Systematic Review

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Impact of PCSK9 Inhibitors on Lipid Profiles and Inflammatory Biomarkers in Patients With Coronary Artery Disease After Percutaneous Coronary Intervention: A Meta-Analysis of Randomized Controlled Trials

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Background: Coronary artery disease (CAD) remains a leading cause of mortality and disability globally, and percutaneous coronary intervention (PCI) is a key revascularization procedure. However, patients often face residual risks, including dyslipidemia and persistent inflammation post-PCI. This meta-analysis aimed to systematically evaluate the effects of Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors on lipid profiles and inflammatory biomarkers in CAD patients after PCI.
Methods: We conducted a systematic literature search of PubMed, Web of Science, and Embase databases, with a cutoff date of September 2025. Only randomized controlled trials (RCTs) were included in the analysis. The methodological quality in the selected studies was assessed using the Cochrane Risk of Bias tool, and the meta-analysis was performed using RevMan software. For continuous outcome, results were expressed as the mean difference (MD) with a 95% confidence interval (CI). Fixed-effect or random-effects models were selected for analysis based on the degree of heterogeneity, as quantified by the I^2 statistic.
Results: A total of 8 RCTs involving 1043 participants were included. The overall quality of evidence was moderate. PCSK9 inhibitors significantly reduced levels of triglycerides (MD = –0.52, 95% CI: –0.92– –0.12; I^2 = 76%), total cholesterol (MD = –0.61, 95% CI: –0.91– –0.32; I^2 = 66%), and low-density lipoprotein cholesterol (LDL-C) (MD = –1.37, 95% CI: –2.24– –0.50; I^2 = 99%). Regarding inflammatory biomarkers, tumor necrosis factor-α (TNF-α) was significantly reduced (MD = –23.65, 95% CI: –28.68– –18.62; I^2 = 67%), while no statistically significant differences were found for high-sensitivity C-reactive protein (hs-CRP) (MD = –1.49, 95% CI: –3.44– 0.46; I^2 = 97%) or interleukin-6 (IL-6) (MD = –6.84, 95% CI: –15.15–1.46; I^2 = 98%).
Conclusion: PCSK9 inhibitors significantly improve lipid parameters and certain inflammatory markers in CAD patients after PCI, suggesting benefits beyond lipid-lowering. Further high-quality trials are needed to confirm these findings and evaluate clinical outcomes.

Keywords: coronary artery disease; PCSK9 inhibitor; percutaneous coronary intervention; lipids; inflammation; meta-analysis

Introduction

Coronary artery disease (CAD) is one of the leading causes of death and disability worldwide [1]. Percutaneous coronary intervention (PCI) is a key method for revascularization, which can effectively open blocked vessels, improve myocardial perfusion, and reduce the mortality rate of patients with acute coronary syndrome [2–4]. Despite receiving PCI and standard drug therapy, patients still face significant residual risks, which are driven by poor lipid control and persistent vascular inflammatory state, factors are closely linked to adverse prognosis, such as heart failure-related re-hospitalization [5,6]. Low-density lipoprotein cholesterol (LDL-C) is a key pathogenic factor for the occurrence and development of atherosclerosis [7]. Moreover, inflammation plays a crucial role in the initiation, progression, and rupture of atherosclerotic plaques [8,9]. Therefore, after PCI, effectively managing dyslipidemia and simultaneously inhibiting vascular inflammation is of great significance for stabilizing plaques and improving long-term prognosis. Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors are a novel class of lipid-lowering agents that work by inhibiting the interaction between PCSK9 and the low-density lipoprotein receptor (LDLR) on hepatocytes. This inhibition reduces LDLR degradation, accelerates the clearance of LDL-C, and thereby significantly lowers serum LDL-C levels [10,11]. Recent basic research also suggests that PCSK9 inhibitors may have multiple effects such as anti-inflammatory properties, for example, inhibiting the secretion of pro-inflammatory factors like tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) by macrophages.

Despite established lipid-lowering efficacy, the specific impact of PCSK9 inhibitors on the high-risk post-PCI population, who exhibit a confluence of residual dyslipidemia and heightened inflammatory activity, remains a critical and less explored area. The post-PCI state is characterized by vascular injury and a consequent inflammatory cascade, which can perpetuate atherosclerosis and increase the risk of restenosis and subsequent events [12]. This unique pathophysiology underscores the need for therapies that address both lipid and inflammatory components of residual risk. Although some randomized controlled trials (RCTs) have explored the application of PCSK9 inhibitors in CAD patients, these studies are often limited by sample sizes. Moreover, their findings regarding the comprehensive effects on both lipid and inflammatory markers specifically in the post-PCI setting are inconsistent and have not been systematically evaluated. A significant knowledge gap exists regarding the consistent anti-inflammatory benefits of PCSK9 inhibitors in this specific clinical context, particularly for key cytokines like TNF-α and IL-6, beyond the conventional marker high-sensitivity C-reactive protein (hs-CRP).

Given these considerations, the present meta-analysis aims to quantitatively synthesize the existing RCT evidence to specifically evaluate the impact of adding PCSK9 inhibitors to standard treatment on both lipid parameters (including triglycerides (TG), total cholesterol (TC), LDL-C) and key inflammatory biomarkers (including high-sensitivity C-reactive protein (hs-CRP), TNF-α, IL-6) in CAD patients after PCI. By focusing exclusively on this high-risk population and integrating evidence on both lipid and inflammatory pathways, this study seeks to provide higher-level evidence regarding the pleiotropic effects of PCSK9 inhibitors post-PCI, thereby informing more targeted and effective clinical management strategies.

Materials and Methods

Search Strategy

A comprehensive and reproducible literature search was performed across three electronic databases: PubMed (https://pubmed.ncbi.nlm.nih.gov/), Embase (https://www.embase.com/), and Web of Science (https://webofscience.com/wos/alldb/basic-search). The search included all studies published from database inception through 10 September 2025. To enhance completeness, we additionally screened the reference lists of included articles and relevant reviews. The search strategy was constructed around the three core concepts of this study: (1) Coronary artery disease (CAD); (2) Percutaneous coronary intervention (PCI); (3) PCSK9 inhibitors. A combination of controlled vocabulary (e.g., MeSH terms in PubMed, Emtree terms in Embase) and free-text keywords was applied. Boolean operators ("AND", "OR") were used to integrate the three concept domains. No language filters were applied initially, but only English and Chinese studies were eligible during screening. The complete search strategies for all databases are presented in **Supplementary Table 1**, ensuring transparency and reproducibility. Two reviewers independently screened all retrieved records through title/abstract and full-text reviews. Any disagreements were resolved through discussion or consultation with a third reviewer.

Eligibility Criteria

Studies were included if they met the following criteria: (1) Population: Adult patients ($\geq$18 years) with a diagnosis of CAD who had received PCI [13]. To precisely define the high-risk post-PCI population of interest, the study participants were required to have initiated the intervention within a specified time frame after PCI (e.g., within 30 days), and their clinical presentation at the time of PCI was explicitly categorized as either Acute Coronary Syndrome (ACS, including ST-segment elevation myocardial infarction [STEMI] or non-ST-segment elevation ACS [NSTE-ACS]) or stable CAD. (2) Intervention: Treatment with a PCSK9 inhibitor (e.g., evolocumab, alirocumab) initiated after PCI, in addition to standard background lipid-lowering therapy (e.g., statins with or without ezetimibe). (3) Comparison: Standard medical therapy (e.g., statins with or without ezetimibe) with or without a matching placebo. (4) Outcomes: Studies must report on at least one of the following outcome measures, presenting data as mean change from baseline or post-intervention values with measures of variance (e.g., standard deviation): Lipid parameters: Triglycerides (TG), Total Cholesterol (TC), Low-Density Lipoprotein Cholesterol (LDL-C); Inflammatory biomarkers: High-sensitivity C-reactive protein (hs-CRP), Tumor Necrosis Factor-alpha (TNF-α), Interleukin-6 (IL-6). (5) The type of study was RCT.

Studies were excluded for any of the following conditions: (1) Non-RCT designs (e.g., observational studies, reviews, editorials, case reports); (2) Duplicate publications or secondary analyses of already included trials; (3) Studies with unavailable or incomplete data necessary for meta-analysis; (4) Studies published in languages other than Chinese or English; (5) Studies that did not specify the duration of PCSK9 inhibitor treatment or the follow-up period for outcome assessment.

Data Extraction

Two researchers independently reviewed the titles and abstracts to determine the relevant studies for the article topic. The eligible literature was fully downloaded and evaluated by two independent assessors, and the data from the included studies were extracted by two independent assessors, with any discrepancies that arose during the process resolved by the assessors reaching a consensus. In case of necessity, a third assessor could also be consulted. The extracted data included (1) the authors, (2) the publication year, (3) the sample size of the participants, (4) the patient

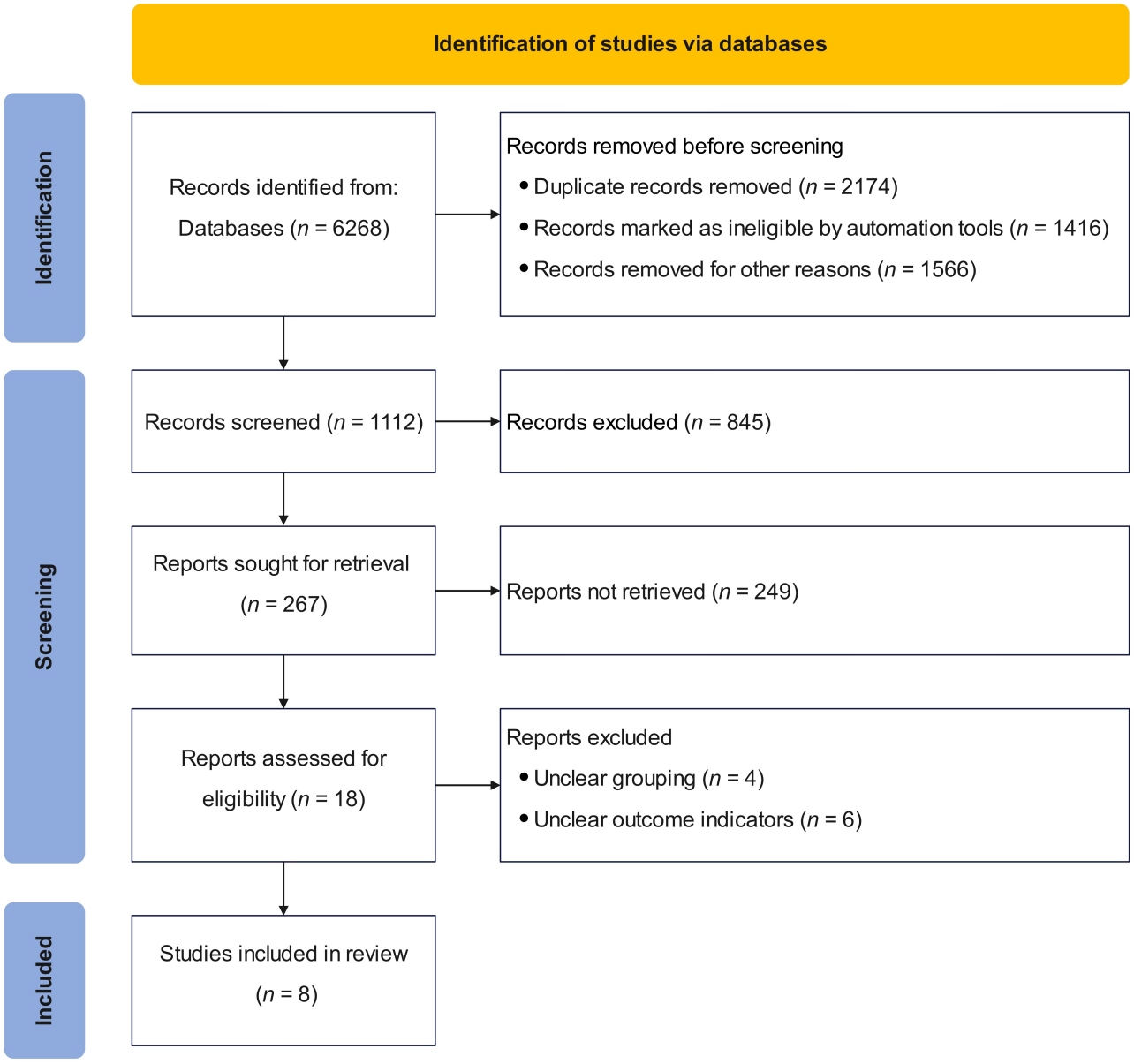

Fig. 1. Flow chart for screening of included studies.

grouping situation and the specific intervention measures adopted by the experimental group and the control group respectively; and (5) the levels of TG, TC, LDL, hs-CRP, TNF-α, and IL-6 of the patients before and after the intervention.

Risk of Bias Assessment

The risk of bias in the included RCTs was independently assessed by two reviewers using the revised Cochrane Risk of Bias tool for randomized trials (RoB 2.0) [14]. This tool evaluates bias across five specific domains: (1) Bias arising from the randomization process; (2) Bias due to deviations from the intended interventions; (3) Bias due to missing outcome data; (4) Bias in measurement of the outcomes; (5) Bias in the selection of the reported results. For each domain, the judgment was guided by a series of signalling questions. Based on the responses, an overall risk-of-bias judgment was assigned for each domain and subsequently for the overall study, categorized as "Low risk", "Unclear", or "High risk". The assessments were performed specifically for the outcome measures relevant to this meta-analysis (lipid profiles and inflammatory biomarkers). Any discrepancies between the two reviewers were resolved through in-depth discussion to reach a consensus. If a consensus could not be reached, a third senior reviewer was consulted for arbitration.

Statistical Analysis

All statistical analyses were performed using Review Manager (RevMan) software, version 5.3 (The Cochrane

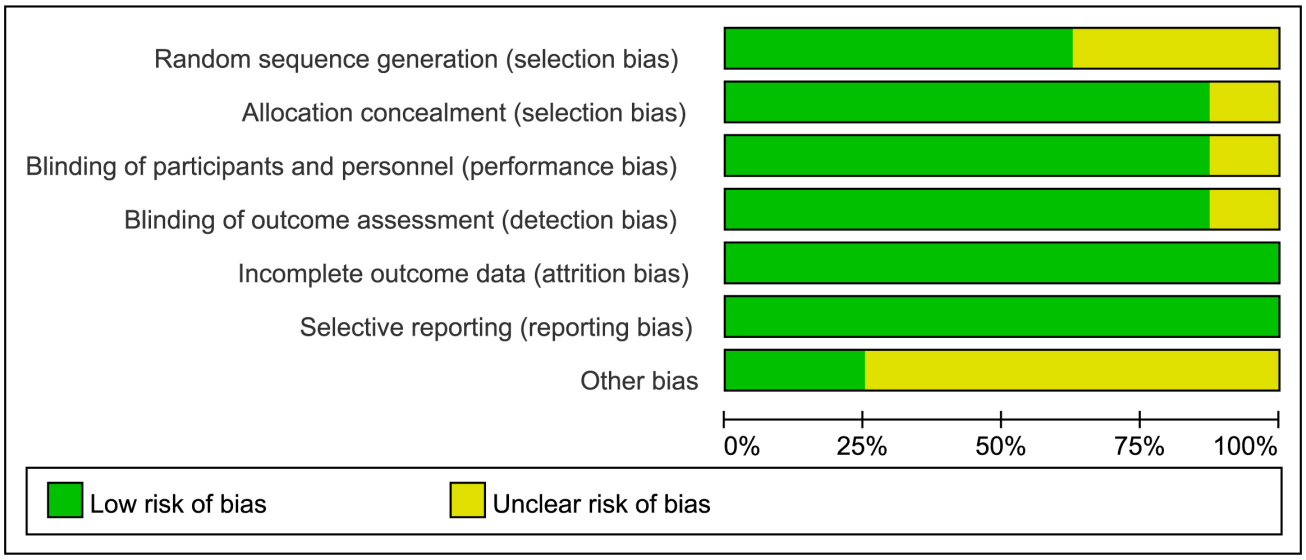

Fig. 2. Risk of bias chart.

Collaboration). For continuous outcomes, including lipid parameters (TG, TC, LDL-C) and inflammatory biomarkers (hs-CRP, TNF-α, IL-6), the intervention effect was estimated using the Mean Difference (MD) with a 95% confidence interval (CI).

Heterogeneity among the included studies was assessed using the Cochran's Q chi-squared test, with a significance level set at $p < 0.10$ indicating significant heterogeneity, as quantified by the I^2 statistic. The degree of heterogeneity was interpreted as follows: I^2 = 0–25% indicated low heterogeneity; I^2 = 25–50% indicated moderate heterogeneity; and $I^2 > 50\%$ indicated substantial heterogeneity. A fixed-effects model was employed when no substantial heterogeneity was present ($I^2 \leq 50\%$). When substantial heterogeneity was present ($I^2 > 50\%$), a random-effects model (using the inverse variance method) was used to obtain a more conservative effect estimate. If significant and unexplained heterogeneity persisted, the results were interpreted with caution and accompanied by a descriptive summary alongside the meta-analysis. A two-tailed p value of <0.05 was considered statistically significant for the overall effect estimate.

Results

Study Selection Process

The systematic literature search across electronic databases (PubMed, n = 3370; Embase, n = 2328; Web of Science, n = 570) initially identified 6268 records. After the exclusion of duplicates (n = 2174), records deemed ineligible by automation tools (n = 1416), and records removed for other reasons (e.g., non-trial articles, irrelevant publication types, n = 1566), the remaining 1112 records underwent title and abstract screening. During the title/abstract screening, 845 records were excluded for not meeting the predefined eligibility criteria. The full texts of the remaining 267 reports were sought; of these, 249 were either unavailable or excluded after detailed assessment. Subsequently, 18 articles underwent full-text eligibility evaluation. Following the full-text review, 10 articles were excluded with specific reasons (including unclear subgroups, n = 4; inconsistent outcome indicators, n = 6). Ultimately, 8 RCT studies were included in the qualitative synthesis and meta-analysis. The study selection process is detailed in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram (Fig. 1). The completed PRISMA checklist is detailed in the **Supplementary Material 1**.

Basic Characteristics and Risk of Bias of Included Studies

A total of 8 RCTs were included in this analysis, comprising 1043 patients who underwent PCI [15–22]. The baseline characteristics and design of these studies are summarized in Table 1 (Ref. [15–22]).

The enrolled studies investigated patients with various coronary artery disease presentations, including acute coronary syndrome (ACS), ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation ACS (NSTE-ACS), and stable CAD with elevated low-density lipoprotein cholesterol (LDL-C). The sample sizes of the individual studies ranged from 32 to 258. Across the studies, the mean age of patients was approximately 60 years, consistent with the epidemiological profile of CAD [23].

The intervention consistently comprised the addition of a proprotein convertase subtilisin/kexin type 9 inhibitor (PCSK9i)—either Evolocumab (140 mg every two weeks) or Alirocumab (75 mg or 150 mg every two weeks)—to background lipid-lowering and standard medical therapy. The control groups received standard care, which typically

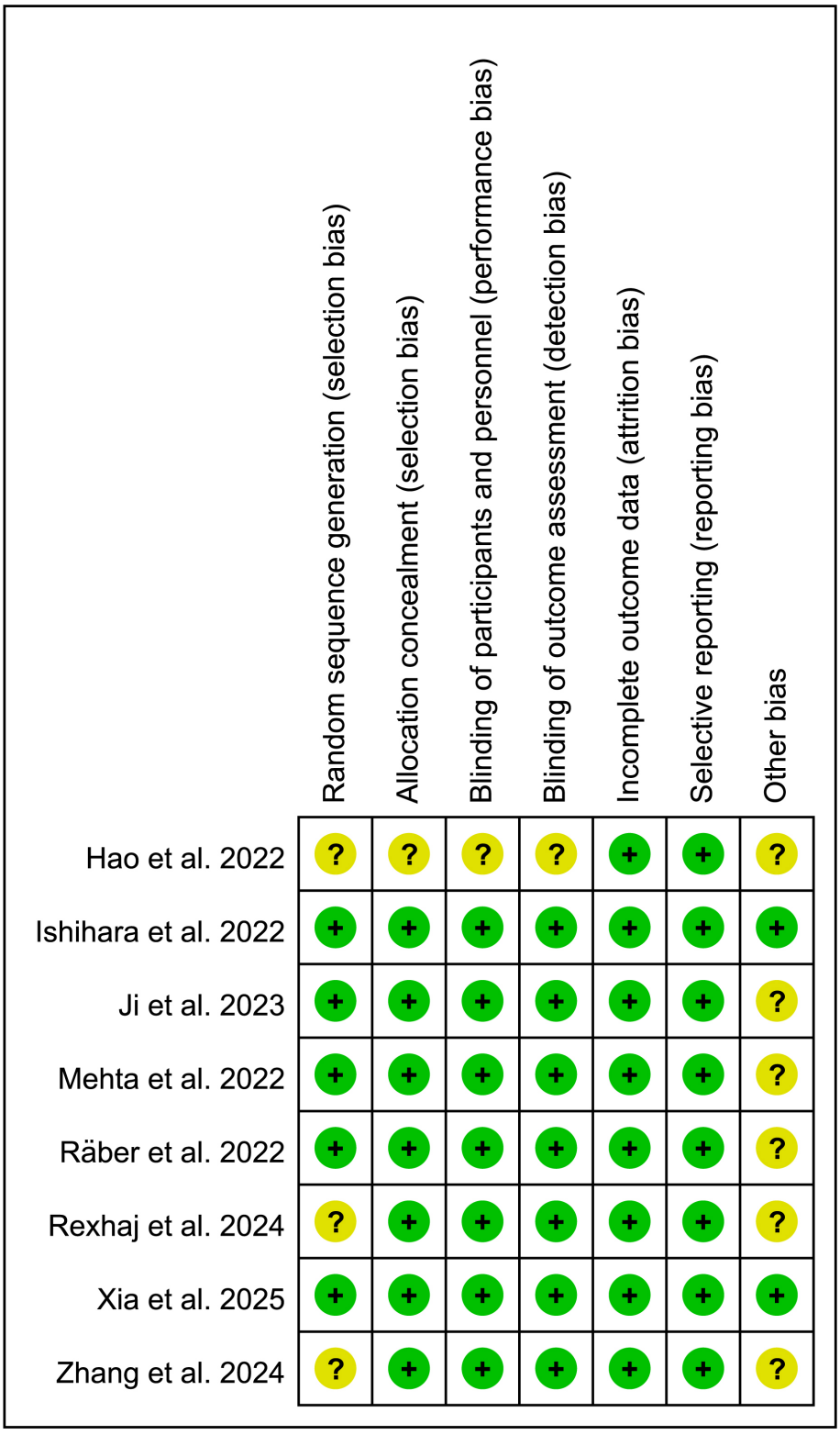

Fig. 3. Summary of risk of bias. Green circle with a plus sign: Low risk of bias; Yellow circle with a question mark: Unclear risk of bias.

involved high-intensity or maximally tolerated statin therapy (e.g., Atorvastatin 20–40 mg/day or Rosuvastatin 20 mg/day), often with a matching placebo to maintain blinding. The follow-up duration varied among the studies, ranging from short-term (3 months) to long-term (52 weeks), allowing for the assessment of both immediate and sustained effects of PCSK9i therapy.

Table 1. Characteristics of the included studies.

Included studies	Patient types	Groups	Amount	Demographics (mean age ± SD; male ratio)	Intervention	Follow-up duration	Outcome indicators	Patient source
Hao *et al*., 2022 [15]	ACS patients after PCI	PCSK9i	68	62.21 ± 12.31; 66.18%	Atorvastatin 40 mg/day + Evolocumab 140 mg q2w	3 months	②③	Qingdao University Hospital
		Control	68	62.22 ± 11.44; 70.59%	Atorvastatin 40 mg/day + Placebo			
Ishihara *et al*., 2022 [16]	Stable CAD patients with high LDL-C undergoing elective PCI	PCSK9i	54	68.1 ± 10.3; 74%	Routine intervention + Evolocumab 140 mg q2w	6 weeks	③	Hyogo College of Medicine
		Control	46	67.0 ± 11.1; 76%	Routine intervention (maximally tolerated statin therapy)			
Ji *et al*., 2023 [17]	NSTE-ACS patients after PCI	PCSK9i	55	60.45 ± 11.67; 69.1%	Atorvastatin 20 mg/day + Evolocumab 140 mg q2w	6 months	①②③④⑤⑥	Henan University of Traditional Chinese Medicine People's Hospital
		Control	55	61.23 ± 10.34; 65.4%	Atorvastatin 20 mg/day			
Mehta *et al*., 2022 [18]	STEMI patients after primary PCI	PCSK9i	38	61.37 ± 11.04; 71.05%	Statins (atorvastatin/rosuvastatin) + Alirocumab 150 mg (baseline, 2 w, 4 w)	12 weeks	③	Hamilton General Hospital
		Control	30	63.63 ± 10.38; 93.33%	Statins + Placebo			
Rexhaj *et al*., 2024 [19]	STEMI patients after PCI	PCSK9i	68	57.5 ± 10.1; 88%	Rosuvastatin 20 mg/day + Alirocumab 150 mg q2w	52 weeks	③	Bern University Hospital Inselspital
		Control	71	58.7 ± 8.4; 80%	Rosuvastatin 20 mg/day + Placebo			
Räber *et al*., 2022 [20]	Acute MI (STEMI/NSTE-ACS) patients after PCI	PCSK9i	126	58.4 ± 10.0; 83.8%	Rosuvastatin 20 mg/day + Alirocumab 150 mg q2w	52 weeks	①③	9 European hospitals
		Control	132	58.6 ± 9.4; 78.3%	Rosuvastatin 20 mg/day + Placebo			
Xia *et al*., 2025 [21]	Acute STEMI after PCI	PCSK9i	16	57.38 ± 10.80; 88%	Routine intervention + Alirocumab 75 mg q2w	6 months	②③	Tongren Hospital
		Control	16	63.13 ± 10.16; 88%	Routine intervention (DAPT, Statin, β-blocker, ACEI/ARB, etc.)			
Zhang *et al*., 2024 [22]	STEMI patients after PCI	PCSK9i	97	60.02 ± 7.79; 40.2%	Routine intervention (statins + antiplatelet drugs) + Evolocumab 140 mg q2w	6 months	①②③④⑤⑥	Qingdao Central Hospital
		Control	103	61.61 ± 8.72; 48.5%	Routine intervention			

① Triglycerides (TG); ② Total Cholesterol (TC); ③ Low-Density Lipoprotein (LDL); ④ High-Sensitivity C-Reactive Protein (hs-CRP); ⑤ Tumor Necrosis Factor-alpha (TNF-α); ⑥ Interleukin-6 (IL-6).
Abbreviations: PCI, percutaneous coronary intervention; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor; ACS, acute coronary syndrome; STEMI, ST-segment elevation myocardial infarction; NSTE-ACS, non-ST-segment elevation acute coronary syndrome; q2w, every 2 weeks.

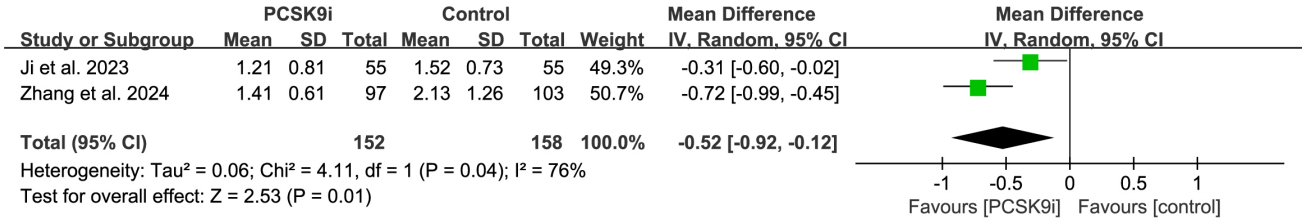

Fig. 4. Forest plot of triglycerides (TG).

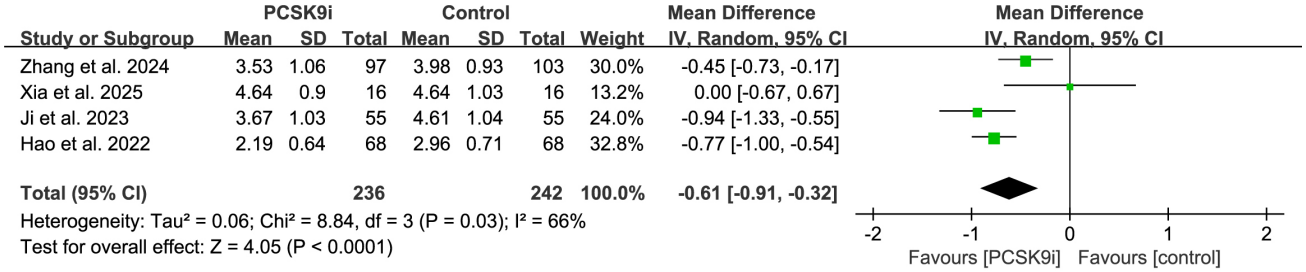

Fig. 5. Forest plot of total cholesterol (TC).

All studies were prospective in design, with and well-balanced baseline demographic characteristics between the PCSK9i and control groups, suggesting a low risk of selection bias. The use of placebo in several trials indicates attention to blinding procedures. The patient populations were recruited from single-center or multi-center hospitals across different geographical regions, including China, Japan, Canada, and Switzerland, as well as a multicenter trial spanning nine European hospitals, which enhances the generalizability of the findings.

In summary, the included literature demonstrates a good level of methodological quality with appropriate randomization, clear intervention protocols, and relevant clinical and laboratory outcome measures, providing a reliable basis for assessing the impact of PCSK9i therapy in PCI-treated patients.

The methodological rigor of the included studies was evaluated through a detailed risk of bias assessment using the Cochrane RoB 2.0 tool. The results of this assessment are presented in Figs. 2,3. Overall, the assessment revealed variability in the reporting and methodology of the included trials. Specifically: Approximately half of the studies were evaluated to have a low risk of bias concerning the randomization process. However, most studies had unclear reporting regarding allocation concealment and the implementation of blinding for participants and personnel, which could potentially influence performance bias. The risks related to missing outcome data and selective reporting were generally low. The risk of bias in outcome measurement was largely reported as low, as the laboratory measurements (lipid levels, inflammatory biomarkers) are objective outcomes. The primary limitation was the insufficient reporting of key methodological design elements in several studies, such as concealment of allocation and blinding procedures, leading to an "unclear" risk-of-bias judgment.

Meta-Analysis Results

Lipid Profiles

Two studies [17,22] comprising 310 patients (PCSK9i group: 152, Control group: 158) assessed the effect of PCSK9 inhibitors on TG levels (Fig. 4). A random-effects model was applied based on substantial heterogeneity (I^2 = 76%). The pooled results demonstrated that a statistically significant reduction in TG levels in the PCSK9 inhibitor group compared to the control group (MD = –0.52, 95% CI: –0.92– –0.12; $p = 0.001$).

Four studies [15,17,21,22] with 478 patients (PCSK9i group: 236, Control group: 242) evaluated the impact of PCSK9 inhibitors on TC levels (Fig. 5). Substantial heterogeneity was observed (I^2 = 66%), and a random-effects model was used. This meta-analysis of 4 studies revealed that a significant reduction in TC levels with PCSK9 inhibitors compared to the control group (MD = –0.61, 95% CI: –0.91– –0.32; $p < 0.0001$).

All 8 studies [15–22] comprising 1043 patients (PCSK9i group: 522, Control group: 521) evaluated the impact of PCSK9 inhibitors on LDL-C levels (Fig. 6). Substantial heterogeneity was present (I^2 = 99%), and a random-effects model was employed. The pooled results demonstrated that LDL-C levels in the PCSK9i group were significantly lower than those in the control group (MD = –1.37, 95% CI: –2.24– –0.50; $p = 0.002$).

Inflammatory Biomarkers

Two studies [17,22] involving 310 patients (PCSK9i: 152, Control: 158) evaluated the impact of PCSK9 in-

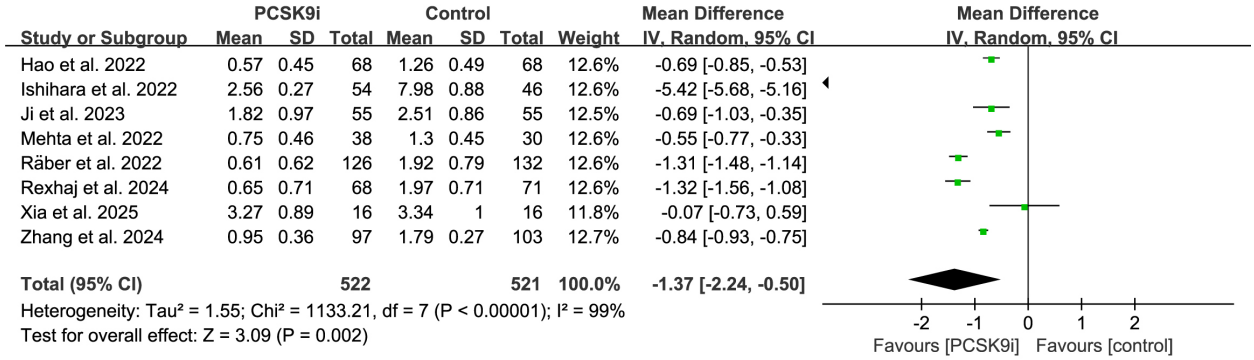

Fig. 6. Forest plot of low-density lipoprotein cholesterol (LDL-C).

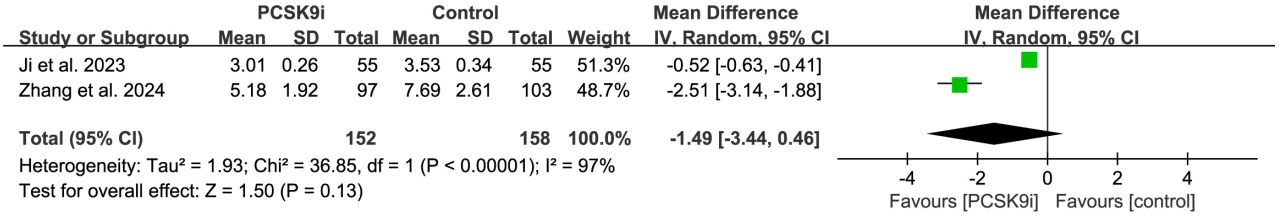

Fig. 7. Forest plot of hs-CRP.

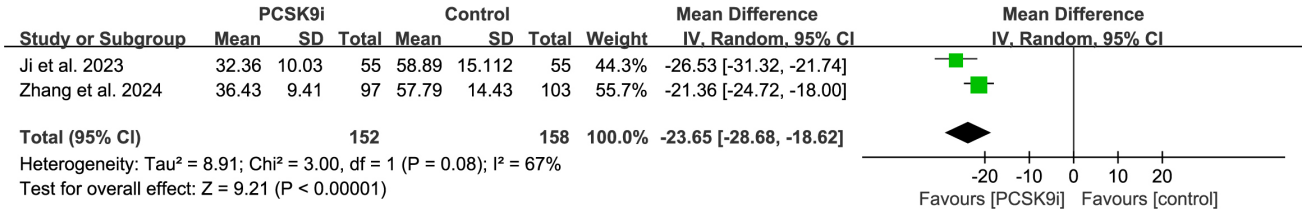

Fig. 8. Forest plot of TNF-α.

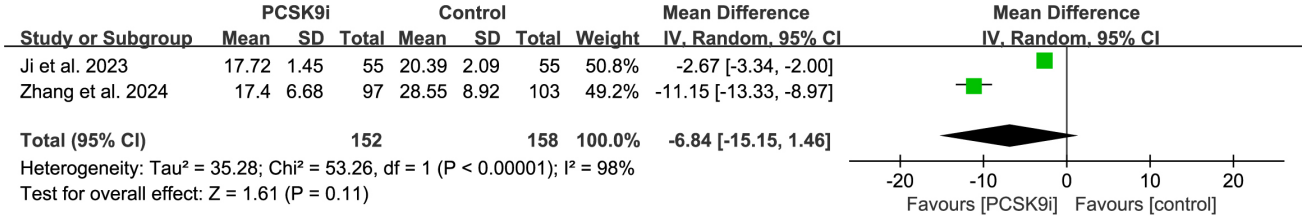

Fig. 9. Forest plot of IL-6.

hibitors on hs-CRP levels (Fig. 7). Substantial heterogeneity was observed (I^2 = 97%), and a random-effects model was applied. The pooled results indicated no significant difference between the PCSK9 inhibitor and control groups (MD = –1.49, 95% CI: –3.44– 0.46; p = 0.13).

Two studies [17,22] with 310 patients (PCSK9i: 152, Control: 158) evaluated the impact of PCSK9 inhibitors on TNF-α levels (Fig. 8). A random-effects model was used based on considerable heterogeneity (I^2 = 67%). A significant reduction in TNF-α was observed in the PCSK9 inhibitor group than the control group (MD = –23.65, 95% CI: –28.68– –18.62; $p < 0.00001$).

Two studies [17,22] comprising a total of 310 patients (PCSK9i: 152, Control: 158) evaluated the impact of PCSK9 inhibitors on IL-6 levels (Fig. 9). The heterogeneity test showed significantly among the included studies (Tau^2 = 35.28; Chi^2 = 53.26, df = 1, $p < 0.00001$; I^2 = 98%). Consequently, a random-effects model was applied for the meta-analysis. The pooled results demonstrated that IL-6 levels in the PCSK9 inhibitor group were lower than those in the control group (MD = –6.84, 95% CI: –15.15–1.46; p = 0.11). This meta-analysis of two studies indicates that PCSK9 inhibitor therapy can reduce IL-6 levels in patients with CAD after PCI compared to the control group.

Notably, none of the included studies reported clinical endpoints, such as major adverse cardiovascular events (MACE), all-cause mortality, myocardial infarction, revascularization, given that the primary focus of the included RCTs was on surrogate biomarkers, including lipid profiles and inflammatory cytokines. Thus, the current meta-analysis is limited to biochemical outcomes, and the impact of PCSK9 inhibitors on clinical outcomes in post-PCI patients remains unaddressed.

Assessment of Publication Bias

Due to the limited number of included studies (<10) for each specific outcome, formal statistical assessments for publication bias (e.g., funnel plot asymmetry tests or Egger's test) were not performed, which aligns with the Cochrane Handbook for Systematic Reviews of Interventions, indicating that tests for funnel plot asymmetry are not reliable when fewer than 10 studies are included in a meta-analysis due to their insufficient statistical power to distinguish real asymmetry from chance variation [24]. Therefore, although we acknowledge publication bias as a potential limitation, a quantitative assessment was not feasible. The results, particularly for outcomes with a smaller number of studies (e.g., TNF-α, IL-6), should be interpreted with this consideration.

Discussion

This meta-analysis of 8 randomized controlled trials demonstrated that the addition of PCSK9 inhibitors to standard medical therapy in patients with CAD following PCI led to significant reductions in key lipid parameters, including TG, TC, and most notably, LDL-C. Furthermore, a significant lowering effect was observed on the inflammatory biomarkers TNF-α and IL-6. It is important to highlight these non-significant findings to avoid selective outcome reporting, as they contribute to a comprehensive understanding of the drug's effects. These findings suggest that PCSK9 inhibitors may exert beneficial effects on both the lipid profile and specific inflammatory pathways in this patient population.

The potent LDL-C-lowering effect of PCSK9 inhibitors observed in our study is consistent with their established mechanism of action. With deepening research in related fields, reports indicate that PCSK9 plays a significant role in atherosclerosis caused by LDL deposition [25,26]. PCSK9 is a protease primarily secreted by hepatocytes [27]. In the human body's LDL-C metabolism process, LDL-C primarily binds to LDLR distributed in hepatocytes to form complexes, which are then internalized by hepatocytes. The LDLR distributed in hepatocytes is subsequently phagocytosed by hepatocytes [28]. PCSK9 can competitively bind to LDLR, promoting its degradation and interfering with the LDL-C metabolic process, thereby increasing serum LDL-C levels in the human body [29].

The novel insight from this analysis pertains to the anti-inflammatory effects. The significant reduction in TNF-α and IL-6, which are central cytokines in the pathogenesis of atherosclerosis, aligns with emerging basic science evidence indicating that PCSK9 may directly promote vascular inflammation. This study targeting specific inflammatory pathways holds significant value. TNF-α and IL-6 are core cytokines mediating the inflammatory cascade in atherosclerosis, with their levels directly correlated to plaque instability [30,31]. The observation that PCSK9 inhibitors significantly reduced TNF-α strongly suggests that the drug's beneficial mechanism may extend beyond its classic lipid-lowering effects. In contrast, the reduction in IL-6, while not statistically significant, showed a strong trend (MD = –6.84, 95% CI: –15.15–1.46; $p = 0.11$), warranting further investigation in larger studies. Recent basic research reveals that PCSK9 not only regulates blood lipids via hepatic LDLR but also directly binds to LDLR on immune cells like macrophages, activating inflammatory signaling pathways, such as NF-κB to promote TNF-α and IL-6 secretion [32,33]. Thus, our clinical meta-analysis results align with this pathophysiological mechanism, providing robust patient-based evidence supporting the hypothesis that "PCSK9 directly contributes to vascular inflammation". This suggests that PCSK9 inhibitors may exert a dual-action role in patients post-PCI: patently reducing the lipid basis of atherosclerosis while directly suppressing local vascular inflammatory responses. These findings thus provide a new theoretical framework for understanding their potential "multifaceted efficacy".

Notably, the non-significant results for hs-CRP, a non-specific systemic inflammatory marker, require careful interpretation. Its lack of significant reduction, despite changes in specific cytokines like TNF-α, may reflect its broader biological variability, its role as a downstream marker of generalized inflammation less specific to the vascular pathobiology targeted by PCSK9 inhibition, or the influence of non-cardiac inflammatory conditions. The substantial heterogeneity (I^2 = 97%) observed in the hs-CRP analysis further complicates its interpretation, suggesting that the effect, if any, is inconsistent across different patient populations or study methodologies.

A critical consideration in interpreting our results is the substantial heterogeneity observed across several analyses, particularly for LDL-C (I^2 = 99%), TC (I^2 = 66%), TG (I^2 = 76%), and hs-CRP (I^2 = 97%). This high degree of heterogeneity limits the consistency and generalizability of the pooled estimates and is a key limitation of our study. Potential sources may include clinical diversity such as variations in patient presentations (ACS vs. stable CAD), the specific type and dosing regimen of PCSK9 inhibitors (evolocumab vs. alirocumab), the timing of initiation post-PCI, intensity of background statin therapy, and differences in follow-up duration. Methodological diversity, including variations in blinding procedures and outcome assessment methods, may

also contribute. Regrettably, the limited number of studies for each outcome precluded meaningful pre-specified subgroup or sensitivity analyses to robustly explore these sources of heterogeneity. Therefore, the inability to conduct these analyses limits the interpretability of our findings, and this constraint must be acknowledged. Future meta-analyses with a larger number of trials should prioritize such analyses to identify moderators of treatment response and enhance the robustness of the conclusions. Similarly, a formal assessment of publication bias (e.g., funnel plots or Egger's test) was not performed for any outcome due to the limited number of studies (<10), as recommended by the Cochrane Handbook. Therefore, the potential for unpublished null results should be acknowledged.

From a clinical perspective, the significant improvement in lipid profiles and the reduction in TNF-α suggest that PCSK9 inhibitors mitigate two key pathophysiological components of post-PCI residual risk: dyslipidemia and vascular inflammation [34]. This pleiotropic effect could theoretically translate into more effective plaque stabilization and improved long-term outcomes. However, this meta-analysis exclusively focused on surrogate biomarkers. A crucial gap in the current evidence base, as highlighted by our study, is the lack of reporting on clinical endpoints such as major adverse cardiovascular events (MACE), all-cause mortality, or repeat revascularization in the included RCTs. While the improvement in surrogate markers is promising, the ultimate clinical benefit of PCSK9 inhibitors on hard outcomes in post-PCI patients remains to be definitively established by future large-scale, outcome-driven randomized trials.

The interpretation of our findings must consider several limitations. First, the limited number of included studies and the total sample size, particularly for some outcomes (e.g., TG, hs-CRP, TNF-α, IL-6), may affect the precision and generalizability of the results. Second, we observed substantial and unexplained heterogeneity ($I^2 > 50\%$) in the analyses of LDL-C, TC, TG, and hs-CRP. Potential sources may include variations in the specific PCSK9 inhibitor used, timing of initiation post-PCI, background statin intensity, and patient characteristics (e.g., ACS vs. stable CAD). The inability to perform subgroup analyses due to the limited data precluded exploration of these sources. Third, the methodological quality of some included studies was compromised by unclear or high risk of bias pertaining to allocation concealment and blinding, as assessed by the Cochrane tool (Figs. 2,3). This could potentially lead to an overestimation of treatment effects. Finally, the focus on surrogate biomarkers and the absence of clinical endpoint data mean that the direct patient-important implications of our findings remain unclear.

Conclusion

This meta-analysis provides evidence that PCSK9 inhibitors significantly improve lipid profiles and may reduce levels of specific pro-inflammatory cytokines, notably TNF-α, in patients with CAD after PCI. These findings reinforce PCSK9 inhibitors' role in managing residual lipid risk and reveal potential pleiotropic anti-inflammatory benefits. However, given the substantial heterogeneity, the limited number of studies for several outcomes, and the focus on surrogate markers, the results, particularly for the inflammatory biomarkers, should be interpreted with caution. Further high-quality RCTs with standardized protocols, larger sample sizes, and clinical outcome measures are needed to confirm these findings and to determine whether the biochemical improvements conferred by PCSK9 inhibitors translate into improved long-term clinical outcomes after PCI.

Abbreviations

CAD, Coronary artery disease; PCI, Percutaneous coronary intervention; PCSK9: Proprotein convertase subtilisin/kexin type 9; LDL-C, Low-density lipoprotein cholesterol; LDLR, Low-density lipoprotein receptor; TNF-α, Tumor necrosis factor-α; IL-6, Interleukin-6; RCT, Randomized controlled trial; TG, Triglycerides; TC, Total cholesterol; hs-CRP, High-sensitivity C-reactive protein; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; MD, Mean difference; CI, Confidence interval.

Availability of Data and Materials

The experimental data used to support the findings of this study are available from the corresponding author upon request.

Author Contributions

YZ: Conceptualization, Study design, Statistical analysis, Data interpretation, Writing – original draft, Final approval. HH: Literature search, Study screening, Data acquisition, Writing – review & editing, Final approval. LX: Data extraction, Risk of bias assessment, Writing – review & editing, Final approval. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.24976/Discov.Med.202638204.22.

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