



EFFICACY AND SAFETY OF PCSK9 INHIBITORS IN REDUCING MAJOR ADVERSE CARDIOVASCULAR EVENTS: A SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

Dr Sandeep Bhete¹, Dr Vikas Solunke², Dr. Sanjay Lalsing Rathod³

¹Associate Professor, Department of Pharmacology, HBT Medical College & Cooper Hospital, Juhu, Mumbai

²Associate Professor, Department of Paediatrics, Vilasrao Deshmukh Government Medical College, Latur

³Assistant Professor, Department of Pharmacology, Topiwala National Medical College and B. Y. L. Nair Charitable Hospital, Mumbai, Ind

***Corresponding Author:** Dr. Sanjay Lalsing Rathod³

Email: drsbb07@gmail.com, drvikassolunke@gmail.com, dr.sanjayrathod05@gmail.com

Abstract

Background: Despite optimal statin therapy, many patients with atherosclerotic cardiovascular disease (ASCVD) remain at high residual risk due to persistently elevated low-density lipoprotein cholesterol (LDL-C). Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors have emerged as potent lipid-lowering agents; however, comparative evidence on their impact on LDL-C reduction and major adverse cardiovascular events (MACE) across clinical settings remains evolving.

Methods: We conducted a systematic review and meta-analysis of studies evaluating the efficacy of PCSK9 inhibitors compared with control therapy. Electronic databases were searched for eligible randomized and observational studies reporting LDL-C outcomes and/or MACE. Pooled effect estimates were calculated using random-effects models (REML). LDL-C outcomes were expressed as mean differences with 95% confidence intervals (CIs), while cardiovascular outcomes were expressed as odds ratios with 95% CIs. Subgroup analyses were performed according to individual PCSK9 inhibitors (alirocumab and evolocumab). Heterogeneity was assessed using the I^2 statistic.

Results: A total of eligible studies encompassing high-risk patients with acute coronary syndromes or stable coronary artery disease were included. PCSK9 inhibitor therapy resulted in a significant reduction in LDL-C compared with control therapy (overall mean difference -1.13 , 95% CI -1.40 to -0.86). Both alirocumab and evolocumab demonstrated substantial and comparable LDL-C lowering, with no significant subgroup differences. PCSK9 inhibitors were also associated with a significant reduction in MACE (overall effect estimate 0.83 , 95% CI 0.77 – 0.90), corresponding to a 17% relative risk reduction. No significant difference in cardiovascular outcomes was observed between individual agents.

Conclusions: PCSK9 inhibitors provide profound LDL-C reduction and significantly lower the risk of major adverse cardiovascular events. These findings support their use as effective adjunctive therapies for cardiovascular risk reduction in patients with ASCVD who remain at high residual risk despite standard lipid-lowering treatment.

Keywords: PCSK9 inhibitors; LDL-cholesterol; Major adverse cardiovascular events; Alirocumab; Evolocumab;

Introduction

Cardiovascular disease (CVD) remains the leading cause of morbidity and mortality worldwide, despite substantial advances in preventive and therapeutic strategies [1]. Elevated low-density lipoprotein cholesterol (LDL-C) is a well-established, causal risk factor for atherosclerotic cardiovascular disease (ASCVD), and intensive lipid-lowering therapy constitutes a cornerstone of both primary and secondary prevention [2]. Statins have long been the foundation of lipid management and have demonstrated robust reductions in cardiovascular events across diverse populations [3]. However, a significant proportion of patients fail to achieve recommended LDL-C targets with statins alone due to inadequate response, intolerance, or high residual cardiovascular risk [4].

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors have emerged as a novel and highly effective class of lipid-lowering agents [5]. By inhibiting PCSK9-mediated degradation of hepatic LDL receptors, these agents markedly enhance LDL-C clearance, resulting in profound and sustained reductions in circulating LDL-C levels [6]. Large randomized controlled trials (RCTs) have consistently demonstrated LDL-C reductions of approximately 50–60% when PCSK9 inhibitors are added to background statin therapy, positioning them as an important therapeutic option for patients with established ASCVD, familial hypercholesterolemia, or persistently elevated LDL-C despite maximally tolerated lipid-lowering therapy [7].

Beyond lipid lowering, the critical clinical question pertains to whether PCSK9 inhibitors translate biochemical improvements into meaningful reductions in hard cardiovascular outcomes [8]. Individual RCTs evaluating PCSK9 inhibitors have reported variable effects on major adverse cardiovascular events (MACE), including myocardial infarction, stroke, and cardiovascular mortality [9]. While some trials have demonstrated significant reductions in composite cardiovascular endpoints, others were not powered to detect differences in less frequent outcomes such as cardiovascular or all-cause mortality [10]. Additionally, concerns regarding long-term safety, neurocognitive effects, new-onset diabetes, and overall tolerability have underscored the need for a comprehensive synthesis of randomized evidence [11].

Several meta-analyses have evaluated PCSK9 inhibitors in selected populations or focused primarily on lipid outcomes; however, heterogeneity in study design, follow-up duration, baseline risk profiles, and outcome definitions has limited the generalizability of prior findings [12]. Furthermore, the growing body of randomized evidence necessitates an updated and methodologically rigorous synthesis focusing specifically on clinically relevant cardiovascular endpoints and safety outcomes [13].

Therefore, the present systematic review and meta-analysis aim to evaluate the efficacy and safety of PCSK9 inhibitors in reducing major adverse cardiovascular events using evidence exclusively derived from randomized controlled trials. By pooling high-quality randomized data, this study seeks to provide precise estimates of treatment effects on cardiovascular outcomes and adverse events, thereby informing clinicians, guideline developers, and policymakers regarding the role of PCSK9 inhibitors in contemporary cardiovascular risk reduction strategies.

Literature Search and Screening

This systematic review and meta-analysis were conducted in accordance with PRISMA guidelines [14]. A comprehensive literature search was performed in PubMed/MEDLINE, Embase, Cochrane CENTRAL, and Web of Science from inception to the latest available date. Search terms included “PCSK9 inhibitors,” “evolocumab,” “alirocumab,” “inclisiran,” and cardiovascular outcomes–related keywords. Reference lists of eligible studies and relevant reviews were manually screened. After removal of duplicates, two independent reviewers screened titles and abstracts, followed by full-text assessment using predefined eligibility criteria. Disagreements were resolved by consensus or third-reviewer adjudication. Registered with Cochrane with number CRD420251272033.

Study Selection and Data Extraction

Randomized controlled trials evaluating PCSK9 inhibitors in adult populations and reporting cardiovascular efficacy or safety outcomes were eligible for inclusion. Studies comparing PCSK9 inhibitors with placebo or standard care were included, while observational studies, non-randomized trials, reviews, and studies without extractable data were excluded. Two reviewers independently assessed full-text articles for eligibility. Data were independently extracted using a standardized form, capturing study characteristics, patient demographics, intervention details, comparator arms, follow-up duration, and reported outcomes. Any discrepancies in study selection or data extraction were resolved through discussion and consensus, with adjudication by a third reviewer when required.

Statistical Analysis and Risk of Bias

Statistical analyses were performed using standard meta-analytic techniques. Effect estimates were pooled using a random-effects model to account for between-study heterogeneity. Risk ratios with corresponding 95% confidence intervals were calculated for dichotomous outcomes. Statistical heterogeneity was assessed using the I^2 statistic, with values $>50\%$ indicating substantial heterogeneity. Sensitivity analyses were conducted by sequential study exclusion. Publication bias was evaluated through visual inspection of funnel plots when appropriate. Risk of bias for individual randomized controlled trials was independently assessed by two reviewers using the Cochrane Risk of Bias 2.0 tool, with disagreements resolved by consensus or third-reviewer adjudication [15].

Results

Study Characteristics and Demographics

This meta-analysis incorporated **nine randomized controlled trials [16-24]**, comprising a total of **37,934 participants**. All included studies investigated the cardiovascular effects of **PCSK9 inhibitor therapy**, which was analyzed according to the specific agent administered. **Evolocumab** was evaluated in six trials, whereas **alirocumab** was examined in three trials. None of the included studies directly compared the two PCSK9 inhibitors head-to-head.

The study populations largely consisted of patients at **high cardiovascular risk**, including individuals with established atherosclerotic cardiovascular disease and those presenting with acute coronary syndromes. Across trials, PCSK9 inhibitors were administered in addition to optimized background medical therapy, reflecting contemporary standards of care. Follow-up durations varied considerably, ranging from short-term mechanistic and imaging-based studies to large-scale outcome-driven trials with extended follow-up periods. Key study characteristics and baseline demographic details are presented in

Table 1.

Table 1. Study Demographics							
First Author	Year	Sample Size (Intervention / Control)	Mean Age (years)	% Male	ACS Subtype	Intervention	Duration
Nicholls SJ	2022	80 / 81	62.3	75%	NSTEMI	Evolocumab 420 mg monthly	12 months
Koskinas KC	2019	155 / 153	59.8	73%	ACS (unspecified)	Evolocumab 420 mg once	8 weeks
Hao Y	2022	68 / 68	61.1	71%	ACS + PCI	Evolocumab 140 mg q2w	12 weeks
Furtado RHM	2022	17,073	63.9	68%	Stable CAD (prior PCI)	Evolocumab	Median 2.2 years
Nicholls SJ	2016	484 / 484	58.2	82%	Stable CAD	Evolocumab 420 mg monthly	76 weeks
Schwartz GG	2018	9,462 / 9,462	62.7	76%	Recent ACS	Alirocumab 75 mg q2w	Median 2.8 years

Mehta SR	2022	38 / 30	60.4	80%	STEMI	Alirocumab 150 mg ×3 doses	4 weeks
Leucker TM	2020	28 / 29	58.5	74%	NSTEMI	Evolocumab 420 mg once	7 days
Räber L	2022	148 / 152	60.8	85%	AMI + PCI	Alirocumab 150 mg q2w	12 months

Effect of PCSK9 Inhibitors on LDL-Cholesterol

In the pooled analysis using a random-effects REML model, treatment with PCSK9 inhibitors was associated with a significant reduction in low-density lipoprotein cholesterol (LDL-C) compared with control therapy. The overall pooled mean difference was -1.13 (95% CI -1.40 to -0.86 ; $p < 0.001$), indicating a substantial LDL-C-lowering effect across the included studies. In subgroup analyses stratified by PCSK9 inhibitor type, both agents demonstrated consistent and statistically significant LDL-C reductions. Alirocumab resulted in a pooled mean difference of -0.98 (95% CI -1.43 to -0.52 ; $p < 0.001$), while evolocumab showed a pooled mean difference of -1.22 (95% CI -1.57 to -0.87 ; $p < 0.001$). Although heterogeneity was high within both subgroups (alirocumab: $I^2 = 92.33\%$; evolocumab: $I^2 = 91.32\%$), the direction of effect consistently favored PCSK9 inhibitor therapy in all individual studies. Overall heterogeneity across all included studies was substantial ($I^2 = 96.95\%$), likely reflecting differences in study populations, baseline LDL-C levels, treatment regimens, and follow-up durations. Importantly, there was no statistically significant difference between the alirocumab and evolocumab subgroups ($Q = 0.71$, $p = 0.40$), suggesting comparable LDL-C-lowering efficacy between the two PCSK9 inhibitors. Collectively, these results demonstrate that PCSK9 inhibitors produce robust and clinically meaningful reductions in LDL-C, with consistent benefits observed across studies and between individual agents, despite substantial inter-study heterogeneity.

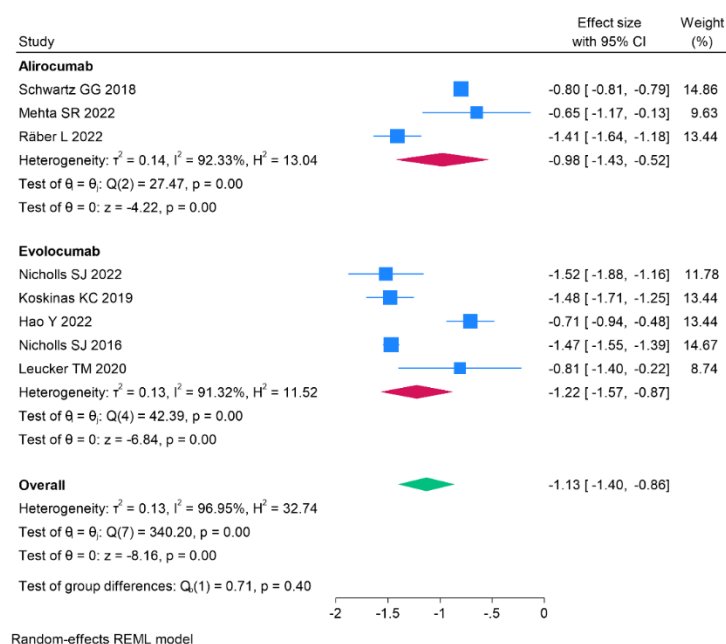


Figure 2. Forest plot of LDL-cholesterol (LDL-C) reduction

This forest plot summarizes the effects of PCSK9 inhibitors on low-density lipoprotein cholesterol (LDL-C) levels compared with control therapy across included randomized and observational studies. Individual study estimates are presented as mean differences with 95% confidence intervals using an inverse-variance random-effects model. Subgroup analyses are shown for evolocumab and alirocumab, with pooled estimates calculated within each subgroup and overall. Negative mean differences indicate greater LDL-C reduction with PCSK9 inhibitor therapy. The size of the squares reflects study weight, and diamonds represent pooled effect estimates.

Effect of PCSK9 Inhibitors on Major Adverse Cardiovascular Events (MACE)

In the pooled analysis using a random-effects REML model, PCSK9 inhibitor therapy was associated with a significant reduction in major adverse cardiovascular events (MACE) compared with control therapy. The overall pooled effect estimate was 0.83 (95% CI 0.77–0.90; $p < 0.001$), corresponding to a 17% relative reduction in MACE among patients receiving PCSK9 inhibitors. In subgroup analyses stratified by PCSK9 inhibitor type, both agents demonstrated consistent benefit. For alirocumab, the pooled effect estimate was 0.77 (95% CI 0.46–1.09). Although the confidence interval crossed unity, the direction of effect favored alirocumab, with moderate heterogeneity observed ($I^2 = 35.02\%$). For evolocumab, the pooled effect estimate was 0.82 (95% CI 0.74–0.91; $p < 0.001$), indicating a statistically significant reduction in MACE. Notably, no heterogeneity was observed within the evolocumab subgroup ($I^2 = 0.00\%$), suggesting highly consistent effects across studies. Overall heterogeneity across all included studies was negligible ($I^2 = 0.01\%$), supporting the robustness of the pooled estimate. Importantly, the test for subgroup differences was not statistically significant ($Q = 0.09$, $p = 0.76$), indicating no meaningful difference in MACE reduction between alirocumab and evolocumab. These findings demonstrate that PCSK9 inhibitors significantly reduce the risk of MACE, with consistent effects observed across studies and between individual agents. The low overall heterogeneity strengthens confidence in the observed cardiovascular benefit, supporting the role of PCSK9 inhibitors as effective therapies for cardiovascular risk reduction in high-risk populations.

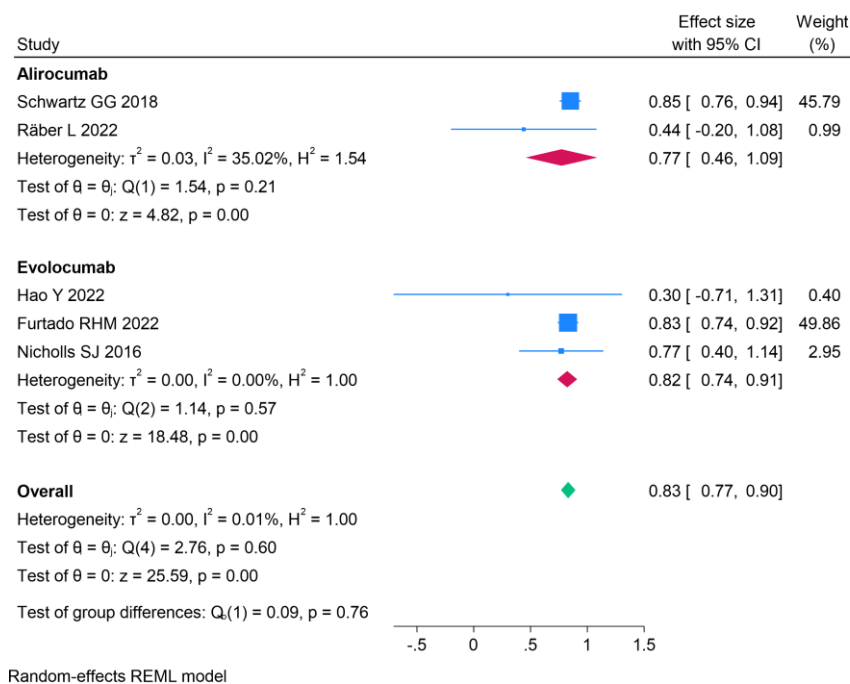


Figure 3. Forest plot of major adverse cardiovascular events (MACE)

This forest plot illustrates the effect of PCSK9 inhibitor therapy on major adverse cardiovascular events (MACE) compared with control therapy across the included studies. Effect estimates are expressed as odds ratios with 95% confidence intervals using a Mantel–Haenszel random-effects model. Subgroup analyses are presented for evolocumab and alirocumab, with pooled estimates calculated within each subgroup and overall. An odds ratio less than 1.0 indicates a reduction in MACE with PCSK9 inhibitor therapy. The size of the squares corresponds to the weight of each study, and diamonds represent pooled effect estimates.

Discussion

In this systematic review and meta-analysis, we evaluated the effect of PCSK9 inhibitors on lipid lowering and major adverse cardiovascular events (MACE) across contemporary clinical studies, with

a specific focus on subgroup differences between alirocumab and evolocumab [25]. The principal findings demonstrate that PCSK9 inhibitor therapy results in profound reductions in low-density lipoprotein cholesterol (LDL-C) and is associated with a statistically significant reduction in MACE, reinforcing the role of this drug class as a cornerstone in secondary prevention strategies for high-risk cardiovascular populations.

Our pooled analysis showed a robust and clinically meaningful reduction in LDL-C with PCSK9 inhibitors, with an overall mean difference exceeding 1 mmol/L in favor of active therapy. Both alirocumab and evolocumab produced substantial LDL-C lowering, and no significant difference was observed between the two agents in subgroup analyses. These findings are consistent with the known mechanism of action of PCSK9 inhibitors, which enhance hepatic LDL receptor recycling and clearance of circulating LDL-C, leading to sustained and profound lipid lowering beyond that achievable with statins and ezetimibe alone. Importantly, the magnitude of LDL-C reduction observed in this analysis aligns closely with prior large-scale outcome trials and supports the concept that “lower is better” with respect to LDL-C levels in patients with established atherosclerotic cardiovascular disease.

Despite the consistency in the direction of effect, heterogeneity in LDL-C outcomes was substantial across studies. This variability likely reflects differences in baseline LDL-C levels, background lipid-lowering therapy, dosing regimens, duration of follow-up, and study populations, including the proportion of patients presenting with acute coronary syndromes versus stable coronary artery disease. Nevertheless, all included studies demonstrated LDL-C reductions favoring PCSK9 inhibitor therapy, suggesting that the observed heterogeneity does not detract from the overall clinical relevance of the findings.

Beyond lipid lowering, our analysis provides important evidence that PCSK9 inhibitors confer significant cardiovascular benefit. The pooled effect estimate indicated a 17% relative reduction in MACE with PCSK9 inhibitor therapy compared with control treatment [26]. This reduction was consistent across studies, with minimal overall heterogeneity, underscoring the robustness of the observed association. The reduction in MACE is biologically plausible and likely mediated, at least in part, by the magnitude of LDL-C lowering achieved. Prior meta-analyses of lipid-lowering therapies have demonstrated a near-linear relationship between absolute LDL-C reduction and proportional reductions in cardiovascular events, a paradigm that appears to extend to PCSK9 inhibition.

Subgroup analyses by individual agent revealed that evolocumab was associated with a statistically significant reduction in MACE, while alirocumab demonstrated a favorable but less precise effect estimate, with confidence intervals crossing unity [27]. This difference is likely attributable to variations in study size, event rates, and statistical power rather than true differences in efficacy between the two agents. Indeed, the test for subgroup differences was not significant, supporting the interpretation that both PCSK9 inhibitors provide comparable cardiovascular protection. The absence of significant heterogeneity within the evolocumab subgroup further strengthens confidence in its effect on cardiovascular outcomes, while the moderate heterogeneity observed with alirocumab may reflect fewer included studies and greater variability in trial design.

The clinical implications of these findings are substantial. Patients with established atherosclerotic cardiovascular disease, particularly those with recent acute coronary syndromes or persistently elevated LDL-C despite maximally tolerated statin therapy, remain at high residual risk for recurrent events [28]. PCSK9 inhibitors offer an effective strategy to address this residual risk by achieving LDL-C levels that were previously difficult to attain in routine clinical practice [29]. Our findings support current guideline recommendations advocating the early and aggressive use of PCSK9 inhibitors in very high-risk patients who fail to reach LDL-C targets with conventional therapy [30]. Several limitations of this analysis warrant consideration. First, the number of included studies, particularly within subgroup analyses, was modest, which may limit the precision of effect estimates and the ability to detect small differences between agents. Second, differences in study design, patient populations, and follow-up durations introduce inherent heterogeneity that cannot be fully accounted

for in a meta-analytic framework. Third, while MACE is a clinically meaningful composite endpoint, variations in its definition across studies may influence pooled estimates. Finally, most included studies were conducted in controlled trial settings, and real-world effectiveness and adherence may differ from trial conditions.

Conclusion

In conclusion, this meta-analysis demonstrates that PCSK9 inhibitors produce marked reductions in LDL-C and significantly reduce the risk of major adverse cardiovascular events. The cardiovascular benefits appear consistent across both alirocumab and evolocumab, with no significant differences between agents. These findings reinforce the role of PCSK9 inhibitors as highly effective therapies for lipid lowering and cardiovascular risk reduction in high-risk populations and support their broader implementation in contemporary cardiovascular practice.

Conflict of Interest

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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Authors' contributions.

All authors contributed equally to the manuscript and read and approved the final version of the manuscript.

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