Lipids in Health and Disease

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Safety and efficacy of antisense oligonucleotides on triglyceride, apolipoprotein C-III, and other lipid parameters levels in hypertriglyceridemia; a network meta-analysis of randomized controlled trials

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Abstract

Background Hypertriglyceridemia is an independent risk factor for cardiovascular diseases. In previous trials, apolipoprotein C-III (APOC3) inhibition through the antisense oligonucleotides volanesorsen, olezarsen, and plozasiran reduced triglyceride levels. However, the three medications' safety and efficacy have yet to be compared.

Methods A network meta-analysis was performed to compare multiple doses of the three medications to each other through the placebo. Randomized controlled trials (RCTs) were retrieved by searching PubMed, EMBASE, Web of Science, SCOPUS, and Cochrane until November 22nd, 2024. The mean difference (MD) and 95% confidence interval (CI) were used for continuous outcomes. The risk ratio (RR) and 95% CI were used for dichotomous outcomes.

Results Ten RCTs with a total of 1,129 patients were included. volanesorsen 300 mg once weekly showed the most significant percent reduction in triglyceride levels (MD = -91.0%, 95% CI: (-109.2%; -72.8%); $P < 0.01$). Only plozasiran once monthly, regardless of the dose, showed a non-significant percent reduction in triglycerides. This finding should be taken cautiously as the data were derived from a phase 1 trial with a small sample size. All the regimens significantly reduced APOC3 levels compared to placebo, with plozasiran 100 mg monthly and volanesorsen 300 mg once weekly showing the most significant reduction (MD range: -92.8% to -88.5%; $P < 0.01$). None of the treatments showed a statistically significant difference in overall adverse events rate compared to the placebo.

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Conclusion APOC3 antisense oligonucleotide inhibitors effectively reduced triglyceride and APOC3 levels in hypertriglyceridemia with an acceptable safety profile. However, the results should be interpreted cautiously due to the small sample size. Further research is needed to confirm the beneficial effects of APOC3 inhibitors and show strong evidence of the impact of each regimen.

Keywords Hyperlipidemia, APOC3, Triglycerides, APOC3 inhibitors, Systematic review, Network meta-analysis

Introduction

Hypertriglyceridemia (HTG), affecting nearly 47% of US adults, independently increases the risk of atherosclerosis, myocardial infarction (MI), atherosclerotic cardiovascular disease (ASCVD), and cardiac mortality—the leading global cause of death [1–6]. Statin is the cornerstone treatment for moderate to severe HTG, and it is also used as a preventive therapy for ASCVD risk of ≥7.5%. However, statins alone are insufficient to prevent elevated triglycerides (TG) from causing acute pancreatitis; because of this, in severe HTG, with fasting TG ≥ 1000 mg/dL, fibrate is essential [7–9]. While combining statins with other drugs like fenofibrate can reduce TG, these combinations come with potential side effects such as myopathies [10–13]. Due to the relative insufficient efficacy and the possible side effects of the available agents, further randomized clinical trials (RCTs) were conducted to find better alternatives.

Apolipoprotein C3 (APOC3) is a small protein molecule that regulates TG metabolism by suppressing the conversion of very low-density lipoprotein (VLDL) to low-density lipoprotein (LDL), as well as the hepatic clearance of VLDL [14–16]. Consequently, high APOC3 levels are associated with multiple hypertriglyceridemic conditions [7–10]. Moreover, triglyceride-rich lipoproteins (TRLs) and their remnants promote atherogenesis partially through the action of APOC3, which is recognized as an independent risk factor for ASCVD and cardiac mortality [14, 16]. Therefore, APOC3 loss of function mutations reduced TG and ASCVD risk [17].

Subsequently, antisense oligonucleotides (ASOs) targeting APOC3, such as olezarsen, volanesorsen, and plozasiran, have emerged as an effective and safe treatment for HTG by selectively targeting APOC3 mRNA, causing a dose-dependent reduction of TG, APOC3, LDL, VLDL, and apolipoprotein B (ApoB) in patients with HTG [19, 20]. Crucially, by improving these serum lipid parameters, ASOs reduce the risk of pancreatitis [15, 18–27]. These findings propel ASOs as potential therapies for HTG and related cardiovascular and non-cardiovascular risks [28–30]. However, the three medications' relative effectiveness and safety have yet to be compared to determine which medication is more appropriate for different conditions. Therefore, this study sought to compare and rank the three medications, volanesorsen, olezarsen, and plozasiran, according to their efficacy and safety through a systematic review and network meta-analysis (NMA) of RCTs.

Methods

Protocol

The study adhered entirely to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [31] and the Cochrane Handbook [32]. The pre-specified protocol was documented in PROSPERO with the ID CRD42024541265.

Databases & search method

The EMBASE, SCOPUS, Web of Science, MEDLINE (PubMed), and Cochrane Central databases were searched until April 20th, 2024, and manually searched the databases for new trials on June 15th, 2024. A final check was performed again on November 22nd, 2024. Two autonomous reviewers employed database searching without using filters. Table S1 shows the complete search strategy.

Eligibility criteria

Inclusion standards

RCTs that met the prespecified PICO criteria were included. The PICO criteria are Population: patients with hyperlipidemia for any cause; Intervention: any ASO against APOC3 including (volanesorsen, plozasiran, and olezarsen); Control: Placebo; and Outcomes: Efficacy outcomes including percent change from baseline in the levels of (Triglycerides, APOC3, Total cholesterol (TC), high-density lipoprotein (HDL), LDL, VLDL, Non-HDL, and ApoB total) and safety outcomes including (Any adverse events, Serious adverse events, Adverse events leading to drug discontinuation, Treatment-related adverse events, Injection site reaction, and Thrombocytopenia (< 140,000)).

Exclusion standards

Non-RCT studies, such as in vitro, conference abstracts, observational, and animal studies, were excluded.

Study identification

Two independent reviewers used Covidence online software for study selection [33]. The software automatically excluded duplicates, and the prevailing studies were screened by the reviewers using the title and abstract of each study. Embraced studies in the last step

were further screened using the full text of each study. Another reviewer was called to settle the discrepancies at each screening step.

Data extraction

Four reviewers independently used an Excel extraction sheet that was generated after going through the full text of the obtained studies to extract the following: Summary characteristics, Baseline characteristics, Efficacy outcomes, and Safety outcomes. More information about the summary and baseline characteristics can be found in (Tables 1 and 2, respectively).

Risk of bias and quality assessment

Four reviewers independently assessed the quality of the studies embraced in the research using the Cochrane ROB2 tool [34]. In case of any discrepancies, the reviewers discussed and settled them via consensus. To estimate the quality of evidence, two reviewers adopted the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) instructions [35, 36].

Statistical analysis

This study employed a frequentist NMA using the Netmeta package in R software. Percent change mean differences and 95% confidence intervals (CIs) for continuous outcomes and risk ratios (RR) with 95% CIs for dichotomous outcomes were computed. Random-effect models weighted by the inverse variance method were applied to account for population diversity in the studies included. Network plots were created to visualize the direct comparisons among treatment arms where each endpoint represents a treatment arm, and the line thickness reflects the number of studies comparing those treatments. Forest plots displayed the network comparison results between each treatment and the control group.

Table 1 Summary characteristics of included studies

Study ID	Used drug	Setting (center, country)	RCT phase	Sample size	Additional hyperlipidemia medications	Conclusion in brief
Ballantyne et al. 2024 [42]	Plozasiran	Multinational	Phase 2b	353	Statin, fibrate, *n* – 3 fatty acids, icosapent ethyl, and PCSK9 inhibitor	Plozasiran, as compared with placebo, significantly reduced triglyceride levels at 24 weeks
Bergmark et al. 2024 [43]	Olezarsen	Multinational	Phase 2b	154	Statin, ezetimibe, fibrate, *n* – 3 fatty acids, niacin, PCSK9 inhibitor	In patients with moderate hypertriglyceridemia and elevated cardiovascular risk, olezarsen significantly reduced triglycerides, and apolipoprotein B, without major safety concerns.
Stroes et al. 2024 [40]	Olezarsen	Multinational	phase 3	66	Statin, fibrate, omega – 3 fatty acids	Olezarsen could offer a new treatment option for reducing plasma triglyceride levels in patients with familial chylomicronemia syndrome.
Tardif et al. 2022 [41]	Olezarsen	Multinational	Phase 2b	114	Statin, ezetimibe, fibrate, omega – 3 fatty acids, niacin, and PCSK9 inhibitor	Olezarsen significantly lowered triglycerides and atherogenic lipoproteins in patients with moderate hypertriglyceridemia and high or established cardiovascular disease risk.
Gaudet et al. 2024 [21]	Plozasiran	Multinational	phase 2b	229	Statin, fibrate, omega – 3 fatty acids, PCSK9 inhibitor	Plozasiran lowered triglycerides below the acute pancreatitis risk level and improved triglyceride-related lipoprotein and safety was favorable. Further studies are needed.
Gaudet et al. 2023 [38]	Plozasiran	Multinational	phase 1	52	Statin, ezetimibe, fibrates, omega-3 fatty acids	No significant toxicities or side effects were reported. Positive changes in lipid parameters were observed in the small patient cohorts, laying the groundwork for larger and longer trials
Gaudet et al. 2014 [16]	Volanesorsen	Multinational	phase 2	57	Statins and fibrates	Treatment with Volanesorsen significantly lowered triglyceride levels in patients with a variety of starting triglyceride levels.
Gouni et al. 2021 [39]	Volanesorsen	Multinational	phase 3	113	Statin, fibrate, fish oils, and ezetimibe	Volanesorsen significantly reduced triglyceride concentrations in patients with multifactorial chylomicronemia and might reduce acute pancreatitis events in these patients.
Oral et al. 2022 [31]	Volanesorsen	Multinational	phase 2	40	Statin, fibrates, and fish oil	Volanesorsen significantly reduced serum triglyceride levels and hepatic steatosis in patients with FPLD.
Witztum et al. 2019 [29]	Volanesorsen	Multinational	phase 3	66	*N* – 3 fatty acids, statins, and fibrates	Volanesorsen lowered triglyceride levels to less than 750 mg per deciliter in 77% of patients with familial chylomicronemia syndrome. Thrombocytopenia and injection site reactions were common adverse events.

FPLD; Familial partial lipodystrophy, PCSK9; Proprotein convertase subtilisin/kexin type 9

Table 2 Baseline characteristics of included studies

Study ID	Doses	Number of patients	Age mean (SD)	Males no. (%)	BMI mean (SD)	Lipid metabolism mean (SD)					Lipid Therapy no. (%)			
						Total triglycerides	Total cholesterol	LDL-C	HDL-C	APOC-III	Statins	Fibrates	Ezetimibe	PCSK-9 Inhibitors
Ballantyne et al. 2024 [42]	plozasiran 10 mg Q12 W	67	60.2 (11.7)	36 (54)	30.5 (5.7)	253.2 (81.4)	NA	105.1 (37.0)	42.2 (11.1)	15.5 (5.5)	61 (91)	10 (15)	NA	3 (4)
	plozasiran 25 mg Q12 W	67	61.3 (11.3)	37 (55)	32.4 (6.7)	234.1 (72.7)	NA	101.6 (43.4)	44.7 (13.6)	15.6 (5.5)	61 (91)	6 (9)	NA	3 (4)
	plozasiran 50 mg Q12 W	66	62.6 (10.5)	37 (56)	32.6 (6.5)	250.3 (81.3)	NA	103.0 (39.7)	42.7 (11.7)	15.0 (5.7)	60 (91)	6 (9)	NA	0
	plozasiran 50 mg Q24 W	66	61.3 (11.8)	43 (65)	32.0 (5.6)	248.0 (80.6)	NA	105.6 (31.8)	40.8 (12.6)	15.0 (5.5)	57 (86)	9 (14)	NA	1 (2)
	Placebo	87	58.9 (9.7)	46 (53)	31.2 (5.4)	237.2 (76.2)	NA	101.6 (38.7)	42.1 (11.1)	14.6 (4.7)	84 (97)	15 (17)	NA	1 (1)
Bergmark et al. 2024 [43]	Olezarsen 50 mg Q4W	58	62.66 (12.92)	34(59)	33.66 (6.61)	248 (113.27)	130.7 (40)	83.1 (35.35)	NA	15.53 (5.54)	49(84)	5 (9)	5 (9)	3 (5)
	Olezarsen 80 mg Q4W	57	61 (11.40)	40(70)	32.2 (6.84)	259.5 (135.37)	128.8 (30.7)	81.5 (30.42)	NA	14.26 (4.86)	46 (81)	9 (16)	2 (4)	1 (2)
	Placebo	39	64 (10.00)	15(38)	33.6 (5.54)	251.1 (50.02)	135.3 (39.6)	82.66 (32.71)	NA	15.9(4.23)	32 (82)	11 (28)	3 (8)	1 (3)
Stroes et al. 2024 [40]	Olezarsen 50 mg Q4W	21	43.2 (12.1)	6(29)	22.4 (3.5)	2684 (1235)	323.4 (100.5)	17.6 (8.5)	15.7 (4.0)	27.7 (10.5)	4 (19)	8 (38)	NA	NA
	Olezarsen 80 mg Q4W	22	47.7 (13.3)	11 (50)	25.1 (6.0)	2613 (1499)	277.4 (99.3)	22.8 (14.1)	14.5 (4.5)	27.5 (11.6)	5 (23)	11 (50)	NA	NA
	Placebo	23	44.0 (14.7)	11 (48)	24.2 (4.1)	2596 (1256)	286.0 (113.9)	16.7 (8.4)	14.7 (3.8)	27.7 (11.7)	7 (30)	11 (48)	NA	NA
Tardif et al. 2022 [41]	Olezarsen 50 mg Q4W	22	62.9 (7.40)	15 (68.2)	32.8 (4.14)	268.4 (85.1)	166.8 (35.3)	76.8 (20.8)	36.8 (10.5)	15.7 (3.3)	19 (86.4)	10 (45.5)	3 (13.6)	2 (9.1)
	Placebo	24	64.6 (7.93)	20 (83.3)	32.1 (4.18)	293.8 (86.7)	144.8 (26.0)	60.2 (27.2)	34.6 (8.6)	16.6 (4.5)	23 (95.8)	8 (33.3)	4 (16.7)	1 (4.2)
Gaudet et al. 2024 [21]	plozasiran 10 mg Q12 W	54	53 (10)	46 (85)	33 (5)	890 (577)	209 (74)	75 (44)	28 (9)	33 (15)	35 (65)	26 (48)	NA	1 (2)
	plozasiran 25 mg Q12 W	55	56 (11)	43 (78)	32 (5)	942 (756)	206 (91)	74 (40)	30 (11)	34 (17)	39 (71)	24 (44)	NA	2 (4)
	plozasiran 50 mg Q12 W	57	54 (11)	41 (72)	32 (5)	908 (653)	196 (88)	72 (42)	31 (13)	32 (16)	39 (70)	28 (50)	NA	1 (2)
	Placebo	60	56 (11)	46 (77)	31 (4)	851 (507)	185 (79)	69 (39)	30 (12)	31 (16)	41 (67)	31 (51)	NA	3 (5)
Gaudet et al. 2023 [38]	plozasiran 10 mg Q4 W	8	53	7 (87.5)	31.9 (4.5)	664 (325.01)	238.3 (105.3)	88.3 (26.6)	26.8 (8.9)	28.4 (10.3)	6 (75.0)	1 (12.5)	NA	NA
	plozasiran 25 mg Q4 W	8	55.5	6 (75.0)	31.5 (3.4)	1252.75 (1007.04)	327.4 (181.1)	76.8 (47.3)	28.8 (8.1)	41.5 (21.6)	5 (62.5)	3 (37.5)	NA	NA
	plozasiran 50 mg Q4 W	8	54.5	4 (50.0)	30.5 (7.0)	723.75 (395.87)	238.8 (82.6)	82.8 (38.1)	30.0 (7.0)	24.5 (12.6)	2 (25.0)	4 (50.0.)	NA	NA
	plozasiran 100 mg Q4 W	8	57.5	6 (75.0)	32.2 (3.6)	688.25 (351.53)	237.0 (59.1)	95.1 (55.7)	33.3 (13.9)	30.2 (14.5)	2 (25.0)	2 (25.0)	NA	NA
	Placebo	8	46.5	6 (75.0)	30.7 (5.0)	680.5 (467.33)	195.0 (48.0)	79.8 (44.5)	27.5 (7.8)	22.8 (7.4)	3 (37.5)	3 (37.5)	NA	NA

Table 2 (continued)

Study ID	Doses	Number of patients	Age mean (SD)	Males no. (%)	BMI mean (SD)	Lipid metabolism mean (SD)					Lipid Therapy no. (%)			
						Total triglycerides	Total cholesterol	LDL-C	HDL-C	APOC-III	Statins	Fibrates	Ezetimibe	PCSK-9 Inhibitors
Gaudet et al. 2014 [16]	volanesorsen 100 mg Q1W	13	52.2 (9.7)	8 (61.54)	29.4 (4.1)	573.2 (248.5)	235.0 (50.3)	95.6 (33.3)	31.5 (4.7)	22.4 (7.7)	6 (46.2)	NA	NA	NA
	volanesorsen 200 mg Q1W	15	49.7 (12.8)	14 (93.33)	30.8 (3.0)	662.0 (299.0)	240.5 (62.7)	79.5 (25.1)	31.9 (4.0)	23.1 (5.3)	4 (26.7)	NA	NA	NA
	volanesorsen 300 mg Q1W	13	52.8 (10.4)	8 (61.54)	30.9 (3.6)	565.6 (213.7)	208.9 (58.7)	70.9 (31.0)	33.2 (8.9)	22.6 (6.3)	5 (38.5)	NA	NA	NA
	Placebo	16	48.6 (11.9)	13 (81.25)	31.1 (3.0)	522.7 (369.7)	241.1 (81.2)	105.1 (56.3)	33.0 (7.5)	22.2 (7.7)	4 (25.0)	NA	NA	NA
Gouni et al. 2021 [39]	volanesorsen 300 mg Q1W	25	50.5 (9)	20 (80)	30.7 (3.8)	1046 (560)	236 (38)	64 (29)	25 (7)	33 (10)	NA	NA	NA	NA
	volanesorsen 300 mg Q2W	50	50 (11.75)	36 (72)	32.1 (6.4)	1251 (838)	267 (110)	64 (29)	25 (7)	36 (17)	NA	NA	NA	NA
	Placebo	38	54 (12.25)	30 (79)	30.3 (4.4)	1414 (1253)	279 (152)	56 (28)	24 (8)	34 (15)	NA	NA	NA	NA
Oral et al. 2022 [31]	volanesorsen 300 mg Q1W	21	46 (10)	14 (73.7)	30.9 (6.4)	1432.25 (952.25)	246 (127)	65 (32)	30 (11)	34.6 (19.3)	NA	NA	NA	NA
	Placebo	19	48 (12)	5 (26.3)	30.6 (5.3)	1838.75 (1223)	254 (120)	74 (32)	24 (8)	37.1 (20.4)	NA	NA	NA	NA
Witztum et al. 2019 [29]	volanesorsen 300 mg Q1W	33	47 (13.25)	16 (48.48)	25.9 (6.5)	2367 (1315)	NA	28 (19)	17 (4)	31.42 (15.29)	NA	NA	NA	NA
	Placebo	33	46 (12)	14 (42.42)	24.1 (4.7)	2152 (1153)	NA	28 (13)	17 (4)	28.94 (13.08)	NA	NA	NA	NA

LDL-C; Low-density Lipoprotein Cholesterol, HDL-C; High-Density Lipoprotein Cholesterol, APOC-III; Apolipoprotein C-III, PCSK-9; Proprotein convertase subtilisin/kexin type 9

To ensure the validity of the NMA, both transitivity and consistency were assessed. Transitivity was examined by comparing various clinical and methodological variables that could influence treatment efficacy, ensuring that patient demographics, disease severity, and study characteristics were similar. Consistency was evaluated through the node-splitting method, which allowed the comparison of direct and indirect evidence for specific treatment comparisons. Heterogeneity within treatment comparisons and overall inconsistency between designs were evaluated using I^2 and Q tests. The treatment ranking probabilities were estimated with the surface under the cumulative ranking curve (SUCRA). A *P* value of less than 0.05 was considered statistically significant.

Results

Search results

The search found 4093 results across the different databases, 530 duplicates were omitted, and 2702 were considered ineligible by Covidence automation tools, leaving 861 records for title and abstract screening. Of these, 827 records were excluded, leaving 34 studies for full-text screening. Of them, 25 were excluded, and nine studies [18–20, 25, 26, 37–40] were included in the review, followed by a new study [41] that was published after finishing the search, ending up with ten studies [18–20, 25, 26, 37–41]. The PRISMA flow diagram records search and selection are discussed in (Fig. 1).

Characteristics of included studies

There were 9 RCTs [18–20, 25, 26, 37–40] with 1,129 patients included in this review. Another RCT was included after the June 15th, 2024 update [41]. No new studies were found during the November 22nd, 2024 update. Four of these studies investigated the effects of volanesorsen [18, 25, 26, 38], three examined the impact of Plozasiran [19, 37, 40], and the remaining three studied olezarsen [20, 39–41]. A complete overview of the summary and baseline characteristics of included RCTs are presented in (Tables 1 and 2, respectively).

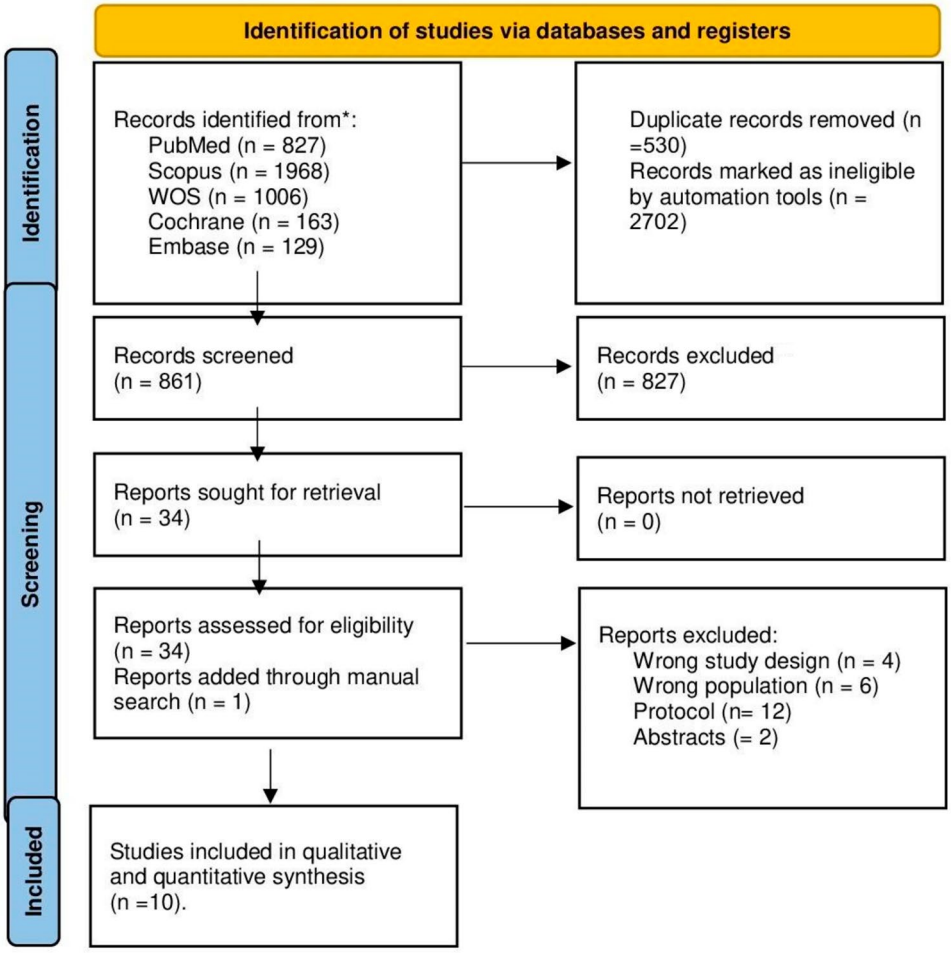

Fig. 1 PRISMA Flow Diagram

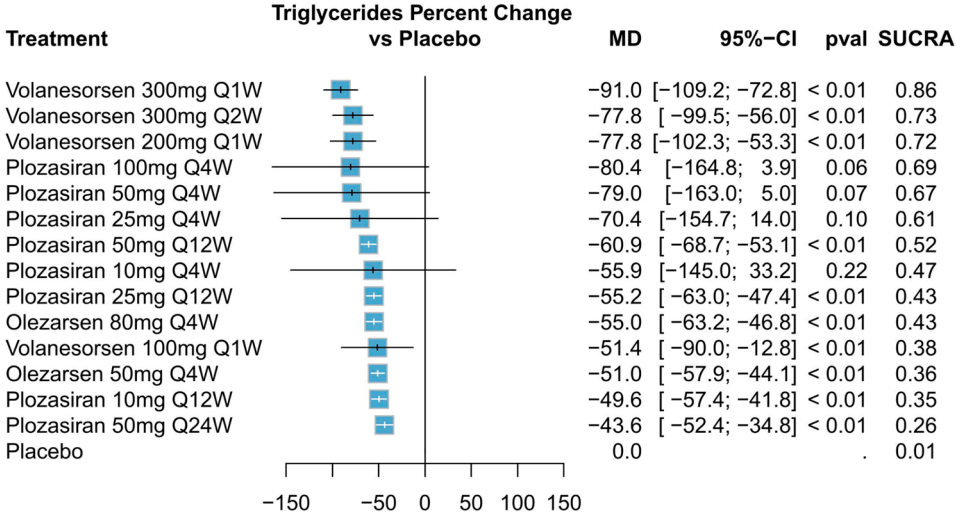

Fig. 2 Forest plot of triglyceride levels percent change

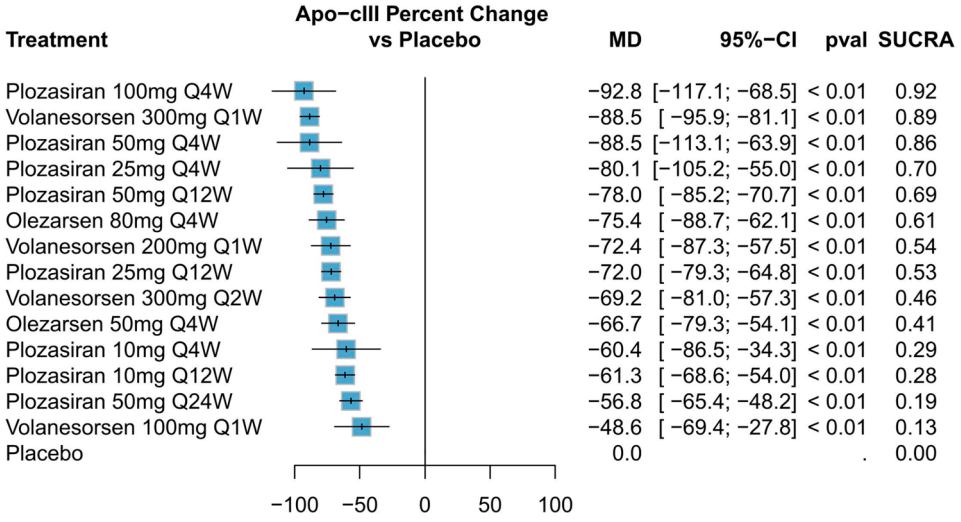

Fig. 3 Forest plot of apolipoprotein CIII levels percent change

Risk of bias and quality assessment

Nine studies showed a low risk of bias (ROB) [18–20, 25, 37–41]. On the other hand, one study showed some concerns [26]. Figure S1 provides more detailed information on ROB assessment. The quality of evidence is illustrated via the GRADE instructions (Table S2).

Efficacy outcomes

Serum TG level

Compared to placebo, volanesorsen at various doses exhibited the most significant percent reduction in TG levels, with 300 mg Q1W dosing having the highest probability of ranking first (MD = -91.0%, 95% CI: -109.2%, -72.8%; $P < 0.0001$). Plozasiran also demonstrated a significant decrease in serum TG level at various doses, with 50 mg Q12W having the most statistically significant profound reduction in serum triglyceride level (MD = -60.9, 95% CI: -68.7; -53.1, $P < 0.01$). Although the plozasiran regimens of 100 mg, 50 mg, and 25 mg dosing Q4W showed higher triglyceride reduction than the 50 mg Q4W regimen, there is significant variability with a wide CI, rendering them not statistically significant. Olezarsen at 80 mg and 50 mg, Q4W also resulted in a significant reduction in serum TG (MD of -55.0% (95% CI: -63.2%, -46.8%; $P < 0.0001$), (MD = -51.0% (95% CI: -57.9%, -44.1%; $P < 0.0001$), respectively (Fig. 2). The heterogeneity of pooled results was low ($I^2 = 0\%$, $P = 0.9746$).

APOC3 serum level percent change

All the ASO drugs showed a significant decrease in APOC3% change with volanesorsen at 300 mg Q1W and plozasiran 100 mg Q4W showing the highest ranking (MD = -88.5% (95% CI: -95.9%, -81.1%; $P < 0.0001$), (MD = -92.5% (95% CI: -116.9%, -68.1%; $P < 0.0001$),

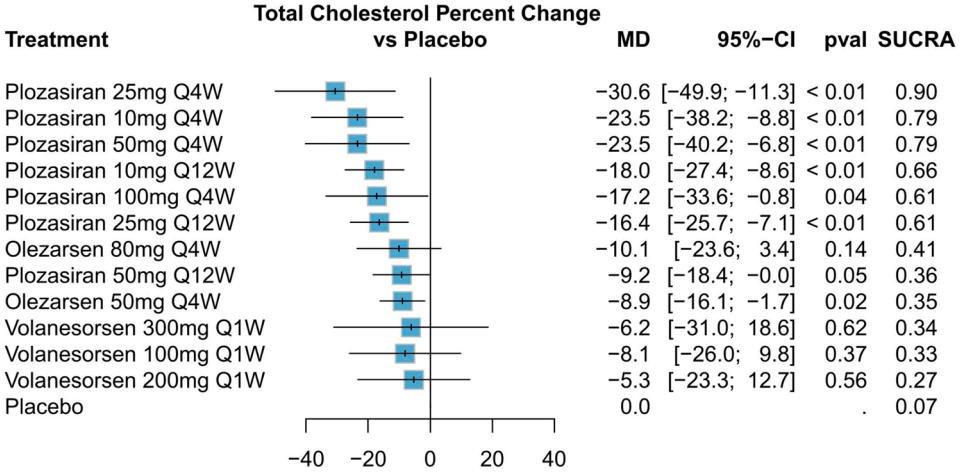

Fig. 4 Forest plot of total cholesterol levels percent change

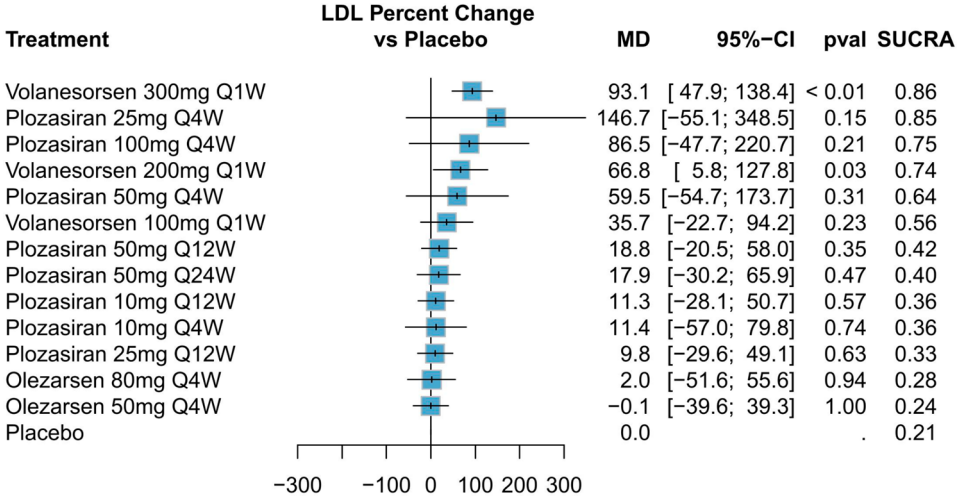

Fig. 5 Forest plot of LDL levels percent change

respectively (Fig. 3). The heterogeneity of pooled results was low (I^2 = 0%, P = 0.9245).

Total cholesterol serum level percent change

Plozasiran at all doses demonstrated a significant decrease in TC level, with the 25 mg Q4W dosing exhibiting the most significant reduction with an MD of -30.6% (95% CI: -49.9%, -11.3%; P = 0.0019). Olezarsen at 50 mg Q4W also showed a significant reduction with an MD of -8.9% (95% CI: -16.1%, -1.7%; P = 0.0154). Volanesorsen, at all doses, failed to achieve a statistically significant decrease in TC level (Fig. 4). The heterogeneity of pooled results was low (I^2 = 0%, P = 0.9904).

LDL serum level percent change

Most of the ASO drugs did not increase serum LDL levels except volanesorsen at 300 mg and 200 mg Q1W, which exhibited a significant increase in serum LDL levels (MD 93.1% (95% CI: 47.9%, 138.4%; P < 0.0001), (MD 66.8%, 95% CI: 5.8%, 127.8%; P = 0.0319), respectively (Fig. 5). The heterogeneity of pooled results was high (I^2 = 79.7%, P < 0.0001).

HDL serum level percent change

All the ASO drugs significantly increased the serum HDL level with plozasiran at 50 mg Q4W and 100 mg Q4W dosing, demonstrating the highest ranking (MD 84.8%, 95% CI: 46.3%, 123.3%; P < 0.0001), (MD 81.8%, 95% CI: 47.3%, 115.3%; P < 0.0001), respectively (Figure SF1). The heterogeneity of pooled results was moderate (I^2 = 64.2%, P = 0.0067).

Non-HDL serum level percent change

Most of the ASO drugs showed a statistically significant reduction in non-HDL. With plozasiran at 50 mg, Q4W exhibited the most significant effect estimate (MD -39.4% (95% CI: -62.1%, -16.7%; P = 0.0007) (Figure SF2). The

heterogeneity of pooled results was moderate (I^2 = 51%, P = 0.0379).

VLDL serum level percent change

Volanesorsen at 200 mg Q1W showed the highest reduction in VLDL levels with an MD of -120.3% (95% CI: -191.4%, -49.1%; P = 0.0009). Other significant reductions were observed with volanesorsen at 300 mg Q1W, volanesorsen at 100 mg Q1W, and plozasiran at 100 mg Q4W (Figure SF3). The heterogeneity of pooled results was high (I^2 = 89.5%, P < 0.0001).

ApoB serum level percent change

Plozasiran at 50 mg Q12W showed the highest reduction in ApoB levels with an MD of -17.0% (95% CI: -23.9%, -10.1%; P < 0.0001). Significant reductions were also noted with plozasiran at 25 mg Q12W, olezarsen at 50 mg Q4W, and plozasiran at 10 mg Q12W (Figure SF4). The heterogeneity of pooled results was low (I^2 = 0%, P = 0.4560). The league tables and the network plots for all efficacy outcomes are included in the Supplementary Material (Figures SL1-SL8 and SN1-SN8, respectively).

Safety outcomes

None of the treatments showed a statistically significant increase in the risk of overall adverse events (Fig. 6), treatment-related adverse events (Figure SF5), or serious adverse events (Figure SF6) compared to placebo. However, volanesorsen at 300 mg Q2W increased the risk of adverse events leading to drug discontinuation (RR = 4.6, 95% CI: 1.5, 14.2; P = 0.009) (Figure SF7). In addition, volanesorsen at 300 mg both Q1W and Q2W dosing significantly increased the risk of injection reactions (RR = 8.4, 95% CI: 3.8, 18.4, P < 0.0001; RR = 7.7, 95% CI: 3.5, 16.9, P < 0.0001, respectively) and thrombocytopenia (RR = 3.1, 95% CI: 1.8, 5.4, P < 0.0001; RR = 4.4, 95% CI: 1.4, 14.2, P = 0.014, respectively) (Fig. 7A and B, respectively). The heterogeneity was insignificant for most safety outcomes except for treatment-related adverse events, which showed high heterogeneity (I^2 = 87.2%, P = 0.0052). All safety outcome league tables and network plots are included in the Supplementary Material (SL9-SL14 and SN9-SN14, respectively).

Discussion

ASOs have emerged as a potential treatment for HTG due to their ability to target APOC3 mRNA. Although several clinical trials have recently evaluated their safety and efficacy, no studies have compared the efficacy and safety of the different ASOs and their various regimens. This systematic review and NMA analyzed data from 10 RCTs conducted between 2015 and 2024 involving 1,129 patients treated with volanesorsen, olezarsen, or plozasiran at different dosage regimens.

Among various doses of volanesorsen, volanesorsen 300 mg Q1W was the most effective regimen for reducing TG by 91% in patients with HTG compared to placebo. Although plozasiran 50 mg Q12W was second to all volanesorsen regimens in reducing TG, thrombocytopenia and injection site reactions associated with frequent dosing of volanesorsen make plozasiran 50 mg Q12W a more favorable option with a better safety profile and convenient dosing schedule. However, this relative discrepancy in medication effects should be considered with caution. Network meta-analyses have inevitable variability in baseline characteristics among the included studies and, subsequently, the indirectly compared medications, which could influence the outcomes.

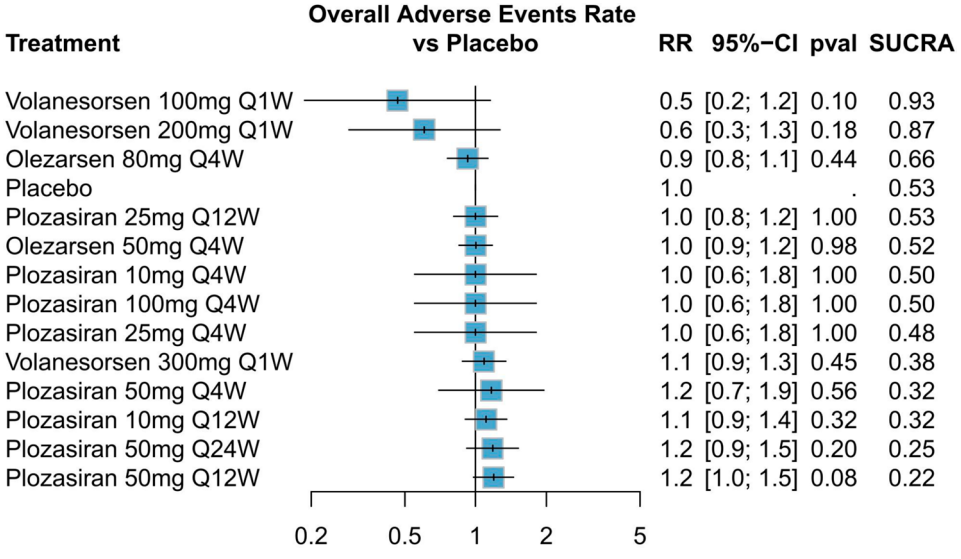

Fig. 6 Forest plot of Overall Drug Adverse Events Rate

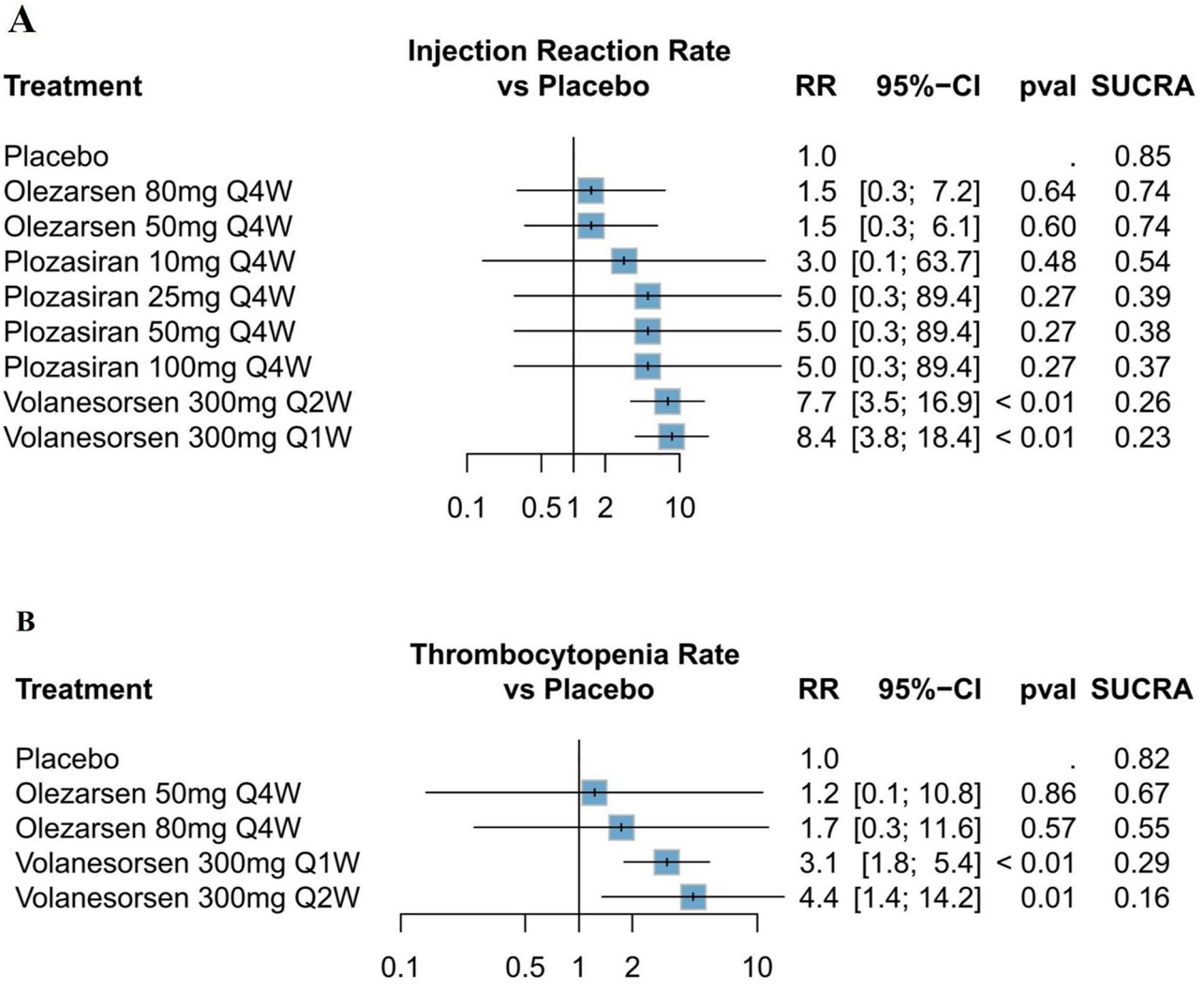

Fig. 7 Forest plot of **A** Injection Reaction; and **B** Thrombocytopenia Rates

However, heterogeneity was low across the included studies in TG levels. The thrombocytopenia observed with volanesorsen could be attributed to off-target effects of the volanesorsen shRNA, immune-mediated damage or suppression of bone marrow cells, direct toxic effects of the ASO on megakaryocytes, or immune activation through complement pathways and toll-like receptors. Therefore, volanesorsen can be recommended in cases of severe HTG or those at risk of acute pancreatitis or high TG-related cardiovascular diseases [42–44].

Compared to existing HTG therapies, the volanesorsen 300 mg Q1W effect on TG has shown a remarkable advance over the 28% reduction recorded in a previous trial that combined niacin and simvastatin in patients with ASCVD and low HDL. Similarly, plozasiran, reducing TG by 60.9%, outpaces the 22% reduction observed with fenofibrate and simvastatin trials in type 2 diabetes mellitus (DM) patients and the 18% reduction seen with evolocumab and statin combination trials. Interestingly, plozasiran surpasses the 18.3% reduction in TG seen with icosapent ethyl and statin combination trials. Hence, volanesorsen and plozasiran can be promising adjunct therapies to reduce triglycerides when used alongside statins or fibrates with or without other therapies, particularly when these treatments are insufficient or not well-tolerated. However, cardiovascular and pancreatic outcome trials are essential to position such a regimen within the existing treatment paradigm for HTG [8, 9, 45, 46].

In conditions where APOC3 and TRL are significant concerns, such as familial chylomicronemia syndrome and mixed dyslipidemia, the efficacy of plozasiran 100 mg Q4W stands out. It reduces APOC3 by 92.5%, surpassing the volanesorsen 300 mg Q1W results. Therefore, plozasiran can lower cardiovascular risk in these patient populations [17].

Lowering TC is crucial for patients at high risk for ASCVD to reduce their risk of cardiovascular events,

including MI and stroke, both fatal and nonfatal [7]. In this analysis, plozasiran 25 mg Q4W was the top choice when managing conditions where elevated TC is a significant risk, such as familial hypercholesterolemia or ASCVD. This regimen outstrips the 25% and 18% reduction reported in two previous RCTs with high-dose atorvastatin and pravastatin, respectively [11, 47]. These findings suggest that plozasiran may be superior to statins in reducing TC, especially in mixed dyslipidemia. Olezarsen 50 mg Q4W is the next best alternative to plozasiran, offering a notable but slightly less reduction in TC. On the other hand, volanesorsen did not affect TC.

The results show that the 120.3% and 104.4% reduction observed in VLDL by volanesorsen 200 mg Q1W and 300 mg Q1W, respectively, establishes this regimen as optimal for conditions like Hyperlipoproteinemia Type V, where elevated VLDL and chylomicrons increase the risk of pancreatitis and cardiovascular diseases. Plozasiran 100 mg Q4W also reduced VLDL, although to a lesser extent. The inconsistency in the effect size between volanesorsen 200 mg Q1W and 300 mg Q1W is likely due to the smaller sample size in the 200 mg Q1W group ($n = 15$) compared to the 300 mg Q1W group ($n = 142$), which is evident in the wider 95% CI for the 200 mg Q1W dose compared to the 300 mg Q1W. Nonetheless, a critical drawback is the consistent increase in LDL levels observed with both doses of volanesorsen, with a 66.8% and 93.1% increase in the 200 mg Q1W and 300 mg Q1W groups, respectively. Such findings raise a major concern for using these drugs in patients with a high risk of LDL-associated cardiovascular diseases such as familial combined hyperlipidemia and ASCVD. Instead, plozasiran 100 mg Q4W is recommended for these patients due to its lack of effect on LDL [48–52]. Notably, statins remain the drugs of choice for strict LDL management, with a 50% reported reduction in LDL [53, 54].

Regarding ApoB reduction, plozasiran 50 mg Q12W was the leading therapeutic option, which would be advantageous in conditions like familial hypercholesterolemia, mixed dyslipidemia, DM, ASCVD, and metabolic syndrome [55–57].

Among the three drugs, plozasiran is the most promising for HDL and non-HDL management, whether at 50 mg or 100 mg Q4W, where it boosts HDL outstripping the increase observed in statin combination with alirocumab in high cardiovascular risk patients. The lower plozasiran dosage reduces non-HDL lipoproteins, including atherogenic LDL, VLDL, and intermediate-density lipoprotein (IDL). This regimen is highly beneficial for HTG, lowering the atherogenic burden by removing cholesterol from arterial walls. However, its scope is limited in ASCVD patients, as it does not lower LDL, a crucial component in ASCVD pathogenesis [58–61].

Strengths and limitations

To the authors' knowledge, this is the first NMA to compare the safety and efficacy of the three ASO ApoC3 inhibitors. The study adopted the PRISMA guidelines and applied the GRADE system to estimate the robustness of the evidence. While NMA allows for indirect comparisons, these comparisons may be less reliable than direct head-to-head trials due to potential differences in study designs, patient populations, or baseline characteristics that can introduce bias.

The low heterogeneity among the primary outcomes suggests consistent and reliable treatment effects on TG, APOC3, and TC. In contrast, the moderate heterogeneity for HDL and non-HDL and the severe heterogeneity for LDL and VLDL reveal some substantial variability that may affect the reliability and generalizability of these outcomes. In addition, the authors could not perform sensitivity analysis to detect the source of heterogeneity due to the low number of studies represented within each arm. Notably, the high number of variable arms at baseline may contribute to this variability, warranting a careful interpretation of the results.

Implications for future research and clinical relevance

The study incorporated a new relevant study published after the initial search, ensuring the most up-to-date evidence was included in the analysis. However, The included studies had differing follow-up periods. Some studies weren't long enough to fully detect the long-term safety and efficacy outcomes. Therefore, future research should confirm the three medications' true and long-term effect estimates on these outcomes. The ASOs have beneficial clinical usage concerning patients with HTG who are not responding to available medications; by normalizing the TG levels in those patients, the risk of related clinical outcomes such as pancreatitis can be reduced significantly, in addition to the favorable effects on other lipid profile parameters which can significantly reduce the ASCVD risk.

Conclusion

In this systematic review and meta-analysis, ASOs significantly reduce TG, APOC3, and TC in patients with HTG. Among these, volanesorsen exhibited the most profound reductions in TG, APOC3, and VLDL. At the same time, plozasiran was superior in reducing TC, ApoB, and increasing HDL, which can help patients with severe HTG who are not responding to currently available medications. The safety of ASOs was generally acceptable, although volanesorsen, particularly at higher doses regimens, was associated with increased LDL levels, injection site reactions, and thrombocytopenia. Future RCTs with longer follow-up periods are needed to confirm the results, conduct direct comparisons with

other available medications, and focus on clinical outcomes, such as cardiovascular ones.

Abbreviations

HTG	Hypertriglyceridemia
MI	Myocardial infarction
ASCVD	Atherosclerotic cardiovascular disease
TG	Triglycerides
TRLs	Triglyceride-rich lipoproteins
APOC3	Apolipoprotein C3
VLDL	Very low-density lipoprotein
LDL	Low-density lipoprotein
ASO	Antisense oligonucleotide
DM	Diabetes mellitus
ApoB	Apolipoprotein B
TC	Total cholesterol
HDL	High-density lipoprotein
NMA	Network Meta-analysis
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	Randomized controlled trial
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
CI	Confidence interval
RR	Risk ratios
SUCRA	Surface under the cumulative ranking curve

Supplementary Information

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Supplementary Material 1

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None.

Author contributions

A.M. conceived the idea. K.A., A.M., and B.A. designed the research workflow. K.A. searched the databases. A.A., K.Al., S.T., and M.R.A screened the retrieved records, and K.A. resolved the conflicts. A.A., K.Al., S.T., and M.R.A extracted relevant data, assessed the quality of evidence, and A.M. resolved the conflicts. Q.N. performed the analysis. A.M., Q.N., and A.A.M. wrote the initial manuscript. K.A. and A.M. wrote the final manuscript. B.A. and J.M supervised the project. All authors have read and agreed to the final version of the manuscript.

Data availability

Data is provided within the manuscript and supplementary information files.

Declarations

Competing interests

The authors declare no competing interests.

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