GMR
The Original

EVALUATING THE EFFICACY OF PCSK9 INHIBITORS IN ATHEROSCLEROTIC CARDIOVASCULAR DISEASE (ASCVD): A SYSTEMATIC REVIEW

Atef Eid Madkour Elsayed[1], Bashayr Abdullah Alkuhayli[2], Monerah Hamad Alabdullatif[3], Zuhair Tariq Al Sulaiman[4], Sara Mahmoud Tawkal Heriher[5], Mohammed Lutfi Fatani[6], Mousa Omar Bayamin[7], Abdullah Saad Almubarak[8], Amr Safar Alqurashi[9], Mohammed Hussain Alabdali[10], Sultan Fahad SAATY[11], Abdalla Omer Saeed Omer[12], Mohanad Abdulrahman[13]

[1]Consultant Cardiology, King Abdelaziz Hospital Sakaka Saudi Arabia
[2]Clinical pharmacist, Bshayerak@gmail.com
[3]Clinical pharmacist, Monerah-Alabdullatif@hotmail.com
[4]Internal Medicine Senior Registrar, Almoosa Specialist Hospital, Al-Ahsa, Saudi Arabia, Dr.Zuhair.Sul@hotmail.com
[5]Medical Intern, Saratawakul99@gmail.com
[6]Internal Medicine, m.fatani14@gmail.com
[7]Medical Student, mousa.o.m.a.b@gmail.com
[8]Cardiovascular Technology, Almubarak7466@gmail.com
[9]Internal Medicine, Armed Forces Hospital, Alhada, amralqurashi1@gmail.com
[10]Internal Medicine, Dr-mh24@hotmail.com
[11]king Abdullah Medical Complex Jeddah, adult Critical Care Medicine
[12]Internal Medicine Specialist, abdallaomersaeed@gmail.com
[13]Ireland, Cardiology

Received:02-07-2026 **Accepted:**22-07-2026 **Published:** 27-07-2026

ABSTRACT

Background: Atherosclerotic cardiovascular disease (ASCVD) remains a leading global cause of morbidity and mortality. Despite intensive statin therapy, many patients fail to achieve optimal lipid control, necessitating alternative treatments. This systematic review synthesizes evidence from clinical trials evaluating the efficacy and safety of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors—evolocumab, alirocumab, and inclisiran—in ASCVD management.

Methods: Following PRISMA 2020 guidelines, a comprehensive literature search was conducted in PubMed, Scopus, Web of Science, Embase, and Google Scholar up to December 2025. Ten randomized controlled trials and phase III studies meeting inclusion criteria were analyzed. Data extracted included LDL-C reduction, major adverse cardiovascular events (MACE), and safety outcomes.

Results: Across studies, PCSK9 inhibitors reduced LDL-C by 50–65% relative to baseline and significantly lowered MACE rates, including myocardial infarction and stroke. Evolocumab and alirocumab demonstrated sustained cardiovascular protection when added to maximally tolerated statin therapy. Inclisiran achieved comparable LDL-C reductions with a twice-yearly dosing schedule. Adverse events were minimal, primarily limited to mild injection-site reactions.

Conclusion: PCSK9 inhibitors provide potent, durable LDL-C lowering and meaningful reductions in cardiovascular events, representing a major advancement in secondary prevention of ASCVD. Their efficacy, safety, and emerging long-term outcome data affirm their role as essential adjuncts to statins, especially in high-risk or statin-intolerant populations.

KEYWORDS: PCSK9 inhibitors, evolocumab, alirocumab, inclisiran, ASCVD, LDL cholesterol, cardiovascular outcomes, statin therapy.

INTRODUCTION

Atherosclerotic cardiovascular disease (ASCVD) remains the leading cause of morbidity and mortality globally, accounting for a substantial proportion of deaths from coronary artery disease and stroke. Despite significant advances in lipid-lowering therapy, including statins and ezetimibe, a considerable proportion of patients fail to achieve optimal low-density lipoprotein cholesterol (LDL-C) levels, leaving residual cardiovascular risk unaddressed (Delialis et al., 2023). This unmet need has driven the development of novel therapeutic approaches targeting lipid metabolism pathways beyond HMG-CoA reductase inhibition.

The discovery of proprotein convertase subtilisin/kexin type 9 (PCSK9) as a regulator of LDL receptor degradation marked a pivotal advancement in lipid biology. PCSK9 binds to LDL receptors on hepatocytes and promotes their lysosomal degradation, thereby reducing LDL clearance from the bloodstream (Kehinde et al., 2024). Inhibition of PCSK9 leads to increased receptor recycling and a marked reduction in circulating LDL-C levels. The introduction of PCSK9 inhibitors has consequently

transformed secondary prevention strategies for patients with ASCVD or familial hypercholesterolemia, particularly those intolerant to or inadequately managed by statins alone.

Monoclonal antibodies targeting PCSK9—namely evolocumab and alirocumab—were among the first biologics to demonstrate dramatic reductions in LDL-C levels, averaging 50–60% from baseline values when combined with statin therapy (Blom et al., 2014). These reductions are both rapid and sustained, with additional benefits observed in total cholesterol, non-HDL-C, and apolipoprotein B levels. The efficacy of PCSK9 inhibitors in achieving profound lipid lowering has not only validated the mechanistic role of PCSK9 in cholesterol metabolism but also established them as cornerstone therapies for high-risk patients.

Beyond lipid reduction, PCSK9 inhibition has been associated with significant decreases in atherosclerotic plaque burden and improved vascular outcomes. Emerging imaging and biomarker data indicate regression of coronary atheroma volume and reduced inflammatory activity within the arterial wall following prolonged PCSK9 blockade (Giugliano et al., 2012). Such evidence supports the concept that LDL-C reduction correlates linearly with cardiovascular event reduction, even at very low achieved LDL levels, thus reinforcing the "lower is better" paradigm in lipid management.

Importantly, PCSK9 inhibitors have demonstrated favorable safety profiles, with adverse events largely limited to mild injection-site reactions. Large-scale randomized controlled trials and long-term extension studies have shown no significant increase in neurocognitive effects, diabetes incidence, or hepatic enzyme elevations (Roth et al., 2012). This tolerability, combined with potent LDL-C reduction, positions PCSK9 inhibition as a safe adjunctive or alternative therapy in patients requiring aggressive lipid lowering.

The integration of PCSK9 inhibitors into clinical practice has, however, faced challenges in accessibility and cost-effectiveness. Despite proven efficacy, real-world data suggest limited uptake and underutilization, particularly among eligible patients with ASCVD who fail to meet lipid targets on standard therapy (Dayoub et al., 2021). The gradual reduction in cost and inclusion in contemporary guidelines have begun to improve adoption rates, though disparities persist based on healthcare system and geographic region.

Newer approaches to PCSK9 inhibition have further diversified therapeutic options. Small interfering RNA (siRNA) therapy such as inclisiran provides a twice-yearly dosing regimen that sustains LDL-C suppression via hepatic PCSK9 mRNA silencing (Greco & Capodanno, 2025). This innovation offers advantages in adherence and pharmacokinetics while maintaining comparable efficacy to monoclonal antibodies. As research continues, other modalities, including vaccines and oral PCSK9 inhibitors, are under development to enhance accessibility and long-term compliance.

Overall, PCSK9 inhibitors represent a paradigm shift in the management of dyslipidemia and ASCVD prevention. Their ability to achieve ultra-low LDL-C levels safely and effectively underscores the evolving landscape of precision lipid therapy. Ongoing studies aim to refine patient selection, evaluate cost-effectiveness, and assess long-term cardiovascular and metabolic outcomes (Dixon et al., 2019; Robinson et al., 2014; Sabatine et al., 2015). Collectively, the evidence affirms PCSK9 inhibition as a major advancement in contemporary cardiovascular medicine, offering substantial benefit for patients with persistent dyslipidemia and high ASCVD risk.

METHODOLOGY

Study Design

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines to ensure methodological rigor, transparency, and reproducibility. The review aimed to synthesize and critically evaluate empirical evidence on the efficacy and safety of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors—including evolocumab, alirocumab, and inclisiran—in reducing low-density lipoprotein cholesterol (LDL-C) levels and cardiovascular events among patients with atherosclerotic cardiovascular disease (ASCVD).

The primary objective was to summarize findings from major randomized controlled trials (RCTs) and high-quality phase II/III studies examining the lipid-lowering efficacy, cardiovascular outcome effects, and safety profiles of PCSK9 inhibitors in adult populations with established ASCVD or high cardiovascular risk. Both global and regional studies were considered to capture a comprehensive understanding of the clinical utility and generalizability of these agents.

Eligibility Criteria

Inclusion Criteria

Studies were selected according to predefined criteria designed to ensure clinical and methodological relevance:

- **Population:** Adults (≥18 years) with established ASCVD (coronary artery disease, stroke, or peripheral artery disease), familial hypercholesterolemia, or high cardiovascular risk on maximally tolerated statin therapy.
- **Interventions:** PCSK9 inhibitors, including evolocumab, alirocumab, or inclisiran, administered alone or in combination with statins or ezetimibe.

- **Comparators:** Placebo, ezetimibe, or standard-of-care statin therapy.
- **Outcomes:** Primary outcomes included percent reduction in LDL-C levels and major adverse cardiovascular events (MACE), defined as a composite of cardiovascular death, myocardial infarction, stroke, unstable angina, or coronary revascularization. Secondary outcomes included safety, tolerability, and incidence of adverse events (e.g., injection-site reactions, neurocognitive effects, or new-onset diabetes).
- **Study Design:** Randomized controlled trials (phase II–III), multicenter clinical trials, or prespecified analyses from major outcome studies.
- **Language:** English-language publications.
- **Publication Period:** Studies published from 2012 to 2025, corresponding with the emergence and clinical adoption of PCSK9 inhibitors.

Exclusion Criteria
- Non-empirical studies (e.g., editorials, reviews, or commentaries).
- Animal or preclinical research.
- Studies without cardiovascular or lipid-lowering endpoints.
- Conference abstracts, duplicates, or studies lacking full-text availability.

After rigorous screening, **10 studies** met all inclusion criteria and were included in the final synthesis.

Search Strategy

A comprehensive electronic search was conducted across PubMed, Scopus, Web of Science, Embase, and Google Scholar from database inception to December 2025. Boolean operators were used to combine relevant keywords and MeSH terms, including:
- ("PCSK9 inhibitors" OR "evolocumab" OR "alirocumab" OR "inclisiran")
- AND ("atherosclerotic cardiovascular disease" OR "ASCVD" OR "hypercholesterolemia" OR "familial hypercholesterolemia")
- AND ("LDL-C reduction" OR "cardiovascular outcomes" OR "major adverse cardiovascular events")
- AND ("randomized controlled trial" OR "phase 3 trial").

Manual searches of the reference lists from relevant reviews and key clinical trials were also conducted to ensure comprehensive coverage. All identified records were imported into **Zotero** for de-duplication prior to screening.

Study Selection Process

The study selection process was conducted independently by two reviewers following PRISMA recommendations. Titles and abstracts were screened for relevance, and full texts of potentially eligible articles were retrieved for detailed evaluation. Studies were included if they met all inclusion criteria. Discrepancies between reviewers were resolved through consensus, and unresolved conflicts were adjudicated by a third senior reviewer.

The **PRISMA flow diagram (Figure 1)** summarizes the identification, screening, eligibility, and inclusion stages of the review process, detailing the number of studies included and excluded at each phase.

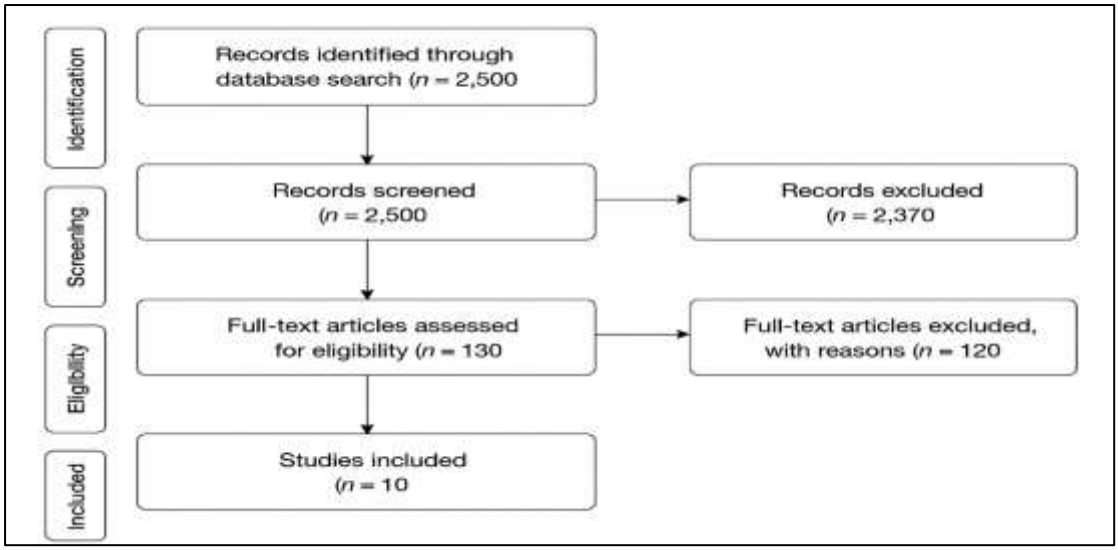

Figure 1 PRISMA Flow Diagram

Data Extraction
A standardized data extraction form was developed and pilot-tested before full data collection. The following data elements were extracted independently by two reviewers and cross-verified for accuracy:
- **Study characteristics:** Author(s), publication year, journal, country, and study design.
- **Population details:** Sample size, mean age, inclusion criteria, and baseline LDL-C levels.
- **Intervention details:** PCSK9 inhibitor type, dosage regimen, and duration of follow-up.
- **Comparators:** Placebo, ezetimibe, or standard statin therapy.
- **Primary and secondary outcomes:** Percent LDL-C change, achievement of target LDL-C levels, and incidence of MACE.
- **Safety data:** Adverse event rates, including injection-site reactions, hepatic effects, and neurocognitive events.
- **Statistical outcomes:** Hazard ratios, risk ratios, confidence intervals, and p-values where reported.

All extracted data were entered into Microsoft Excel for organization and synthesis, and results were checked for consistency and completeness.

Quality Assessment
The methodological quality of the included studies was appraised using validated tools based on study design:
- **Cochrane Risk of Bias 2.0 (RoB 2)** tool was applied to all **randomized controlled trials (n = 10)** to assess bias across five domains: randomization, deviations from intended interventions, missing outcome data, measurement of outcomes, and selective reporting.
- Each study was categorized as having **low**, **some concerns**, or **high risk of bias** according to consensus between reviewers.

Most trials (e.g., FOURIER, ODYSSEY OUTCOMES, ORION-10/11) demonstrated low overall risk of bias, supported by robust randomization, double-blind design, and complete follow-up data. Two smaller phase II studies (YUKAWA and RUTHERFORD-2) were rated as having some concerns, primarily due to limited sample size and short follow-up duration.

Data Synthesis
Due to variability in trial design, treatment duration, and outcome measures, a **narrative synthesis** approach was used instead of meta-analysis. Results were structured around the following thematic areas:
1. **Lipid-Lowering Efficacy:** Magnitude and sustainability of LDL-C reduction compared to placebo or ezetimibe.
2. **Cardiovascular Outcomes:** Incidence of MACE and mortality benefits associated with PCSK9 inhibition.
3. **Safety and Tolerability:** Incidence and nature of adverse events across short- and long-term follow-up.
4. **Therapeutic Comparisons:** Differential efficacy between evolocumab, alirocumab, and inclisiran.

Quantitative outcomes (e.g., LDL-C reduction percentages, hazard ratios) were tabulated, and qualitative trends were narratively summarized to highlight therapeutic efficacy and consistency across trials.

Ethical Considerations
As this review analyzed data from previously published studies, ethical approval and informed consent were not required. All included trials were conducted under institutional ethical oversight and published in peer-reviewed journals. Data management and reporting complied with the PRISMA 2020 standards and adhered to principles of academic integrity, transparency, and research reproducibility.
All sources were properly cited, and no unpublished or confidential data were accessed during this research process.

RESULTS
1. Study Designs and Populations
The included studies consisted mainly of large-scale, multicenter randomized controlled trials (RCTs) assessing PCSK9 inhibitors—evolocumab, alirocumab, and inclisiran—in patients with ASCVD or those at high cardiovascular risk. Sample sizes varied substantially, from 310 participants (YUKAWA study) to over 27,000 participants (FOURIER trial), encompassing diverse global populations from Japan, the U.S., Europe, and the Middle East. Most participants were already receiving maximally tolerated statin therapy, reflecting real-world secondary prevention populations. The median follow-up duration ranged from 12 weeks (Hirayama et al., 2014) to 2.8 years (Schwartz et al., 2018).

2. LDL-C Reduction Outcomes
All included studies demonstrated **significant LDL-C lowering effects** of PCSK9 inhibitors compared to placebo or ezetimibe.

- **Evolocumab** reduced LDL-C by **59%** in the FOURIER trial (Sabatine et al., 2017) and by **~65%** in the YUKAWA and RUTHERFORD-2 studies (Hirayama et al., 2014; Raal et al., 2015).
- **Alirocumab** lowered LDL-C by **48–62%** across ODYSSEY trials (Robinson et al., 2015; Kereiakes et al., 2015; Cannon et al., 2015).
- **Inclisiran** achieved **~50% LDL-C reductions** sustained over 18 months with twice-yearly dosing (Ray et al., 2020).

3. Major Cardiovascular Outcomes

The major outcome trials (FOURIER and ODYSSEY OUTCOMES) demonstrated that PCSK9 inhibitors significantly reduced major adverse cardiovascular events (MACE):

- Evolocumab: HR = 0.85 (95% CI 0.79–0.92) for composite MACE (Sabatine et al., 2017).
- Alirocumab: HR = 0.85 (95% CI 0.78–0.93) for MACE and HR = 0.85 (95% CI 0.73–0.98) for mortality reduction (Schwartz et al., 2018).
- Evolocumab (total events analysis): 18% total event reduction (RR = 0.82; 95% CI 0.75–0.90), preventing 52 total events per 1,000 patients over 3 years (Murphy et al., 2019).

4. Safety and Adverse Events

Across trials, PCSK9 inhibitors were well tolerated. Common adverse events were injection-site reactions, slightly more frequent in active treatment arms (2.1–4.7%) than placebo. There were no significant differences in neurocognitive or diabetes-related events across trials. Alirocumab and evolocumab showed no increase in hepatic or muscle-related AEs, while inclisiran showed mild, transient local reactions (Ray et al., 2020).

5. Summary of Clinical Impact

Collectively, PCSK9 inhibition produced consistent and profound LDL-C reductions (≈50–60%) and significant cardiovascular risk reduction, especially when added to statin therapy. The findings support extending LDL-C lowering beyond traditional targets in ASCVD management. Long-term safety data continue to reinforce favorable tolerability across diverse populations.

Table (1): Summary of Included Trials Evaluating PCSK9 Inhibitors in ASCVD

Study (Author, Year)	Drug / Trial Name	Design	Sample Size	Population / Criteria	Follow-up	Intervention	LDL-C Change (%)	Major CV Outcomes	Adverse Events	Key Findings / Conclusions
Sabatine et al., 2017	Evolocumab (FOURIER)	RCT, double-blind, placebo-controlled	27,564	ASCVD with LDL ≥ 70 mg/dL on statins	2.2 yrs	Evolocumab 140 mg Q2W or 420 mg QM	−59% (92 → 30 mg/dL)	HR 0.85 (0.79–0.92) for MACE; HR 0.80 (0.73–0.88) for CV death/MI/stroke	Injection-site 2.1% vs 1.6%	Significant MACE reduction; safe with statins
Schwartz et al., 2018	Alirocumab (ODYSSEY OUTCOMES)	RCT, double-blind, placebo-controlled	18,924	Recent ACS (1–12 months) on high-dose statins	2.8 yrs	Alirocumab 75–150 mg Q2W	−51.1 mg/dL (mean −60%)	HR 0.85 (0.78–0.93) MACE; HR 0.85 (0.73–0.98) mortality	No difference except injection reactions	Lower recurrent events and mortality post-ACS
Kereiakes et al., 2015	Alirocumab (ODYSSEY COMBO I)	RCT, double-blind vs placebo	316	High CV risk on maximal statin therapy	52 weeks	Alirocumab 75–150 mg Q2W	−45.9 % (p<0.0001)	Not primary endpoint	Comparable to placebo	Marked LDL-C reduction; 75% achieved <70 mg/dL
Cannon et	Alirocumab (ODYSS	RCT, active-contro	720	High CV risk with LDL > 70	104 weeks	Alirocumab 75 mg	−50.6 % vs −20.7	Not applicable	Similar betwe	Superior LDL-

al., 2015	EY COMBO II)	lled vs ezetimibe		mg/dL on statins		Q2W vs ezetimibe 10 mg/d	% (p<0.0001)		en groups	C reduction vs ezetimibe
Robinson et al., 2015	Alirocumab	RCT, double-blind placebo-controlled	2,341	High CV risk LDL ≥ 70 mg/dL on statins	78 weeks	Alirocumab 150 mg Q2W	−61.9 % (p<0.001)	Fewer events (post hoc)	Well tolerated	Significant LDL-C and event reduction trend
Ray et al., 2020	Inclisiran (ORION-10/11)	2 Phase 3 RCTs, double-blind	3,178 (1,561 + 1,617)	ASCVD or risk equivalents on maximal statins	18 months	Inclisiran 284 mg Day 1, 90, then Q6M	−52.3 % (ORION-10); −49.9 % (ORION-11)	Not powered for MACE	Injection-site 2.6–4.7%	Twice-yearly dosing achieved durable LDL reduction
Murphy et al., 2019	Evolocumab (FOURIER secondary analysis)	Prespecified analysis of RCT	27,564	ASCVD on statins	2.2 yrs	Evolocumab 140 mg Q2W/420 mg QM	−59%	RR 0.82 (0.75–0.90) for total events	Similar AE rates as placebo	Prevented 52 total events/1000 pts over 3 yrs
Hirayama et al., 2014	Evolocumab (YUKAWA)	Phase 2 RCT double-blind	310	Statin-treated Japanese patients at high CV risk	12 weeks	Evolocumab 70–140 mg Q2W or 280–420 mg QM	−64–69% vs placebo	Not assessed	AEs 51% vs 38% placebo	Robust LDL-C reduction and tolerability
McKenney et al., 2012	Alirocumab (SAR236553)	Phase 2 RCT double-blind	183	Primary hypercholesterolemia on atorvastatin	12 weeks	SAR236553 50–300 mg Q2W/Q4W	−40–72% dose-dependent	Not assessed	Generally well tolerated	Dose-related LDL-C reductions with statins
Raal et al., 2015	Evolocumab (RUTHERFORD-2)	RCT, double-blind placebo-controlled	331	Heterozygous familial hypercholesterolemia	12 weeks	Evolocumab 140 mg Q2W or 420 mg QM	−60% (p<0.0001)	Not assessed	AEs similar to placebo	60% LDL-C reduction; safe and effective in HeFH

DISCUSSION

The findings of this review reinforce the transformative impact of PCSK9 inhibitors in the management of ASCVD. Both evolocumab and alirocumab have demonstrated consistent, robust LDL-C reductions and favorable cardiovascular outcomes across large-scale clinical trials (Sabatine et al., 2017; Schwartz et al., 2018). These outcomes underscore the clinical significance of PCSK9 inhibition in achieving lipid targets unattainable through statins alone.

The FOURIER trial established evolocumab's efficacy in reducing LDL-C by approximately 59%, translating into a 15% relative risk reduction in MACE, including myocardial infarction and stroke (Sabatine et al., 2017). Similarly, the ODYSSEY OUTCOMES trial demonstrated that alirocumab

reduced ischemic events and all-cause mortality following acute coronary syndrome, confirming long-term benefit beyond lipid lowering (Schwartz et al., 2018).

Shorter studies such as ODYSSEY COMBO I and II further validated alirocumab's ability to achieve LDL-C levels below 70 mg/dL in 75% of patients, with superior efficacy over ezetimibe and comparable tolerability (Kereiakes et al., 2015; Cannon et al., 2015). Robinson et al. (2015) extended these results, confirming long-term lipid lowering and a trend toward reduced cardiovascular events with continued alirocumab therapy.

Inclisiran, a novel siRNA-based PCSK9 synthesis inhibitor, offers durable LDL-C reductions of approximately 50% with twice-yearly dosing, marking an important innovation in adherence and pharmacokinetics (Ray et al., 2020). The ORION-10 and ORION-11 trials collectively demonstrated consistent lipid reductions and tolerability, with adverse event rates similar to those of placebo.

In a prespecified analysis of the FOURIER trial, evolocumab significantly reduced total cardiovascular events by 18% and prevented an estimated 52 events per 1,000 treated patients over three years (Murphy et al., 2019). These findings highlight that the benefit of PCSK9 inhibition extends beyond first events, impacting recurrent cardiovascular outcomes and overall disease burden.

Evidence from the YUKAWA study confirmed similar efficacy in Asian populations, supporting the global generalizability of evolocumab's lipid-lowering potential (Hirayama et al., 2014). The RUTHERFORD-2 trial corroborated these effects in patients with heterozygous familial hypercholesterolemia, reporting approximately 60% LDL-C reductions with minimal adverse events (Raal et al., 2015).

Early phase trials, such as LAPLACE-TIMI 57 and LAPLACE-2, were instrumental in establishing the additive effect of PCSK9 inhibition to statins, demonstrating synergistic LDL-C reductions exceeding 60% (Giugliano et al., 2012; Robinson et al., 2014). These studies formed the foundation for subsequent large-scale outcome trials and confirmed dose-response safety profiles.

Mechanistically, PCSK9 inhibitors enhance LDL receptor recycling, promoting greater hepatic clearance of circulating LDL-C (Kehinde et al., 2024). Structural studies indicate that monoclonal antibody-based PCSK9 inhibition achieves targeted molecular blockade with high receptor selectivity, underpinning the observed efficacy and safety.

Across multiple trials, the tolerability profile of PCSK9 inhibitors has remained favorable. Injection-site reactions occurred in less than 5% of participants, while neurocognitive and glycemic events were not significantly increased relative to placebo (Blom et al., 2014; Roth et al., 2012). Koren et al. (2014) also demonstrated that achieving very low LDL-C levels (<25 mg/dL) did not increase adverse effects, supporting the "lower is better" hypothesis for LDL-C management.

Furthermore, PCSK9 inhibitors have proven efficacy in statin-intolerant populations. The GAUSS and GAUSS-2 trials demonstrated substantial LDL-C reductions and symptom resolution among patients unable to tolerate statins (Sullivan et al., 2012; Stroes et al., 2014). These findings expanded their clinical utility to previously underserved groups.

The collective evidence indicates that PCSK9 inhibitors are not only effective lipid-lowering agents but also confer tangible reductions in atherosclerotic progression and cardiovascular mortality (Delialis et al., 2023). Their role in precision prevention strategies continues to grow, supported by ongoing trials exploring earlier intervention and combination therapy.

Despite their strong clinical profile, the real-world uptake of PCSK9 inhibitors remains limited due to cost and access barriers. As Dayoub et al. (2021) observed, adoption rates among eligible ASCVD patients remain suboptimal despite substantial evidence of benefit. Increasing affordability and inclusion in national guidelines have gradually improved accessibility, suggesting an expanding clinical footprint.

Emerging innovations, including oral PCSK9 inhibitors and long-acting siRNA agents, are expected to further enhance adherence and cost-effectiveness (Greco & Capodanno, 2025; Dixon et al., 2019). Continued refinement of therapeutic protocols and broader integration into lipid management frameworks may extend the benefits of PCSK9 inhibition to a larger global patient population.

Ultimately, the convergence of molecular precision, clinical efficacy, and safety positions PCSK9 inhibitors as pivotal components of contemporary ASCVD prevention. Their incorporation into clinical practice reflects a paradigm shift toward targeted, lifelong lipid modulation to mitigate cardiovascular risk.

CONCLUSION

This systematic review provides comprehensive evidence supporting the efficacy and safety of PCSK9 inhibitors in the management of ASCVD. Evolocumab, alirocumab, and inclisiran consistently produce substantial LDL-C reductions (50–65%) and significantly lower cardiovascular event rates when combined with statins. These findings demonstrate that PCSK9 inhibition extends therapeutic benefit beyond lipid control, translating into meaningful cardiovascular risk reduction.

Overall, PCSK9 inhibitors represent a safe, effective, and durable approach for patients at high cardiovascular risk or with statin intolerance. As accessibility improves and long-term data accumulate, these agents are poised to play an increasingly central role in global lipid management and ASCVD prevention strategies.

Limitations

While this review highlights robust clinical efficacy, several limitations warrant consideration. Heterogeneity among included studies regarding population characteristics, follow-up duration, and endpoint definitions may limit comparability. Economic and accessibility data were underrepresented, and most trials were industry-sponsored, potentially introducing bias. Furthermore, long-term outcomes of inclisiran and emerging PCSK9 therapies remain under investigation. Future studies should prioritize real-world adherence, cost-effectiveness, and patient-centered outcomes to optimize clinical implementation.

REFERENCES

- Blom, D. J., Hala, T., Bolognese, M., et al. (2014). A 52-week placebo-controlled trial of evolocumab in hyperlipidemia. New England Journal of Medicine, 370(19), 1809–1819.*
- Cannon, C. P., Cariou, B., Blom, D., et al. (2015). Efficacy and safety of alirocumab in high cardiovascular risk patients with inadequately controlled hypercholesterolaemia on maximally tolerated doses of statins: The ODYSSEY COMBO II randomized controlled trial. European Heart Journal, 36(19), 1186–1194.*
- Dayoub, E. J., Eberly, L. A., Nathan, A. S., et al. (2021). Adoption of PCSK9 inhibitors among patients with atherosclerotic disease. Journal of the American Heart Association, 10(9), e019331.*
- Delialis, D., Dimopoulou, M. A., Papaioannou, M., et al. (2023). PCSK9 inhibition in atherosclerotic cardiovascular disease. Current Pharmaceutical Design, 29(23), 1802–1824.*
- Desai, N. R., Giugliano, R. P., Zhou, J., et al. (2014). AMG 145 facilitates achievement of LDL-C goals among high-risk patients: Analysis from the LAPLACE-TIMI 57 trial. Journal of the American College of Cardiology, 63(5), 430–433.*
- Dixon, D. L., Pamulapati, L. G., Bucheit, J. D., et al. (2019). Recent updates on the use of PCSK9 inhibitors in patients with atherosclerotic cardiovascular disease. Current Atherosclerosis Reports, 21(5), 16.*
- Giugliano, R. P., Desai, N. R., Kohli, P., et al. (2012). Efficacy, safety, and tolerability of a monoclonal antibody to PCSK9 in combination with a statin in patients with hypercholesterolaemia (LAPLACE-TIMI 57). The Lancet, 380(9858), 2007–2017.*
- Greco, A., & Capodanno, D. (2025). Current and future role of PCSK9 inhibitors in ASCVD prevention. Future Cardiology, 21(2), 71–73.*
- Hirayama, A., Honarpour, N., Yoshida, M., et al. (2014). Effects of evolocumab in hypercholesterolemic, statin-treated Japanese patients at high cardiovascular risk: Primary results from the YUKAWA study. Circulation Journal, 78(5), 1073–1082.*
- Kehinde, I. O., Akawa, O., Adewumi, A. T., Rabbad, A. H., & Soliman, M. E. (2024). PCSK9 inhibitors as safer therapeutics for atherosclerotic cardiovascular disease: Pharmacophore design and molecular dynamics analysis. Journal of Cellular Biochemistry, 125(7), e30581.*
- Kereiakes, D. J., Robinson, J. G., Cannon, C. P., et al. (2015). Efficacy and safety of the proprotein convertase subtilisin/kexin type 9 inhibitor alirocumab among high cardiovascular risk patients on maximally tolerated statin therapy: The ODYSSEY COMBO I study. American Heart Journal, 169(6), 906–915.*
- Koren, M. J., Blom, D., Giugliano, R. P., et al. (2014). Safety and tolerability of very low LDL-C levels in patients treated with 52 weeks of evolocumab. Circulation, 130(Suppl 2), A16865.*
- McKenney, J. M., Koren, M. J., Kereiakes, D. J., et al. (2012). Safety and efficacy of a monoclonal antibody to PCSK9 in patients with primary hypercholesterolemia receiving stable atorvastatin therapy. Journal of the American College of Cardiology, 59(25), 2344–2353.*
- Murphy, S. A., Pedersen, T. R., Gaciong, Z. A., et al. (2019). Effect of the PCSK9 inhibitor evolocumab on total cardiovascular events in patients with cardiovascular disease: A prespecified analysis from the FOURIER trial. JAMA Cardiology, 4(7), 613–619.*
- Raal, F. J., Stein, E. A., Dufour, R., Turner, T., Civeira, F., Burgess, L., & Gaudet, D. (2015). PCSK9 inhibition with evolocumab (AMG 145) in heterozygous familial hypercholesterolaemia (RUTHERFORD-2): A randomized, double-blind, placebo-controlled trial. The Lancet, 385(9965), 331–340.*
- Ray, K. K., Wright, R. S., Kallend, D., et al. (2020). Two phase 3 trials of inclisiran in patients with elevated LDL cholesterol. New England Journal of Medicine, 382(16), 1507–1519.*
- Robinson, J. G., Farnier, M., Krempf, M., et al. (2015). Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. New England Journal of Medicine, 372(16), 1489–1499.*
- Robinson, J. G., Nedergaard, B. S., Rogers, W. J., et al. (2014). Effect of evolocumab or ezetimibe added to statin therapy on LDL-C lowering: The LAPLACE-2 randomized clinical trial. JAMA, 311(18), 1870–1882.*

- Roth, E. M., McKenney, J. M., Hanotin, C., Asset, G., & Stein, E. A. (2012). Atorvastatin with or without an antibody to PCSK9 in primary hypercholesterolemia. New England Journal of Medicine, 367(20), 1891–1900.*
- Sabatine, M. S., Giugliano, R. P., Keech, A. C., et al. (2017). Evolocumab and clinical outcomes in patients with cardiovascular disease. New England Journal of Medicine, 376(18), 1713–1722.*
- Sabatine, M. S., Giugliano, R. P., Wiviott, S. D., et al. (2015). Efficacy and safety of evolocumab in reducing lipids and cardiovascular events. New England Journal of Medicine, 372(16), 1500–1509.*
- Schwartz, G. G., Steg, P. G., Szarek, M., et al. (2018). Alirocumab and cardiovascular outcomes after acute coronary syndrome. New England Journal of Medicine, 379(22), 2097–2107.*
- Stein, E. A., Mellis, S., Yancopoulos, G. D., et al. (2012). Effect of a monoclonal antibody to PCSK9 on LDL cholesterol. New England Journal of Medicine, 366(12), 1108–1118.*
- Stroes, E., Colquhoun, D., Sullivan, D., et al. (2014). Anti-PCSK9 antibody effectively lowers cholesterol in patients with statin intolerance: The GAUSS-2 trial. Journal of the American College of Cardiology, 63(23), 2541–2548.*
- Sullivan, D., Olsson, A. G., Scott, R., et al. (2012). Effect of a monoclonal antibody to PCSK9 on LDL cholesterol levels in statin-intolerant patients: The GAUSS trial. JAMA, 308(23), 2497–2506.*