ORIGINAL ARTICLE

Current Evidence on the Lipid-Lowering Efficacy and Safety of Oral PCSK9 Inhibitors: A Systematic Review and Meta-analysis

Evidencia actual sobre la eficacia hipolipemiante y seguridad de los inhibidores orales de PCSK9: revisión sistemática y metaanálisis

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ABSTRACT

Background: Inhibition of the proprotein convertase subtilisin/kexin type 9 (PCSK9) is a well-established therapeutic strategy for significantly reducing low-density lipoprotein cholesterol (LDL-C) levels. In recent years, new oral PCSK9 inhibitors have been developed, providing emerging evidence regarding their lipid-lowering efficacy and safety profile.
Objective: The aim of this study was to update the available evidence on the efficacy and safety of oral PCSK9 inhibitors.
Methods: A systematic review and meta-analysis was conducted following the PRISMA statement guidelines. Randomized clinical trials evaluating oral PCSK9 inhibitors versus placebo or other lipid-lowering drugs were included. Percent changes in lipid parameters and the occurrence of adverse events were analyzed. Studies that could not be included in the quantitative analysis were described qualitatively.
Results: Ten randomized clinical trials were included in the qualitative analysis, of which six met the criteria for inclusion in the meta-analysis. Five oral PCSK9 inhibitors were identified. Three of them (enlicitide, laroprovstat and NNC0385-0434) provided data for the quantitative analysis, while the other two (DC371739 and CVI-LM001) were evaluated descriptively. Compared with placebo, oral PCSK9 inhibitors were associated with significant reductions in LDL-C [mean difference (MD) -57.83%; 95% confidence interval (CI) -60.48% to -5.18%; I^2 = 23%] and apolipoprotein B (MD -49.02%; 95% CI -53.61 to -44.42%; I^2 = 76.3%). Similarly, decreases were observed in non-HDL cholesterol (MD -53.48%; 95% CI -57.61% to -49.36; I^2 = 56.5%), triglycerides (MD -15.44%; 95% CI -15.96% to -14.92%; I^2 = 0.0%) and lipoprotein(a) (MD -24.86%; 95% CI -29.50% to -20.21; I^2 = 99.2%). No significant differences in the incidence of adverse events were observed between oral PCSK9 inhibitors and placebo in the included studies.
Conclusion: Oral PCSK9 inhibitors appear to offer lipid-lowering efficacy comparable to that achieved with currently approved subcutaneous therapies, without any relevant safety concerns.

Key words: Oral PCSK9 inhibitors - LDL cholesterol - Safety - Meta-analysis

RESUMEN

Introducción: La inhibición de la proproteína convertasa subtilisina/kexina tipo 9 (PCSK9) constituye una estrategia terapéutica bien establecida para reducir de manera significativa los niveles de colesterol asociado a lipoproteínas de baja densidad (C-LDL). En los últimos años han surgido nuevos inhibidores de PCSK9 de administración oral, que aportan evidencia emergente sobre su eficacia hipolipemiante y su perfil de seguridad.
Objetivo: Actualizar la evidencia disponible sobre la eficacia y seguridad de los inhibidores orales de PCSK9 .
Métodos: Se realizó una revisión sistemática con metaanálisis siguiendo las recomendaciones de la declaración PRISMA. Se incluyeron ensayos clínicos aleatorizados que evaluaron inhibidores orales de PCSK9 versus placebo u otras drogas hipolipemiantes. Se analizaron los cambios porcentuales de los parámetros lipídicos y la aparición de eventos adversos. Los estudios que no pudieron incluirse en el análisis cuantitativo se describieron de forma cualitativa.
Resultados: Se incluyeron diez ensayos clínicos aleatorizados en el análisis cualitativo, de los cuales seis cumplieron los criterios para ser incorporados en el metaanálisis. Se identificaron cinco inhibidores orales de PCSK9. Tres de ellos (enlicitide, laroprovstat y NNC0385-0434) aportaron datos para el análisis cuantitativo, mientras que los otros dos (DC371739 y CVI-LM001) fueron evaluados de forma descriptiva. En comparación con placebo, los inhibidores orales de PCSK9 se asociaron con reducciones significativas del C-LDL [diferencia de medias (DM) -57,83 %; intervalo de confianza (IC) 95% -60,48 % a -5,18 %; I^2 = 23%] y de la apolipoproteína B

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(DM -49,02 %; IC 95% -53,61% a -44,42 %; I^2 = 76,3%). Asimismo, se observaron descensos en el colesterol no-HDL (DM -53,48 %; IC 95% -57,61% a -49,36; I^2 = 56,5%), en los triglicéridos (DM -15,44 %; IC 95% -15,96% a -14,92 %; I^2 = 0,0%) y en la lipoproteína(a) (DM -24,86 %; IC 95% -29,50% a -20,21; I^2 = 99,2%). No se evidenciaron diferencias significativas en la incidencia de eventos adversos entre los inhibidores orales de PCSK9 y placebo en los estudios incluidos.

Conclusión: Los inhibidores orales de PCSK9 parecen ofrecer una eficacia hipolipemiante comparable a la alcanzada con las terapias actualmente aprobadas de administración subcutánea, sin evidenciar señales relevantes de seguridad.

Palabras clave: Inhibidores orales de PCSK9 - Colesterol LDL - Seguridad - Metaanálisis

INTRODUCTION

Elevated concentrations of lipoproteins with atherogenic potential are consistently associated with both the initial onset and recurrence of cardiovascular events. (1) The available, robust, and reproducible clinical and genetic evidence has conclusively established low-density lipoprotein cholesterol (LDL-C) as a causal factor in the development of atherosclerotic cardiovascular disease. (2)

According to current clinical practice guidelines, the initial management of dyslipidemia in patients at high cardiovascular risk is based on the use of statins at the maximum tolerated dose. (3–5) When, despite this intervention, LDL-C levels do not reach therapeutic targets—particularly in patients with established atherosclerotic cardiovascular disease or severe forms of hypercholesterolemia—it is recommended to intensify treatment by adding other lipid-lowering agents, including ezetimibe, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, and bempedoic acid.

Pharmacological inhibition of PCSK9 has established itself as an effective strategy for achieving substantial reductions in LDL-C and lowering cardiovascular risk. Subcutaneous administration of monoclonal antibodies, such as evolocumab and alirocumab, on a biweekly or monthly strategies, has demonstrated reductions of nearly 60% in LDL-C levels, along with a significant decrease in cardiovascular events in high-risk patients on statin therapy. (6, 7) Similarly, the small interfering RNA, inclisiran, enables approximately 50% sustained reductions in LDL-C through a regimen that includes an initial dose, a second administration at 3 months, and subsequent maintenance doses every 6 months. (8, 9) Furthermore, safety assessments of these drugs (monoclonal antibodies and inclisiran) have not identified any significant signs of concern. The most common adverse events were injection-site reactions, the vast majority of mild intensity that did not require any intervention.

Although both therapeutic strategies have been shown to be capable of enabling most patients at high or very high cardiovascular risk to achieve the recommended LDL-C targets, their widespread implementation is limited by their high cost and the need for subcutaneous administration. In this context, the development of small, orally administered PCSK9 inhibitors could represent a more accessible and practical alternative for the treatment of hypercholesterolemia. (10) Although information on the price of these drugs once they are marketed is not yet available, the introduction of new therapeutic alternatives could promote greater competition in the market and, thereby, help reduce the costs of currently available treatments, regardless of their final price.

In recent years, new data have emerged providing evidence on the lipid-lowering efficacy and safety profile of these emerging agents, (11–20) and our research group published a systematic review on this topic. (21) However, given the emergence of new evidence over the past year, the objective of the present study was to provide an update through a systematic review and meta-analysis of the available evidence on the efficacy and safety of oral PCSK9 inhibitors.

OBJECTIVES

The aim of this study was to identify and reach consensus on therapeutic strategies for patients > 80 years with AF or ACS, stratified by robustness, mild frailty, and moderate frailty.

METHODS

Search and Data Collection Strategy

This systematic review was conducted in accordance with the recommendations of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement (22) and was registered in PROSPERO. A comprehensive literature search was conducted to identify studies evaluating oral PCSK9 inhibitors published up to April 20, 2026. Two independent reviewers searched various databases, including PubMed/MEDLINE, Scielo, Latindex, and the Cochrane Library, using both MeSH terms and relevant keywords, including “oral PCSK9 inhibitors,” “AZD0780,” “Laroprovstat,” “MK-0616,” “Enlicitide,” “CVI-LM001,” “NNC0385-0434,” and “DC371739.” In PubMed, Boolean operators were applied as follows: ("PCSK9 Inhibitors"[MeSH Terms] OR "PCSK9 inhibitor"[tiab]) AND (oral[tiab] OR orally[tiab]). In the SciELO and Latindex databases, free-text searches were conducted using terms in English and their Spanish equivalents, such as “PCSK9 inhibitors” and “inhibidores de PCSK9,” combined with the term “oral.” Subsequently, a manual review of titles and abstracts was conducted to identify relevant clinical studies. In the Cochrane Library, the search was conducted in the CENTRAL database (Cochrane Central Register of Controlled Trials), using terms such as “PCSK9 inhibitors” and “oral,” with the aim of identifying randomized clinical trials.

Grey literature was also explored, including records on ClinicalTrials.gov, congress presentations, and material available on pharmaceutical company websites. Additionally, the reference tracking (snowballing) technique was used to identify additional publications. There were no language restrictions.

Inclusion and exclusion criteria

Clinical trials in humans were considered eligible, specifically randomized studies evaluating the lipid-lowering efficacy and safety of oral PCSK9 inhibitors compared with placebo or other lipid-lowering drugs. Opinion articles, narrative or systematic reviews, and observational studies were excluded.

Outcome variables

Percent changes in lipid parameters and the incidence of clinically relevant adverse events were analyzed. The lipid markers evaluated included LDL-C, non-HDL cholesterol, apolipoprotein B (ApoB), triglycerides, and lipoprotein(a) [Lp(a)]. Safety was assessed by analyzing all reported adverse events. Additionally, serious adverse events were considered, defined as those resulting in death, being life-threatening, requiring hospitalization or prolonging hospitalization, causing significant disability, or being considered clinically relevant by the investigator.

Quality Assessment

The risk of bias was analyzed using the Cochrane Collaboration tool designed for this purpose. (23) The RoB-2 tool assesses five domains: randomization process, deviations from the planned intervention, incomplete data, outcome measurement, and selection of reported outcomes. Each domain was classified as "low risk," "high risk," or "some concerns," and an overall score was assigned to each study.

Statistical Analysis

Initially, a qualitative synthesis was performed of the studies that met the inclusion criteria. Subsequently, a meta-analysis was conducted on those studies that reported sufficient data for quantitative pooling. Regarding the doses included, the maximum reported doses were considered for NNC0385-0434 and laroprovstat (AZD0780), since the optimal dose in advanced stages has not yet been defined and both drugs demonstrated acceptable safety profiles. In the case of enlicitide (MK-0616), the 18-mg dose was selected from the study by Ballantyne et al., (11) due to its similarity to the dose used in subsequent studies [20 mg in the CorReef program and in the Johns et al. study (17)]. For each study, the percent changes in lipid parameters and the frequency of relevant adverse events were calculated. The results were expressed as mean difference (MD) or relative risk (RR), with their respective 95% confidence intervals (95% CI). When data were not reported as mean and standard deviation, conversion methods previously described in the literature were used. (24) Heterogeneity among studies was assessed using the I^2 statistic. Fixed-effect or random-effect models were used depending on the degree of heterogeneity observed. The Z-test was used to compare effects between subgroups. A p-value <0.05 (two-sided) was considered statistically significant. The analysis was performed using the R statistical software (version 3.5.1). (25)

Sensitivity Analysis

The sensitivity analysis was restricted to those lipid markers for which five or more studies were available, since, in contexts with a small number of studies, the exclusion of a single study could disproportionately alter the pooled estimates and compromise the robustness of results.

Publication bias

No formal assessment of publication bias was conducted due to the small number of included studies, which limits the validity of tools such as funnel plots or specific statistical tests, whose use is recommended only when enough studies are available.

RESULTS

The search strategy identified a total of 239 registries. After excluding 211 duplicates and irrelevant studies, 28 full-text articles were evaluated, of which 18 were excluded for failing to report the exposure or outcomes of interest. The study selection process is presented in Figure 1.

The qualitative analysis included two abstracts (11, 17) and eight full-text articles, (12-16, 18-20) and six of the latter provided sufficient information on lipid parameters to be included in the quantitative synthesis (meta-analysis) (13-15, 17–19). Table 1 summarizes the main characteristics of the studies considered in this systematic review.

The quality of the evaluated studies is shown in Figure 2. It should be noted that studies available only as abstracts were not evaluated, due to the limited information, which prevents an adequate assessment of the risk of bias. Overall, three studies were classified as having a low risk of bias, while five raised some concerns, mainly related to biases arising from deviations from the planned intervention, absence of complete data on outcomes, and the selection of reported results.

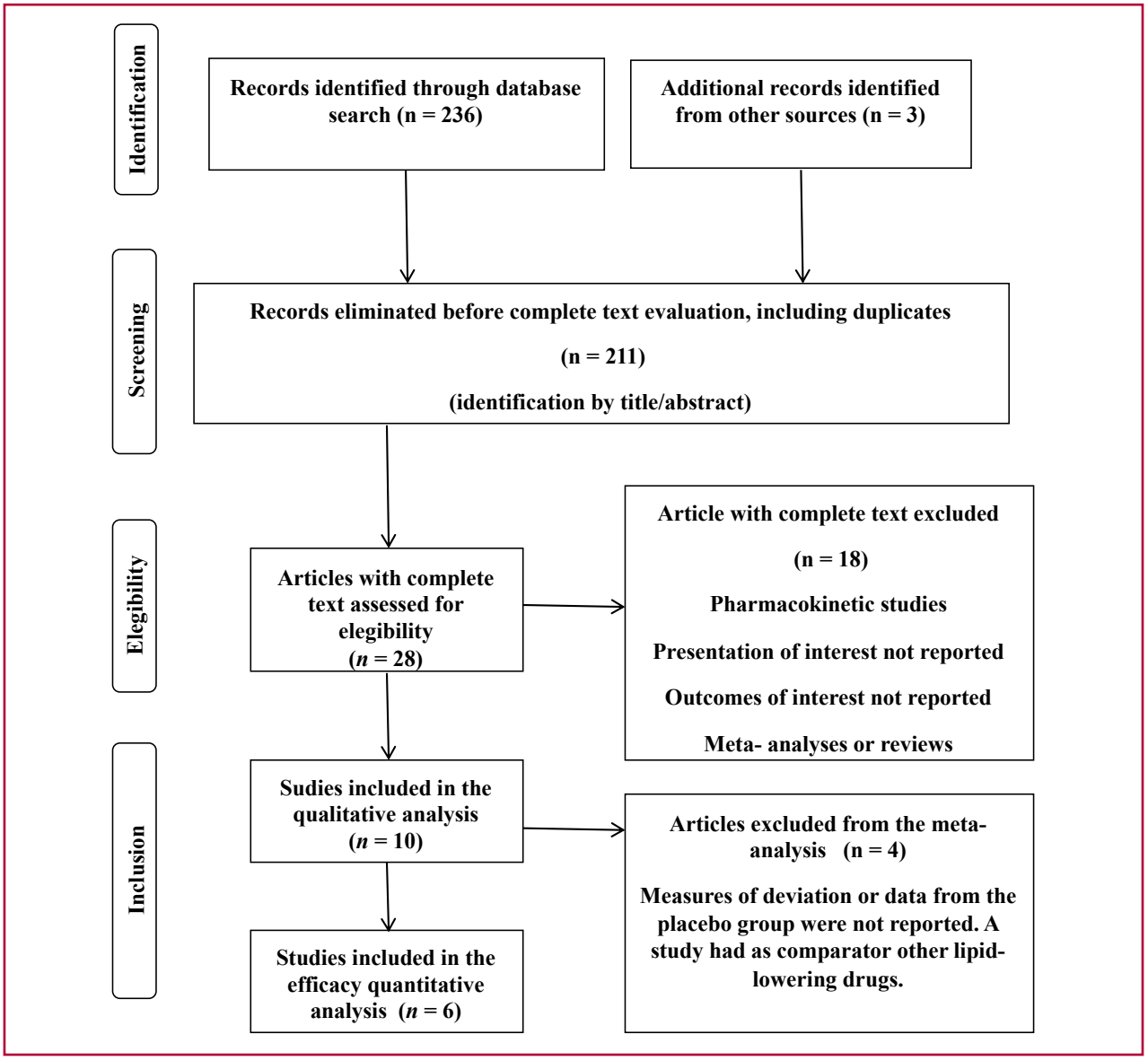
Regarding the assessment of lipid-lowering efficacy, four of the studies included in the qualitative synthesis could not be incorporated into the quantitative analysis.

One of these was a Phase 1 trial designed to evaluate the safety, tolerability, and pharmacokinetic and pharmacodynamic profiles of laroprovstat, administered both as monotherapy and in combination with standard treatment (rosuvastatin). (16) In a subgroup of 35 participants with hypercholesterolemia (LDL-C between 100 and 190 mg/dL), rosuvastatin 20 mg daily was administered for 3 weeks, followed by administration of laroprovstat 30 mg or placebo for an additional period. Following this initial phase with rosuvastatin, laroprovstat 30 mg achieved a 52% reduction in LDL-C (95% CI: -57% to -45%). This study was not included in the meta-analysis because the number of patients assigned to each group was not clearly specified, nor were the percent changes in lipid levels in the placebo group reported.

The second study was a small, placebo-controlled Phase Ib clinical trial. (11) In this study, administration of CVI-LM001 at a dose of 300 mg reduced LDL-C and ApoB levels by 26.3% and 17.4%, respectively, compared with baseline values in subjects with hypercholesterolemia. However, it was not possible to include this study in the quantitative analysis due to the absence of measures of dispersion and the lack of detailed data from the placebo group.

A third study evaluated DC371739 in the context of a Phase I clinical trial. (12) In this study, LDL-C showed a significant decrease of 19.1% compared with placebo, while triglycerides and ApoB were reduced by

Fig. 1. Flowchart of the study selection process.



27.1% and 25.3%, respectively. Once again, the available information proved insufficient for quantitative analysis, which prevented its inclusion in the meta-analysis.

Finally, a fourth study was not included in the meta-analysis. (20) Unlike the previous studies, its exclusion was not due to incomplete data but rather to its specific methodological nature, as it is the only study identified comparing an oral PCSK9 inhibitor with other lipid-lowering strategies, which limited its comparability with the rest of the included evidence. This was a phase III, randomized, double-blind, active-controlled trial including adults on statin therapy with a history of atherosclerotic cardiovascular disease or high cardiovascular risk and elevated LDL-C levels. Participants were randomized to receive enlicitide, bempedoic acid, ezetimibe, or a combination of the latter two for 56 days. Enlicitide achieved a 64.6% reduction in LDL-C (95% CI: -68.3% to -60.9%), which was significantly greater than that observed with bempedoic acid (-6.3%; 95% CI: -13.5% to 0.8%), ezetimibe (-27.8%; 95% CI: -32.3% to -23.4%) or their combination (36.5%; 95% CI: -40.8% to -32.2%), with consistent results also observed for ApoB, and non-HDL cholesterol (all $p < 0.001$). The incidence of adverse events was similar across the groups.

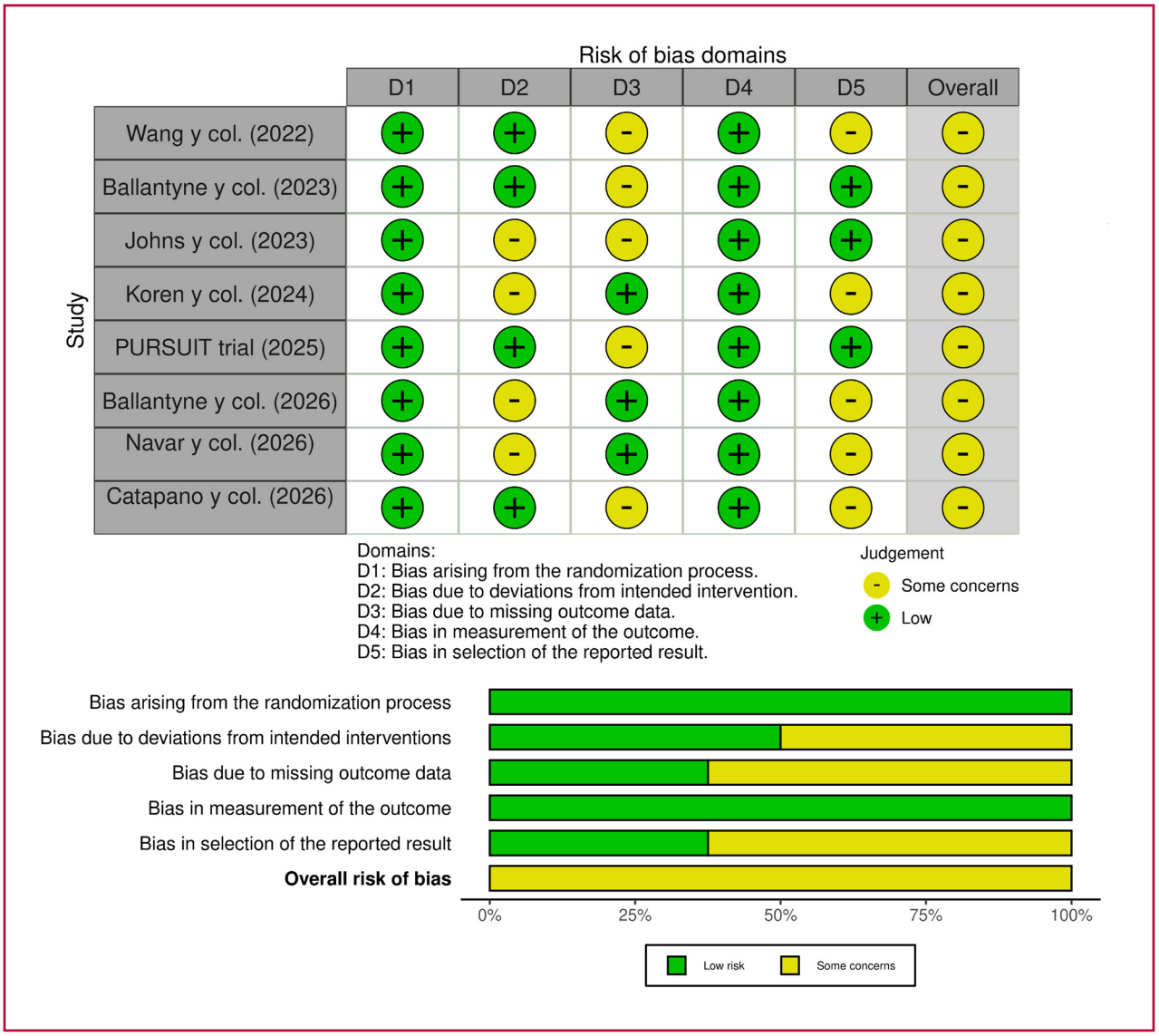
The remaining studies (n = 6) could be quantitatively assessed. In this case, our study showed that oral PCSK9 inhibitors significantly reduced LDL-C levels compared with placebo (MD -57.83%; 95% CI: -60.48% to -55.18%; I^2 = 23 .0%), as well as ApoB levels (MD -49.02%; 95% CI: -53.61% to -44.42%; I^2

Table 1. Characteristics of the studies included in the systematic review

Study (year)	Intervention	n	Population	Follow-up (weeks)
Liu et al. (2020) (11)	CVI-LM001, 200 or 300 mg/day versus placebo.	32	Chinese subjects aged 18 to 65 years with mild hypercholesterolemia (LDL-C ≥ 3.2 mmol/L and ≤ 4.88 mmol/L).	4
Wang et al. (2022) (12)	DC371739, 40 mg/day versus placebo.	20	Chinese subjects with hypercholesterolemia.	4
Johns et al. (2023) (13)	Enlicitide, 10 or 20* mg/day versus placebo.	40	Patients on statin therapy. Mean age was 57.7 years, and 67.5% were men.	2
Ballantyne et al. (2023) (14)	Enlicitide, 18 mg/day* versus placebo.	152#	Participants aged ≥18 and ≤80 years who had to fall into one of the following categories: 1) clinical atherosclerotic cardiovascular disease with LDL-C ≥70 and ≤160 mg/dL; 2) intermediate or high risk with LDL-C ≥100 and ≤200 mg/dL; or 3) borderline risk with LDL-C ≥130 and ≤250 mg/dL. Participants were also on stable lipid-lowering therapy. Mean age was 62 years, and 51% were men.	8
Koren et al. (2024) (15)	NNC0385-0434, 100 mg/day* versus placebo.	107#	Individuals with established atherosclerotic cardiovascular disease (≥40 years) or at high risk of developing it (>50 years), with LDL-C levels of at least 70 mg/dL and receiving statins at the maximum tolerated dose and stable lipid-lowering therapy. Mean age was 64.3 years, and 69% were men	12
Vega et al. (2024) (16)	Laroprovstat, 30 mg/day* versus placebo.	35	Subjects with hypercholesterolemia (LDL-C ≥100 mg/dL and ≤190 mg/dL) treated with 20 mg of rosuvastatin.	4
PURSUIT trial. (2025) (17)	Laroprovstat, 30 mg/day* versus placebo.	172#	Patients with LDL-C levels ≥70 mg/dL and <190 mg/dL, and triglycerides <400 mg/dL, on stable doses of moderate- or high-intensity statins, with or without ezetimibe at the start of the study. Mean age was 62.4 years, and 52.1% were men.	12
Ballantyne et al. (2026) (18)	Enlicitide 20 mg/day versus placebo.	303	Participants aged 18 years or older with heterozygous familial hypercholesterolemia, receiving lipid-lowering therapy (at least moderate- or high-intensity statins), and who had an LDL-C levels ≥55 mg/dL with a history of atherosclerotic cardiovascular disease, or an LDL-C level ≥70 mg/dL without a history of atherosclerotic cardiovascular disease. Mean age was 52.4 years, and 49% were men.	52
Navar et al. (2026) (19)	Enlicitide 20 mg/day versus placebo.	2,909	Adults with a history of atherosclerotic cardiovascular disease and LDL-C levels ≥55 mg/dL, as well as those with intermediate/high cardiovascular risk and LDL-C levels ≥70 mg/dL. Mean age was 62.8 years, and 60.7% were men.	52
Catapano et al. (2026) (20)	Enlicitide 20 mg/day versus ezetimibe 10 mg/day, bempedoic acid 180 mg/day, or the combination of bempedoic acid and ezetimibe at those doses.	301	Adults with a history of atherosclerotic cardiovascular disease and LDL-C levels ≥55 mg/dL, as well as those with intermediate/high cardiovascular risk and LDL-C levels ≥70 mg/dL. Mean age was 64.5 years, and 63% were men.	8

*This dose was selected for inclusion in the quantitative lipid analysis.
Sum of participants in the selected active arm and the placebo arm.

Fig. 2. Quality assessment of the studies included in the review.



= 76.3%) (Figure 3). Similarly, treatment with these drugs was associated with significant reductions in non-HDL cholesterol (DM -53.48%; 95% CI: -57.61% to -49.36%; I^2 = 56.5%), triglycerides (DM -15.44%; 95% CI: -15.96% to -14.92%; I^2 = 0 .0%), and Lp(a) (MD -24.86%; 95% CI: -29.50% to -20.21%; I^2 = 99.2%) compared with placebo. (Figure 4)

Regarding safety, of the nine studies comparing an oral PCSK9 inhibitor with placebo, six reported total adverse events and eight reported serious adverse events, allowing for a combined quantitative analysis. Our findings showed no significant differences in the outcomes assessed between oral PCSK9 inhibitors and placebo. (Figure 5)

Sensitivity analysis confirmed the robustness of the findings regarding LDL-C, ApoB and LP(a) (Figures 6 and 7).

DISCUSSION

In this systematic review and meta-analysis, treatment with oral PCSK9 inhibitors was associated with significant reductions in lipid levels, with no observed differences in the incidence of adverse events compared with placebo.

The binding of PCSK9 to the low-density lipoprotein receptor (LDLR) directs this receptor toward lysosomal degradation, preventing its recycling to the hepatocyte surface and thereby decreasing the clearance of circulating LDL-C. (26) Consequently, PCSK9 inhibition increases the availability of functional LDLRs on the cell membrane, resulting in greater removal of LDL-C from the plasma.

To date, various lipid-lowering therapeutic strategies aimed at inhibiting PCSK9 have been developed and approved. (27) All of them are administered sub-

Fig. 3. Percentage reduction in LDL-C and apolipoprotein B levels with oral PCSK9 inhibitors. Fixed- and random-effects models, mean difference (MD), 95% confidence intervals (CI), and I² statistic.

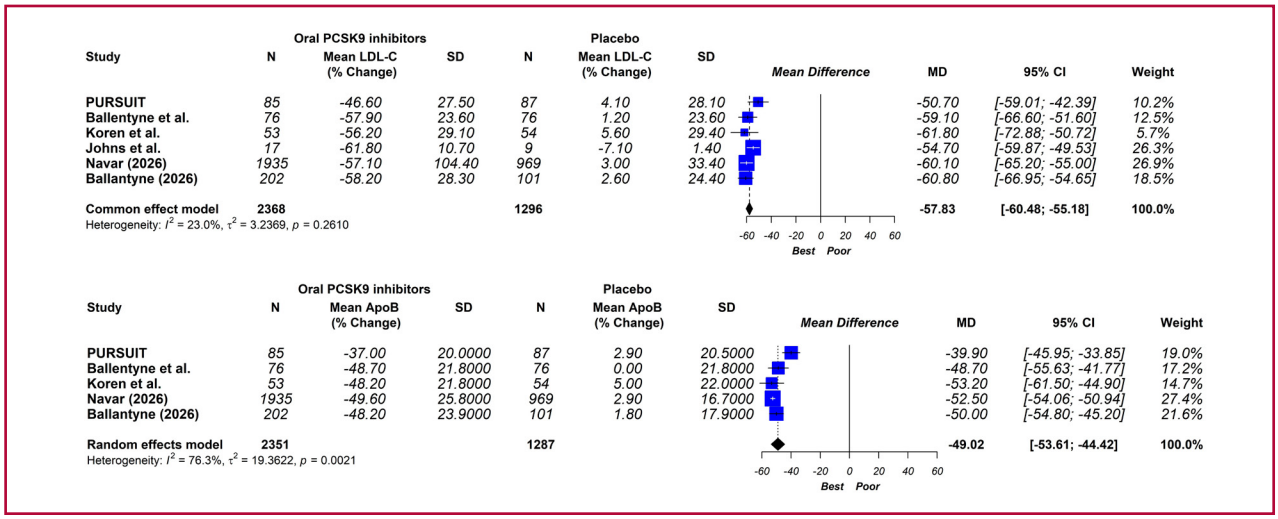
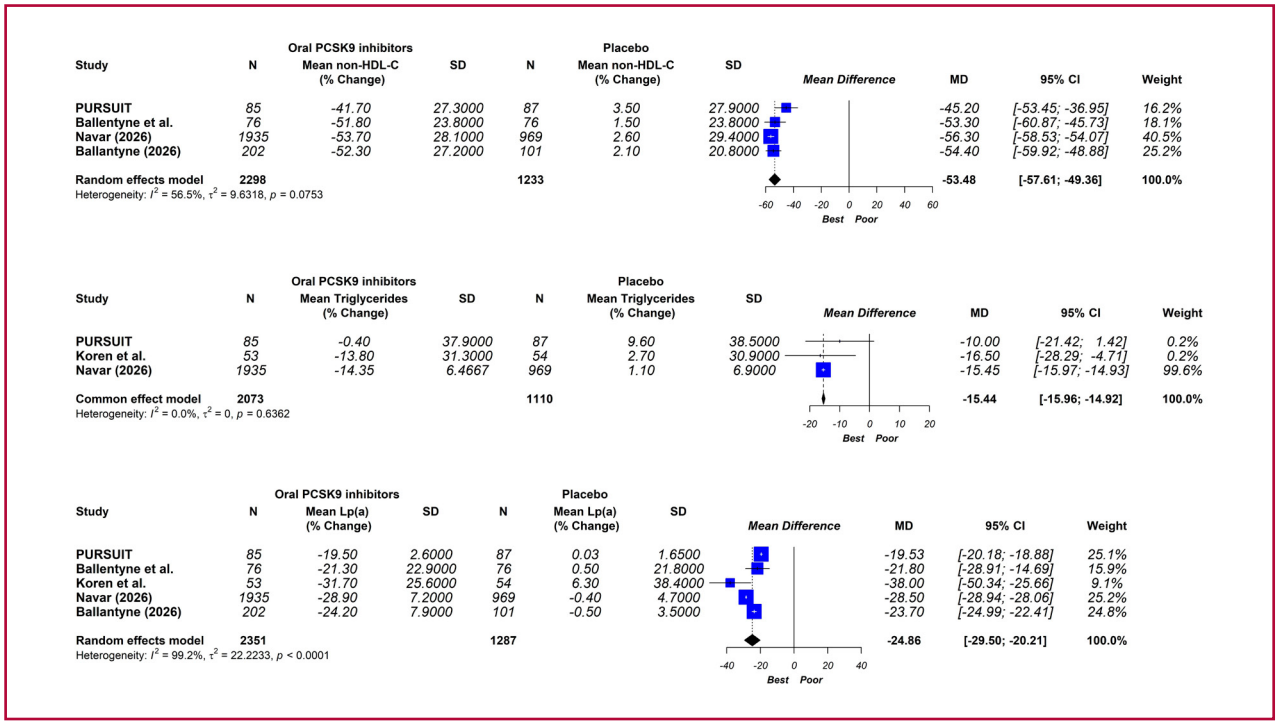


Fig. 4. Percentage reduction in non-HDL cholesterol, triglyceride, and lipoprotein(a) levels with oral PCSK9 inhibitors. Fixed- and random-effects models, mean difference (MD), 95% confidence intervals (CI), and I² statistic.



cutaneously and act through two main mechanisms: inhibition of PCSK9 functional activity in the extracellular space via monoclonal antibodies (alirocumab and evolocumab), or reduction of its hepatic synthesis at the intracellular level via a small double-stranded interfering RNA (inclisiran). Recently, an additional agent with an innovative mechanism of action has been approved: lerodalcibep, a recombinant protein engineered by fusing human serum albumin with a PCSK9-specific adnectin-like binding domain. (28) This molecule has been shown to reduce LDL-C levels by 50% in patients with heterozygous familial hypercholesterolemia, as well as in individuals with cardiovascular disease or at high cardiovascular risk. (29, 30) In addition, a fifth drug has been evaluated in two clinical trials conducted in China, which have

Fig. 5. Safety analysis. Fixed-effect and random-effects models, relative risk (RR), 95% confidence intervals (CI), and I² statistic.

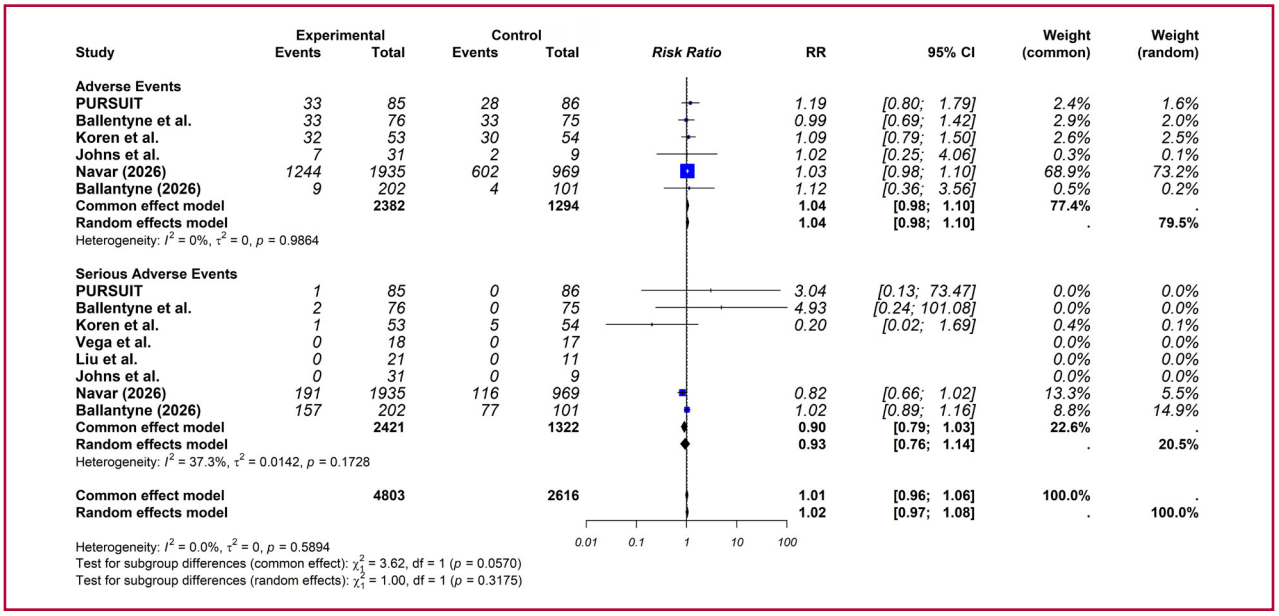
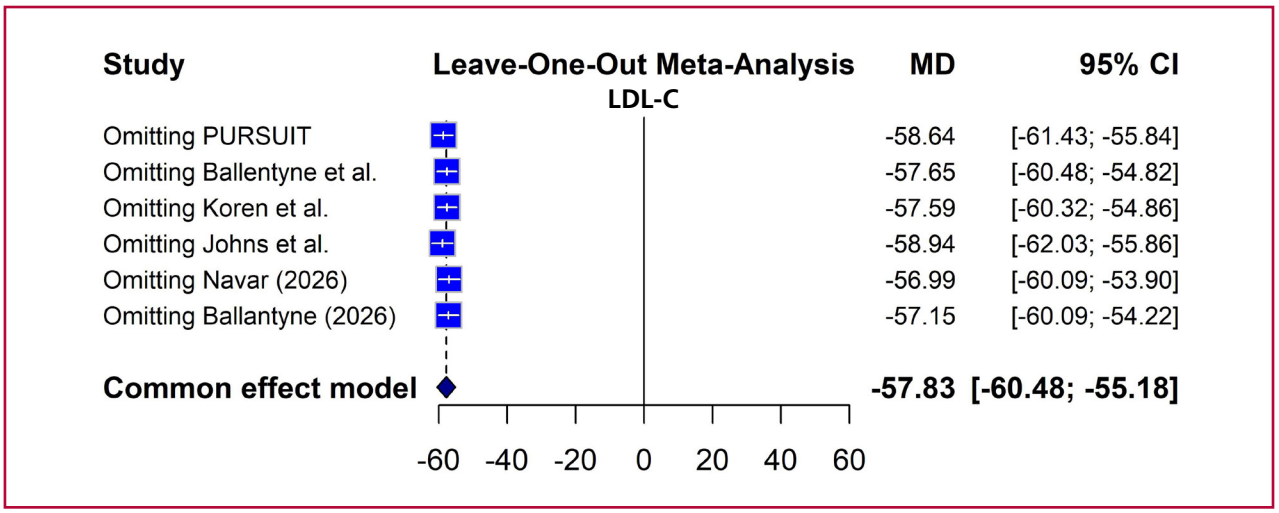


Fig. 6. Sensitivity analysis of studies evaluating the percentage reduction in LDL-C.

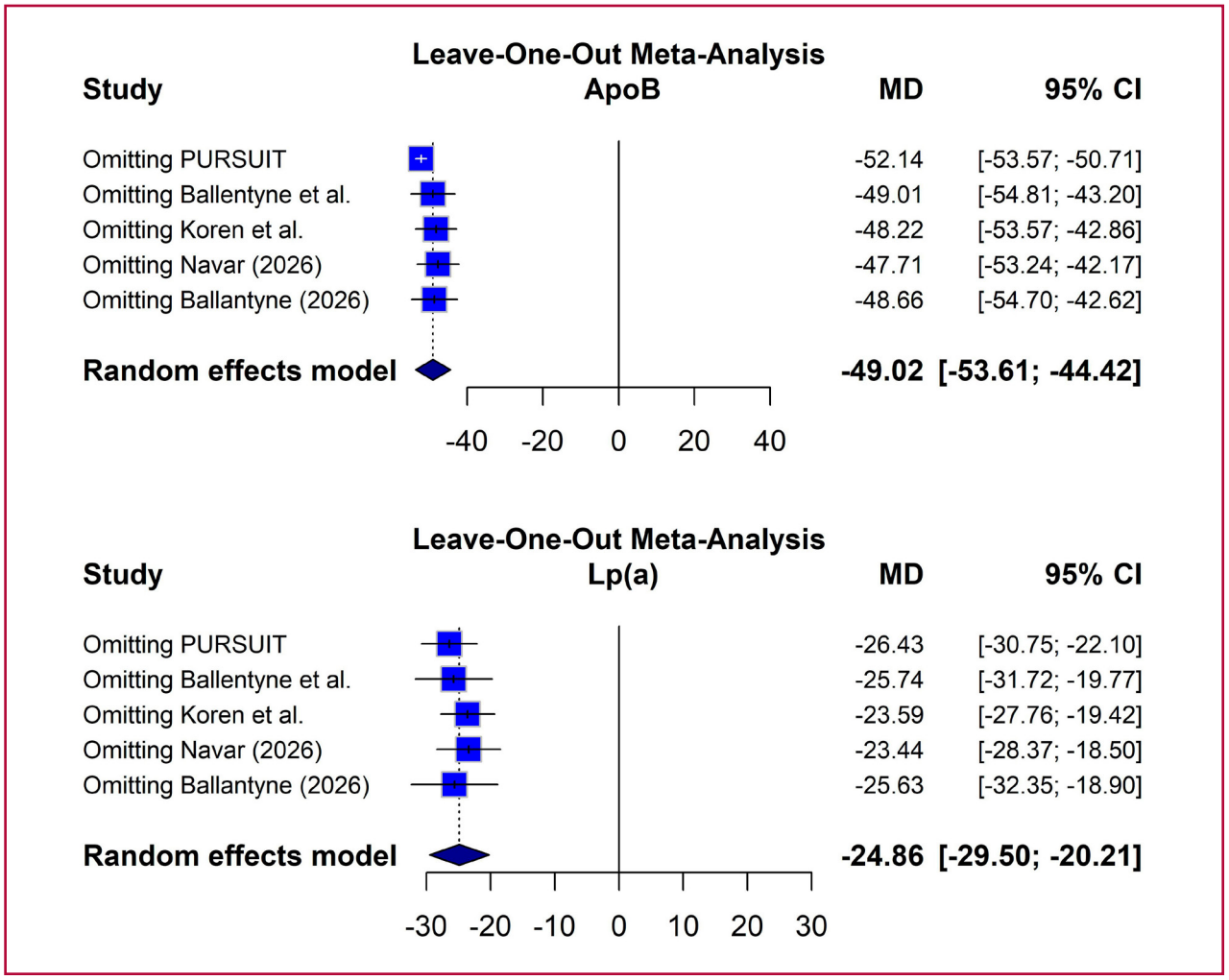


shown that recaticimab—a humanized monoclonal antibody with a prolonged half-life and less frequent dosing—reduces LDL-C levels by approximately 50% as monotherapy and by up to 62% when added to statin therapy. (31, 32)

Subcutaneous administration can be uncomfortable and poorly tolerated by many patients. Furthermore, current PCSK9-targeted therapies are considerably more expensive than other available options, particularly oral lipid-lowering agents, constituting a significant barrier for access to these treatments. (33) In this context, there has been growing interest in the development of oral PCSK9 inhibitors for reducing LDL-C. (10)

Our study evaluated the currently available evidence on five oral PCSK9 inhibitors. Three agents (enlicitide, laroprovstat, and NNC0385-0434) were included in the quantitative analysis, showing significant reductions in LDL-C and ApoB levels, consistent with those reported for injectable PCSK9 inhibitors. (34, 35) A ≥50% reduction in LDL-C levels constitute a clinically relevant outcome, as it represents a target strongly recommended by current guidelines, especially in patients at high or very high cardiovascular risk. (3–5) Moreover, the observed reduction in ApoB levels is also of great clinical importance, as this marker reflects more accurately the total number of atherogenic particles and has been proposed as an

Fig. 7. Sensitivity analysis of studies that evaluated the percentage reduction in apolipoprotein B (ApoB) and lipoprotein(a) [Lp(a)].



additional lipid target in high-risk patients who have already achieved the LDL-C target. (4, 36) While the development and research of enlicitide and laroprovstat continue to advance, it is important to note that, at the end of 2022, the development of NNC0385-0434 was discontinued by the sponsor for strategic reasons. (37) In contrast, LDL-C reduction with the other two agents (DC371739 and CVI-LM001) was more modest, ranging from approximately 19% to 26%.

The variability observed among the different drugs could be attributed, at least in part, to differences in their underlying mechanisms of action. Oral PCSK9 inhibitors comprise structurally diverse molecules that act at different levels of the PCSK9–LDLR axis. (10) Transcriptional inhibitors, such as DC371739 and CVI-LM001, reduce PCSK9 expression by interfering with transcription mediated by hepatocyte nuclear factor 1α and by stabilizing the LDLR mRNA; (38, 39) additionally, CVI-LM001 activates hepatic AMPK, reducing triglyceride synthesis and promoting fatty acid oxidation. In contrast, laroprovstat binds directly to PCSK9, while macrocyclic peptides such as enlicitide and NNC0385-0434 mimic the EGF-A domain of the LDLR or bind to the catalytic site of PCSK9, thereby blocking the interaction between PCSK9 and the LDLR. (40)

Another important finding of our meta-analysis is that oral PCSK9 inhibitors can significantly reduce Lp(a) levels by approximately 25%. This effect is consistent with what has been previously reported for other PCSK9 inhibition strategies, such as monoclonal antibodies (29%) and inclisiran (22%). (41) However, although some preliminary data suggest that the cardiovascular benefit associated with PCSK9 inhibition may be more pronounced in patients with elevated baseline Lp(a) levels, the clinical impact of this reduction on Lp(a) has not yet been fully defined. (42)

The CORALreef AddOn study demonstrated that

the PCSK9 inhibitor enlicitide achieved significantly greater reductions in LDL-C compared with standard non-statin oral therapies (bempedoic acid, ezetimibe, and their combination) in patients on statins. (20) Although this study was not included in the quantitative analysis due to the absence of a placebo group, the analysis of the arm treated with the oral PCSK9 inhibitor showed, at 8 weeks, a mean LDL-C reduction of 64.6%. This magnitude is comparable to that previously observed in studies with injectable monoclonal antibodies and is consistent with the overall findings of this meta-analysis. Similar findings are evidenced when analyzing other atherogenic markers, such as ApoB, non-HDL cholesterol, and Lp(a).

Finally, this meta-analysis did not reveal any significant safety concerns. Oral administration of these drugs eliminates the injection-site reactions typical of the subcutaneous route used by their predecessors, which constitutes a potential clinical advantage. However, the short follow-up period in many of the included studies limits the ability to fully assess long-term safety. In fact, randomized clinical trials are not the most appropriate design for detecting and evaluating rare, late-onset, and/or unexpected adverse effects related to drug safety. (43) Furthermore, the highly homogeneous populations resulting from restrictive inclusion criteria means that these studies are not suitable for comprehensively describing the safety profile of the medications.

In the context of increasingly stringent lipid-lowering targets that are often not achieved in clinical practice, (44,45) the development of new lipid-lowering therapies represents a significant advance. Future large-scale studies will be necessary to confirm their efficacy and safety, as well as to assess the cardiovascular impact of these new drugs. (46)

This meta-analysis has several limitations. First, clinical heterogeneity was observed among the studies, stemming from differences in the characteristics of the included populations, and in some cases, considerable statistical heterogeneity was also evident. Second, the lack of detailed information in some original studies limited a comprehensive assessment of their methodological quality. Third, the small number of studies included reduces the power of formal tests to detect publication bias and limits the ability to perform sensitivity analyses, which in this study were restricted to LDL-C, ApoB, and Lp(a). Finally, for some of the agents evaluated, the optimal dose has not yet been definitively established in more advanced-phase clinical trials.

CONCLUSION

According to the evidence synthesized in this systematic review, oral PCSK9 inhibitors may offer lipid-lowering efficacy comparable to that observed with other subcutaneously administered PCSK9 inhibition strategies. In addition, a randomized clinical trial demonstrated that, in patients treated with statins, these drugs are more effective than other alternatives such as ezetimibe or bempedoic acid for reducing LDL-C. In terms of safety, no relevant signals were identified. However, it is important to note that the evidence available to date remains limited and preliminary, based on a small number of studies. In this context, the clinical trials currently underway will be key to providing more robust and definitive information.

DECLARATIONS

Authorship

All authors listed meet the authorship criteria established by the International Committee of Medical Journal Editors (ICMJE) for this article, assume responsibility for the integrity of the work as a whole and have approved the final version for publication.

Author Contributions

WM and ML participated in the conception and design of the study. WM, LB, and GG contributed to data collection. The interpretation of the results and statistical analysis were performed by WM and ML. WM, ML, JPN, and GG drafted the manuscript. All authors critically reviewed the final draft.

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Conflicts of interest

None declared.

(See authors' conflict of interests forms on the web).

Ethical Approval

This work is based on previously published studies and does not include research conducted by the authors on humans or animals.

Use of Artificial Intelligence

During the preparation of the manuscript, an artificial intelligence tool (ChatGPT, OpenAI) was used exclusively to improve aspects of style and writing. The tool did not intervene in the generation of scientific content, data analysis, or the interpretation of results. The authors assume full responsibility for the final content of the article.

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