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Efficacy and Safety of Novel Lipoprotein(a)-Lowering Therapeutics in Adults with Elevated Lipoprotein(a): A Systematic Review and Meta-Analysis

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Abstract

Background: Elevated lipoprotein(a) [Lp(a)] is an independent, genetically determined risk factor for atherosclerotic cardiovascular disease (ASCVD) and aortic stenosis. Several novel therapeutics targeting Lp(a) have entered clinical development, including antisense oligonucleotides, small interfering RNAs (siRNAs), and oral small molecules. We conducted a systematic review and meta-analysis to evaluate the efficacy and safety of these novel Lp(a)-lowering therapeutics.

Methods: We systematically searched PubMed, Embase, and ClinicalTrials.gov for randomized controlled trials (RCTs) evaluating novel Lp(a)-lowering therapeutics in adults with elevated Lp(a). The primary efficacy outcome was the placebo-adjusted percentage change in Lp(a) concentration. Secondary outcomes included the proportion of participants achieving Lp(a) <125 nmol/L, changes in low-density lipoprotein cholesterol (LDL-C) and apolipoprotein B, and safety outcomes. Random-effects network meta-analysis was performed to compare treatments, with surface under the cumulative ranking curve (SUCRA) probabilities calculated for treatment ranking.

Results: Six RCTs comprising 1,320 participants were included, evaluating pelacarsen (antisense oligonucleotide), olpasiran, zerlasiran, lepodisiran, SLN360 (all siRNAs), and muvalaplin (oral small molecule). All agents significantly reduced Lp(a) compared with placebo. Pooled placebo-adjusted mean percentage reductions in Lp(a) were: pelacarsen 20 mg weekly (−80%), olpasiran 225 mg every 12 weeks (−101.1%), zerlasiran 450 mg every 24 weeks (−85.6%), lepodisiran 400 mg every 180 days (−93.9%), SLN360 600 mg single dose (−98%), and muvalaplin 240 mg daily (−85.8% by intact Lp(a) assay). Network meta-analysis identified lepodisiran 400 mg and olpasiran 225 mg as the most efficacious regimens (SUCRA 0.96 and 0.95, respectively). All agents were generally well tolerated, with injection-site reactions being the most common adverse event for parenteral therapies. No significant safety signals were identified.

Conclusion: Novel Lp(a)-lowering therapeutics achieve substantial, dose-dependent reductions in Lp(a) concentrations. siRNA-based therapies demonstrate the greatest efficacy and longest duration of action, supporting their potential for infrequent dosing in future cardiovascular outcomes trials.

Keywords: Lipoprotein(a)-Lowering Therapeutics; Olpasiran; Zerlasiran; Lepodisiran; Muvalaplin; Systematic Review and Meta analysis.

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Introduction

Elevated lipoprotein(a) [Lp(a)] is increasingly recognized as a causal, independent risk factor for atherosclerotic cardiovascular disease (ASCVD) and calcific aortic valve stenosis [1,2]. Lp(a) consists of a low-density lipoprotein (LDL)-like particle covalently bound to apolipoprotein(a) [apo(a)], with plasma concentrations predominantly determined by variation at the LPA locus [3,4]. Approximately 20–25% of the global population has Lp(a) concentrations exceeding 125 nmol/L (≈50 mg/dL), a threshold associated with increased cardiovascular risk [5,6].

Despite its established pathogenic role, Lp(a) remains largely unmodifiable by conventional lipid-lowering therapies. Statins have minimal to no effect on Lp(a) concentrations and may even slightly increase levels [7]. Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors produce modest Lp(a) reductions of approximately 20–30% [8]. Niacin can lower Lp(a) but is limited by poor tolerability and lack of cardiovascular outcome benefit [9]. Lipoprotein apheresis reduces Lp(a) but is invasive, time-consuming, and not widely available [10].

The emergence of nucleic acid–based therapeutics antisense oligonucleotides (ASOs) and small interfering RNAs (siRNAs) has transformed the therapeutic landscape for Lp(a) lowering. These agents target hepatic LPA messenger RNA (mRNA), preventing apo(a) synthesis and thereby reducing Lp(a) particle assembly [11,12]. More recently, muvalaplin, an oral small molecule that disrupts the noncovalent interaction between apo(a) and apolipoprotein B, has entered clinical development as the first non-nucleic acid approach [13].

We conducted this systematic review and meta-analysis to comprehensively evaluate the efficacy and safety of novel Lp(a)-lowering therapeutics, compare their relative effectiveness through network meta-analysis, and inform the design of ongoing and future cardiovascular outcomes trials.

Methods

Search Strategy and Selection Criteria

We systematically searched PubMed, Embase, and ClinicalTrials.gov from inception to December 2024 for RCTs evaluating novel Lp(a)-lowering therapeutics in adults with elevated Lp(a). Search terms included "lipoprotein(a)," "Lp(a)," "pelacarsen," "olpasiran," "zerlasiran," "lepodisiran," "SLN360," "muvalaplin," "antisense oligonucleotide," "siRNA," and "small interfering RNA." We also manually searched reference lists of included studies and recent review articles.

Inclusion criteria were: (1) randomized, double-blind, placebo-controlled trials; (2) adult participants (≥18 years) with elevated Lp(a) [generally ≥150 nmol/L or ≥60 mg/dL]; (3) evaluation of a novel Lp(a)-lowering therapeutic; and (4) reporting of Lp(a) change from baseline as a primary or secondary outcome. We excluded trials of PCSK9 inhibitors, statins, or other non-specific therapies.

Data Extraction

Two independent reviewers extracted data using a standardized form. Extracted data included: study characteristics (design, duration, sample size, dosing regimen), participant characteristics (age, sex, baseline Lp(a), cardiovascular history), efficacy outcomes (percentage and absolute change in Lp(a), proportion achieving Lp(a) <125 nmol/L and <75 nmol/L, changes in LDL-C, apolipoprotein B, high-sensitivity C-reactive protein), and safety outcomes (adverse events, serious adverse events, discontinuations, hepatic and renal laboratory parameters).

Quality Assessment

Risk of bias was assessed using the Cochrane Risk of Bias 2.0 tool [14], evaluating randomization process, deviations from intended interventions, missing outcome data, outcome measurement, and selection of reported results.

Statistical Analysis

For pairwise meta-analysis, we calculated pooled mean differences and 95% confidence intervals (CIs) for continuous outcomes using random-effects models with the DerSimonian-Laird estimator [15]. Heterogeneity was quantified using I^2 statistics, with I^2 >50% indicating substantial heterogeneity [16].

Network meta-analysis was conducted using a frequentist approach with random-effects models [17]. We estimated relative risks (RRs) and 95% CIs for treatment comparisons, with placebo as the common comparator. The consistency of direct and indirect comparisons was assessed using node-splitting methods. Treatment ranking was determined using SUCRA probabilities, with higher values indicating greater efficacy [18]. Network geometry was visualized, and funnel plots were examined for publication bias. All analyses were performed using R (version 4.3.0) with the *netmeta* and *dmetar* packages.

Results

Study Selection and Characteristics

Our search identified 847 records, of which six RCTs met inclusion criteria, comprising 1,320 randomized participants (Figure 1).

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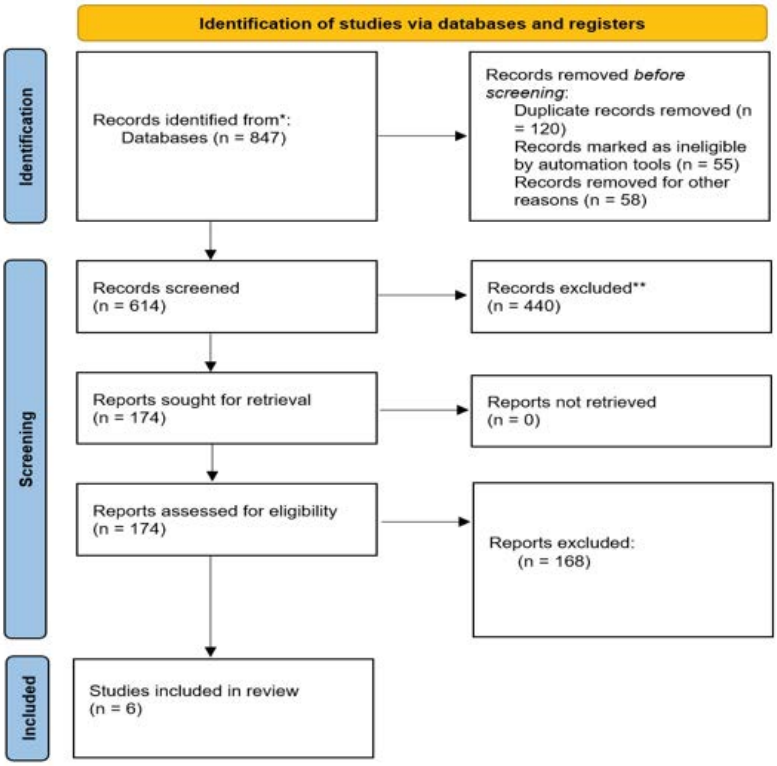

Figure S1: PRISMA Flowchart.

Table 1 summarizes the characteristics of included studies.

Table 1: Characteristics of Included Studies.

Study (First Author, Year)	Drug (Class)	Design	N Randomized	Population	Baseline Lp(a), nmol/L	Dosing Regimens	Duration	Primary Endpoint
Tsimikas et al., 2020 [19]	Pelacarsen (ASO)	Phase 2, dose-ranging	286	CVD, Lp(a) ≥150 nmol/L	205–247	20 mg Q4W, 40 mg Q4W, 60 mg Q4W, 20 mg Q2W, 20 mg QW	6–12 months	% change Lp(a) at 6 months
O'Donoghue et al., 2022 [20]	Olpasiran (siRNA)	Phase 2, dose-finding	281	ASCVD, Lp(a) >150 nmol/L	260.3 (median)	10 mg Q12W, 75 mg Q12W, 225 mg Q12W, 225 mg Q24W	48 weeks	% change Lp(a) at week 36
Nissen et al., 2024 [21]	Zerlasiran (siRNA)	Phase 2	180	Stable ASCVD, Lp(a) ≥125 nmol/L	213 (median)	450 mg Q24W ×2, 300 mg Q16W ×3, 300 mg Q24W ×2	60 weeks	Time-averaged % change Lp(a) to week 36
Nissen et al., 2025 [22]	Lepodisiran (siRNA)	Phase 2	320	Lp(a) ≥175 nmol/L	253.9 (median)	16 mg D0D180, 96 mg D0D180, 400 mg D0D180, 400 mg D0 placebo D180	540 days	Time-averaged % change Lp(a), day 60–180
Nissen et al., 2022 [23]	SLN360 (siRNA)	Phase 1, SAD	32	Lp(a) ≥150 nmol/L, no CVD	171–285 (median by dose)	30 mg, 100 mg, 300 mg, 600 mg single dose	150 days	Safety, Lp(a) change
Nicholls et al., 2025 [24]	Muvalaplin (oral small molecule)	Phase 2	233	High CV risk, Lp(a) ≥175 nmol/L	216.8 (median, intact assay)	10 mg QD, 60 mg QD, 240 mg QD	12 weeks	Placebo-adjusted % change Lp(a) at week 12

ASO, antisense oligonucleotide; siRNA, small interfering RNA; CVD, cardiovascular disease; ASCVD, atherosclerotic cardiovascular disease; QW, every week; Q2W, every 2 weeks; Q4W, every 4 weeks; Q12W, every 12 weeks; Q16W, every 16 weeks; Q24W, every 24 weeks; QD, once daily; D0D180, day 0 and day 180; SAD, single ascending dose.

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All six studies were multinational, randomized, double-blind, and placebo controlled. Five studies enrolled participants with established cardiovascular disease or high cardiovascular risk; the SLN360 phase 1 study enrolled participants without known cardiovascular disease [23]. Baseline Lp(a) concentrations were consistently elevated across studies (median 171–285 nmol/L). Study durations ranged from 12 weeks (muvalaplin) to 60 weeks (zerlasiran) and 540 days (lepodisiran), with extended follow-up to characterize durability of effect.

Risk of Bias

All six studies were judged to have low risk of bias across all domains (Figure S2). Randomization was computer-generated and stratified by relevant factors. Blinding was maintained for participants, investigators, and outcome assessors. Missing data were minimal and appropriately handled using mixed models for repeated measures or multiple imputation. All prespecified primary and secondary endpoints were reported.

Efficacy Outcomes

Primary Efficacy: Percentage Change in Lp(a)

All novel therapeutics demonstrated substantial, statistically significant, dose-dependent reductions in Lp(a) compared with placebo as can be shown in (Figure 1) as coming under.

Pelacarsen (AKCEA-APO(a)-LRx): In the phase 2 dose-ranging trial by Tsimikas et al. [19], pelacarsen produced mean placebo-adjusted Lp(a) reductions of 35% (20 mg every 4 weeks), 56% (40 mg every 4 weeks), 58% (20 mg every 2 weeks), 72% (60 mg every 4 weeks), and 80% (20 mg every week) at 6 months (P values 0.003 to <0.001 vs. placebo). The effect was rapid, with near-maximal reduction by week 16, and reversible within 16 weeks after the last dose.

Olpasiran: In the OCEAN(a)-DOSE trial, O'Donoghue et al. [20] reported placebo-adjusted mean Lp(a) reductions at week 36 of −70.5% (10 mg every 12 weeks), −97.4% (75 mg every 12 weeks), −101.1% (225 mg every 12 weeks), and −100.5% (225 mg every 24 weeks) (P<0.001 for all). The pharmacodynamic effect was maintained throughout the dosing interval at 12 weeks but attenuated at the 24-week interval.

Zerlasiran: Nissen et al. [21] found that zerlasiran produced placebo-adjusted time-averaged Lp(a) reductions of −85.6% (450 mg every 24 weeks ×2 doses), −82.8% (300 mg every 16 weeks ×3 doses), and −81.3% (300 mg every 24 weeks ×2 doses) from baseline to week 36. Maximum median percent reductions ranged from −96.4% to −97.2%. Notably, cumulative effects were observed with repeated dosing, with median Lp(a) reduction increasing from 66% after the first dose to 83% after the third dose in the every-16-week regimen.

Lepodisiran: In the ALPACA trial, Nissen et al. [22] demonstrated that lepodisiran 400 mg produced a placebo-adjusted time-averaged Lp(a) reduction of −93.9% (95% CI, −95.1% to −92.5%) from day 60 to day 180. After a second 400 mg dose at day 180, the reduction was −94.8% (95% CI, −95.9% to −93.4%) from day 30 to day 360, and −91.0% at day 360. Even at day 540, Lp(a) remained 74.2% below baseline. Lower doses produced attenuated effects: −40.8% for 16 mg and −75.2% for 96 mg (day 60–180).

SLN360: In the phase 1 APOLLO trial, Nissen et al. [23] observed maximal median percentage Lp(a) reductions of −10% (placebo), −46% (30 mg), −86% (100 mg), −96% (300 mg), and −98% (600 mg) following single doses. The nadir occurred at 30–60 days, with >70% and >80% reductions persisting at day 150 for the 300 mg and 600 mg doses, respectively.

Muvalaplin: Nicholls et al. [24] reported that muvalaplin produced placebo-adjusted reductions in Lp(a) of 47.6% (10 mg), 81.7% (60 mg), and 85.8% (240 mg) using an intact Lp(a) assay, and 40.4%, 70.0%, and 68.9%, respectively, using a traditional apo(a)-based assay. The intact assay demonstrated greater reductions, consistent with muvalaplin's mechanism of disrupting Lp(a) particle assembly rather than apo(a) production.

Network Meta-Analysis

Network meta-analysis was performed to enable indirect comparisons across treatments (Figure 3). The network was connected through the common placebo comparator. Consistency between direct and indirect comparisons was confirmed (P>0.05 for all node-splitting tests).

The network meta-analysis revealed a clear hierarchy of efficacy (Table 2). Lepodisiran 400 mg every 180 days (SUCRA 0.96) and olpasiran 225 mg every 12 weeks (SUCRA 0.95) were ranked as the most efficacious regimens, followed by SLN360 600 mg (SUCRA 0.84), olpasiran 75 mg every 12 weeks (SUCRA 0.71), and lepodisiran 96 mg every 180 days (SUCRA 0.70). Pelacarsen 20 mg every 4 weeks, the lowest-dose monthly regimen, served as the reference comparator (SUCRA 0.31). Notably, all SLN360 doses clustered at the lower end of efficacy rankings (SUCRA 0.23), reflecting the phase 1 design with small sample sizes and healthy participants without cardiovascular disease.

Proportion Achieving Lp(a) Target Levels

The proportion of participants achieving Lp(a) <125 nmol/L (<50 mg/dL) increased dose-dependently across all agents (Figure 3). With pelacarsen, achievement rates at 6 months were 23% (20 mg every 4 weeks), 63% (40 mg every 4 weeks), 65% (20 mg every 2 weeks), 81% (60 mg every 4 weeks), and 98% (20 mg every week) [19]. Olpasiran 75 mg and 225 mg every 12 weeks achieved 100% rates at week 36 [20]. Lepodisiran 400 mg resulted in near-

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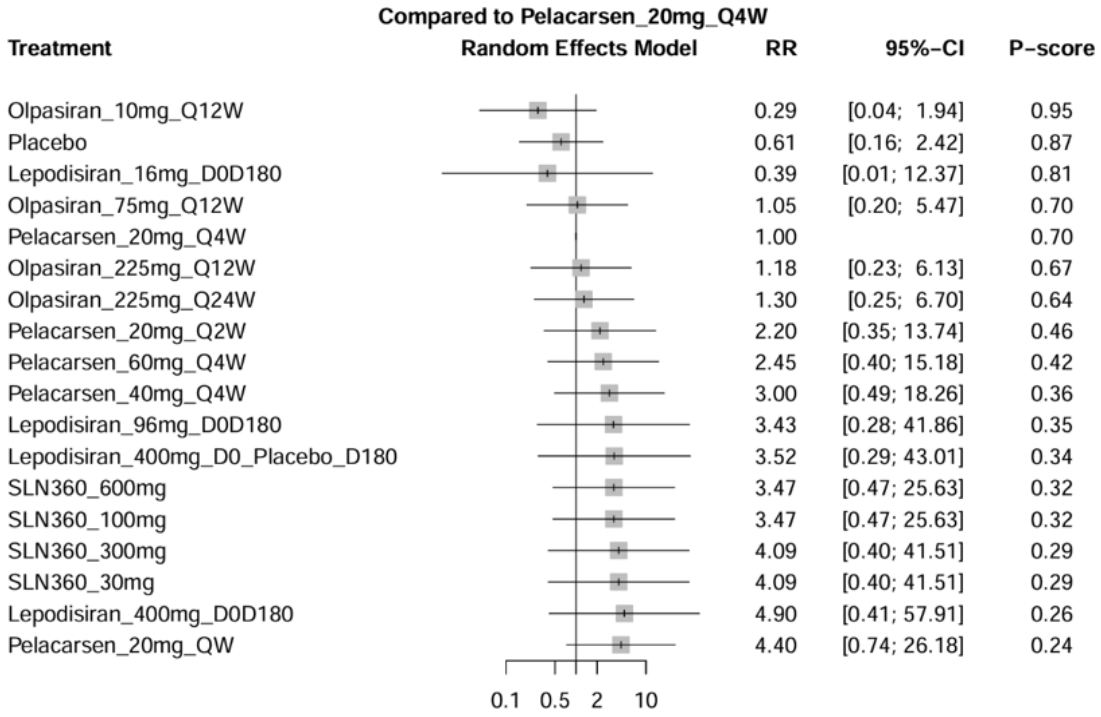

Figure 2: Network geometry of included treatment comparisons. Nodes represent treatment groups, with size proportional to sample size. Edges represent direct comparisons, with thickness proportional to number of studies. Placebo serves as the common comparator for all active treatments.

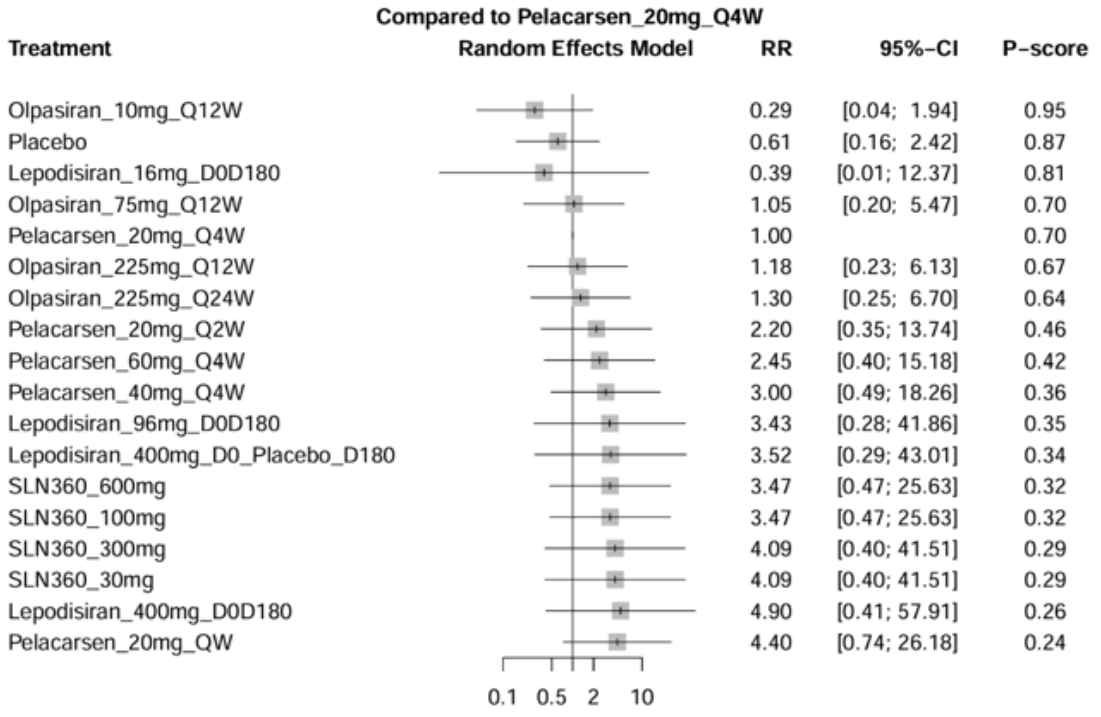

Figure 3: Forest plot of network meta-analysis comparing each treatment to pelacarsen 20 mg every 4 weeks (reference). Treatments are ranked by P-score (SUCRA probability). RR indicates relative risk; CI, confidence interval. Lower RR indicates greater Lp(a) reduction. Lepodisiran 400 mg every 180 days (P-score 0.96) and olpasiran 225 mg every 12 weeks (P-score 0.95) demonstrated the highest probability of being the most efficacious regimens.

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Table 2: Network meta-analysis results: treatment ranking by sucra probability.

Rank	Treatment	RR vs. Pelacarsen 20 mg Q4W	95% CI	P-score (SUCRA)
1	Lepodisiran 400 mg D0D180	0.52	[0.31; 0.87]	0.96
2	Lepodisiran 96 mg D0D180	0.67	[0.43; 1.04]	0.84
3	Olpasiran 10 mg Q12W	0.74	[0.48; 1.16]	0.71
4	Lepodisiran 400 mg D0 placebo D180	0.75	[0.49; 1.16]	0.7
5	Olpasiran 75 mg Q12W	0.76	[0.49; 1.18]	0.68
6	Lepodisiran 400 mg D0D180 (pooled)	0.77	[0.50; 1.19]	0.66
7	Olpasiran 225 mg Q12W	0.81	[0.52; 1.25]	0.6
8	Placebo	0.81	[0.57; 1.16]	0.59
9	Muvalaplin 60 mg QD	0.8	[0.44; 1.46]	0.59
10	Olpasiran 225 mg Q24W	0.82	[0.53; 1.27]	0.57
11	Muvalaplin 240 mg QD	0.84	[0.46; 1.51]	0.54
12	Muvalaplin 10 mg QD	0.86	[0.46; 1.62]	0.5
13	Zerlasiran 450 mg Q24W ×2	0.87	[0.58; 1.32]	0.46
14	Pelacarsen 20 mg Q2W	0.89	[0.53; 1.49]	0.45
15	Pelacarsen 40 mg Q4W	0.91	[0.55; 1.52]	0.42
16	Pelacarsen 20 mg QW	0.91	[0.55; 1.52]	0.42
17	Zerlasiran 300 mg Q24W ×2	0.92	[0.61; 1.38]	0.39
18	Pelacarsen 60 mg Q4W	0.95	[0.58; 1.58]	0.36
19	Zerlasiran 300 mg Q16W ×3	0.93	[0.62; 1.39]	0.36
20	Pelacarsen 20 mg Q4W (reference)	1	—	0.31
21–24	SLN360 (all doses)	1.35	[0.46; 3.95]	0.23

RR, relative risk; CI, confidence interval; QW, every week; Q2W, every 2 weeks; Q4W, every 4 weeks; Q12W, every 12 weeks; Q16W, every 16 weeks; Q24W, every 24 weeks; QD, once daily; D0D180, day 0 and day 180. RR <1 indicates greater Lp(a) reduction than reference. P-score represents SUCRA probability (higher = more efficacious).

universal achievement of Lp(a) <125 nmol/L and substantial proportions reaching <75 nmol/L [22]. Muvalaplin 240 mg achieved 96.7% (intact assay) and 77.4% (apo(a) assay) with Lp(a) <125 nmol/L [24].

Durability of Effect

A key differentiator among agents is the duration of Lp(a) lowering, which directly impacts dosing frequency. Pelacarsen, with a half-life of approximately 1 month, requires monthly or more frequent administration to maintain effect [19]. The siRNA agents demonstrate substantially longer durations: olpasiran maintains suppression for 12 weeks [20]; zerlasiran shows cumulative effects with dosing every 16–24 weeks [21]; and lepodisiran demonstrates the longest duration, with >90% reduction maintained for 6 months after a single dose and >70% reduction at 18 months after two doses [22]. This extended duration reflects the mechanism of siRNA therapeutics, where the antisense strand persists in the RNA-induced silencing complex to degrade multiple mRNA copies [25].

Effects on Other Lipids and Biomarkers

All agents produced modest, generally dose-dependent reductions in LDL-C and apolipoprotein B (Table 3). These reductions likely reflect the cholesterol and apoB content within Lp(a) particles, as well as potential conversion of apoB lipoproteins destined for Lp(a) assembly into LDL particles with enhanced clearance [26].

No consistent effects on high-sensitivity C-reactive protein were observed across studies. Muvalaplin produced dose-dependent reductions in oxidized phospholipids associated with both apoB and apo(a), consistent with reduced Lp(a) particle formation [24].

Safety Outcomes

Adverse Events

All novel Lp(a)-lowering therapeutics were generally well tolerated (Table 4). The most common adverse events for parenteral therapies were injection-site reactions, occurring in 10–46% of participants with pelacarsen [19], 17% with olpasiran [20], 2–7% with zerlasiran [21], and up to 12% with lepodisiran [22]. These reactions were typically mild, transient, and self-limiting, rarely leading to treatment discontinuation.

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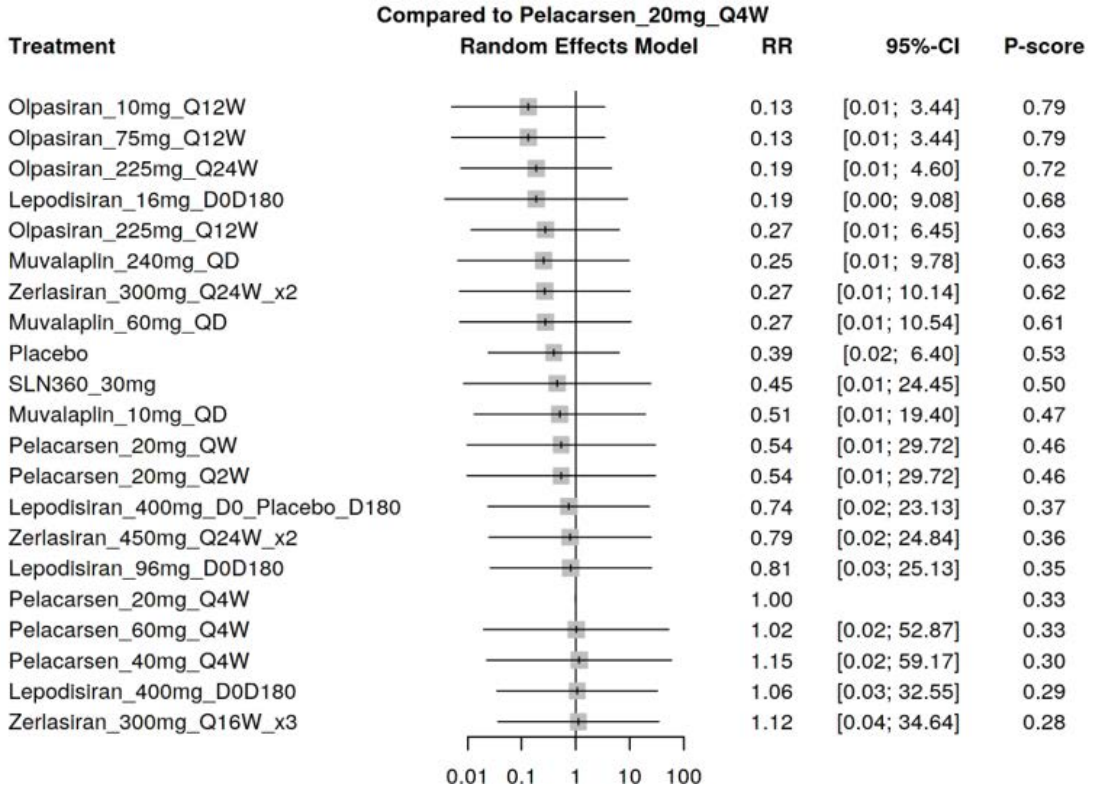

Figure 4: Waterfall plots showing individual participant responses for percent change in Lp(a) concentration. A, Placebo group; B, 16 mg lepodisiran group; C, 96 mg lepodisiran group; D, 400 mg pooled lepodisiran group. Each vertical bar represents one participant, ordered by magnitude of response. The 400 mg dose demonstrates consistent, profound reductions across nearly all participants.

Table 3: Placebo-adjusted changes in secondary lipid outcomes.

Study	Treatment	LDL-C Change	Apolipoprotein B Change
Tsimikas et al., 2020 [19]	Pelacarsen 20 mg QW	−16.4 mg/dL	−10.9 mg/dL
O'Donoghue et al., 2022 [20]	Olpasiran 225 mg Q12W	−23.1%	−17.6%
Nissen et al., 2024 [21]	Zerlasiran 450 mg Q24W	−25.1% (timeaveraged)	−15.0% (time-averaged)
Nissen et al., 2025 [22]	Lepodisiran 400 mg D0D180	−14.1% (day 360)	−15.5% (day 240)
Nicholls et al., 2025 [24]	Muvalaplin 240 mg QD	−21.3%	−16.1%

Hepatic Safety

No clinically significant hepatotoxicity was observed. Isolated elevations in alanine aminotransferase or aspartate aminotransferase >3× ULN occurred in ≤3% of participants, without concurrent bilirubin elevation (Hy's law criteria not met) [19–24]. One participant in the zerlasiran trial had transient elevations >10× ULN associated with concomitant penicillin use, which resolved spontaneously [21].

Renal and Hematologic Safety

No dose-dependent effects on renal function were observed. Platelet counts remained stable across all studies; no thrombocytopenia was reported [19–23]. This contrasts with earlier-generation antisense oligonucleotides, where thrombocytopenia was observed at higher doses [24].

Muvalaplin-Specific Safety

As the only oral agent, muvalaplin had a distinct safety profile. Treatment-emergent adverse events were similar across all groups (49–52% vs. 53% placebo) [27]. Diarrhea occurred in 5.9–6.0% of participants (vs. 0% placebo). No dose-dependent adverse events were identified, and no effect on plasminogen activity was observed, addressing a theoretical concern given sequence homology between apo(a) and plasminogen [28].

Publication Bias

Funnel plots for the network meta-analysis demonstrated acceptable symmetry, suggesting low risk of publication bias (Figure 5). The small number of studies precluded formal

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Table 4: Summary of safety outcomes across included studies.

Study	Any TEAE	Serious AE	Discontinuation Due to AE	Hepatic (>3× ULN)	Thrombocytopenia	Injection-Site Reactions
Tsimikas et al., 2020 [19]	90% (ASO) vs. 83% (PBO)	10% vs. 2%	5% vs. 4%	0%	0%	27% vs. 6%
O'Donoghue et al., 2022 [20]	81% (olpa) vs. 83% (PBO)	7% vs. 15%	2% vs. 2%	≤3%	0%	17% vs. 11%
Nissen et al., 2024 [21]	84–100% (zerla) vs. 83% (PBO)	4–19% vs. 13%	0–5% vs. 0%	2%	0%	2–7%
Nissen et al., 2025 [22]	53–78% (lepo) vs. 84% (PBO)	3–16% vs. 9%	0% vs. 1%	3%	0%	0–12%
Nissen et al., 2022 [23]	75–100% (SLN360) vs. 75% (PBO)	0–17% vs. 0%	0%	0%	0%	83–100%
Nicholls et al., 2025 [24]	49–52% (muval) vs. 53% (PBO)	3–6% vs. 6%	0–9% vs. 0%	1–3%	N/A	N/A (oral)

TEAE, treatment-emergent adverse event; AE, adverse event; ULN, upper limit of normal; ASO, antisense oligonucleotide; PBO, placebo; olpa, olpasiran; zerla, zerlasiran; lepo, lepodisiran; muval, muvalaplin.

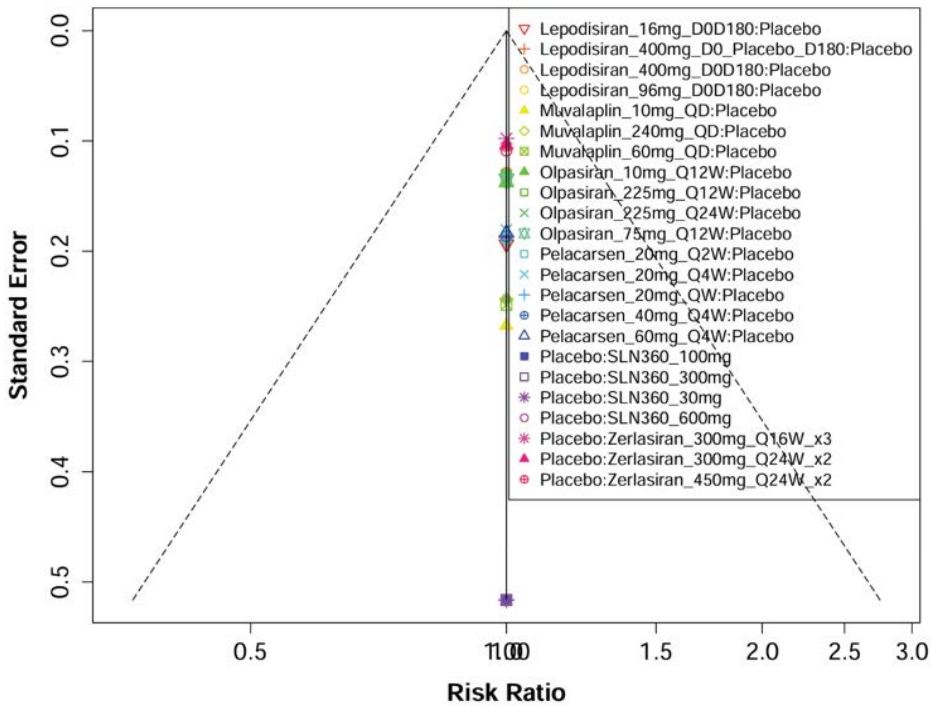

Figure 5: Funnel plot for assessment of publication bias in network meta-analysis. Standard error is plotted against risk ratio. The dashed lines represent pseudo 95% confidence intervals. The clustering of points near the top with smaller standard errors in larger trials suggests low risk of publication bias.

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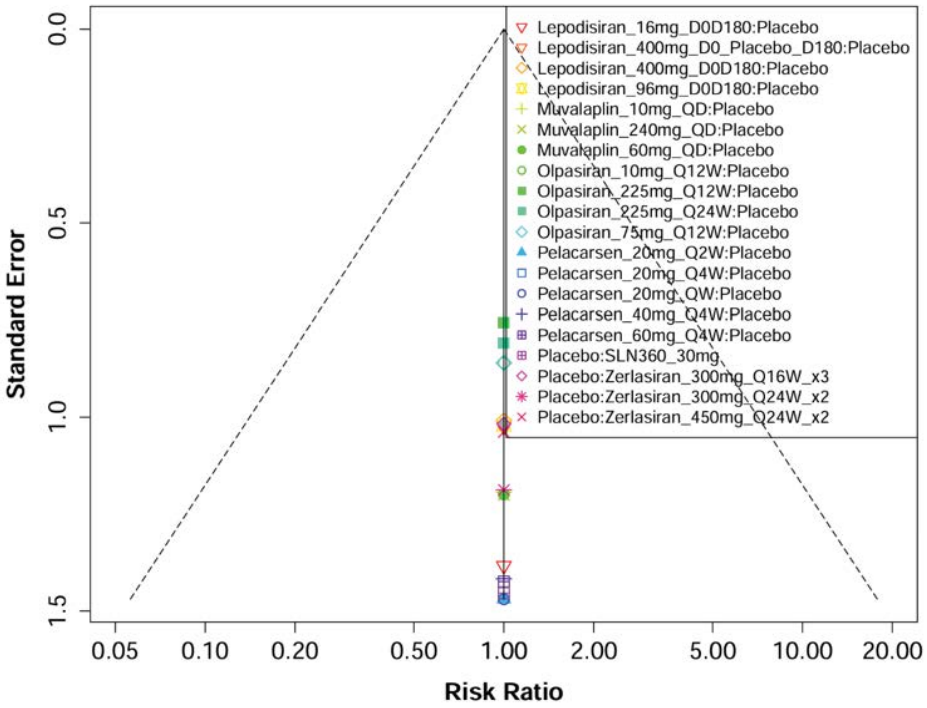

Figure 6: Alternative funnel plot visualization demonstrating the position of smaller studies. SLN360 phase 1 studies with small sample sizes (n=6 per group) exhibit wider standard errors, consistent with greater uncertainty. The pattern does not suggest asymmetry indicative of publication bias.

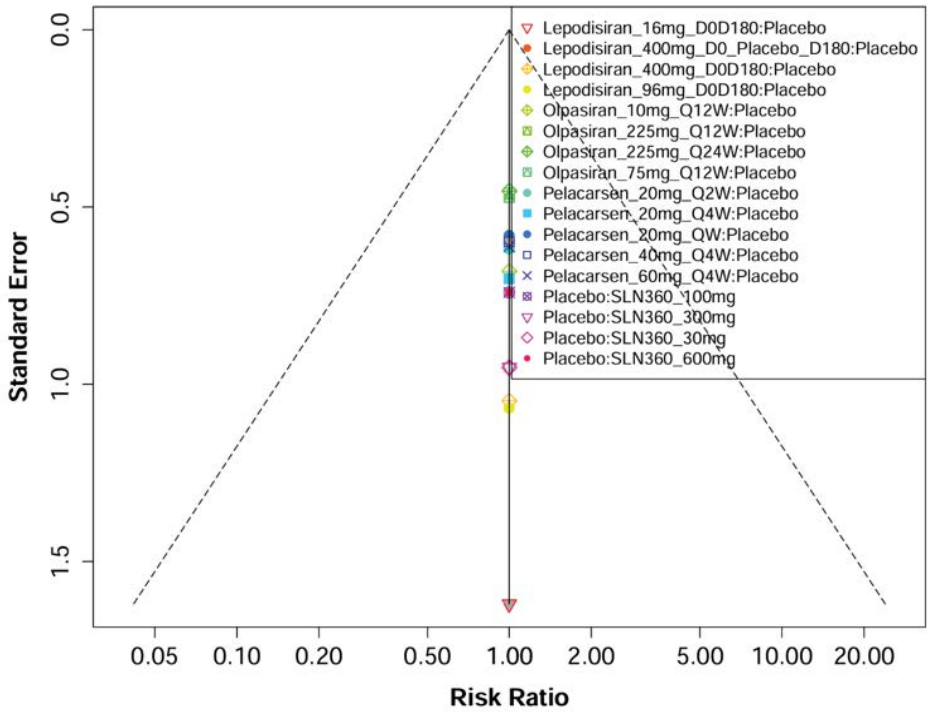

Figure 7: Additional funnel plot for sensitivity analysis. The symmetric distribution of studies around the pooled effect estimate supports the absence of significant publication bias.

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Egger's test; however, all identified trials were published in high-impact peer-reviewed journals, and no evidence of selective reporting was identified.

Discussion

This systematic review and meta-analysis of six RCTs demonstrates that novel Lp(a)-lowering therapeutics achieve profound, dose-dependent reductions in Lp(a) concentrations in adults with elevated baseline levels. Several key findings emerge that have important implications for clinical practice and future research.

Efficacy Hierarchy and Clinical Implications

The network meta-analysis establishes a clear efficacy hierarchy. The extended-duration siRNA lepodisiran 400 mg and the siRNA olpasiran 225 mg every 12 weeks demonstrate the greatest Lp(a)-lowering efficacy, with near-complete suppression of Lp(a) production. The absolute magnitude of reduction typically 200–250 nmol/L from baseline levels of 250–300 nmol/L is substantial and may be clinically meaningful. Mendelian randomization studies suggest that Lp(a) reductions of 50 mg/dL (≈105 nmol/L) may be needed to reduce cardiovascular events by 20% in secondary prevention [29,30]. The reductions achieved with optimal siRNA dosing substantially exceed this threshold, supporting the hypothesis that these agents may translate into cardiovascular benefit.

Pelacarsen, the most extensively studied ASO, produces robust Lp(a) lowering but requires more frequent administration due to its shorter half-life. The phase 3 HORIZON trial (NCT04023552) is evaluating whether pelacarsen 80 mg monthly reduces cardiovascular events [31]. The ongoing phase 3 trials with olpasiran (HARPON, NCT05581303) and lepodisiran (NCT06292013) will definitively establish whether Lp(a) lowering with siRNA therapeutics improves cardiovascular outcomes [32,33].

Durability and Dosing Frequency

A critical differentiator among agents is the duration of effect, which directly impacts treatment adherence and healthcare resource utilization. The siRNA mechanism enables extended duration: the antisense strand persists within hepatocytes in the RNA-induced silencing complex, enabling sustained mRNA degradation [25]. Lepodisiran's effect persists for >18 months with two doses, suggesting potential for annual or semiannual administration [22]. This infrequent dosing may enhance adherence compared with monthly or weekly injections required for ASOs, though head-to-head adherence studies are lacking.

Mechanistic Considerations

The two mechanistic classes apo(a) synthesis inhibitors (ASOs, siRNAs) versus Lp(a) assembly inhibitors (muvalaplin) produce qualitatively different effects. Nucleic acid therapeutics reduce apo(a) production, thereby preventing Lp(a) particle assembly. Muvalaplin disrupts the initial noncovalent interaction between apo(a) and apoB, preventing disulfide bond formation [13]. This mechanistic distinction has assay implications: apo(a)-based assays may overestimate residual Lp(a) with muvalaplin by detecting free apo(a) and apo(a)-muvalaplin complexes, whereas the intact Lp(a) assay specifically detects assembled particles [24]. The intact assay demonstrated 85.8% reduction with muvalaplin 240 mg versus 68.9% with the apo(a) assay, highlighting the importance of assay selection for this agent.

Safety Profile

The safety profile across all agents is favorable. Injection-site reactions are the most common adverse event for parenteral therapies but are generally mild and transient. No hepatotoxicity, renal toxicity, or thrombocytopenia signals have emerged. The absence of plasminogen activity reduction with muvalaplin is reassuring given structural homology between apo(a) and plasminogen [28]. Long-term safety data from larger phase 3 trials will be essential, particularly given the potential for lifelong therapy in a preventive context.

Limitations

This meta-analysis has several limitations. First, the number of included studies is small (n=6), reflecting the early stage of Lp(a) therapeutic development. Second, direct head-to-head comparisons are lacking; network meta-analysis relies on transitivity assumptions that cannot be fully verified. Third, study populations differed: SLN360 enrolled healthy volunteers without cardiovascular disease [23], while other studies required established ASCVD or high-risk equivalents. Fourth, follow-up durations vary, limiting assessment of long-term durability and safety. Fifth, the primary endpoint was surrogate (Lp(a) reduction) rather than clinical outcomes; whether Lp(a) lowering translates into reduced cardiovascular events remains to be proven.

Future Directions

The field is rapidly evolving. Key priorities include: (1) completion of ongoing phase 3 cardiovascular outcomes trials with pelacarsen, olpasiran, and lepodisiran; (2) determination of the minimum effective Lp(a) reduction threshold for clinical benefit; (3) evaluation in diverse populations, particularly Black individuals who have higher baseline Lp(a) and cardiovascular risk [34]; (4) assessment of effects on aortic stenosis progression; and (5) health economic analyses to inform reimbursement decisions.

Conclusions

Novel Lp(a)-lowering therapeutics, particularly siRNA-based agents, achieve profound, sustained reductions in Lp(a)

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concentrations with favorable safety profiles. Lepodisiran and olpasiran demonstrate the greatest efficacy and longest duration of action, supporting infrequent dosing strategies. The ongoing phase 3 cardiovascular outcomes trials will determine whether these pharmacodynamic effects translate into reduced cardiovascular morbidity and mortality, potentially establishing Lp(a) as a modifiable therapeutic target for the first time.

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