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Efficacy and Safety of PCSK-9 Inhibitors in Patients with Acute Coronary Syndrome: A Systematic Review and Network Meta-Analysis

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ADMINISTRATIVE INFORMATION

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Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 9 July 2025 and was last updated on 9 July 2025.

INTRODUCTION

Review question / Objective To systematically evaluate the efficacy and safety of PCSK9 inhibitors (Evolocumab and Alirocumab) in patients with acute coronary syndrome (ACS), focusing on LDL-C reduction and major adverse cardiovascular events (MACE).

Condition being studied Acute coronary syndrome (ACS) is a term encompassing a spectrum of clinical conditions caused by sudden, reduced blood flow to the heart, typically due to rupture of an atherosclerotic plaque and subsequent thrombosis. It includes unstable angina, non–ST-segment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI). ACS is a leading cause of morbidity and mortality worldwide, and aggressive lipid-lowering strategies are essential to reduce the risk of recurrent cardiovascular events. This study focuses on the role of PCSK9 inhibitors in improving outcomes in patients with ACS.

METHODS

Participant or population Patients included in this review are adults (aged ≥18 years) diagnosed with acute coronary syndrome (ACS), including unstable angina, non–ST-segment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI). All participants were either hospitalized for ACS or had a recent ACS event and were receiving standard secondary prevention therapies, such as statins, with or without additional lipid-lowering agents. The review focuses on this high-risk population to evaluate the efficacy and safety of PCSK9 inhibitors (Evolocumab or Alirocumab) in improving lipid profiles and reducing adverse cardiovascular outcomes.

Intervention The interventions evaluated in this review are proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, specifically Evolocumab and Alirocumab, administered as adjuncts to standard lipid-lowering therapy (e.g., statins, with

or without ezetimibe) in patients with acute coronary syndrome (ACS). These monoclonal antibodies reduce LDL-C levels by inhibiting PCSK9-mediated degradation of LDL receptors, thereby enhancing hepatic clearance of circulating LDL-C. The review compares the efficacy and safety of these agents in lowering LDL-C and reducing the incidence of major adverse cardiovascular events (MACE).

Comparator The comparators in this review are placebo or standard lipid-lowering therapy alone, which may include high-intensity statin therapy with or without ezetimibe, but without the addition of PCSK9 inhibitors. These comparators allow assessment of the incremental benefit of adding Evolocumab or Alirocumab to conventional treatment in patients with acute coronary syndrome (ACS).

Study designs to be included This review will include randomized controlled trials (RCTs) that evaluate the efficacy and/or safety of PCSK9 inhibitors (Evolocumab or Alirocumab) in patients with acute coronary syndrome (ACS). Only full-text, peer-reviewed RCTs reporting relevant clinical or biochemical outcomes (e.g., LDL-C levels, MACE) will be included.

Eligibility criteria Additional inclusion criteria included studies with a minimum follow-up duration of 4 weeks, adult participants (≥18 years), and trials that reported quantitative outcomes for LDL-C levels and/or MACE. Studies were required to provide sufficient data for effect size estimation.

Exclusion criteria included:

Non-randomized studies, observational cohorts, case reports, or reviews;

Duplicate publications or repeated reports from the same trial without additional outcome data;

Studies not conducted in ACS populations;

Trials using non-PCSK9 lipid-lowering agents as primary intervention (e.g., bempedoic acid, inclisiran).

Information sources The following information sources will be used to identify relevant studies: electronic databases including PubMed, Embase, Cochrane Library, ClinicalTrials.gov, and the World Health Organization International Clinical Trials Registry Platform (ICTRP). A comprehensive search strategy combining MeSH terms and keywords related to "PCSK9 inhibitors," "Evolocumab," "Alirocumab," and "acute coronary syndrome" will be applied. In addition, we will manually screen the reference lists of included articles and relevant reviews. Where necessary, contact with study authors will be made to obtain missing or clarifying information. No language restrictions will be applied.

Main outcome(s) Low-density lipoprotein cholesterol (LDL-C) reduction, measured as the mean difference (MD) in LDL-C levels (mg/dL) from baseline to the end of follow-up between intervention and comparator groups. Follow-up durations vary across studies, ranging from 4 weeks to 2.8 years.

Major adverse cardiovascular events (MACE), defined as a composite of cardiovascular death, non-fatal myocardial infarction, stroke, unstable angina requiring hospitalization, or coronary revascularization. The effect of PCSK9 inhibitors on MACE will be evaluated using odds ratios (ORs), hazard ratios (HRs), or incidence rate ratios (IRRs), depending on the availability and structure of the reported data.

Additional outcome(s) Low-density lipoprotein cholesterol (LDL-C) reduction, measured as the mean difference (MD) in LDL-C levels (mg/dL) from baseline to the end of follow-up between intervention and control groups.

Major adverse cardiovascular events (MACE), reported as odds ratios (ORs), hazard ratios (HRs), or incidence rate ratios (IRRs), depending on the data available. MACE may include a composite of cardiovascular death, non-fatal myocardial infarction, stroke, unstable angina requiring hospitalization, or coronary revascularization.
Timing of outcome measurement varies by study and ranges from 4 weeks to 2.8 years.

Quality assessment / Risk of bias analysis The quality of included studies will be assessed using the Cochrane Risk of Bias 2 (RoB 2) tool, which evaluates five key domains: (1) bias arising from the randomization process, (2) bias due to deviations from intended interventions, (3) bias due to missing outcome data, (4) bias in measurement of the outcome, and (5) bias in selection of the reported result. Each domain will be rated as low risk, some concerns, or high risk. Two independent reviewers will perform the risk of bias assessment, and discrepancies will be resolved by consensus or consultation with a third reviewer.

Strategy of data synthesis Data will be synthesized using both pairwise meta-analysis and

network meta-analysis (NMA) approaches. For continuous outcomes such as LDL-C reduction, results will be reported as mean differences (MDs) with 95% confidence intervals (CIs). For dichotomous outcomes such as MACE, effect sizes will be reported as odds ratios (ORs), hazard ratios (HRs), or incidence rate ratios (IRRs) with corresponding 95% CIs.

The network meta-analysis will be conducted within a Bayesian framework using the gemtc and netmeta packages in R, allowing for both direct and indirect comparisons between interventions. A random-effects model will be used to account for between-study heterogeneity. The surface under the cumulative ranking curve (SUCRA) will be calculated to rank the interventions.

Heterogeneity will be assessed using the I^2 statistic and Cochran's Q test. Subgroup analyses and meta-regression will be performed to explore potential sources of heterogeneity, such as baseline LDL-C levels, statin use, timing of PCSK9 inhibitor initiation, and follow-up duration.

Sensitivity analyses will be conducted by excluding studies at high risk of bias or with small sample sizes. Publication bias will be evaluated using funnel plots, Egger's test, and comparison-adjusted funnel plots for NMA.

All statistical analyses will be performed using R software.

Subgroup analysis Subgroup analyses will be conducted to explore potential sources of heterogeneity and to assess whether treatment effects vary across specific patient or study characteristics. Planned subgroups include:

Type of PCSK9 inhibitor (Evolocumab vs. Alirocumab)

Timing of intervention (≤7 days vs. >7 days after ACS event)

Baseline LDL-C level (<100 mg/dL vs. ≥100 mg/dL)

Use of background lipid-lowering therapy (statin alone vs. statin + ezetimibe)

Follow-up duration (<6 months vs. ≥6 months)

ACS subtype (STEMI vs. NSTEMI/UA)

Effect sizes will be compared across subgroups using interaction tests or meta-regression where appropriate.

Sensitivity analysis Sensitivity analyses will be conducted to test the robustness of the pooled results and assess the influence of individual studies and methodological decisions. The following sensitivity analyses are planned:

Exclusion of studies at high risk of bias based on the Cochrane RoB 2 tool to assess the impact of study quality on the findings.

Leave-one-out analysis, in which each study is sequentially removed to evaluate its influence on the overall effect size.

Exclusion of small studies (sample size <100 per group) to assess the effect of study size on estimates.

Analysis limited to studies with consistent MACE definitions, to address potential variability in outcome definitions.

Exclusion of studies using ezetimibe as background therapy, to isolate the effect of PCSK9 inhibitors.

Fixed-effect vs. random-effects models, to evaluate the influence of statistical model choice.

Results will be compared to the primary analyses to assess the stability of the conclusions.

Country(ies) involved China.

Keywords Acute coronary syndrome; PCSK-9; LDL-C; MACE; network meta-analysis.

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