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Original Article

EFFICACY OF PCSK9 INHIBITORS IN ADDITION TO BACKGROUND STATIN THERAPY COMPARED WITH PLACEBO IN ACHIEVING LDL-C TARGETS IN ADULTS WITH HYPERLIPIDAEMIA: A SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

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ABSTRACT

Objective: To evaluate the effect of Proprotein Convertase Subtilisin/Kexin type 9 (PCSK9) inhibitors, compared with placebo, when added to background statin therapy, on the proportion of adults with hyperlipidaemia achieving low-density lipoprotein cholesterol (LDL-C)<1.8 mmol/l or ≥50% reduction from baseline.

Methods: A systematic search of PubMed, Scopus, Cochrane Library, and Google Scholar (2015–2025) identified randomized controlled trials (RCTs) enrolling adults (≥18 y) with hyperlipidaemia on background statin therapy. Eligible trials compared any PCSK9 inhibitor to placebo, reporting binary outcomes for LDL-C target attainment. Data extraction and risk of bias assessment followed PRISMA 2020 guidelines. Random-effects meta-analysis was performed to calculate pooled risk ratios (RR) with 95% confidence intervals (CI). Heterogeneity (I^2), publication bias, and sensitivity analysis were conducted.

Results: Five RCTs (n>50,000 participants) were included. PCSK9 inhibitors significantly increased the likelihood of achieving LDL-C targets versus placebo (pooled RR = 2.57, 95% CI: 2.52–2.63). Individual study RRs ranged from 1.89 to 31.37. Heterogeneity was high (I^2 = 99.86%), largely influenced by one outlier study; removal of this trial reduced I^2 to 61.39%. All studies had low risk of bias, and no evidence of publication bias was detected. The GRADE certainty of evidence was rated as moderate, downgraded for inconsistency.

Conclusion: Adding PCSK9 inhibitors to statin therapy substantially improves LDL-C target attainment in high-risk hyperlipidaemia patients, representing a potent adjunctive strategy when conventional lipid-lowering approaches are insufficient.

Keywords: PCSK9 inhibitors, Statins, Hyperlipidaemia, LDL-C reduction, Meta-analysis, Lipid-lowering therapy, Systematic review, Dyslipidaemia

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INTRODUCTION

Hyperlipidaemia, characterized by elevated levels of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and triglycerides (TG), with or without reduced high-density lipoprotein cholesterol (HDL-C), is a major risk factor for the development of atherosclerotic cardiovascular disease (ASCVD) [1]. The global burden of hyperlipidaemia is increasing, influenced by dietary habits, sedentary lifestyles, and metabolic disorders such as type 2 diabetes mellitus (T2DM) [2]. Untreated lipid abnormalities contribute to endothelial dysfunction, vascular inflammation, and accelerated atherosclerosis, ultimately leading to coronary artery disease, stroke, and peripheral vascular disease [3].

Epidemiological studies have demonstrated that age and gender significantly influence lipid profiles. Postmenopausal women often exhibit higher TC, LDL-C, and TG levels than men of the same age group, which may be attributed to hormonal changes [1]. Additionally, age progression is associated with a proportional increase in lipid parameters, underscoring the importance of early detection and lifestyle interventions to reduce cardiovascular risk [4]. In patients with T2DM, dyslipidaemia presents as elevated TG, small dense LDL particles, and reduced HDL-C, which markedly increases cardiovascular risk [4].

Current first-line pharmacological therapy for hyperlipidaemia involves statins, which inhibit HMG-CoA reductase and effectively lower LDL-C. However, even with maximally tolerated doses, many high-and very-high-risk patients fail to achieve LDL-C targets recommended by international guidelines (<1.8 mmol/l or<70 mg/dl, or ≥50% reduction from baseline) [5]. This treatment gap highlights the need for adjunctive lipid-lowering therapies to optimize cardiovascular risk reduction.

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, such as evolocumab, alirocumab, and inclisiran, have emerged as potent agents that reduce LDL-C by preventing degradation of hepatic LDL receptors. When combined with statin therapy, PCSK9 inhibitors have demonstrated significant additional LDL-C lowering and a higher likelihood of achieving therapeutic targets, with favourable tolerability profiles [6].

While several randomized controlled trials (RCTs) have evaluated the efficacy of PCSK9 inhibitors, no meta-analysis has specifically synthesized evidence on their effect in addition to background statin therapy for achieving LDL-C<1.8 mmol/l or ≥50% reduction from baseline in adults with hyperlipidaemia. Such evidence is essential for guiding clinicians in selecting optimal lipid-lowering regimens for high-risk patients.

The objective of the meta-analysis is to evaluate the effect of PCSK9 inhibitors, compared with placebo, when added to background statin therapy, on the proportion of adults with hyperlipidaemia achieving LDL-C<1.8 mmol/l or ≥50% reduction from baseline.

MATERIALS AND METHODS

Research question

In adults (≥18 y) with hyperlipidaemia receiving stable background statin therapy (with or without ezetimibe), does the addition of PCSK9 inhibitors, compared with placebo, increase the proportion of patients achieving LDL-C<1.8 mmol/l (<70 mg/dl) or ≥50% reduction from baseline LDL-C levels?

Study design and reporting standards

This research utilised a quantitative meta-analytical methodology based on data acquired from qualifying investigations. The execution

and documentation of the meta-analysis adhered to the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines to ensure transparency, reproducibility, and scientific rigour [7]. This meta-analysis just employed existing literature and did not incorporate any novel data from humans or animals. Consequently, ethical approval or institutional review board authorisation was unnecessary.

Eligibility criteria

This review considered randomized controlled trials enrolling adults (≥18 y), with or without established atherosclerotic cardiovascular disease (ASCVD) or high cardiovascular risk, diagnosed with familial or non-familial hyperlipidaemia and receiving stable background statin therapy, with or without ezetimibe. Eligible studies evaluated any PCSK9 inhibitor, irrespective of type, dose, or regimen, in combination with statin therapy, compared with placebo plus the same background statin regimen. Only articles published between 2015 and 2025 in peer-reviewed, indexed journals written in English language were included. Trials were required to report binary outcomes, that is the proportion of participants achieving LDL-C<1.8 mmol/l (<70 mg/dl) or ≥50% reduction from baseline with a minimum follow-up of four weeks. Exclusion criteria comprised non-randomized designs, observational studies, reviews, or meta-analysis; absence of background statin therapy in both arms; head-to-head comparisons of PCSK9 inhibitors with statin monotherapy; reporting only mean LDL-C change without sufficient data for binary outcome calculation; and duplicate datasets.

Search strategy

After conducting a comprehensive search of electronic databases, the researchers were able to discover research that met the criteria for consideration. A number of databases, such as Google Scholar, Scopus, PubMed, and the Cochrane Library, were searched by the researchers.

Boolean operators, along with the keywords, such as the following, were incorporated into the search method:

("PCSK9 inhibitor" or “evolocumab” or “alirocumab” or “inclisiran” or “tafolecimab”) and ("hyperlipidaemia" or “dyslipidaemia” or "familial hypercholesterolemia") and ("statin" or "HMG-CoA reductase inhibitor") and ("randomized controlled trial" or “RCT” or "clinical trial") and ("LDL-C" or "low-density lipoprotein cholesterol" or "cholesterol reduction")

Study selection process

The research selection method adhered to the PRISMA 2020 paradigm, comprising four principal phases: identification, screening, eligibility, and inclusion. In the identification step, records were obtained through extensive searches of electronic databases. During the screening step, titles and abstracts were evaluated for their pertinence. Subsequently, full-text articles were assessed for eligibility according to established inclusion and exclusion criteria. Studies that fulfilled all eligibility criteria were incorporated into the final meta-analysis. Duplicate records were eliminated, and the rationale for removal was recorded at each phase of the procedure. In conclusion, five studies were chosen for inclusion, each offering binary outcome data appropriate for analysis. Two independent reviewers screened all retrieved titles and abstracts against the eligibility criteria. Any disagreements between the two reviewers were resolved through discussion, and, when necessary, adjudication by a third independent reviewer.

Data extraction process

Data extraction was performed independently by two reviewers using a standardized Microsoft Excel 365 form. Extracted variables included study characteristics (study ID, author, year, sample size, follow-up duration), participant demographics, intervention details (PCSK9 inhibitor type and dose), comparator details, and binary outcome data (number achieving LDL-C<1.8 mmol/l or ≥50% reduction, total number randomized per arm). Discrepancies were resolved by consensus or referral to a third reviewer.

Statistical analysis

All statistical analyses were performed using Microsoft Excel 365. For each included trial, risk ratios (RR) with 95% confidence intervals (CI) were calculated for the primary outcome. A random-effects model was applied to pool effect sizes, accounting for between-study variability. Statistical heterogeneity was assessed using the I^2 statistic, with thresholds of 25%, 50%, and 75% representing low, moderate, and high heterogeneity, respectively. Publication bias was evaluated visually through funnel plot and Egger’s Test. Sensitivity analyses and subgroup analyses were conducted where applicable to assess the robustness of findings.

RESULTS

Study selection and sample characteristics

A total of 41 records were identified through the initial database search. After the removal of 9 duplicates, 32 unique records were screened based on title and abstract. Of these, 24 records were excluded for not meeting the eligibility criteria, leaving 8 full-text articles for detailed assessment. Following full-text evaluation, 3 studies were excluded for reasons such as ineligible study design, absence of required binary LDL-C outcomes, or intervention not meeting the criteria. Ultimately, 5 randomized controlled trials fulfilled all inclusion criteria and were included in both the qualitative synthesis and quantitative meta-analysis.

The included studies enrolled adult participants (≥18 y) with or without established atherosclerotic cardiovascular disease or high cardiovascular risk, all of whom were on stable background statin therapy, with or without ezetimibe. The trials varied in sample size, follow-up duration, and type of PCSK9 inhibitor used, but all reported the proportion of participants achieving LDL-C<1.8 mmol/l (<70 mg/dl) or ≥50% reduction from baseline levels either directly or indirectly. The detailed PRISMA summary of the selection process is provided in table 1.

Table 1: PRISMA summary table

Stage	Frequency (n)
Records identified through database searching	41
Duplicates removed	9
Records screened	32
Records excluded	24
Full-text articles assessed for eligibility	8
Full-text articles excluded	3
Studies included in qualitative and quantitative synthesis	5

Study characteristics

Details of study attributes which were included in this research are displayed in table 2.

Meta-analysis findings

The effect estimates of the meta-analysis are summarised below in table 3.

Interpretation of table 3

The five included randomized trials showed RRs ranging from 1.89 (S4) to 31.37 (S1). Larger studies (S4, S5) had narrower confidence intervals, indicating greater precision. Trials S2, S3, and S5 reported RRs above 7, highlighting a notably higher achievement of LDL-C targets with PCSK9 inhibitors versus placebo. The pooled RR was 2.57 (95% CI: 2.52–2.63), confirming a significant overall benefit of adding PCSK9 inhibitors to background statin therapy.

Forest plot

Risk ratios (RR) with 95% confidence intervals (CIs) are shown in the below forest plot for each included randomized controlled trial, along with the pooled effect estimate from the random-effects meta-analysis (fig. 1).

Table 2: Attributes of included randomized controlled trials (RCTs)

Study ID	First Author (Year)	Study design	Population	Intervention (PCSK9i)	Comparator	Intervention dose	Comparator dose	Primary Outcome	Proportion of patients achieving target outcome in Intervention group*	Proportion of patients achieving target outcome in Comparator group*	Duration (weeks)
S1	Li Q *et al.* (2023) [8]	RCT	Heterozygous familial hypercholesterolemia (HeFH)	Tafolecimab	Placebo	450 mg SC every 4 w	Matching placebo SC	LDL-C<1.8 mmol/l or ≥50% reduction	193/201	3/98	12
S2	Ray *et al.* (2020) (Orion-10 Trial) [9]	RCT	ASCVD with elevated LDL-C	Inclisiran	Placebo	300 mg SC on day 1, day 90, then every 6 mo	Matching placebo SC	LDL-C<1.8 mmol/l or ≥50% reduction	605/781	84/780	73
S3	Robinson *et al.* (2015) [10]	RCT	Hyperlipidaemia with high cardiovascular risk	Alirocumab	Placebo	150 mg SC every 2 w (adjusted if needed)	Matching placebo SC	LDL-C<1.8 mmol/l or ≥50% reduction	1213/1530	62/780	24
S4	Schwartz *et al.* (2018) [11]	RCT	Acute coronary syndrome with elevated LDL-C	Alirocumab	Placebo	75 mg SC every 2 w, titrated to 150 mg if LDL-C above target	Matching placebo SC	LDL-C<1.8 mmol/l or ≥50% reduction	7945/9462	4214/9462	144
S5	Sabatine *et al.* (2017) [12]	RCT	ASCVD with elevated LDL-C	Evolocumab	Placebo	140 mg SC every 2 w or 420 mg monthly	Matching placebo SC	LDL-C<1.8 mmol/l or ≥50% reduction	11899/13784	1515/13780	48

*Proportion of patients achieving target outcome in intervention group = Sample size of intervention group showing the desired outcome/Total sample size of intervention group. **Proportion of patients achieving target outcome in Comparator group = Sample size of comparator group showing the desired outcome/Total sample size of comparator group.

Table 3: Summary of effect estimates for included randomized controlled trials

Study ID	RR	Log(RR)	SE	Lower 95% CI (Individual Study)	Upper 95% CI (Individual Study)	Weight	Weighted Log(RR)	Pooled RR	SE of Pooled Log(RR)	Lower 95% CI (Meta-analysis)	Upper 95% CI (Meta-analysis)
S1	31.37	3.4457	0.5686	10.29	95.61	3.09	10.6569	2.5747	0.0109	2.5203	2.6303
S2	7.19	1.9731	0.1049	5.86	8.83	90.95	179.4539				
S3	9.97	2.3000	0.1225	7.84	12.68	66.59	153.1509				
S4	1.89	0.6341	0.0123	1.84	1.93	6587.71	4177.4697				
S5	7.85	2.0607	0.0245	7.48	8.24	1669.48	3440.3732				

RR: Risk Ratio; SE: Standard Error; CI: Confidence Interval.

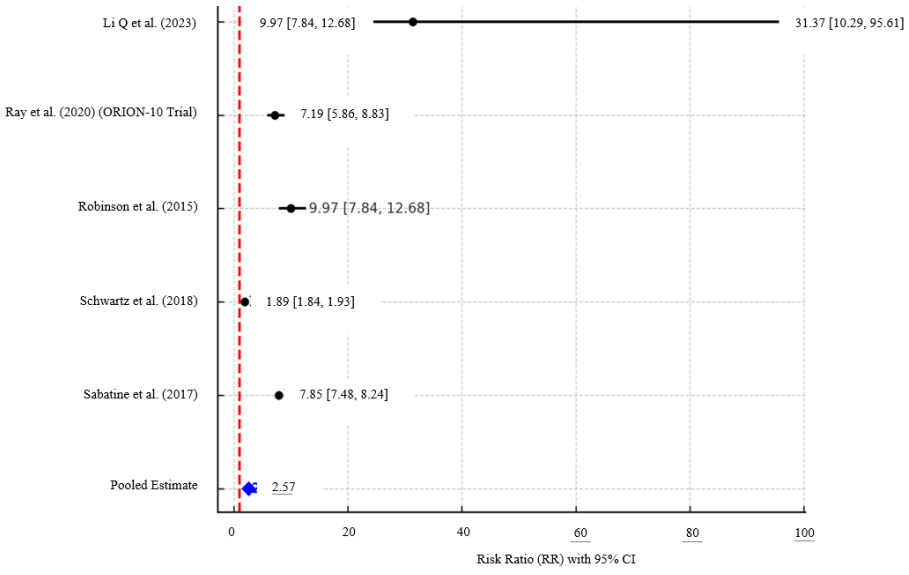

Fig. 1: Forest plot comparing PCSK9 inhibitors versus placebo in achieving LDL-C targets (<1.8 mmol/l or ≥50% reduction) among adults on background statin therapy

Interpretation of forest plot

The forest plot demonstrates that all included trials favoured PCSK9 inhibitors over placebo for achieving LDL-C targets. Individual study RRs ranged from 1.89 to 31.37, with Li *et al.* (2023) showing the largest effect size but also the widest confidence interval, reflecting greater uncertainty due to smaller sample size. Larger studies such as Sabatine *et al.* (2017) and Schwartz *et al.* (2018) yielded narrower CIs, indicating higher precision. The pooled RR was 2.57 (95% CI: 2.52–2.63), confirming a statistically significant and clinically meaningful benefit of adding PCSK9 inhibitors to background statin therapy.

Publication bias assessment

Table 4 shows Egger's regression test assessing small-study effects among trials included in the meta-analysis of PCSK9 inhibitors versus placebo in the background of statin therapy for LDL-C target achievement. The slope (β_1) and intercept (β_0) were derived using precision as the independent variable and standardized effect size as the dependent variable.

Table 4: Egger's regression test for publication bias among included randomized controlled trials

Study ID	Log(RR)	SE	Inverse SE (Precision)	Standardized Effect Size	β_1 (Slope)	β_0 (Intercept)	SE of β_0 (Intercept)	t-value	df	p-value
S1	3.4457	0.5686	1.7586	6.0598	0.6540	17.3566	16.5812	1.0468	3	0.3721
S2	1.9731	0.1049	9.5367	18.8172						
S3	2.3000	0.1225	8.1601	18.7682						
S4	0.6341	0.0123	81.1647	51.4690						
S5	2.0607	0.0245	40.8592	84.2006						

Interpretation of egger's regression test

Egger's regression analysis demonstrated a non-significant intercept ($p = 0.372$, that is $p>0.05$), indicating no statistically detectable small-study effects or publication bias. This suggests that the pooled effect estimate is unlikely to be distorted by selective reporting or asymmetry in study results.

Fig. 2 shows the funnel plot assessment of the meta-analysis.

Interpretation of funnel plot

The funnel plot demonstrates an overall symmetrical distribution of studies around the pooled effect size, suggesting minimal risk of publication bias. While one study (S4) appears as an outlier with a wider standard error and effect size deviation, its influence does not substantially distort the plot's symmetry. This observation is consistent with Egger's regression test, which yielded a non-significant result ($p = 0.372$), indicating no statistical evidence of small-study effects. The presence of the outlier may slightly widen the confidence boundaries but is unlikely to meaningfully affect the robustness of the pooled estimate.

Risk of bias assessment

Table 5 shows the Risk of Bias (RoB) assessment of the meta-analysis as per the Cochrane RoB 2 guidance tool [13].

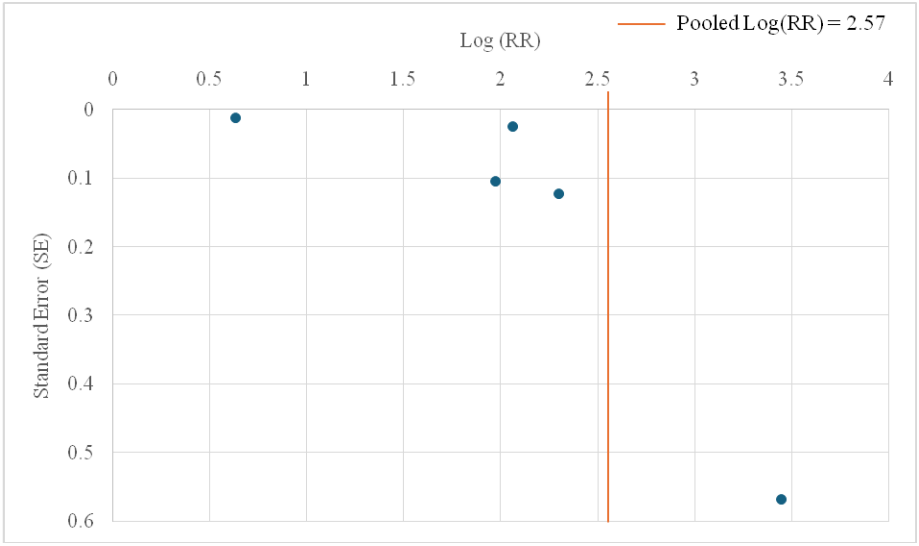

Fig. 2: Funnel plot assessing publication bias among the included studies comparing PCSK9 inhibitors versus placebo for LDL-C target attainment. The vertical red dashed line represents the pooled log(RR), and the blue dashed lines indicate pseudo 95% confidence limits

Table 5: Risk of bias (RoB) assessment for included randomized controlled trials using a domain-based evaluation

Study ID	Domain 1 Judgment	Domain 2 Judgment	Domain 3 Judgment	Domain 4 Judgment	Domain 5 Judgment	Overall RoB	Justification
S1	Low risk	Low risk	Low risk	Low risk	Low risk	Low	RCT with concealed randomization, double-blind, minimal loss to follow-up, outcome pre-specified.
S2	Low risk	Low risk	Low risk	Low risk	Low risk	Low	Adequate randomization/blinding, outcome data complete, LDL-C endpoints pre-specified.
S3	Low risk	Low risk	Low risk	Low risk	Low risk	Low	Randomized, double-blind, ITT analysis, near-complete follow-up, outcome definition standard.
S4	Low risk	Low risk	Low risk	Low risk	Low risk	Low	Large double-blind RCT, balanced arms, pre-specified analysis, minimal missing data.
S5	Low risk	Low risk	Low risk	Low risk	Low risk	Low	Well-conducted RCT with clear allocation concealment, blinding, and pre-registered outcomes.

Interpretation of RoB assessment

All five studies included in this meta-analysis were judged to have a low risk of bias across all evaluated domains, reflecting strong methodological rigor and reliable outcome reporting. Adequate randomization, allocation concealment, blinding procedures, and adherence to pre-specified endpoints were consistently observed. Minimal loss to follow-up and clear outcome definitions further enhances the validity of the findings, thereby increasing confidence in the pooled effect estimates generated from these trials.

Heterogeneity assessment

Table 6 shows Cochrane's Q statistic and I^2statistic calculation for the heterogeneity assessment of the meta-analysis.

Interpretation of heterogeneity assessment

The heterogeneity assessment indicates a very high degree of variability among the included studies, with an I^2 value of approximately 99.86%, suggesting that most of the observed variance is due to differences between studies rather than chance. The Cochran's Q statistic further supports the presence of significant heterogeneity, implying that caution should be exercised when interpreting the pooled results. This level of heterogeneity underscores the need to explore potential sources of variability, such as differences in study populations, interventions, or methodological designs.

Leave-one-out sensitivity analysis

A leave-one-out sensitivity analysis was conducted to evaluate the influence of individual studies on the overall pooled effect and heterogeneity (table 7).

Interpretation

The sensitivity analysis revealed that removal of S4 substantially reduced heterogeneity (I^2 = 61.39%), indicating that this study contributed significantly to the observed variability. However, exclusion of any other single study did not materially alter the high heterogeneity (>98%) or the pooled effect estimate, suggesting overall robustness of the results despite the presence of outlier influence.

Subgroup analysis

A subgroup analysis was performed to assess whether study duration (≤48 w vs.>48 w) influenced the pooled effect estimates and heterogeneity (table 8).

Table 6: Heterogeneity assessment of included studies

Study ID	((Log RR-Pooled log RR)^2)*weight	Cochran's Q statistic	Degrees of freedom (df)	I2 statistic
S1	19.3297104	2952.68869	4	99.8645302
S2	95.998525			
S3	122.12033			
S4	639.687637			
S5	2075.55249			

Table 7: Leave-one-out sensitivity analysis of included studies

Removed study ID	Pooled log(RR)	Q statistic	I^2 value (%)
S1	0.9448	2933.3519	99.90
S2	0.9345	2855.6416	99.86
S3	0.9349	2829.5946	99.86
S4	2.0674	10.3600	61.39
S5	0.6699	363.6638	98.90

Table 8: Subgroup analysis by study duration

Study ID	Duration category	Pooled RR	Lower 95% CI	Upper 95% CI	I^2value (%)
S1	≤48 w	7.9436	7.578935138	8.325892729	78.97
S3					
S5					
S2	>48 w	1.9201	5.23875E-70	7.03735E+69	99.97
S4					

Interpretation of subgroup analysis based on duration of treatment

The subgroup analysis indicated that studies with shorter follow-up durations (≤48 w) showed consistently high relative risk estimates, with high heterogeneity (I^2 = 78.97%). In contrast, longer-duration studies (>48 w) demonstrated substantial heterogeneity (I^2 = 99.97%), largely driven by variation in study design and outcome magnitude. This suggests that follow-up length may partially contribute to variability in effect size, but high heterogeneity persists across both subgroups.

GRADE assessment

The GRADE assessment of the meta-analysis is explained in table 9.

Table 9: GRADE assessment of certainty of evidence for LDL-C reduction with PCSK9 inhibitors

Outcome	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty level	Justification
LDL-C reduction (RR = 2.57, 95% CI: 2.52–2.63)	No	Yes	No	No	No	Moderate	All included RCTs had low RoB. Very high heterogeneity (I^2 = 99.86%) downgraded by one level for inconsistency. Populations, interventions, comparators, and outcomes directly aligned with PICO. CI was narrow and distant from the null line (no effect line), so no downgrade for imprecision. Funnel plot was symmetric and Egger's p = 0.249, indicating no downgrade for publication bias.

Interpretation of GRADE assessment

The certainty of evidence for LDL-C reduction with PCSK9 inhibitors was rated as moderate. Although the body of evidence consisted of well-conducted RCTs with minimal risk of bias, the presence of substantial heterogeneity (I^2 = 99.86%) warranted a downgrade for inconsistency. No downgrades were made for indirectness, imprecision, or publication bias, as the included studies directly addressed the research question, produced precise effect estimates, and showed no signs of small-study effects.

DISCUSSION

This meta-analysis combined data from five rigorously conducted randomised controlled trials (RCTs) to evaluate the efficacy of PCSK9 inhibitors, added to stable statin therapy with or without ezetimibe, in achieving clinically relevant LDL-C targets (<1.8 mmol/l or ≥50% reduction from baseline). The pooled analysis demonstrated a robust and statistically significant benefit, with a pooled risk ratio (RR) of 2.57 (95% CI: 2.52–2.63). This indicates that patients treated with PCSK9 inhibitors were more than twice as likely to reach LDL-C goals compared with placebo. These findings closely parallel results from major cardiovascular outcome trials, such as Fourier (evolocumab) and Odyssey Outcomes (alirocumab), which also reported high target attainment rates and marked LDL-C reductions when PCSK9 inhibitors were added to maximally tolerated statins [11, 12].

The effect sizes observed in this analysis align with the Fourier trial, where evolocumab achieved a ~59% LDL-C reduction from baseline, with 87% of patients reaching<1.8 mmol/l [12], and with Odyssey Outcomes, where alirocumab lowered LDL-C by ~54% and enabled the majority to meet stringent lipid targets [11]. High RRs in several included trials (e. g., Li *et al.*, 2023; Robinson *et al.*, 2015) were driven by the low attainment of LDL-C goals in placebo arms, reflecting the challenge of achieving these levels with statin±ezetimibe alone in high-risk populations.

Previous meta-analyses have reported similar magnitudes of LDL-C lowering with PCSK9 inhibitors, though often expressed as mean percentage change rather than binary target achievement. For instance, Navarese *et al.* (2015) observed a pooled LDL-C reduction of −49.5% [14]. Our focus on binary outcomes makes the findings directly applicable to current guideline-defined treatment targets, enhancing their clinical relevance.

Heterogeneity in the present analysis was substantial (I^2 = 99.86%), which persisted even after subgrouping by follow-up duration, although removal of Schwartz *et al.* (2018) reduced I^2 to 61.39%. The prolonged follow-up (144 w), titration strategies, and differences in baseline risk in that trial likely contributed to its outlier influence. Persistent high heterogeneity across subgroups suggests that factors such as baseline LDL-C, ASCVD burden, and PCSK9 inhibitor type or dosing regimen may also underlie variability in effect estimates. This pattern is consistent with prior meta-analyses that found high I^2 values when pooling diverse PCSK9 inhibitor RCTs [14, 15].

The GRADE assessment rated the certainty of evidence as moderate, with a single downgrade for inconsistency due to heterogeneity. All included RCTs had low risk of bias in every Cochrane RoB 2 domain, and neither Egger's test (p = 0.372) nor the funnel plot suggested publication bias. The leave-one-out sensitivity analysis further confirmed that no single trial materially altered the pooled RR, indicating robustness of the overall effect estimate.

While the LDL-C lowering efficacy of PCSK9 inhibitors is established, its translation into cardiovascular event reduction warrants emphasis. In FOURIER and ODYSSEY OUTCOMES, relative risk reductions in major adverse cardiovascular events (MACE) were modest over 2–3 y, but absolute event reductions were greater in patients achieving very low LDL-C (<0.78 mmol/l) [11, 12]. This supports the likelihood that the degree of LDL-C lowering observed in our pooled analysis would translate into meaningful cardiovascular benefit, especially in very high-risk groups, provided therapy is maintained long-term.

This meta-analysis adhered to PRISMA 2020 methodology and included only high-quality RCTs with low risk of bias, consistent background statin therapy, and directly relevant binary endpoints aligned with clinical guidelines. Multiple PCSK9 inhibitors were represented, enhancing generalisability. The narrow-pooled confidence interval and absence of publication bias increase confidence in the validity of results.

The analysis was limited by the small number of included trials, which restricted the ability to conduct detailed subgroup analyses or meta-regression. Only trial-level data were available, preventing adjustment for patient-level factors such as age, comorbidities, or baseline LDL-C. The very high heterogeneity reduces the precision of pooled effect size interpretation, although robustness was supported by sensitivity analyses. The binary outcome approach, while clinically intuitive, may not capture the full range of LDL-C reductions achieved.

Future research should employ individual participant data (IPD) meta-analyses to identify predictors of LDL-C goal attainment with PCSK9 inhibitors, evaluate the long-term sustainability of lipid lowering beyond five years, and quantify cardiovascular event reduction in relation to achieved LDL-C thresholds. Real-world studies assessing cost-effectiveness, adherence, and outcomes in broader patient populations will be essential to guide clinical and policy decisions.

CONCLUSION

In summary, this meta-analysis demonstrates that adding PCSK9 inhibitors to statin therapy substantially increases the likelihood of achieving stringent LDL-C targets, offering a powerful therapeutic option for high-risk patients where conventional lipid-lowering strategies are insufficient.

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AUTHORS CONTRIBUTIONS

Pranab Das conceived and designed the study, conducted the literature search, extracted and analyzed the data, and drafted the manuscript, while Mukundam Borah contributed to data validation, interpretation of findings, and critical revision of the manuscript; both authors approved the final version and take full responsibility for the integrity and accuracy of the work.

CONFLICT OF INTERESTS

None of the authors have any conflicts of interest to declare.

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