Original Article

Althea Medical Journal
ISSN Online: 2337-4330
https://doi.org/10.15850/amj.v12n3.4209

Therapeutic Effects of Proprotein Convertase Subtilisin/Kexin Type 9 Inhibitors in Dyslipidemia: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Nur Hafidha Hikmayani,[1] Ratih Puspita Febrinasari,[1] Ariq Ratya Satwika2[2]

[1]Department of Pharmacology, Faculty of Medicine, Universitas Sebelas Maret, Surakarta, Indonesia

[2]Faculty of Medicine, Universitas Sebelas Maret, Surakarta, Indonesia

Abstract

Background: Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors represent a novel class of medications for managing dyslipidemia. Although previous meta-analyses have confirmed their efficacy in lowering low-density lipoprotein cholesterol (LDL-C), few have evaluated their effects on broader lipid parameters. Moreover, most studies focus on the general dyslipidemic population, provided limited insight into specific subgroups. This study specifically investigated the effects of PCSK9 inhibitors on multiple lipid parameters in individuals with dyslipidemia who were statin-intolerant, statin-resistant, or required intensified lipid-lowering treatment.

Methods: This study systematically searched PubMed, ScienceDirect, and the Cochrane Library for phase 3 randomized controlled trials (2013–2023), evaluating PCSK9 inhibitors against placebo or non-statin standard care in dyslipidemic patients aged ≥18 years. The main outcome was the changes from baseline in lipid parameters. Random-effects meta-analyses were conducted using RevMan.

Results: Eight studies involving 2,343 participants met eligibility criteria. PCSK9 inhibitors significantly reduced LDL-C (MD -46.8, 95% CI [-53.2; -40.4]), non-HDL-C (MD -41.1 [-46.9; -35.3]), total cholesterol (MD -31.5 [-37.8; -25.2]), triglycerides (MD -11.7 [-15.0; -8.4], Lp(a) (MD -19.2 [-25.7; -12.6]), and ApoB (MD -39.4 [-45.0; -33.7]). PCSK9 inhibitors also significantly increased HDL-C (MD 6.3 [4.7; 7.9]) and ApoA-I (MD 4.1 [2.8; 5.5]).

Conclusions: PCSK9 inhibitors significantly improve a broad spectrum of lipid parameters, including non-traditional markers such as non-HDL-C, ApoA-I, ApoB, and Lp(a), underscoring their potential role in managing dyslipidemia, particularly in patients inadequately controlled with standard therapies

Keywords: Alirocumab, cholesterol, dyslipidemia, evolocumab, PCSK9 inhibitors

Althea Medical Journal.
2025;12(3):161–171

Received: May 16, 2025
Accepted: August 29, 2025
Published: September 30, 2025

Correspondence:
Nur Hafidha Hikmayani,
Department of Pharmacology,
Faculty of Medicine,
Universitas Sebelas Maret,
Jl. Ir. Sutami 36A, Kentingan,
Surakarta 57126, Indonesia

E-mail:
hafidha@staff.uns.ac.id

Introduction

Dyslipidemia, a key component of metabolic syndrome, is associated with a two-fold increase in cardiovascular disease (CVD) morbidity and mortality.[1,2] Elevated low-density lipoprotein cholesterol (LDL-C) levels are strongly linked to a higher risk of atherosclerotic CVD,[3] which in 2016 was the leading cause of death worldwide, accounting for 31% of all deaths.[4] Managing dyslipidemia involves both primary and secondary prevention strategies, including lifestyle modifications and pharmacologic interventions to reduce LDL-C levels.[5]

Statins remain the first-line treatment for dyslipidemia due to their proven efficacy in lowering LDL-C. However, many patients fail to achieve target levels due to statin resistance,[6] and 10–15% discontinue treatment because of intolerance.[7] Second-line therapies such as ezetimibe, fibrates, and nicotinic acid are used when statins are insufficient or poorly tolerated. Recently, non-statin lipid-lowering

therapies (LLTs) such as proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors have gained attention for their ability to substantially reduce LDL-C, either alone or in combination with other agents.[8]

PCSK9 inhibitors, including evolocumab and alirocumab, are monoclonal antibodies that enhance LDL receptor expression, thereby lowering LDL-C levels.[9] These agents are particularly beneficial for patients with familial hypercholesterolemia and statin intolerance, including those with poorly controlled triglyceride.[6] Although PCSK9 inhibitors may cause local injection site reactions, they do not induce muscle toxicity or elevate creatine kinase or hepatic enzymes.[10] PCSK9 inhibitors are currently approved as adjuncts to dietary modifications and maximally tolerated statin therapy.[11]

Previous meta-analyses have demonstrated the efficacy of PCSK9 inhibitors in lowering and improving cardiovascular outcomes.[12,13] However, few have comprehensively evaluated their effects on additional lipid parameters such as high-density lipoprotein cholesterol (HDL-C), total cholesterol, and apolipoproteins. Furthermore, limited emphasis has been placed on the role of PCSK9 inhibitors in subgroups such as statin-intolerant or statin-resistant patients, and several reviews relied on older data without incorporating recent phase 3 trial updates.

This systematic review and meta-analysis aimed to address these gaps by evaluating the therapeutic effects of PCSK9 inhibitors on a comprehensive range of lipid parameters using updated evidence from randomized controlled trials (RCTs) published up to 2023. Special emphasis was placed on patients who are statin-intolerant, statin-resistant, or require intensified lipid-lowering treatment. Subgroup analyses by type of PCSK9 inhibitor, comparator, prior LLTs exposure, and study quality were also conducted to explore potential differences in efficacy.

Methods

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines.[14] A comprehensive literature search was performed in PubMed, ScienceDirect, and the Cochrane Library to identify relevant studies published between January 2013 and December 2023. The keywords used the Medical Subject Headings (MeSH) terms or relevant keywords, combined with Boolean operators and database-specific filters (Table 1). In addition, the reference lists of related reviews were screened to capture additional eligible studies.

Eligible studies were phase 3 randomized controlled trials (RCTs) that enrolled patients aged ≥18 years with dyslipidemia, including those with statin intolerance, statin resistance, or requiring intensified lipid-lowering therapy. Interventions included PCSK9 inhibitors

Table 1 Databases and Search Strategy

Database	MeSH Terms or Keywords	Filters
PubMed	(dyslipidemia OR hyperlipidemia OR hypercholesterolemia OR hyperlipoproteinemia OR hypertriglyceridemia OR (elevated low-density lipoprotein cholesterol) OR (elevated triglyceride)) AND ((proprotein convertase subtilisin-kexin type 9 inhibitors) OR (PCSK9 inhibitors) OR evolocumab OR alirocumab) AND ((low-density lipoprotein cholesterol) OR (high-density lipoprotein cholesterol) OR (total cholesterol) OR triglyceride OR (*lipoprotein))	Publication date: 10 years; Article type: Randomized controlled trial; Text availability: Free full text; Language: English; Species: Human.
ScienceDirect	((pcsk9 inhibitor) AND dyslipidemia AND (randomized controlled trial))	Years: 2013-2023; Article type: Research articles.
Cochrane Library	((pcsk9 inhibitor) AND dyslipidemia)	

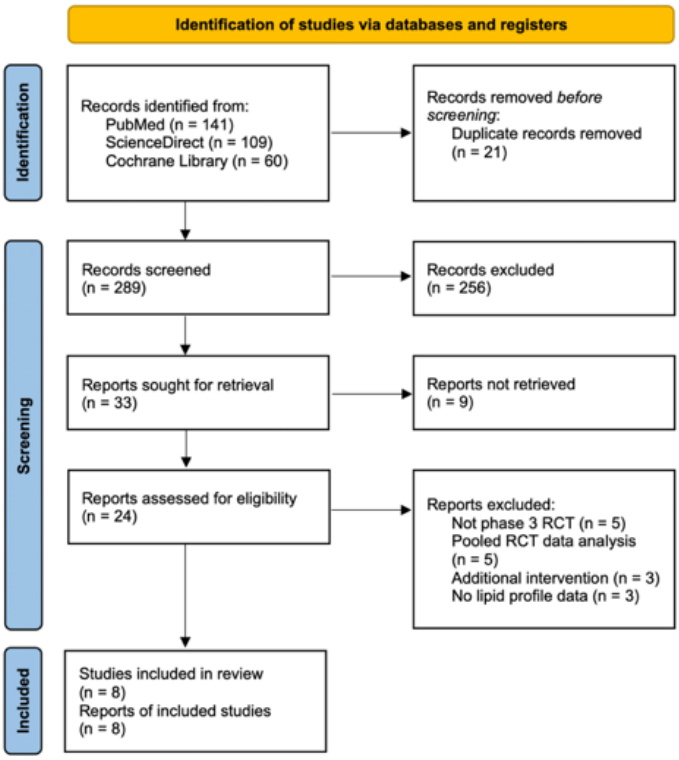

Figure 1 PRISMA Flow Diagram

(alirocumab or evolocumab), administered either as monotherapy or in combination with background therapy. Comparators consisted of placebo or other LLTs. Outcomes of interest were changes from baseline in lipid parameters, including LDL-C, HDL-C, total cholesterol, triglycerides, non-HDL-C, apolipoprotein A-I (ApoA-I), apolipoprotein B (ApoB), and lipoprotein(a) [Lp(a)]. These outcomes were pre-specified prior to data extraction based on clinical relevance and frequent reporting in lipid-related studies.

Only phase 3 RCTs published in English and reporting at least one lipid outcome were included. Non-randomized studies, observational studies, reviews, conference abstracts, studies in pediatric populations, studies involving patients with controlled dyslipidemia or comorbidities, or early phase clinical trials (phase 1 or 2), or trials without lipid outcome data were excluded.

Two independent reviewers (ARS and NHH) screened the articles, extracted the relevant data, and assessed study quality using the Cochrane's Risk of Bias 2.0 tool, Discrepancies were resolved by consensus or by consulting a third reviewer. Extracted data included study characteristics (the first author's name, year of publication, study name and location, study design, study and control drugs, sample size, study duration), patients demographics, and clinical outcomes.

Meta-analyses were conducted using Review Manager (RevMan) version 5.4. Mean differences (MD) with 95% confidence intervals (CI) were calculated for continuous outcomes. Random-effects models were applied to account for potential heterogeneity among studies, and statistical significance was set at $p<0.05$. Heterogeneity was assessed using the I^2 statistics, with values ≥50% indicating substantial heterogeneity. Subgroup analyses were conducted according to the type of PCSK9 inhibitor, comparator, prior LLT use, predominant racial composition, and study quality. Publication bias was evaluated with funnel plots.

The certainty of evidence for each outcome was assessed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach, which considers five domains: risk of bias, inconsistency, indirectness, imprecision, and publication bias. The quality of evidence was rated as high, moderate, low, or very low. The summary of findings (SoF) table was generated using the GRADEpro GDT software (https://gradepro.org).

Table 2 Characteristics of Included Studies

Author, (Year)	Study Name (Country)	Study Design	Study Drug	Control Drug	Sample Size	Duration (Weeks)	Inclusion Criteria
Koba, et al.,[21] (2020)	GAUSS-4 (Japan)	Double-blind RCT (1:1) + open-label RCT (extended)	Evolocumab (140 mg or 420 mg) + placebo	Ezetimibe + placebo	61	12 (extended to 1 year)	- Age 20-80 years - LDL-C ≥140 - TG ≤400 - Statins intolerance - No comorbidity
Stiekema, et al. [22] (2019)	ANITSCHKOW (The Netherlands)	Double-blind RCT (1:1)	Evolocumab 420 mg	Placebo	129	16	- Age ≥50 years - LDL-C ≥100 - Lp(a) ≥50*
Roth, et al.[15] (2016)	ODYSSEY CHOICE I (Multicountry)	Double-blind RCT (4:2:1)	Alirocumab 75 mg or 300 mg	Placebo	803	48	- Age ≥18 years -Uncontrolled hyperlipidemia - Statins intolerance
Stroes, et al.[16,] (2016)	ODYSSEY CHOICE II (Multicountry)	Double-blind RCT, double dummy (1:2:1)	Alirocumab 75 mg or 150 mg	Placebo	233	24	- Age ≥18 years - LDL-C ≥70 + high CVD risk - LDL-C ≥100 + moderate CVD risk - Statins intolerance or no statins history
Ginsberg, et al. [17] (2016)	ODYSSEY HIGH FH (Multicountry)	Double-blind RCT (1:1)	Alirocumab 150 mg	Placebo	107	78 (primary endpoint at week 24)	- HeFH - LDL-C ≥160 - TG ≤400 -Maximally tolerated dose statins
Roth, et al.[18] (2014)	ODYSSEY MONO (Multicountry)	Double-blind RCT, double dummy (1:1)	Alirocumab 75 mg (or up-titrated to 150 mg if needed)	Placebo	103	24	- Age ≥18 years - LDL-C ≥100 - No LLT in 4 weeks
Koren, et al.[19] (2014)	MENDEL-2 (Multicountry)	Double-blind RCT (1:1:1:1:2:2)	Evolocumab (140 mg or 420 mg) + placebo	(Oral placebo + SC placebo) or (Ezetimibe + placebo)	614	12	- Age ≥18 years - LDL-C 100-190 - TG ≤400
Stroes, et al.[20] (2014)	GAUSS-2 (Multicountry)	Double-blind RCT (2:2:1:1)	Evolocumab (140 mg or 420 mg) + placebo	Ezetimibe + placebo	307	12	- Age ≥18 years - LDL-C ≥70 + high CVD risk) or - LDL-C ≥100 + moderate CVD risk - Statins intolerance

Note: ApoA-1: apolipoprotein A-1; ApoB: apolipoprotein B; HDL-C: high-density lipoprotein cholesterol; HeFH: heterozygote familial hypercholesterolemia; LDL-C: low-density lipoprotein cholesterol; LLT: lipid-lowering therapy; Lp(a): lipoprotein(a); TC: total cholesterol; TG: triglyceride. All lipid profiles stated in mg/dl unless marked by * (in nmol/L).

The review protocol was not registered with PROSPERO because the literature search had already been initiated at the time the protocol was developed. However, to ensure ethical and methodological oversight, approval for this review was sought and granted by the Research Ethics Committee of Dr. Moewardi General Hospital, Surakarta (No. 2.819/XII/HREC/2024).

Results

A comprehensive search to identify original articles meeting the inclusion criteria is outlined in Figure 1. A total of 289 records were retrieved from PubMed, ScienceDirect, and the Cochrane Library after de-duplication. Following the screening of titles and abstracts, 24 reports were selected for full-text review. After eligibility assessment, 16 studies were excluded, leaving eight studies (involving 2,343 participants) for inclusion in this systematic review.

The characteristics of the included studies are summarized in Table 2. Most studies were multicenter trials[15–20] with a minimum duration of 12 weeks. Five studies specifically enrolled statin-intolerant participants,[15–17,20,22] one of which exclusively included heterozygous familial hypercholesterolemia (HeFH) patients[17] while the others targeted high-risk individuals.[18,19,21] Four studies investigated

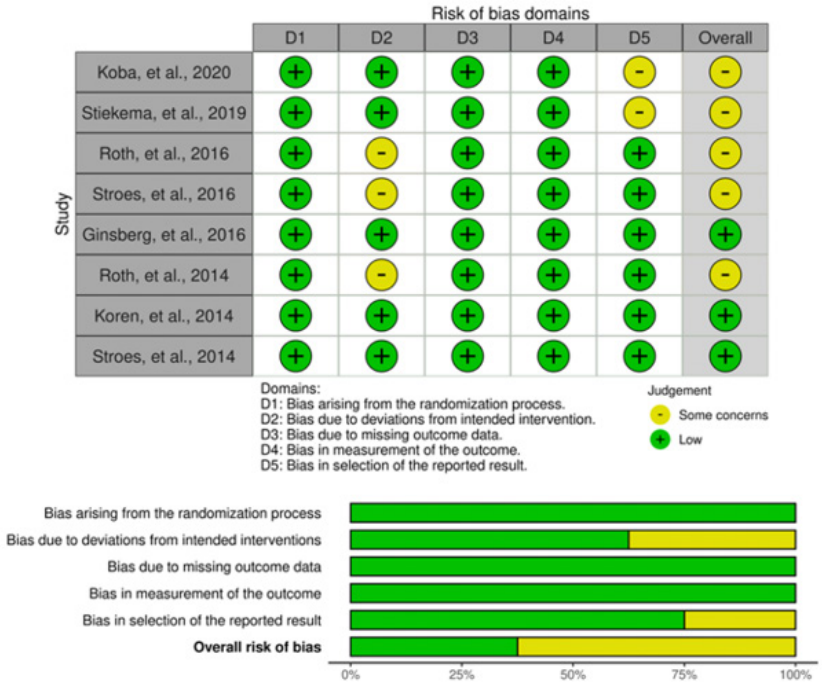

Figure 2 Risk of Bias in the Reviewed Articles

alirocumab,[15–18] while the remaining four focused on evolocumab.[19–22] Three studies used ezetimibe, either alone or in combination with placebo[19–21] while the others used placebo as the comparator. All studies employed a double-blind design, with two also incorporating a double dummy approach.[16,18]

All studies showed a low risk of bias in key areas, namely randomization, management of missing data, and outcome measurement. However, three studies raised concerns about deviations from intended intervention [15,16,18] and two had potential issues with result reporting.[21,22] Figure 2 presents the risk of bias summaries for the included studies.

As illustrated in Figure 3, our analysis indicated that, compared to placebo or ezetimibe, PCSK9 inhibitors significantly reduced all lipid parameters studied, including LDL-C (MD -46.8, 95% CI -53.2 to -40.4, p<0.00001, I^2=93%), non-HDL-C (MD -41.1 [-46.9 to -35.3], p<0.00001, I^2=88%), total cholesterol (MD -31.5 [-37.8 to -25.2], p<0.00001, I^2=89%), triglycerides (MD -11.7 [-15.0 to -8.4], p<0.00001, I^2=0%), Lp(a) (MD -19.2 [-25.7 to -12.6], p<0.0001, I^2=79%), and ApoB levels (MD -39.4 [-45.0 to -33.7], p<0.00001, I^2=92%). PCSK9 inhibitors also significantly increased HDL-C (MD 6.3 [4.7 to 7.9], p<0.00001, I^2= 6%) and ApoA-I levels (MD 4.1 [2.8 to 5.5], p=0.00001, I^2 =0%).

The direction of treatment effects was consistent across subgroup analyses, although the magnitude differed by certain moderators such as type of PCSK9 inhibitor, comparator, and prior LLT exposure. For instance, alirocumab showed a greater impact on most lipid outcomes, and the effect size of PCSK9 inhibitors was more pronounced when compared with placebo than with ezetimibe (forest plots not shown). However, significant heterogeneity persisted for most lipid outcomes, indicating that between-study variability was not fully accounted for by the examined moderators. The corresponding p-values and I2 statistics from subgroup analyses are presented in Table 3. In some subgroups, the I2 statistic was even higher than in the main pooled analysis, which likely reflects the reduced number of studies within subgroups and residual variability across trials, rather than indicating a true increase in heterogeneity. Table 4 presents the GRADE-based summary of findings, showing the effect estimates and high-certainty ratings for all assessed lipid parameters.

Further analysis indicated potential publication bias for several outcomes, as

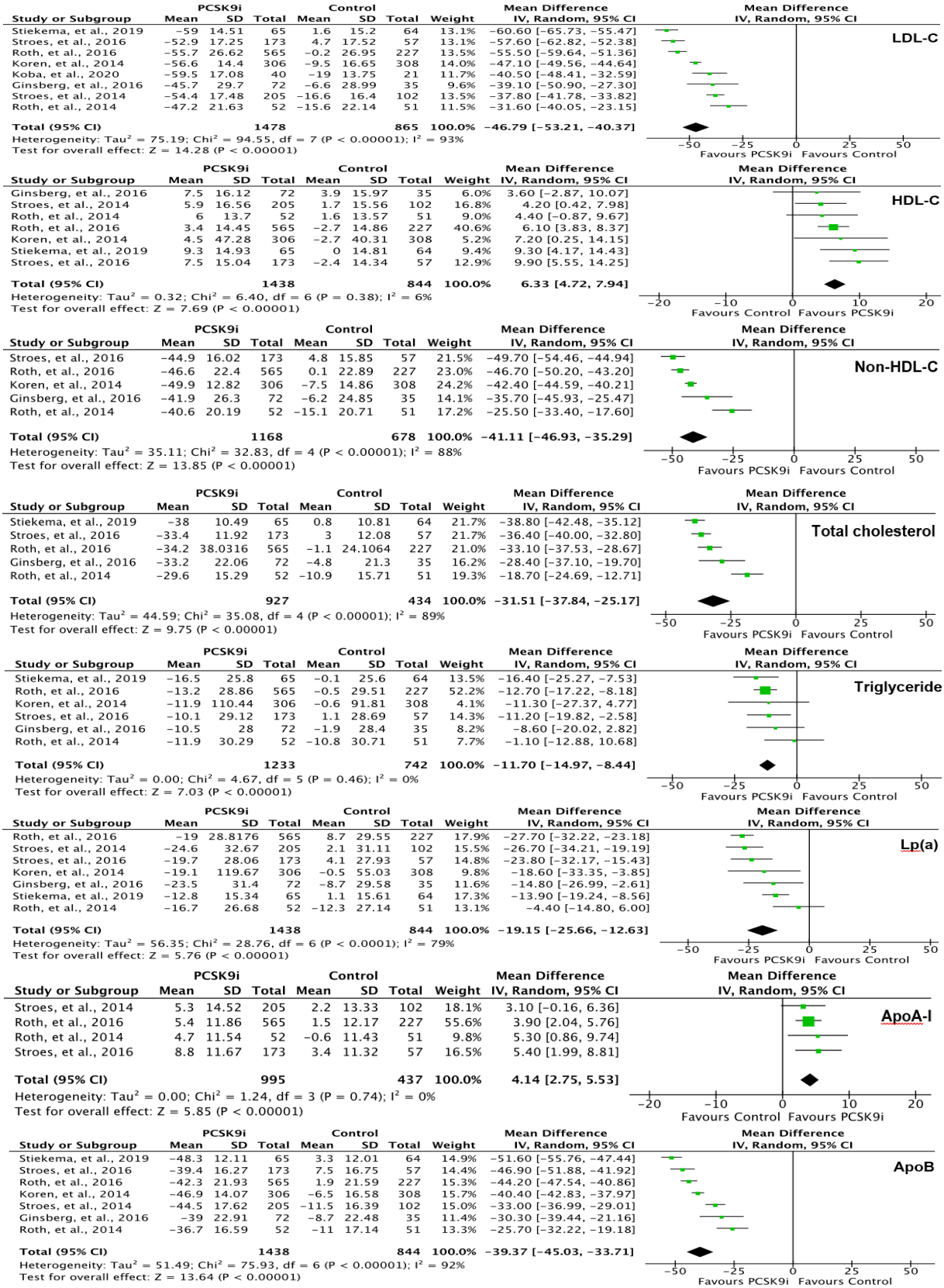

Figure 3 Forest Plots Showing the Mean Difference for Lipid Outcomes Comparing PCSK9 IIhibitors (PCSK9i) with Control (No PCSK9i)

Table 3 Summary of P-Values and I2 Statistics from Subgroup Analyses by Moderators

Lipid Parameter	P-values, I^2 Statistics (%)#				
	PCSK9i Type[a]	Comparator Type[b]	Prior Use of LLT[c]	Predominant Race[d]	Study Quality[e]
LDL-C	*, 100	*, 93.7	0.004, 82.3	0.19, 43.0	0.59, 0
HDL-C	0.04, 77.2	*, 98.5	0.48, 0	n/a, n/a	0.18, 43.8
Non-HDL-C	*, 99.9	*, 99.8	0.20, 39.4	n/a, n/a	0.97, 0
Total cholesterol	*, 99.8	*, 98.8	*, 93.7	n/a, n/a	0.52, 0
Triglyceride	0.11, 61.6	*, 98.3	0.2, 37.1	n/a, n/a	0.69, 0
Lp(a)	*, 99.9	0.90, 0	0.002, 84.2	n/a, n/a	0.57, 0
ApoA-I	*, 97.2	0.73, 0	0.59, 0	n/a, n/a	0.49, 0
ApoB	*, 99.7	0.005, 81.3	0.002, 83.7	n/a, n/a	0.20, 38.7

Note: [a]Alirocumab versus Evolocumab; [b]Ezetimibe versus Placebo versus Combined; [c]Prior LLT use versus No prior LLT use versus Mixed; [d]White versus Asian; [e]Low risk of bias versus Some concerns. *p<0.00001. #p value and I2 statistics were obtained via test for subgroup differences.

suggested by the funnel plots (Figure 4). Visual inspection revealed varying degrees of asymmetry. While some outcomes, such as HDL-C and ApoA-I, showed relatively symmetrical dispersion within the 95% confidence limits, others suggested possible small-study effects. Due to the limited number of included studies per outcome (generally <10), formal statistical tests for asymmetry, for example, Egger's test, were not performed, in line with PRISMA and Cochrane guidelines. Therefore, while there was no definitive evidence of publication bias, the observed asymmetry in certain plots warrants cautious interpretation of pooled estimates.

Discussion

This systematic review and meta-analysis demonstrates that PCSK9 inhibitors significantly improve multiple lipid parameters in individuals who are statin-intolerant,

Table 4 Summary of Findings (SoF) (GRADE Approach)

Outcomes	Anticipated absolute effects* (95% CI)		№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with Control	Risk with PCSK9 inhibitor		
Change in LDL-C levels follow-up: range 12 to 78 weeks	The mean change in LDL-C levels was **0**	MD **48.2 lower** (49.8 lower to 46.6 lower)	2343 (8 RCTs)	⊕⊕⊕⊕ High[a,b,c]
Change in HDL-C levels follow-up: range 12 to 78 weeks	The mean change in HDL-C levels was **0**	MD **6.3 higher** (4.8 higher to 7.8 higher)	2282 (7 RCTs)	⊕⊕⊕⊕ High[a,b]
Change in non-HDL-C levels follow-up: range 12 to 78 weeks	The mean change in non-HDL-C levels was **0**	MD **43.3 lower** (45 lower to 41.7 lower)	1846 (5 RCTs)	⊕⊕⊕⊕ High[a,c]
Change in total cholesterol levels follow-up: range 16 to 78 weeks	The mean change in total cholesterol levels was **0**	MD **34 lower** (36 lower to 31.9 lower)	1361 (5 RCTs)	⊕⊕⊕⊕ High[a,b,c]
Change in triglyceride levels follow-up: range 12 to 78 weeks	The mean change in triglyceride levels was **0**	MD **11.7 lower** (15 lower to 8.4 lower)	1975 (6 RCTs)	⊕⊕⊕⊕ High[a,b,c]
Change in Lp(a) levels follow-up: range 12 to 78 weeks	The mean change in Lp(a) levels was **0**	MD **21.1 lower** (23.8 lower to 18.4 lower)	2282 (7 RCTs)	⊕⊕⊕⊕ High[a,b,c]
Change in ApoA-I levels follow-up: range 12 to 48 weeks	The mean change in ApoA-I levels was **0**	MD **4.1 higher** (2.8 higher to 5.5 higher)	1432 (4 RCTs)	⊕⊕⊕⊕ High[a]
Change in ApoB levels follow-up: range 12 to 78 weeks	The mean change in ApoB levels was **0**	MD **41.1 lower** (42.6 lower to 39.6 lower)	2282 (7 RCTs)	⊕⊕⊕⊕ High[a,b,c]

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **MD:** mean difference

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.

Explanations
a. Minor deviations from intended interventions were noted but did not justify downgrading for risk of bias
b. Minor concerns about selective reporting were observed but did not warrant downgrading for risk of bias
c. Not downgraded for publication bias due to the limited number of included studies and lack of formal statistical testing

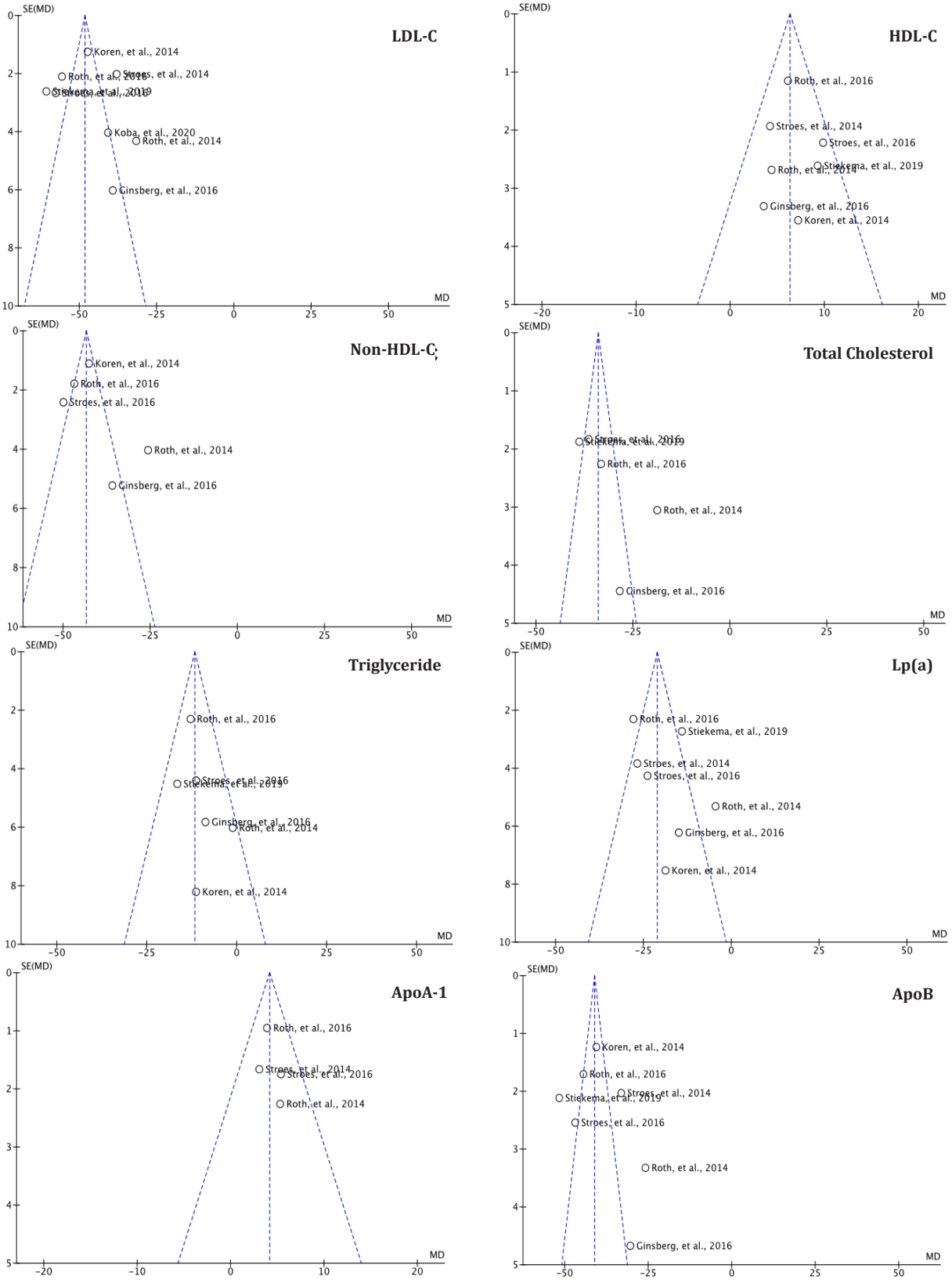

Figure 4 Funnel Plots Showing Publication Bias in the Reviewed Studies

statin-resistant, or require intensified LLT. The substantial heterogeneity observed across trials indicates that treatment effects are not uniform and may be influenced by clinical and methodological factors. Variability between PCSK9 inhibitor types could reflect differences in molecular structure, binding affinity, and pharmacokinetic properties, which may result in varying lipid-lowering effects. In addition, differences by comparator are likely influenced by the background intensity of LLT. Trials employing placebo capture the full therapeutic effect of PCSK9 inhibitors, whereas studies using active comparators estimate only the incremental benefit beyond standard therapy, which may attenuate the observed treatment effects. These findings underscore the importance of tailoring therapy to specific patient populations and highlight the need for more standardized trial design to improve comparability. Nevertheless, all outcomes were supported by high-certainty evidence according to the GRADE assessment, indicating that further research is unlikely to change the estimated effects.

The superior efficacy of PCSK9 inhibitors over ezetimibe, as partially observed in this review, aligns with findings from other studies.[22–25] PCSK9, a circulating protein, plays a pivotal role in regulating LDL-C levels by modulating LDL receptor expression on hepatocyte surfaces. Normally, LDL receptors recycle to the cell surface, bind LDL-C, and facilitate its clearance. PCSK9, secreted by hepatocytes, binds to LDL receptors and promotes their lysosomal degradation, reducing receptor expression and impairing LDL-C clearance.[9,26] Inhibiting PCSK9 enhances LDL receptor expression, providing an effective mechanism for substantial LDL-C reduction.[26]

In addition to LDL-C, PCSK9 inhibitors improved other lipid parameters. Atherogenic lipoproteins, such as ApoB and Lp(a), contribute significantly to residual cardiovascular risk. The differing magnitude of LDL-C and ApoB reductions may reflect their distinct roles in lipid metabolism.[23] While LDL-C represents the cholesterol content of LDL particles, ApoB indicates the total number of circulating LDL, very low-density lipoprotein (VLDL), and other atherogenic lipoproteins. By preventing LDL receptor degradation, PCSK9 inhibitors enhance hepatic LDL-C uptake. However, since LDL particles and other atherogenic lipoproteins contain ApoB, the reductions in LDL-C and ApoB may not always align, leading to dissociation in their respective trends.[23]

Decreased levels of Lp(a) have been associated with reduced CVD risk.[23,27] Statins do not affect Lp(a) concentrations, whereas PCSK9 inhibitors lower Lp(a) by approximately 20–30%.[27] Our findings reflected similar reductions. Although the mechanism remains unclear, some studies suggest that Lp(a) reduction is correlated with LDL-C lowering, indicating a significant role for LDL receptors in Lp(a) clearance.[27,28]

Hypertriglyceridemia, particularly when combined with low HDL-C, is a strong contributor to cardiovascular risk.[27] The included trials in our analysis showed triglyceride reductions ranging from 9.2% to 21% with evolocumab, and 1.2% to 10.6% with alirocumab.[15–19,22] Increased LDL receptor activity induced by PCSK9 inhibitors enhances the catabolism of LDL and VLDL particles and stimulates other lipoprotein receptors, including VLDL, apolipoprotein E2 (ApoE2), LDL-related protein (LRP), and cluster of differentiation 36 (CD36). This facilitates clearance of chylomicrons and VLDL remnants, contributing to reduced triglyceride levels.[27]

ApoA-I, the principal structural and functional protein of HDL-C, was modestly elevated by PCSK9 inhibitors.[27,29] Our review identified studies reporting similar findings, with evolocumab increasing HDL-C[19,22] and ApoA-I.[20] Meanwhile alirocumab also increased HDL-C[15–18] and ApoA-I,[15,16,18] though to a slightly lesser extent. The increase in HDL-C is likely due to a reduction in LDL particles, diminishing cholesterol transfer from HDL to LDL.[27]

This review has several limitations. First, the literature search may not have captured all relevant studies due to database accessibility. Second, variability in sample sizes, study duration, and inclusion criteria may affect the generalizability. Although some studies reported race and geographic location, data were insufficient to assess diversity across populations. Moreover, most trials were conducted in high-income countries, limiting applicability to low- and middle-income settings. Third, while all included studies used approved therapeutic doses of PCSK9 inhibitors, dosing regimens varied. Subgroup analyses by dose were not feasible, but effect sizes were consistent across studies, suggesting minimal impact of dosing differences. Substantial heterogeneity in several outcomes highlights the values of individual participant data (IPD) meta-analyses or meta-regression in future research to better explore additional sources of variability, such as baseline LDL-C, age, treatment duration, drug dosing,

and sample size. Additionally, funnel plot asymmetry suggested potential publication bias for some outcomes, although formal testing was not conducted due to the small number of studies. Finally, future research should assess safety, clinical outcomes, and economic implications of PCSK9 inhibitors in management of dyslipidemia, particularly in statin-resistant or statin-intolerant populations to provide a more comprehensive evaluation of PCSK9 inhibitors in real-world practice.

In conclusion, PCSK9 inhibitors significantly improve a broad spectrum of lipid parameters, including non-traditional markers such as non-HDL-C, ApoA-I, ApoB, and Lp(a), underscoring their potential role in managing dyslipidemia, particularly in patients inadequately controlled with standard therapies.

Funding Source
This paper did not receive any funding.

Conflict of Interests
The authors declare no conflict of interest.

References

1. Eckel R. The metabolic syndrome. In: Kasper D, Fauci A, Hauser S, Longo D, Jameson J, editors. 2015 Harrison's principles of internal medicine. 19th ed. New York; McGraw-Hill Education; 2015. p.2449–54
2. Motillo S, Filion K, Genest J, Joseph L, Pilote L, Poirier P, et al. The metabolic syndrome and cardiovascular risk: a systematic review and meta-analysis. J Am Coll Cardiol. 2010;56(14):1113–32. doi: 10.1016/j.jacc.2010.05.034.
3. Silverman M, Ference B, Im K, Wiviott S, Giugliano R, Grundy S, et al. Association between lowering LDL-C and cardiovascular risk reduction among different therapeutic interventions: a systematic review and meta-analysis. JAMA. 2016;316(12):1289–97. doi: 10.1001/jama.2016.13985.
4. World Health Organization (WHO). Non-communicable diseases country profiles 2018. WHO; 2018. [Cited 2023 Nov 17]. Available from: https://iris.who.int/handle/10665/274512.
5. Perkumpulan Endokrinologi Indonesia (PERKENI). Panduan pengelolaan dislipidemia di Indonesia 2021. Jakarta: PB PERKENI; 2021. [Cited 2023 Dec 15]. Available from: https://pbperkeni.or.id/wp-content/uploads/2022/02/23-11-21-Website-Panduan-Dislipidemia-2021-Ebook.pdf .
6. Zodda D, Giammona R, Schifilliti S. Treatment strategy for dyslipidemia in cardiovascular disease prevention: focus on old and new drugs. Pharmacy. 2018;6(1):10. doi: 10.3390/pharmacy6010010.
7. Ward NC, Watts GF, Eckel RH. Statin toxicity: mechanistic insights and clinical implications. Circ Res. 2019;124(2):328–50. doi: 10.1161/CIRCRESAHA.118.312782.
8. Bardolia C, Amin N, Turgeon J. Emerging non-statin treatment options for lowering low-density lipoprotein cholesterol. Front Cardiovasc Med. 2021;8:789931. doi: 10.3389/fcvm.2021.789931.
9. Pokhrel B, Yuet W, Levine S. PCSK9 inhibitors. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 [Cited 2023 Nov 10]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK448100/.
10. Chhetry M, Jialal I. Lipid- lowering drug therapy. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 [Cited 2023 Dec 19]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK541128/.
11. American College of Cardiology. FDA approves first of novel cholesterol-lowering drugs. ACC News Story. 2015 [Cited 2023 Oct 12]. Available from: https://www.acc.org/latest-in-cardiology/articles/2015/07/24/16/01/fda-approves-first-of-novel-cholesterol-lowering-drugs.
12. Zhang Y, Suo Y, Yang L, Zhang X, Yu Q, Zeng M, et al. Effect of PCSK9 inhibitor on blood lipid levels in patients with high and very-high CVD risk: a systematic review and meta-analysis. Cardiol Res Pract. 2022;8729003. doi: 10.1155/2022/8729003.
13. Toth PP, Worthy G, Gandra SR, Sattar N, Bray S, Cheng LI, et al. Systematic review and network meta-analysis on the efficacy of evolocumab and other therapies for the management of lipid levels in hyperlipidemia. J Am Heart Assoc. 2017;6(10):e005367. doi: 10.1161/JAHA.116.005367.
14. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71. doi: 10.1136/bmj.n71.

15. Roth E, Moriarty P, Begeron J, Langslet G, Manvelian G, Zhao J, et al. A phase III randomized trial evaluating alirocumab 300 mg every 4 weeks as monotherapy or add-on to statin: ODYSSEY CHOICE I. Atherosclerosis. 2016;254:254–62. doi: 10.1016/j.atherosclerosis.2016.08.043.
16. Stroes E, Guyton J, Lepor N, Civeira F, Gaudet D, Watts G, et al. Efficacy and safety of alirocumab 150 mg every 4 weeks in patients with hypercholesterolemia not on statin therapy: the ODYSSEY CHOICE II study. J Am Heart Assoc. 2016;5(9):e003421. doi: 10.1161/JAHA.116.003421.
17. Ginsberg H, Rader D, Raal F, Guyton J, Baccara-Dinet M, Lorenzato C, et al. Efficacy and safety of alirocumab in patients with heterozygous familial hypercholesterolemia and LDL-C of 160 mg/dl or higher. Cardiovasc Drugs Ther. 2016;30(5):473–83. doi: 10.1007/s10557-016-6685-y.
18. Roth E, Taskinen M, Ginsberg H, Kastelein J, Colhoun H, Robinson J, et al. Monotherapy with the PCSK9 inhibitor alirocumab versus ezetimibe in patients with hypercholesterolemia: results of a 24-week, double-blind, randomized phase 3 trial. Int J Cardiol. 2014;176(1):55–61. doi: 10.1016/j.ijcard.2014.06.049.
19. Koren M, Lundqvist P, Bolognese M, Neutel J, Monsalvo M, Yang J, et al. Anti-PCSK9 monotherapy for hypercholesterolemia the MENDEL-2 randomized, controlled phase III clinical trial of evolocumab. J Am Coll Cardiol. 2014;63(23):2531–40. doi: 10.1016/j.jacc.2014.03.018.
20. Stroes E, Colquhoun D, Sullivan D, Civeira F, Rosenson RS, Watts GF, et al. Anti-PCSK9 antibody effectively lowers cholesterol in patients with statin intolerance: the GAUSS-2 randomized, placebo-controlled phase 3 clinical trial of evolocumab. J Am Coll Cardiol. 2014;63(23):2541–8. doi: 10.1016/j.jacc.2014.03.019.
21. Koba S, Inoue I, Cyrille M, Lu C, Inomata H, Shimauchi J, et al. Evolocumab vs. ezetimibe in statin-intolerant hyperlipidemic Japanese patients: phase 3 GAUSS-4 trial. J Atheroscler Thromb. 2020;27(5):471–84. doi: 10.5551/jat.50963.
22. Stiekema LCA, Stroes ESG, Verweij SL, Kassahun H, Chen L, Wasserman SM, et al. Persistent arterial wall inflammation in patients with elevated lipoprotein(a) despite strong low-density lipoprotein cholesterol reduction by proprotein convertase subtilisin/kexin type 9 antibody treatment. Eur Heart J. 2019;40(33):2775–81. doi: 10.1093/eurheartj/ehy862.
23. Huang YT, Ho LT, Hsu HY, Tu YK, Chen KL. Efficacy and safety of proprotein convertase subtilisin/kexin type 9 inhibitors as adjuvant treatments for patients with hypercholesterolemia treated with statin: a systematic review and network meta-analysis. Front Pharmacol. 2022;13:832614. doi: 10.3389/fphar.2022.832614.
24. Wang X, Wen D, Chen Y, Ma L, You C. PCSK9 inhibitors for secondary prevention in patients with cardiovascular diseases: a Bayesian network meta-analysis. Cardiovasc Diabetol. 2022;21(1):107. doi: 10.1186/s12933-022-01542-4.
25. McDonagh M, Peterson K, Holzhammer B, Fazio S. A systematic review of PCSK9 inhibitors alirocumab and evolocumab. J Manag Care Spec Pharm. 2016;22(6):641–53q. doi: 10.18553/jmcp.2016.22.6.641.
26. Burger A, Pogran E, Muthspiel M, Kaufmann C, Jäger B, Huber K. New treatment targets and innovative lipid-lowering therapies in very-high-risk patients with cardiovascular disease. Biomedicines. 2022;10(5):970. doi: 10.3390/biomedicines10050970.
27. Filippatos T, Kei A, Rizos C, Elisaf M. Effects of PCSK9 inhibitors on other than low-density lipoprotein cholesterol lipid variables. J Cardiovasc Pharmacol Ther. 2018;23(1):3–12. doi: 10.1177/1074248417724868.
28. Reyes-Soffer G, Pavlyha M, Ngai C, Thomas T, Holleran S, Ramakrishnan R, et al. Effects of PCSK9 inhibition with alirocumab on lipoprotein metabolism in healthy humans. Circulation. 2017;135(4):352–62. doi: 10.1161/CIRCULATIONAHA.116.025253.
29. Mangaraj M, Nanda R, Panda S. Apolipoprotein A-I: a molecule of diverse function. Indian J Clin Biochem. 2016;31(3):253–9. doi: 10.1007/s12291-015-0513-1.