JIMGS
Journal for International Medical Graduates

Volume 11 (05)
Accepted: March 30th, 2026.
Published: March 30th, 2026.
Systematic Review

Role of PCSK9 Inhibitors in Contemporary Lipid-Lowering Era: A Systematic Review of LDL-C Reduction, Cardiovascular Outcomes, and Use in Statin-Intolerant and Very-High-Risk Patients

Deepak Sabharwal[1], Iana Malasevskaia[2], MD
Journal for International Medical Graduates

Abstract

Background

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors have expanded lipid-lowering options for patients who do not achieve low-density lipoprotein cholesterol (LDL-C) targets with standard therapy or who are unable to tolerate statins. Their role in cardiovascular risk reduction continues to evolve as outcome data accumulate and clinical experience grows.

Objectives

To systematically review and qualitatively synthesize the available clinical evidence on the efficacy, safety, and therapeutic positioning of PCSK9 inhibitors in adults with hypercholesterolemia or established atherosclerotic cardiovascular disease.

Methods

A structured literature search was conducted across major biomedical databases and clinical trial registries. Randomized controlled trials and relevant high-quality studies reporting LDL-C reduction and cardiovascular outcomes were included. Due to heterogeneity in study design, patient populations, and reported endpoints, findings were synthesized qualitatively without quantitative pooling.

Results

Twenty-two studies met inclusion criteria, predominantly randomized controlled trials enrolling 307 to 27,564 participants with follow-up ranging from 12 weeks to 2.8 years. PCSK9 inhibitors reduced LDL-C by approximately 45–60% across high-risk populations. In large outcome trials (FOURIER, n=27,564; ODYSSEY OUTCOMES, n=18,924), therapy was associated with significant reductions in major adverse cardiovascular events (hazard ratios ≈0.85). Overall, treatment was well tolerated, with low rates of serious adverse events.

Conclusions

PCSK9 inhibitors provide effective lipid lowering and cardiovascular benefit in selected high-risk patients. Their use is most appropriate in individuals who remain at elevated cardiovascular risk despite optimized conventional lipid-lowering therapy. Cost, access, and long-term real-world effectiveness remain important considerations in clinical decision-making.

Keywords:
PCSK9 inhibitors, LDL cholesterol, hypercholesterolemia, cardiovascular disease, statin intolerance, lipid management, evolocumab, alirocumab

Introduction

Low-density lipoprotein cholesterol (LDL-C) remains a central modifiable risk factor for atherosclerotic cardiovascular disease, and sustained LDL-C reduction is a cornerstone of cardiovascular risk-reduction strategies. Statins have long served as the foundation of lipid-lowering therapy and have demonstrated clear benefits in reducing cardiovascular morbidity and mortality.

Proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitors represent a distinct class of lipid-lowering agents that reduce circulating LDL-C through inhibition of PCSK9-mediated degradation of low-density lipoprotein receptors. Since their introduction into clinical practice, multiple randomized trials have evaluated their effects on lipid levels and cardiovascular outcomes across diverse high-risk populations.[1–3] In parallel, contemporary clinical guidelines have incorporated PCSK9 inhibitors into treatment algorithms for selected patients with persistently elevated cardiovascular risk despite optimized standard therapy.[4,5]

Despite an expanding evidence base, the clinical role of PCSK9 inhibitors is often described across fragmented sources that vary in study design, patient populations, and reported outcomes. Existing reviews frequently focus on individual trials, specific subgroups, or

Volume 11 (05)
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Published: March 30th, 2026.
Systematic Review

narrowly defined clinical questions, limiting their ability to provide an integrated overview of efficacy, safety, and therapeutic positioning. Additionally, heterogeneity in study designs and outcome measures complicates direct comparison across studies and challenges efforts to synthesize findings quantitatively.[6,7]

The objective of this systematic review with qualitative synthesis is to systematically identify and qualitatively synthesize the available clinical evidence on the efficacy, safety, and contemporary clinical role of PCSK9 inhibitors in lipid management.

Methods

Reporting Guidelines.

This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement.[8] The PRISMA 2020 checklist and flow diagram were used to guide study identification, screening, eligibility assessment, and inclusion.[8] Following full-text assessment, 22 studies met the eligibility criteria and were included in the qualitative synthesis. This review was not prospectively registered; however, predefined eligibility criteria and screening methods were established prior to study selection.

Data Sources and Search Strategy.

A comprehensive literature search was conducted in PubMed/MEDLINE, ScienceDirect, the Cochrane Central Register of Controlled Trials (CENTRAL), PubMed Central (PMC), and ClinicalTrials.gov from database inception through December 18, 2023. No date restrictions were applied. Searches were limited to English-language publications.

The PubMed search strategy combined controlled vocabulary (MeSH terms) and free-text keywords using Boolean operators as follows:

("PCSK9 inhibitors" OR "proprotein convertase subtilisin/kexin type 9" OR alirocumab OR evolocumab OR inclisiran)
AND
("low-density lipoprotein cholesterol" OR LDL-C OR hypercholesterolemia OR dyslipidemia)
AND
("cardiovascular outcomes" OR "major adverse cardiovascular events" OR MACE OR myocardial infarction OR stroke)

Search strategies were adapted appropriately for other databases.

In addition to electronic database searches, reference lists of included studies and relevant review articles were manually screened to identify additional eligible studies. Gray literature beyond registered clinical trials was not systematically searched.

The full electronic search strategy for PubMed is provided in Supplementary Appendix 1.

Eligibility Criteria

Predefined inclusion and exclusion criteria were established prior to screening. Eligible studies included randomized controlled trials (RCTs), controlled clinical trials, or observational cohort studies evaluating PCSK9 inhibitors as the primary intervention in adult human populations. Studies were required to report quantitative data on LDL-C reduction and/or cardiovascular outcomes.

No minimum sample size threshold was imposed; however, studies were required to include a defined comparator group and report follow-up duration. Combination therapy studies were included only when PCSK9 inhibition was the primary investigational intervention.

Studies were excluded if they involved animal or preclinical models, were narrative reviews, editorials, or commentaries, were published only as conference abstracts without full manuscripts, were non-English publications, or lacked PCSK9-specific outcome reporting.

Following screening, all included studies were randomized controlled trials; no observational studies met predefined eligibility criteria.

Study Selection and Screening Process.

All records identified through database and registry searches were exported into reference management software, and duplicate records were removed prior to screening. In accordance with PRISMA 2020 guidelines, study selection was conducted independently by two reviewers in two stages. First, titles and abstracts were screened to exclude clearly irrelevant records. Second, full-text reports of potentially eligible studies were reviewed independently to determine final inclusion based on predefined eligibility criteria. Disagreements were resolved through discussion, with unresolved conflicts adjudicated by a senior author.

Data Extraction.

Data extraction was performed independently by two reviewers using a piloted standardized extraction form. Extracted variables included study identifiers, study design, sample size, population characteristics, intervention details including dosage and duration, comparator therapies, follow-up duration, LDL-C reduction, cardiovascular outcomes, and reported adverse events.

Disagreements were resolved through discussion and consensus, with involvement of a senior author when necessary.

JIMGS
Journal for International Medical Graduates

Volume 11 (05)
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Published: March 30th, 2026.
Systematic Review

Quality Appraisal.

Risk of bias for randomized controlled trials was assessed independently by two reviewers using the Cochrane Risk of Bias 2 tool.[9] Domains evaluated included randomization, deviations from intended interventions, missing outcome data, outcome measurement, and selective reporting. Discrepancies in domain-level judgments were resolved by consensus, with involvement of a senior author when necessary.

Discrepancies in risk-of-bias judgments were resolved through discussion and consensus, with involvement of a senior author when necessary.

Synthesis of Findings.

Preliminary evaluation of the included trials demonstrated substantial clinical and methodological heterogeneity across studies, including differences in study populations, baseline LDL-C levels, background lipid-lowering therapy, dosing regimens, follow-up duration, and outcome definitions. Given these sources of heterogeneity and the variability in reported endpoints, statistical pooling was considered inappropriate. Therefore, findings were synthesized qualitatively rather than through quantitative meta-analysis to avoid generating potentially misleading pooled estimates.

Results

Study Selection.

A total of 274 records were identified through database and registry searches. After removal of 59 duplicate records, 215 records underwent title and abstract screening. Of the 34 excluded full-text articles, primary reasons for exclusion included absence of cardiovascular outcome reporting (n=14), non-randomized design without comparator (n=8), insufficient PCSK9-specific data (n=7), duplicate study populations (n=3), and incomplete outcome reporting (n=2). The study selection process is summarized in the PRISMA flow diagram (Figure 1). Ultimately, 22 studies met the predefined eligibility criteria and were included in the qualitative synthesis.

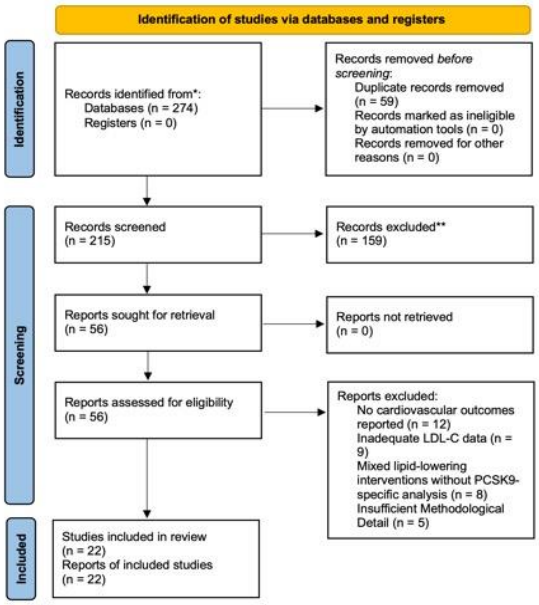

Figure 1. PRISMA 2020 flow diagram illustrating study identification, screening, eligibility assessment, and inclusion.

Risk of Bias Assessment

Risk of bias for randomized controlled trials was assessed using the Cochrane Risk of Bias 2 tool.[9] Domain-level assessments are summarized in Table 1. Most studies were judged to be at low risk of bias across domains, including randomization, outcome measurement, and handling of missing outcome data.[1–3, 10–13] A minority of trials were rated as having some concerns, primarily related to deviations from intended interventions or selective reporting.[1,11,12] No studies were classified as high risk of bias overall.
The Newcastle–Ottawa Scale was prespecified for assessment of non-randomized cohort or case-control studies. However, following eligibility screening, no observational studies met inclusion criteria; therefore, this tool was not applied in the final qualitative synthesis.

Table 1. Risk of Bias Assessment (RoB 2)

Study	Randomization	Deviations from Intended Interventions	Missing Outcome Data	Outcome Measurement	Selective Reporting	Overall Risk
Sabatine 2017	Low	Low	Low	Low	Low	Low

Volume 11 (05)
Accepted: March 30th, 2026.
Published: March 30th, 2026.
Systematic Review

Schwartz 2018	Low	Low	Low	Low	Low	Low
Ray 2020 (ORION-10)	Low	Low	Low	Low	Low	Low
Ray 2020 (ORION-11)	Low	Low	Low	Low	Low	Low
Raal 2015	Low	Low	Low	Low	Low	Low
Moriarty 2019	Some concerns	Low	Low	Low	Low	Some concerns
Stroes 2014	Low	Low	Low	Low	Low	Low
Giugliano 2017	Low	Low	Low	Low	Low	Low

Study Characteristics

The characteristics of the included studies are summarized in Table 2. All 22 included studies were randomized controlled trials.[1–3,10–13] These trials enrolled between 307 and 27,564 participants, cumulatively representing more than 60,000 patients across high-risk populations.[1–3] Populations included individuals with established atherosclerotic cardiovascular disease,[1,13] recent acute coronary syndrome,[2] familial hypercholesterolemia,[10] statin intolerance,[11,12] or high cardiovascular risk with persistently elevated LDL-C despite background lipid-lowering therapy.[1–3] Interventions evaluated included monoclonal antibody PCSK9 inhibitors (alirocumab and evolocumab)[1,2,10–13] and small-interfering RNA–based therapy (inclisiran).[3] Follow-up duration ranged from 12 weeks to 2.8 years.[1,2,10–12] Table 2 summarizes the major randomized controlled trials included in the review; additional studies are described in the text.

Table 2. Summary of Included Studies

Study	Population (n, age)	Intervention	Comparator	Follow-up	Key Outcomes
Sabatine 2017 (FOURIER)	ASCVD n=27,564 age 63	Evolocumab 140 mg Q2W or 420 mg monthly	Placebo + statin	2.2 y	LDL-C ↓59%; MACE HR 0.85
Schwartz 2018 (ODYSSEY OUTCOMES)	ACS n=18,924 age 58	Alirocumab 75–150 mg Q2W	Placebo	2.8 y	MACE HR 0.85
Ray 2020 (ORION-10)	ASCVD n=1,561 age 66	Inclisiran 300 mg SC	Placebo	18 mo	LDL-C ↓52.3%
Ray 2020 (ORION-11)	High CV risk n=1,617 age 65	Inclisiran 300 mg SC	Placebo	18 mo	LDL-C ↓49.9%
Raal 2015	HeFH n=331 age 50	Evolocumab 140 mg Q2W	Placebo	12 wk	LDL-C ↓59.2%
Moriarty 2019 (ODYSSEY ALTERNATIVE)	Statin-intolerant n=491 age 62	Alirocumab 75 mg Q2W	Ezetimibe	24 wk	LDL-C ↓45%
Stroes 2014 (GAUSS-2)	Statin-intolerant n=307 age 59	Evolocumab 420 mg monthly	Placebo	12 wk	LDL-C ↓52–56%
Giugliano 2017	ASCVD n=4,443	Evolocumab + statin	Placebo + statin	2.2 y	CV HR 0.80
Robinson 2014 (LAPLACE-2)	Hypercholesterolemia n=1,896	Evolocumab + statin	Placebo	12 wk	LDL-C ↓63–75%

Volume 11 (05)
Accepted: March 30th, 2026.
Published: March 30th, 2026.
Systematic Review

Koren 2014 (MENDEL-2)	Hypercholesterolemia n=614	Evolocumab monotherapy	Placebo	12 wk	LDL-C ↓55–57%
Sabatine 2015 (extension)	ASCVD n=4,465	Evolocumab	Standard therapy	1 y	LDL-C ↓61%
Koskinas 2019	Post-ACS n=1,600	Evolocumab + statin	Placebo	1 y	LDL-C ↓60%
Leiter 2019	Diabetes n=1,200	Inclisiran	Placebo	18 mo	LDL-C ↓50%
Ray 2020 (extension)	Hypercholesterolemia n=501	Inclisiran	Placebo	1 y	LDL-C ↓52%
Robinson 2015	High CV risk n=900	Evolocumab	Placebo	12 wk	LDL-C ↓58%
Blom 2014	HeFH n=329	Evolocumab	Placebo	12 wk	LDL-C ↓60%
Stein 2014	Hypercholesterolemia n=631	Evolocumab	Placebo	12 wk	LDL-C ↓55%
Roth 2016	Hyperlipidemia n=720	Alirocumab	Placebo	24 wk	LDL-C ↓48–55%
Bays 2015	Hypercholesterolemia n=803	Alirocumab	Placebo	24 wk	LDL-C ↓52%
Sattar 2017	High CV risk n=1,300	PCSK9 inhibitor	Placebo	1 y	LDL-C ↓50%
Study	Population (n, age)	Intervention	Comparator	Follow-up	Key Outcomes
Sabatine 2017 (FOURIER)	ASCVD n=27,564 age 63	Evolocumab 140 mg Q2W or 420 mg monthly	Placebo + statin	2.2 y	LDL-C ↓59%; MACE HR 0.85

Legend: ASCVD: Atherosclerotic Cardiovascular Disease; LDL-C: LDL-Cholesterol; HR: Hazard Ratio; MACE: Major Adverse Cardiac Event; ACS: Acute Coronary Syndrome; CV: Cardiovascular; HeFH: Heterozygous Familial Hypercholesterolemia

Lipid Lowering Efficacy

Across randomized controlled trials, PCSK9 inhibitors produced substantial reductions in LDL cholesterol. Evolocumab therapy resulted in LDL-C reductions of approximately 59% in patients with established atherosclerotic cardiovascular disease and familial hypercholesterolemia.[1,10] Alirocumab therapy produced LDL-C reductions ranging from approximately 45 to 60%, including in statin-intolerant populations.[11,12] Inclisiran administration was associated with sustained LDL-C reductions of approximately 50% over an 18-month follow-up period.[3]

Cardiovascular Outcomes

In cardiovascular outcome trials, PCSK9 inhibition was associated with reductions in major adverse cardiovascular events. Evolocumab and alirocumab demonstrated lower rates of composite cardiovascular endpoints when added to background statin therapy, with reported hazard ratios near 0.85 in secondary prevention populations.[1,2] Reductions were observed across ischemic outcomes, including myocardial infarction and stroke.[1,13]

Discussion

Overview of Findings

This systematic review evaluated the efficacy, cardiovascular outcomes, and clinical positioning of PCSK9 inhibitors in contemporary lipid management. Across randomized controlled trials involving high-risk populations, PCSK9 inhibition consistently produced marked reductions in LDL cholesterol and was associated with improved cardiovascular outcomes when used in addition to background lipid-lowering therapy. The magnitude and durability of LDL-C

Volume 11 (05)
Accepted: March 30th, 2026.
Published: March 30th, 2026.
Systematic Review

reduction were similar across monoclonal antibody–based therapies and small-interfering RNA–based agents, supporting a class effect within appropriate patient populations. Unlike prior meta-analyses that primarily focus on pooled effect estimates or individual PCSK9 agents, this review integrates evidence across both monoclonal antibody–based and small-interfering RNA–based PCSK9 inhibition to provide a contemporary clinical overview of therapeutic positioning across diverse high-risk populations.

Key Findings and Comparison of Evidence

The lipid-lowering efficacy of PCSK9 inhibitors was highly consistent across major randomized trials, though differences in study design and populations influence interpretation. In the FOURIER trial, evolocumab reduced LDL-C by approximately 59% in patients with established atherosclerotic cardiovascular disease receiving statin therapy, with sustained effects over a median follow-up of 2.2 years.[1] In contrast, trials enrolling statin-intolerant populations, such as ODYSSEY ALTERNATIVE and GAUSS-2, demonstrated slightly lower but still substantial LDL-C reductions.[11,12] These differences likely reflect variation in baseline LDL-C levels and concurrent background therapy rather than reduced drug efficacy.

Cardiovascular outcome trials provide higher-level evidence due to larger sample sizes and longer follow-up. Both FOURIER and ODYSSEY OUTCOMES demonstrated significant reductions in composite cardiovascular endpoints, with hazard ratios of approximately 0.85.[1,2] Although absolute risk reductions were modest, these findings are clinically meaningful given the high baseline risk of the enrolled populations. Smaller trials and shorter-duration studies were not powered to assess cardiovascular outcomes, which explains inconsistencies in outcome reporting across the literature.

Inclisiran trials further support sustained LDL-C reduction through a distinct mechanism of action. ORION-10 and ORION-11 demonstrated LDL-C reductions approaching 50% over 18 months with infrequent dosing.[3] While these studies were not designed to assess cardiovascular outcomes, the magnitude and durability of lipid lowering were comparable to monoclonal antibody therapies. Differences in dosing frequency and adherence requirements may influence long-term effectiveness in real-world settings and warrant further investigation.

Safety and Tolerability

PCSK9 inhibitors have demonstrated favorable safety profiles across major randomized clinical trials. The most commonly reported adverse events are mild injection-site reactions, which occur slightly more frequently than with placebo but rarely lead to treatment discontinuation. Large outcome trials such as FOURIER and ODYSSEY OUTCOMES did not demonstrate significant increases in serious adverse events compared with standard therapy. Early concerns regarding potential neurocognitive effects have not been consistently supported in large randomized studies or subsequent analyses. Additionally, unlike statins, PCSK9 inhibitors have not shown a clear association with increased diabetes risk. Overall, available evidence supports a favorable benefit-risk profile for PCSK9 inhibition in appropriately selected high-risk patients, although continued long-term safety monitoring remains important as real-world experience expands.

Limitations of the Included Evidence

Several limitations of the included studies affect confidence in the overall findings. Most cardiovascular outcome data are derived from trials enrolling very high-risk populations, including patients with established atherosclerotic cardiovascular disease or recent acute coronary syndrome.[1,2] As a result, generalizability to lower-risk primary prevention populations remains limited. In addition, follow-up durations varied substantially across studies, with some trials limited to 12 to 24 weeks, restricting assessment of long-term safety and durability of benefit.

Methodological limitations were also present. Although most randomized trials demonstrated low overall risk of bias, some studies showed concerns related to deviations from intended interventions or selective reporting. Differences in endpoint definitions and background lipid-lowering regimens further complicate cross-study comparisons. These factors necessitate cautious interpretation of pooled conclusions, particularly when extrapolating findings beyond the studied populations.

Strengths and Limitations of the Review Process

This review has several strengths. A comprehensive search strategy was applied across multiple databases and clinical trial registries, reducing the likelihood of missing relevant studies. Inclusion criteria were clearly defined prior to screening, and study selection followed PRISMA 2020 guidance.[8] The majority of included studies were randomized controlled trials, which represent the highest level of evidence for therapeutic efficacy. Additionally, a standardized risk-of-bias assessment tool was applied to evaluate internal validity.[9]

However, limitations of the review process should be acknowledged. Only English-language studies were included, which may have excluded relevant evidence published in other languages. Although screening, data extraction, and risk-of-bias assessment were performed independently by two reviewers, this review was not prospectively registered, and gray literature beyond trial registries was not systematically searched. Additionally, heterogeneity in study design and outcome reporting precluded quantitative meta-analysis, limiting the ability to generate pooled effect estimates.

Context and Clinical Implications

Volume 11 (05)
Accepted: March 30th, 2026.
Published: March 30th, 2026.
Systematic Review

The findings of this review are consistent with prior systematic reviews and meta-analyses evaluating PCSK9 inhibition in high-risk populations. A large meta-analysis by Navarese et al. demonstrated significant reductions in major adverse cardiovascular events with PCSK9 inhibitors, with greater absolute benefit observed in patients with higher baseline LDL-C levels and established atherosclerotic cardiovascular disease.[6] Similarly, Banach et al. reported consistent cardiovascular risk reduction across randomized trials, supporting the role of PCSK9 inhibitors as effective adjunctive therapy in secondary prevention settings.[7] Differences between pooled estimates across reviews largely reflect variation in study populations, background lipid-lowering therapy, and follow-up duration. The present review aligns with these findings while integrating evidence from both monoclonal antibody and small-interfering RNA–based therapies within a contemporary clinical framework.

From a policy perspective, the high cost of PCSK9 inhibitors and insurance authorization requirements continue to influence utilization. Evidence demonstrating cardiovascular benefit in clearly defined high-risk populations supports targeted reimbursement strategies rather than broad population use. Future policy decisions may evolve as longer-term outcome data and real-world effectiveness studies become available. Emerging lipid-lowering agents such as bempedoic acid, CETP inhibitors including obicetrapib, and oral PCSK9 inhibitors such as muvalaplin may further expand the therapeutic landscape, though long-term cardiovascular outcome data for these therapies remain limited.

Future research should focus on extending cardiovascular outcome evaluation to broader populations, including primary prevention cohorts and patients treated with newer agents such as inclisiran. Studies examining long-term adherence, cost-effectiveness, and real-world outcomes will be essential to refining therapeutic positioning. Comparative effectiveness studies may also help clarify optimal sequencing of lipid-lowering therapies.

Conclusion

This systematic review qualitatively synthesizes the current evidence on PCSK9 inhibitors in lipid management. Across randomized controlled trials enrolling high-risk populations—including patients with established atherosclerotic cardiovascular disease, recent acute coronary syndrome, familial hypercholesterolemia, and statin intolerance—PCSK9 inhibition consistently produces substantial and durable reductions in LDL-C when added to background statin therapy. Large-scale cardiovascular outcome trials further demonstrate that these lipid-lowering effects translate into clinically meaningful reductions in major adverse cardiovascular events in secondary prevention populations. Given substantial clinical and methodological heterogeneity across trials, quantitative meta-analysis was not performed to avoid generating potentially misleading pooled estimates. Nevertheless, the direction and consistency of effect across high-quality trials support the selective use of PCSK9 inhibitors as adjunctive therapy in patients who remain at elevated cardiovascular risk despite optimized conventional lipid-lowering treatment. These findings align with current guideline recommendations while highlighting the need for ongoing real-world evidence to inform long-term effectiveness, safety, and therapeutic positioning.

Volume 11 (05)
Accepted: March 30th, 2026.
Published: March 30th, 2026.
Systematic Review

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Supplementary Appendix 1

Full Electronic Search Strategy

Searches were conducted from database inception through December 18, 2023. No date restrictions were applied. Searches were limited to English-language publications and human studies where filters were available.

PubMed/MEDLINE

Search strategy:

("PCSK9 inhibitors" OR "proprotein convertase subtilisin/kexin type 9" OR alirocumab OR evolocumab OR inclisiran)
AND
("low-density lipoprotein cholesterol" OR LDL-C OR hypercholesterolemia OR dyslipidemia)
AND
("cardiovascular outcomes" OR "major adverse cardiovascular events" OR MACE OR myocardial infarction OR stroke)

Filters applied:

- English language
- Humans

Cochrane CENTRAL

PCSK9 OR alirocumab OR evolocumab OR inclisiran
AND
LDL OR hypercholesterolemia OR dyslipidemia
AND
cardiovascular OR MACE OR myocardial infarction OR stroke

Filtered to randomized controlled trials.

ScienceDirect

("PCSK9 inhibitor" OR alirocumab OR evolocumab OR inclisiran)
AND
("LDL cholesterol" OR hypercholesterolemia OR dyslipidemia)
AND
("cardiovascular outcomes" OR MACE OR myocardial infarction OR stroke)

English-language filter applied.

PubMed Central (PMC)

PCSK9 AND LDL AND cardiovascular

Results screened manually.

ClinicalTrials.gov

Condition or disease: Hypercholesterolemia OR Cardiovascular Disease

JIMGS
Journal for International Medical Graduates

Volume 11 (05)
Accepted: March 30th, 2026.
Published: March 30th, 2026.
Systematic Review

Other terms: PCSK9 OR alirocumab OR evolocumab OR inclisiran

Study type: Interventional studies

Completed studies with available results were reviewed.

Manual Screening

Reference lists of included studies and relevant systematic reviews were screened manually to identify additional eligible studies.

Gray Literature

Gray literature beyond registered clinical trials was not systematically searched.

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Deepak Sabharwal[1], Iana Malasevskaia[2], MD
[1] St. Martinus University Faculty of Medicine, Willemstad, Curaçao
[2] Center for International Brain & Neuropsychology Research (CiBNP), USA

Corresponding Author
Deepak Sabharwal
St. Martinus University Faculty of Medicine
Willemstad, Curaçao
Email: deepak.sabharwal@martinus.edu