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Efficacy and safety of antisense oligonucleotide therapies targeting APoC-III in patients with severe hypertriglyceridemia: a meta-analysis of randomized controlled trials

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Abstract

Hypertriglyceridemia (HTG) increases cardiovascular and pancreatitis risk. Antisense oligonucleotide (ASO) therapies like volanesorsen and olezarsen target ApoC-III mRNA to reduce ApoC-III, enhancing lipoprotein lipase activity and lowering triglycerides (TGs). This meta-analysis evaluates the efficacy and safety of these ASOs in severe HTG. A systematic review (PROSPERO: CRD42024577110) was conducted following PRISMA, sourcing studies from PubMed, Scopus, Cochrane CENTRAL, and ClinicalTrials.gov until July 2024. Randomized controlled trials (RCTs) involving severe HTG (200 mg/dL) treated with volanesorsen or olezarsen *vs.* placebo were included. Data were synthesized using a random effects model in RevMan 5.4, and bias was assessed with the Cochrane tool. Of 31 identified articles, 9 RCTs (341 patients treated with ASOs, 209 controls) were included. ASOs significantly reduced TG levels [mean difference (MD): -53.72; 95% confidence interval (CI): -77.04 to -30.40; p<0.00001]. Reductions were also seen in very low-density lipoprotein cholesterol (MD: -55.76; p<0.00001), ApoC-III (MD: -74.78; p<0.00001), and APOB48 (MD: -69.45; p<0.00001). Olezarsen uniquely reduced APOB (MD: -15.60; p<0.00001). Non-high-density lipoprotein cholesterol (HDL-C) decreased (MD: -23.25; p<0.00001), while HDL-C increased (MD: +42.14; p<0.00001). Volanesorsen was linked to higher low-density lipoprotein-cholesterol (MD: +62.74; p=0.004). For safety, local injection reactions, thrombocytopenia, and nausea were more common with volanesorsen. Acute pancreatitis occurred only in the placebo group (relative risk: 0.15; p=0.0004), indicating ASO protection. This meta-analysis confirms that ASOs effectively lower TGs and improve lipid profiles in severe HTG.

Key words: hypertriglyceridemia, antisense oligonucleotides, cardiovascular risk.

Introduction

Triglycerides (TGs) are vital lipids that serve as the body's primary energy reservoir and are crucial for various physiological functions. They originate from three main sources: dietary intake, liver synthesis, and adipose tissue mobilization. Dietary TGs are hydrolyzed by pancreatic lipase and absorbed by enterocytes as chylomicrons, which transport these TGs to peripheral tissues. Lipoprotein lipase (LPL), located on the capillary endothelium in muscle and adipose tissue, hydrolyzes TGs for storage and metabolism, a process activated by Apo-CII on chylomicrons and very low-density lipoproteins (VLDLs) [1-3].

The liver synthesizes TGs from fatty acids or carbohydrates, which are either stored, or released into the bloodstream as VLDLs, where they undergo LPL-mediated hydrolysis in peripheral tissues. Additionally, hormone-sensitive lipase in adipose tissue mobilizes stored TGs, contributing to blood TG levels [4].

Apolipoproteins, particularly ApoC-III, play a significant role in regulating TG metabolism. ApoC-III, a hydrophobic protein produced by the liver and encoded by the ApoC-III gene on chromosome 11q23.3, inhibits LPL activity by competing with Apo-CII for binding sites on chylomicrons and VLDLs. This inhibition leads to reduced TG hydrolysis, contributing to elevated serum TG levels, a condition known as hypertriglyceridemia [5-7]. It also influences triglyceride-rich lipoprotein (TRL) remnant clearance by the liver and impacts the conversion of VLDL to IDL and HDL through hepatic lipase [8-13].

ApoC-III not only blocks LPL binding but also interacts with LPL itself, altering its structure and further reducing its catalytic efficiency, exacerbating hypertriglyceridemia [7]. Mutations that impair ApoC-III gene function result in lower ApoC-III levels, reducing serum TGs. This discovery prompted the development of antisense oligonucleotide (ASO) therapies targeting ApoC-III to lower TG levels [14].

Volanesorsen was the first antisense oligonucleotide (ASO) specifically designed to inhibit the expression of apolipoprotein C-III (ApoC-III), as introduced by Mark J. Graham and colleagues [15]. ASO therapies, such as Volanesorsen and Olezarsen, operate by binding to ApoC-III mRNA, resulting in the formation of a DNA/RNA duplex that is then degraded by RNAse H. This process leads to a reduction in ApoC-III levels, thereby enhancing lipoprotein lipase (LPL) activity and contributing to lower serum triglyceride (TG) levels [16].

Importantly, elevated triglyceride-rich lipoproteins and their remnants are increasingly recognized as independent risk factors for atherosclerotic cardiovascular disease (ASCVD), including coronary artery disease, ischemic stroke, and peripheral arterial disease [17]. Epidemiological and

genetic studies have shown that even modest reductions in TG levels can significantly decrease cardiovascular risk, particularly in patients with residual hypertriglyceridemia despite statin therapy [18]. Therefore, TG-lowering interventions targeting ApoC-III offer not only biochemical benefits but also potential cardiovascular protection [19].

Despite significant research on the effectiveness of ASO therapies in reducing TGs, there has been no specific meta-analysis conducted to evaluate effectiveness of Olezarsen. Most previous meta-analyses have focused solely on Volanesorsen alone [20,21], leaving a gap in understanding the combined effects of these therapies on severe hypertriglyceridemia. Given the emergence of new studies, our meta-analysis aims to assess both the efficacy and safety of ASO treatments targeting ApoC-III in patients with severe hypertriglyceridemia, integrating the latest data to enhance the robustness of our findings.

Methods

This meta-analysis was registered with PROSPERO, The International Prospective Register of Systematic Reviews (Registration ID CRD42024577110), and was conducted following the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)* guidelines to ensure transparency and comprehensive reporting of the review process [22].

Search strategy and selection criteria

A systematic search was performed in the following electronic databases: PubMed, Scopus, the Cochrane Central Register of Controlled Trials (CENTRAL), and ClinicalTrials.gov from inception through August 1, 2024. In addition to database searches, the reference lists of relevant studies were also screened to identify any additional sources. The search strategy utilized a combination of keywords and MeSH terms such as *Volanesorsen*, *Olezarsen*, *ISIS 304801*, *ISISApoCIIIRx*, *IONIS-ApoCIIIRx*, *IONIS-APOCIII-LRx*, *AKCEA-APOCIII-LRx*, *antisense oligonucleotide*, *hypertriglyceridemia*, *familial chylomicronaemia syndrome*, and *anti-ApoC-III mRNA*. A detailed search strategy is mentioned in the supplementary file.

The inclusion criteria for eligible studies were defined as follows: Population: Adult patients diagnosed with severe hypertriglyceridemia (HTG), characterized by triglyceride levels of 200 mg/dl; Intervention: Studies must involve the use of Volanesorsen or Olezarsen for lowering triglyceride levels; Comparator: Placebo; and Study type: Only randomized controlled trials (RCTs) were considered to ensure the highest level of evidence for the assessment of treatment efficacy.

Study selection and data extraction

The search results were imported into Rayyan, a web-based tool for systematic review management [23]. After removing duplicates, two reviewers (AM and AQ) independently screened the titles and abstracts of the studies. Full texts of potentially eligible studies were reviewed to confirm inclusion, with discrepancies between reviewers resolved through discussion or with the assistance of a third reviewer (AS) when necessary.

For data extraction, two reviewers (ZK and HS) independently populated a pre-piloted data extraction sheet. The extracted data included study characteristics such as the author, year, sample size, study design, and study duration, as well as patient characteristics like age, sex, baseline triglyceride levels, and comorbid conditions. The outcomes of interest included the primary efficacy outcome, which was the mean percentage change in triglyceride (TG) levels from baseline in patients receiving Volanesorsen or Olezarsen compared to placebo. Secondary outcomes encompassed changes in ApoC-III, LDL-C, HDL-C, VLDL-C, non-HDL-C, Apo-B, Apo-B48, Apo-A1, chylomicron TG levels, and safety outcomes which assessed the incidence of adverse events, including injection site reactions, muscle-related side effects, reduction in platelet count, acute pancreatitis, abdominal pain, nausea, fatigue, headache, abnormal liver or renal function, and hypersensitivity reactions.

Risk of bias assessment

The quality of included RCTs was evaluated using the Cochrane Risk of Bias Tool (RoB 2.0), which assesses potential bias in five domains: randomization process, blinding and protocol deviations, loss of outcome data, outcome assessment, and selection of reported results. Based on this tool, trials were categorized as having low, some concerns, or high risk of bias [24].

Data synthesis

The meta-analysis was performed using RevMan 5.4 software (The Cochrane Collaboration, Copenhagen, Denmark) under a random effects model [25]. Results were expressed as the mean difference (MD) with a 95% confidence interval (CI) for continuous outcomes, while risk ratios (RR) with a 95% CI were used for safety outcomes. The I^2 statistic was applied to assess heterogeneity among studies. Low heterogeneity was defined as an I^2 value less than 25%, moderate heterogeneity as a value of 25–50%, and high heterogeneity as a value larger than 50%.

Results

Study selection and characteristics of included studies

After removing duplicate results, the search yielded 31 articles. Of these, 20 were excluded due to being irrelevant based on their title and/or abstract, being reviews/comments/case reports, or lacking the required data. In total, 9 studies [26-34] involving 341 patients treated with Volanesorsen or Olezarsen and 209 patients receiving a placebo were included in the final analysis (Figure 1). Five studies [26,31-34] administered Volanesorsen in addition to maximal standard therapy. One study [30] featured both a monotherapy arm (Volanesorsen alone) and an arm with Volanesorsen as add-on therapy. Three studies [27-29] used Olezarsen as an add-on treatment. All 9 studies were randomized controlled trials, and the key characteristics of the study populations are presented in Table 1.

Risk of bias in included studies

Three RCTS were found to be at a low risk of bias, while the rest were rated as having some concerns of bias (*Supplementary Figure 1*).

Synthesis of results

Triglyceride reduction

The nine studies [26-34] included in the analysis showed a significant reduction in triglycerides with ASO ApoC-III inhibitors in comparison to placebo (MD: -53.72%; 95% CI: -77.04%, -30.40%; $p<0.00001$). The results are consistent across the sub-groups, depicting a significant reduction with Volanesorsen (-59.06%; 95% CI: -95.32%, -22.79%) and with Olezarsen (-50.04%; 95% CI: -60.27%, -39.81%) as shown in Figure 2. Heterogeneity for triglyceride reduction was high (I^2=98%).

VLDL-C level reduction

There was a significant reduction in VLDL-C levels (MD: -55.76; 95% CI: -59.82%, -51.71, $p<0.00001$) with ASO ApoC-III inhibitors in comparison to placebo. The results are consistent across the sub-groups, depicting a significant reduction with Volanesorsen (-62.97%; 95% CI: -74.15%, -51.80%) and with Olezarsen (-52.47%; 95% CI: -60.27%, -44.67%) as shown in *Supplementary Figure 2*. Heterogeneity for VLDL-C reduction was low (I^2=2%).

APO-CIII level reduction

A significant reduction was observed in Apo-CIII levels (MD: -74.78%; 95% CI: -78.94%, -70.61%; p<0.00001) with ASO ApoC-III inhibitors in comparison to placebo. The results are consistent across the sub-groups, depicting a significant reduction with Volanesorsen (-78.59%; 95% CI: -84.87%, -72.31%) and with Olezarsen (-71.63%; 95% CI: -76.01%, -67.24%) as shown in *Supplementary Figure 3*. Heterogeneity for APO-CIII level reduction was moderate (I^2=33%).

APO-B48 level reduction

The analysis showed a significant reduction in APO-B48 levels (MD: -69.45%; 95% CI: -92.40%, -46.51%; p<0.00001) with ASO ApoC-III inhibitors in comparison to placebo. The results are consistent across the sub-groups, depicting a significant reduction with Volanesorsen (-72.98%; 95% CI: -100.51%, -45.46%) and with Olezarsen (-58.70%; 95% CI: -108.40%, -8.99%). Heterogeneity for APO-B48 level reduction was high (I^2=75%).

APO-B level reduction

A significant reduction in Apo-B levels was not observed with ASO ApoC-III inhibitors (MD: -5.37%; 95% CI: -14.51%, 3.76%; p=0.25) in comparison to placebo. However, a substantial reduction in APO-B levels was observed in the Olezarsen subgroup (MD: -15.60%; 95% CI: -21.04%, -10.17%). Heterogeneity for APO-B level reduction was high (I^2=80%).

Non-HDL cholesterol level reduction

Non-HDL cholesterol levels were reduced (MD: -23.25%; 95% CI: -29.18%, -17.31%; p<0.00001) with ASO ApoC-III inhibitors in comparison to placebo. The results are consistent across the sub-groups, depicting a significant reduction with Volanesorsen (-24.06%; 95% CI: -37.94%, -10.18%) and with Olezarsen (-21.97%; 95% CI: -27.08%, -16.85%). Heterogeneity for non-HDL level reduction was moderate (I^2=45%).

Chylomicron triglyceride level reduction

Three studies [26,32,33] demonstrated a considerable decrease in chylomicron triglyceride levels (MD: -86.56; 95% CI: -104.11%, -69.01; p<0.00001) with Volanesorsen in comparison to placebo. Heterogeneity for chylomicron TG level reduction was low (I^2=1%).

HDL-C level increase

In parallel, we observed a significant increase in HDL-C levels (MD: +42.14%; 95% CI: +35.98%, +48.30%; p<0.00001) with ASO ApoC-III inhibitors in comparison to placebo. The results are consistent across the sub-groups, depicting a significant increase with Volanesorsen (+46.49%; 95% CI: +38.64%, +54.34%) and with Olezarsen (+37.02%; 95% CI: +29.19%, +44.85%) as shown in *Supplementary Figure 4*. Heterogeneity for HDL-C level increase was low (I^2=23%).

APO-A1 level increase

A significant increase in APO-A1 levels was also noted (MD: +13.03; 95% CI: +10.48%, +15.59; p<0.00001) with ASO ApoC-III inhibitors in comparison to placebo. The results are consistent across the sub-groups, depicting a significant increase with Volanesorsen (+12.44%; 95% CI: +8.53%, +16.36%) and with Olezarsen (+13.48%; 95% CI: +10.10%, +16.86%). Heterogeneity for APO-A1 level increase was negligible (I^2=0%).

LDL-C level changes

A significant increase in LDL-C levels was observed (MD: +62.74; 95% CI: +19.57%, +105.90; p<0.004) in the Volanesorsen subgroup. However, no significant change in LDL-C levels (MD: -2.83%; 95% CI: -14.56%, +8.90; p=0.64) was observed with Olezarsen. Overall, a significant increase in LDL-C levels was observed (MD: +36.79; 95% CI: +9.75%, +63.83; p=0.008) with ASO ApoC-III inhibitors in comparison to placebo as shown in *Supplementary Figure 5*. Heterogeneity for LDL-C level increase was high (I^2=91%).

Safety outcomes

Six studies [26-30,33] reported data on the incidence of local injection site reactions (*Supplementary Figure 6*), which were mostly mild and significantly more common with Volanesorsen (RR: 9.93, 95% CI: 2.35, 41.90; p=0.0003, I^2=13%) in comparison to placebo. Moreover, treatment with Volanesorsen was associated with a higher rate of thrombocytopenia (RR: 4.36, 95% CI: 1.78, 10.72; p=0.001, I^2=0%, *Supplementary Figure 7*), and nausea (RR: 4.01, 95% CI: 1.05, 15.37; p=0.04, I^2=0%, *Supplementary Figure 8*), as compared to placebo. However, there was no significant difference between Olezarsen and placebo in the rates of local injection site reactions (RR: 2.22, 95% CI: 0.85, 5.82) and thrombocytopenia (RR: 1.29, 95% CI: 0.25, 6.53). Derangements in RFTs were more common with placebo in comparison to Olezarsen (RR: 0.21, 95% CI: 0.08, 0.59; p=0.003, I^2=0%). In the four studies [26,28,32,33] included, thirteen

events of acute pancreatitis were reported in the placebo group while none with Volanesorsen and Olezarsen (RR: 0.15, 95%CI: 0.04, 0.55; p=0.0004, I^2=0%, *Supplementary Figure 9*).

Discussion

In this meta-analysis, we evaluated the efficacy and safety of antisense oligonucleotide therapies, specifically Volanesorsen and Olezarsen, targeting apolipoprotein C-III in patients with severe hypertriglyceridemia (HTG). These innovative therapies represent a focused approach to lipid regulation, with ApoC-III serving as a critical regulator of triglyceride metabolism. Unlike previous meta-analyses that focused solely on Volanesorsen, this study is the first to comprehensively evaluate the impact of both Volanesorsen and Olezarsen, providing a more complete understanding of these therapeutic options [20,21].

Summary of the key findings

Both Volanesorsen and Olezarsen show a significant reduction in triglyceride levels, which is a primary target in the treatment of hypertriglyceridemia. The significant decrease observed in both treatments underlines the potent effect of ApoC-III inhibition in enhancing the clearance of triglyceride-rich particles. Significant decrease in other lipoprotein fractions like VLDL-C, ApoB48 and non-HDL cholesterol was also observed with both therapies suggesting a broad impact on lipid metabolism, enhancing the clearance of triglyceride-rich particles from the bloodstream. We also found a significant increase in HDL-C levels, an effect that could confer additional cardiovascular protection [35]. The impact on LDL levels was mixed; Volanesorsen showed significant increases, while Olezarsen did not. This differential effect might be attributed to variations in drug design or molecular targets that influence lipoprotein particle dynamics beyond ApoC-III inhibition.

Comparison with conventional therapies

Currently available therapies such as statins, ezetimibe, fibrates, and Omega−3 fatty acids typically lower triglyceride levels by 10% to 40% [36]. In contrast, ApoC-III ASO such as Volanesorsen and Olezarsen offer significantly greater reductions, achieving up to 70-80%, which is particularly advantageous for patients with severe hypertriglyceridemia. Conventional therapies also demonstrate limited efficacy in individuals with lipoprotein lipase (LPL) impairments, whereas ApoC-III ASOs address this gap, likely through involvement of both LPL-dependent and LPL-independent pathways of triglyceride clearance [37]. Furthermore, fibrates and omega-3 fatty

acids have a minimal effect on atherogenic lipoproteins such as ApoB and non-HDL cholesterol, while ApoC-III ASOs significantly reduce these lipoproteins, providing superior cardiovascular risk reduction [14]. Fibrates, omega-3 fatty acids, and statins often cause side effects like gastrointestinal issues, muscle toxicity, and elevated LDL-C with omega-3s, limiting their long-term use [38]. In contrast, ApoC-III ASOs such as Volanesorsen and Olezarsen offer a more favorable safety profile. While Volanesorsen is associated with injection site reactions and reversible thrombocytopenia, both therapies generally present fewer risks compared to conventional treatments, with Olezarsen showing an even fewer adverse events and better safety profile, making it a safer long-term option [26,27,33,39].

Pancreatitis risk reduction

Volanesorsen has shown particular success in reducing the risk of acute pancreatitis (AP) in patients with familial chylomicronemia syndrome (FCS), up to tenfold compared to placebo [40]. This highlights its therapeutic benefit in reducing triglyceride-induced complications and is particularly valuable in clinical settings where patients present with recurrent pancreatitis due to severely elevated triglyceride levels [41].

Olezarsen, a newer ApoC-III ASO, also showed significant triglyceride reductions at higher doses, offering a promising alternative with a more favorable safety profile, including fewer cases of thrombocytopenia.

Cardiovascular implications

Another important aspect of ApoC-III inhibition is the reduction of cardiovascular and thrombogenic risk. ApoC-III plays a significant role in the atherogenic process by influencing multiple pathways, including monocyte adhesion to endothelial cells, smooth muscle cell proliferation, oxidative stress enhancement, and interactions with LDL particles that increase their atherogenic potential [42]. Elevated triglyceride-rich lipoproteins and remnants independently predict incident coronary artery disease, ischemic stroke, and peripheral arterial disease [43,44]. Thus, the robust TG reductions achieved with Volanesorsen and Olezarsen may result into meaningful reductions in atherosclerotic plaque burden, plaque vulnerability, and downstream ischemic events. Although more research is needed to establish its impact on cardiovascular events, Olezarsen's efficacy in lowering atherogenic lipids and its favorable safety profile position it as a promising therapeutic option.

However, a potentially concerning aspect to consider here is the increase in LDL-C levels with antisense therapy, driven mainly by Volanesorsen. We found a statistically significant increase in LDL-C (MD: +62.74; $p<0.004$) in the Volanesorsen group, whereas Olezarsen produced no significant change. The plausible explanation is likely related to lipoprotein remodeling. ApoC-III inhibition accelerates hepatic clearance of TRLs, thereby lowering circulating TG levels. This shift may secondarily increase the presence of LDL particles in the bloodstream [30,35]. It is also important to note that the studies included in our review did not characterize LDL particle size, which could help distinguish between larger LDL particles of de novo synthesis and small dense LDL particles that have a greater atherogenic effect [45]. However, the exact mechanism for these lipid changes remains incompletely understood. Given the atherogenic potential of increased LDL, especially in longer-term therapy, clinicians should monitor LDL-C carefully. Further long-term studies focused on cardiovascular outcomes are needed to determine whether the LDL-C increase translates into excess atherosclerotic events which could further clarify its safety profile.

Safety profile

ApoC-III ASOs demonstrate an overall favorable safety profile, yet the analysis reveals a nuanced profile for each agent. The safety profile of Olezarsen was observed to be slightly better compared to its predecessor, Volanesorsen. Injection site reactions were significantly more common with Volanesorsen, pointing to potential issues with the drug's administration that might not be as pronounced with Olezarsen. This could influence patient compliance and preference. Thrombocytopenia, a serious adverse event, was also significant with Volanesorsen but not reported for Olezarsen, indicating a need for careful monitoring of blood parameters in patients treated with Volanesorsen.

Strengths and Limitations

The current analysis represents a comprehensive systematic review and meta-analysis of the available clinical trials for the antisense oligonucleotides Volanesorsen and Olezarsen in the treatment of familial chylomicronemia syndrome. By including trials conducted across diverse geographic regions, the analysis also allows evaluation of the consistency of effects. However, as with the previously published Volanesorsen meta-analysis [21], the current review is limited by the relatively small number of available studies, which restricts the ability to perform subgroup analysis or meta-regressions to explore potential sources of heterogeneity.

The majority of the research appears to have been conducted in Western countries, with limited participation from Asian, African, or other non-Caucasian ethnic groups. This reduces the generalizability of the results to the broader global population affected by this rare disorder.

Future Recommendations

Future RCTs should aim to include participants from different racial and ethnic backgrounds to ensure generalizability across a broader patient demographic and should explore the long-term cardiovascular outcomes associated with ApoC-III inhibition, such as the incidence of myocardial infarction and stroke and if there is any mortality benefit akin to statins Additionally, head-to-head comparisons between these ApoC-III inhibitors and other emerging therapies would be valuable to determine the optimal treatment strategy for patients with severe hypertriglyceridemia.

Conclusions

In conclusion, the findings from this analysis underscore the significant efficacy of antisense oligonucleotide (ASO) inhibitors of ApoC-III, specifically Volanesorsen and Olezarsen, in lowering triglyceride levels compared to placebo. Both therapies effectively reduce atherogenic lipids, including VLDL-C, APO-CIII, and APO-B48, while enhancing HDL-C and APO-A1 levels, indicating an overall improvement in lipid profiles. Notably, Olezarsen maintains a favorable safety profile by not elevating LDL-C levels and demonstrating lower rates of thrombocytopenia, unlike Volanesorsen. Importantly, the absence of acute pancreatitis cases in the treatment groups, contrasted with multiple events in the placebo group, suggests a protective benefit against this serious complication.

In clinical practice, patients with severe hypertriglyceridemia often remain at high residual cardiovascular risk despite standard lipid-lowering therapies. By delivering profound and sustained reductions in triglycerides and remnant cholesterol, which are the key drivers of inflammation and endothelial dysfunction, ApoC-III ASOs are expected to lower the incidence of major adverse cardiovascular events, such as myocardial infarction and stroke. These results highlight the potential of ApoC-III inhibitors as valuable therapeutic options for patients with hypertriglyceridemia and related cardiovascular risks.

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Online supplementary material:
Supplementary Figure 1. Risk of Bias of included studies
Supplementary Figure 2. Changes in very low-density lipoprotein-cholesterol levels.
Supplementary Figure 3. Changes in APOC3 levels.
Supplementary Figure 4. Changes in high-density lipoprotein levels.
Supplementary Figure 5. Changes in low-density lipoprotein-cholesterol levels.
Supplementary Figure 6. Local injection site reactions.
Supplementary Figure 7. Thrombocytopenia.
Supplementary Figure 8. Nausea.
Supplementary Figure 9. Acute pancreatitis.

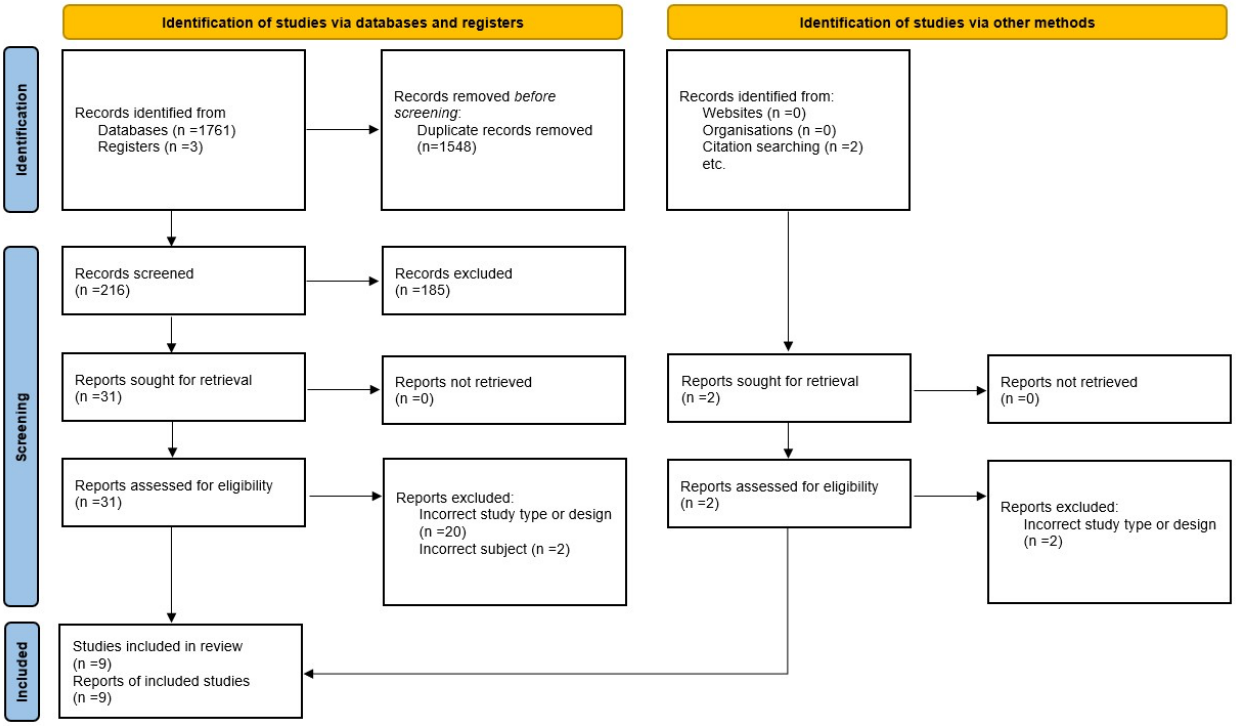

Figure 1. PRISMA flow-chart for inclusion and exclusion of studies.

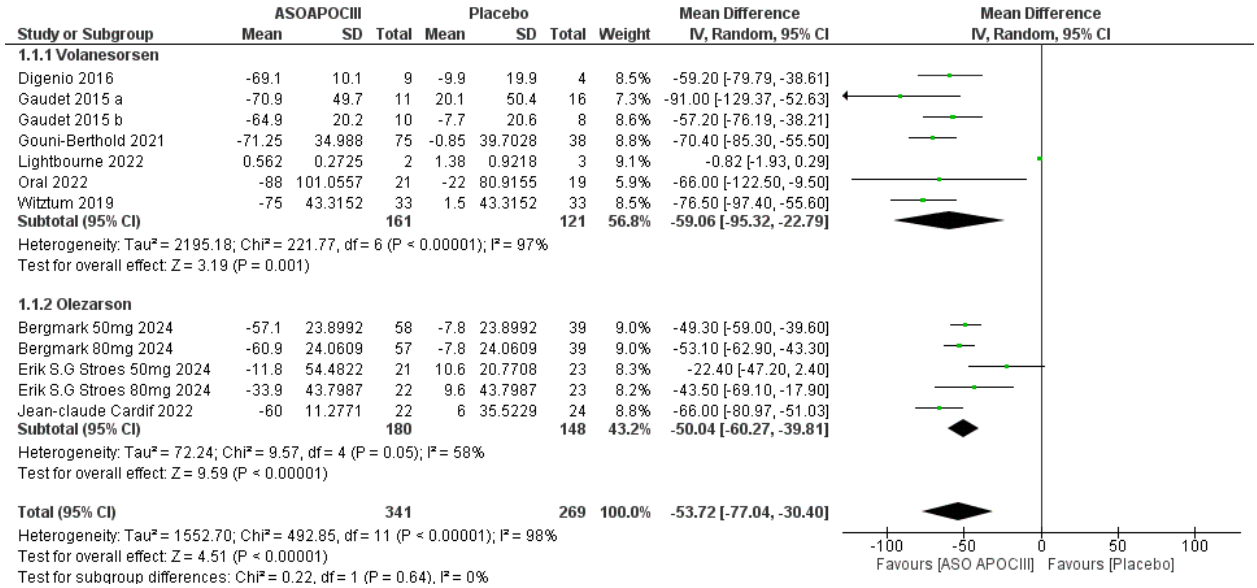

Figure 2. Changes in triglyceride levels.

Table 1. Study characteristics.

Study ID	Trial phase	Number of patients (intervention *vs.* placebo)	Age (mean + SD)	Male (%)	Patient population	Body Mass Index	Baseline TG threshold	Baseline lipid lowering therapy
Volanesorsen								
Witztum, 2019 (30)	phase 3	33 *vs*. 33	46 (20–75)	45.50	Familial chylomicronemia syndrome	25.0±5.7	750 mg/dL	Add on to LLT
Lightbourne, 2022 (31)	Phase 2	2 *vs*. 3	39 ± 11	0	Partial lipodystrophy	30.8±5.4	500 mg/dL or 200 mg/dL with hemoglobin A1c (A1c) >7%	Add on to LLT
Gaudet, 2015 (27)	Phase 2	11 *vs*. 16	50.5 (11.3)	73	Severe Hypertriglyceridemia	31.1	>350 mg/dL and <2000 mg/dL	No background LLT
Gaudet, 2015 (27)	Phase 2	10 *vs*. 8	56.0 (14.8)	70	Severe Hypertriglyceridemia	32.9	>350 mg/dL and <2000 mg/dL	Add on to fibrate
Oral, 2022 (29)	Phase 2/3	21 *vs*. 19	47(11)	11 (27.5%)	FPLD,Hypertriglyceridemia and Diabetes	30.7 (5.9)	500 mg/dL	Add on to LLT
Gouni-Berthold, 2021 (23)	phase 3	75 *vs*. 38	51 (22-73)-median and range	86 (76%)	Severe HTG (including FCS)	31.2	>500 mg/dL	Add on to LLT
Digenio, 2016 (28)	phase 2	10 *vs*. 5	56.5 (7.5)	20	HTG and type 2 diabetes	33.1	>200 mg/dL	Add on to LLT
Olezarsen								
Bergmark, 2024 (24)	2b	50mg:58 *vs*. 39 80mg: 57 *vs*. 39	62 (54-71) median and range	55.60	Moderate HTG and at high ASCVD risk or severe HTG	32.8 (8)	500 mg/dL or 150 to 499 mg/dL with elevated ASCVD risk	Add on to LLT
Stroes, 2024 (25)	Phase 3	80 mg = 22 *vs*. 23 50 mg = 21 *vs*. 23	45 (13.4)	42.42	Familial chylomicronemia syndrome	23.9 (4.7)	880 mg/dL	Add on to LLT
Cardif, 2022 (26)	Phase 2	22 *vs*. 24	63.8±7.6	30.70%	Established or at high risk of ASCVD and HTG	32.4 (4.1)	>200 mg and <500 mg	Add on to LLT