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Review Article

# Treatment of Severe Hypertriglyceridemia

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## Abstract

Elevated triglycerides are associated with an increased risk of ASCVD. Drugs that reduce triglyceride levels have not been shown to reduce ASCVD events more than statin therapy alone. Severe hypertriglyceridemia (>500 mg/dL) increases the risk of pancreatitis, but the currently available triglyceride lowering drugs have not been shown to prevent pancreatitis. While the prevalence of severe hypertriglyceridemia is rare, the burden of disease in these patients is high. Several biologic agents are currently in development for the treatment of severe hypertriglyceridemia. While several drugs have reached testing in phase 3 trials and one agent is approved in Europe for Familial Chylomicronemia Syndrome (FCS), none of these agents have been approved in the US. Further development of agents that alter the adverse outcomes associated with hypertriglyceridemia remains an important area of discovery.

**Keywords: Triglycerides; Hypertriglyceridemia; Familial chylomicronemia syndrome; Pancreatitis**

## Introduction

Elevated triglyceride levels are a known risk factor for Atherosclerotic Cardiovascular Disease (ASCVD) [1]. Multiple outcome trials combining statins with different triglyceride lowering drugs have failed to further reduce ASCVD risk [1]. As a result, triglycerides are no longer a target of drug therapy to reduce ASCVD risk. Elevated triglycerides suggest, however, that other lipid-related risk factors such as triglyceride-rich lipoproteins and lipoprotein remnants need to be evaluated to assess and manage ASCVD risk [2].

Triglyceride levels (>500 mg/dL) are a known risk factor for acute pancreatitis [3,4]. While treatment of severe hypertriglyceridemia is recommended, evidence that traditional lipid lowering drugs reduce the risk of pancreatitis is lacking. Several drugs with novel mechanisms of action directed at reducing triglyceride levels with the potential to reduce the risk of pancreatitis are in development [5]. The purpose of this review is to summarize the efficacy and safety of these drugs in the treatment of severely elevated triglycerides with the goal of preventing pancreatitis.

## Definition of Hypertriglyceridemia

Triglyceride levels are reported either as mmol/L or mg/dL. Conversion from mmol/L to mg/dL requires multiplication of the value in mmol/L by a factor of 88.57 to report the triglyceride value in mg/dL. While there are generally small variations in triglyceride levels obtained under fasting and non-fasting conditions, measuring triglyceride levels in the fasting state minimizes potential variability [1]. Triglyceride levels have historically been stratified into different categories of severity based on the risk of ASCVD (Table 1) [1,6]. Current evidence does not support the use of drugs for the treatment of moderately elevated triglyceride levels [1].

There is no agreed upon absolute triglyceride threshold above which pancreatitis risk becomes certain. In a large population study, the adjusted hazard ratio for acute pancreatitis was 1.5 and 3.2 times greater with triglyceride levels 150-499 mg/dL and ≥ 500 mg/dL, respectively, compared to triglycerides <150 mg/dL [7]. This study also observed that for every 100 mg/dL increase in triglyceride levels, the incident risk of pancreatitis increased by 4%. In studies of patients with triglyceride levels >1000 mg/dL, the incidence of acute pancreatitis has been reported to be as high as 20% to 30% [8,9]. Severely elevated triglyceride levels are defined as >500 mg/dL or >5 nmol/L (440 mg/dL) with very severe levels defined as >1000 mg/dL or >10 nmol/L (880 mg/dL) [1,3,4]. These lipid guidelines recommend intervention to reduce the risk of pancreatitis when triglyceride levels are >500 mg/dL with a greater urgency in lowering triglycerides when even more severe hypertriglyceridemia (>1000 mg/dL) exists.

## Etiology and Prevalence

Elevated triglyceride levels are most often associated with secondary causes such as diets high in fat and/or with excessive caloric intake, excessive alcohol intake, obesity, metabolic syndrome, and uncontrolled diabetes mellitus. Less frequent secondary causes include hypothyroidism, nephrotic syndrome, rheumatoid arthritis, psoriasis, and certain medications (i.e., estrogens, corticosteroids, retinoids, antiretrovirals, antipsychotics, etc.) [6]. Patients with severe hypertriglyceridemia are more likely to have a Multifactorial Chylomicronemia Syndrome (MCS) attributed to polygenic gene mutations in combination with one or more secondary causes of elevated triglycerides [10].

Familial Chylomicronemia Syndrome (FCS) results from a rare single gene mutation that results in deficiencies in one of several enzymes (i.e., lipoprotein lipase, Apo CII, etc.) responsible for clearance of chylomicrons [4]. Homozygous loss of function mutations in lipoprotein lipase result in severe elevations in plasma

**Table 1:** Classification of Triglyceride Levels [1,17].

| | |
|---|---|
| Desirable (Normal) | <150 mg/dL |
| Moderate | 150 to 499 mg/dL |
| Severe | 500 to 999 mg/dL |
| Very Severe | >1000 mg/dL |

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triglycerides (predominately as chylomicrons) that exceed 1000 mg/dL and are frequently higher [11-13]. Clinical manifestations appear in childhood or adolescence and are characterized by the development of xanthomas, lipemia retinalis, neurologic symptoms, abdominal pain, hepatosplenomegaly, and pancreatitis.

About one-third of adults in the US have elevated triglycerides (>150 mg/dL) [6]. The prevalence of adults in the US with triglycerides >500 mg/dL is estimated to 1.1%. Men, age 40 to 60 years, and Hispanics have a slightly higher prevalence of triglycerides >500 mg/dL [6]. The incidence of severe hypertriglyceridemia is estimated to occur in 1:600 individuals, while the incidence of FCS is estimated to be 1:1,000,000 [11].

## Pathophysiology

The pathophysiology of elevated triglycerides in the development of ASCVD is complex. Triglycerides are a marker of other lipid abnormalities (elevated triglyceride-rich lipoproteins) which are in turn more closely linked to atherosclerosis and increased ASCVD risk [1-4]. The specific mechanism of triglyceride-induced pancreatitis is not well defined. One proposed mechanism is that a high concentration of triglycerides hydrolyzed by pancreatic lipase results in an excessive free fatty acid concentration in the pancreas [12]. This leads to inflammation and ischemia in acinar cells and capillaries. Another proposed mechanism is that high concentrations of plasma chylomicrons lead to increased viscosity in pancreatic capillaries causing ischemia. Neither hypothesis has been clearly established as the cause of pancreatitis in the clinical setting. Pancreatitis associated with hypertriglyceridemia is often cited as being more severe than that seen with gallstones or alcohol [9].

## Triglyceride Lowering Therapy

Lifestyle interventions including diet, exercise, and weight loss can produce substantial reductions in triglycerides [12,13]. The traditional drugs used in patients with hypertriglyceridemia include the statins, fibric acid derivatives, niacin, and the omega-3 fatty acids. All of these drugs may be reasonable options alone and/or in combination in patients with severe hypertriglyceridemia. Each drug has specific limitations (i.e., adverse effects, drug interactions) that need to be considered in the treatment of specific patients. Table 2 summarizes the average effect of these drugs on specific lipid fractions [1,3,12,13]. Patients with genetic mutations leading to hypertriglyceridemia (i.e., FCS) typically do not respond well to these therapies [11].

Statins are used primarily to lower LDL-C and ASCVD risk but also typically reduce triglyceride levels by 10% to 15% [12,13]. Greater reductions (up to 30%) are achieved when baseline triglyceride levels are higher. While statins apparently inhibit synthesis of VLDL the exact cellular mechanism of triglyceride reduction is unknown. Statins are primarily used in patients with elevated triglycerides to reduce vascular risk rather than for their specific effects on triglyceride levels [3,4,13].

**Table 2:** Effect of Lipid Lowering Drugs on Lipids (% change).

| Drug Class | LDL-C Reduction | HDL-C Increase | Triglyceride Reduction |
|---|---|---|---|
| Statin | 18-65 | 5-15 | 10-30 |
| Fibrates | Variable | 2-10 | 20-50 |
| Niacin | 15-25 | 15-30 | 20-35 |
| Omega-3 Fatty Acids | Neutral/Increase | 5 | 20-50 |
| PCSK9 Inhibitors | 55-65 | Neutral | Neutral |
| Ezetimibe | 18 | Neutral | 8 |
| Bempedoic acid | 15-20 | Neutral | 10-13 |

Fibrates stimulate the Peroxisome Proliferator Activated Receptor-alpha (PPAR-alpha) which activates lipoprotein lipase and reduces production of apoprotein C-III (an inhibitor of lipoprotein lipase activity) [13,14]. Fibrates generally reduce triglycerides by 20%-50%. There is limited data with fibrates in severe hypertriglyceridemia. In one unpublished placebo-controlled study conducted in 44 patients with a mean baseline triglyceride level of ~700 mg/dL, fenofibrate 145 mg/d reduced triglycerides by 54% compared to an increase of 7% with placebo [15]. This study also found that fenofibrate increased LDL-C by 45% resulting from conversion of VLDL to LDL-C. The long-term implications of this effect have not been well established, but baseline LDL-C levels in severe hypertriglyceridemia are typically low.

There are no reported studies demonstrating that fibrates prevent pancreatitis. In a report of 17 patients with a history of pancreatitis due to severe hypertriglyceridemia (baseline levels >1000 mg/dL), the use of a fibrate (fenofibrate or ciprofibrate) combined with a nicotinic acid analog (acipimox), achieved triglyceride levels of 100-230 mg/dL [16]. Over a 42-month follow-up period, only 1 of 17 patients had a recurrence of pancreatitis. It should also be noted that fibrate therapy has been associated with triggering acute pancreatitis secondary to cholesterol-based gallstones [17].

Niacin has been largely abandoned as a lipid modifying drug as it failed to reduce ASCVD risk when combined with statins. While niacin reduces LDL-C, raises HDL-C, and lowers triglycerides, its mechanism of action is not well defined [12,13]. It has been proposed to increase lipoprotein lipase activity and decrease the rate of hepatic synthesis of VLDL and LDL-C. In patients with mixed dyslipidemia, the extended-release formulation of niacin produced a dose-dependent reduction in triglycerides from 8% at 500 mg/d up to 35% at 2000 mg/d [18]. Data with niacin is lacking in severe hypertriglyceridemia. But as previously discussed, a niacin analog was combined with a fibrate for prevention of recurrent pancreatitis [16]. Niacin is limited by a substantial burden of adverse effects including gastrointestinal intolerance, flushing, impaired glucose tolerance, hepatotoxicity, and hyperuricemia.

The omega-3 fatty acids (EPA and DHA) increase fatty acid oxidation which reduces hepatic lipogenesis and VLDL production [1,19]. They also increase lipoprotein lipase activity resulting in increased triglyceride clearance. Two prescription omega-3 products are currently approved for the treatment of severe hypertriglyceridemia. The EPA/DHA combination is dosed at 4 g/d while the EPA-only (icosapent ethyl) product is given at 2 g twice daily for severe hypertriglyceridemia. Both products should be taken with food, swallowed whole and not opened, crushed, dissolved, or chewed. Both products have been studied in patients with severe hypertriglyceridemia. The combination EPA/DHA product dosed at 4 g/d reduced triglycerides from a mean baseline of 800 mg/dL by 45% (52% placebo-corrected) [18]. Icosapent ethyl given at 2 g/d and 4 g/d doses reduced triglycerides from a baseline of 700 mg/dL by 7% (20% placebo-subtracted) and 27% (33% placebo-subtracted), respectively [20]. No head-to-head comparative studies on triglyceride reduction with the two products have been conducted. Adverse reactions include an increase in the risk of atrial fibrillation and the potential for increased bleeding risk especially in patients treated with concomitant anticoagulants and/or antiplatelet agents [3,4]. Gastrointestinal side effects (eructation, dyspepsia, and taste perversion) can occur, but are substantially more common with dietary supplement omega-3 fatty

**Table 3:** Potential Therapies for Severe Hypertriglyceridemia.

| Agent | Mechanism of Action | Dose | Status |
|---|---|---|---|
| Apo-CIII inhibitors | | | |
| Volanesorsen | ASO inhibiting APOC3 | 300 mg SC once weekly or biweekly | Approved in EU and UK, denied FDA approval in 2018 |
| Olezarsen | ASO inhibiting APOC3 | 10-50 mg SC every 4 weeks | Phase 3 |
| ARO-APOC3 | siRNA inhibiting APOC3 | 50 mg SC every 12 weeks | Phase 3 |
| ANGPTL3 inhibitors | | | |
| ARO-ANG3 | ASO inhibiting ANGPTL3 | 100-300 mg SC every 12 weeks | Phase 2 |
| LY3475766 | Monoclonal antibody targeting ANGPTL3/8 complex | Multiple IV and SC doses | Phase 1 |

acids [21].

## Novel Triglyceride Lowering Therapy

Lifestyle interventions, management of secondary causes, and the use of traditional triglyceride lowering drugs should be the initial approach to patients with severe hypertriglyceridemia [12,13]. These interventions frequently fail to reduce triglycerides to levels associated with reductions in the risk of pancreatitis. Several drugs are being developed to treat severe hypertriglyceridemia and potentially reduce the risk of pancreatitis. These include drugs that alter the biologic activity of Apolipoprotein-CIII (APOCIII) and Angiopoietin-Like Protein 3 (ANGPTL3).

APOCIII is a glycoprotein synthesized in the liver and intestine whose activity is controlled by the *APOC3* gene [5,11]. APOCIII increases triglycerides by reducing lipoprotein lipase and hepatic lipase activity and increasing hepatic synthesis of VLDL. Volanesorsen is an Antisense Oligonucleotide (ASO) which inhibits *APOC3* mRNA translation given by the subcutaneous (SC) route [22]. It is metabolized by endonucleases to form shorter, inactive oligonucleotides which are cleared renally. It is not a substrate, inhibitor, or inducer of cytochrome P450 enzyme systems or other known cellular transport systems (i.e., PGP). There are no known pharmacokinetic interactions.

The APPROACH study randomized 66 patients with FCS to volanesorsen 300 mg SC weekly or placebo for 52 weeks [23]. Eligibility was based either on genetic testing or documentation of low LPL activity and baseline triglyceride levels ≥ 750 mg/dL. Baseline characteristics included a mean triglyceride level of 2209 mg/dL, genetic mutations were identified in 79%, fibrates and/or omega-3 fatty acids were used in 53%, and a history of pancreatitis had occurred in 76%. Triglycerides were reduced by 77% with volanesorsen compared to an 18% increase with placebo after 3 months of treatment ($p<0.001$). Triglyceride reductions with volanesorsen were 53% and 40% at 6 and 12 months, respectively. This relatively lesser effect was attributed to interruption of drug therapy and dosage adjustments for adverse effects rather than loss of efficacy. Volanesorsen did not reduce the maximal intensity of abdominal pain or the composite of pancreatitis and moderate-to-severe abdominal pain. The most common side effects were injection site reactions and reduced platelet counts. Treatment discontinuation occurred in 42% (n=14) of volanesorsen patients and 6% (n=2) of placebo patients. Nine patients discontinued volanesorsen due to adverse reactions with thrombocytopenia occurring in 5 patients. Platelet levels <100,000/μL were observed in 16 volanesorsen patients (48%) and in no patients who received placebo. Two additional patients developed platelet counts <25,000/μL which recovered after treatment discontinuation. No major bleeding events were observed. Five patients withdrew from the study for issues related to requirements of the protocol. Only 6 patients (18%) remained on the 300 mg dose for 52 weeks.

The COMPASS study randomized 113 patients with severe hypertriglyceridemia with triglyceride levels ≥ 500 mg/dL in a 2:1 ratio to volanesorsen 300 mg subcutaneously (n=75) or placebo (n=38) given weekly for 26 weeks [24]. Approximately a year after enrollment began, the protocol was amended based on reports of thrombocytopenia occurring in the APPROACH study. After 13 weekly treatments at the start of the study, the frequency of treatments was reduced to every 2 weeks for the remaining 13 weeks. At baseline, the mean triglyceride level was 1261 mg/dL, 65% of patients were taking a statin, fibrate, or both, 33% were taking fish oil, 5% were taking ezetimibe, and 24% had a history of pancreatitis. After 3 months of treatment, the mean reduction in triglycerides was 71% (absolute decrease of 869 mg/dL) with volanesorsen and a 0.9% decrease with placebo. At 6 months, volanesorsen reduced triglyceride levels by 78% in patients completing the weekly treatment (n=25) and 62% in patients switched to biweekly treatment (n=50). Seven (6%) patients were identified as having FCS and 22 (19%) patients had heterozygous loss-of-function genetic mutations. The magnitude of triglyceride lowering with volanesorsen was not substantially different in individuals with and without genetic mutations. Pancreatitis occurred in 3 placebo patients (5 episodes) and in no patients receiving volanesorsen. Treatment discontinuation occurred in 24 (32%) volanesorsen patients and 4 (10%) placebo patients. Treatment related adverse reactions resulting in treatment discontinuation were seen in 15 (20%) volanesorsen patients and 3 (8%) placebo patients. The most common reasons for volanesorsen discontinuation included injection site reactions in 9 patients and thrombocytopenia in 1 patient. Platelet counts <100,000/μL occurred in 9 volanesorsen patients and 1 placebo patient. One patient had a platelet count <50,000/μL (42,000 μ/L) requiring drug discontinuation with resultant recovery of the platelet count after drug discontinuation.

The APPROACH OLE (Open Label Extension) is a longitudinal follow-up of FCS patients originally treated in the APPROACH (n=44) and COMPASS (n= 5) studies as well as a group of treatment-naïve patients allowed to receive open-label volanesorsen [25]. Triglyceride reductions at 2 years in these patients were approximately 50%. An analysis of the impact of volanesorsen on pancreatitis was conducted comparing the 5 years prior to starting volanesorsen to the time after the start of treatment. A substantial reduction was observed in both the number of patients with pancreatitis and the number of pancreatitis episodes. Prior to treatment, 33 patients had 82 episodes of pancreatitis while only 4 patients had 4 episodes of pancreatitis while on treatment. The IN-FOCUS study was a web-based disease burden survey open to patients with FCS [26]. In the 166 patients who completed the survey, significant clinical and psychosocial burdens were associated with a poor quality of life which limited employment and social interactions. The ReFOCUS study was a survey conducted in a fashion similar to the IN-FOCUS survey that assessed the impact of volanesorsen on the quality of life of 22 FCS patients in the

APPROACH OLE [27]. Patients treated with volanesorsen reported a general improvement in symptoms such as steatorrhea, abdominal pain, anxiety, and interference with work as well as a decrease in hospitalizations for pancreatitis.

While no serious bleeding events were reported in the APPROACH and COMPASS studies, volanesorsen-treated patients did experience an overall higher incidence of any bleeding events compared with placebo in the APPROACH (49% *vs.* 12%) and COMPASS (28% *vs.* 16%) studies [22]. Most events consisted of epistaxis, petechiae, and injection site bleeding. Bleeding may have been more common in the APPROACH study as patients with FCS are more likely to have platelet abnormalities. The lower bleed risk in the COMPASS study may have also been associated with a reduction in thrombocytopenia resulting from the reduction in volanesorsen dose.

Volanesorsen received regulatory approval for patients with genetically confirmed FCS in the European Union and UK with some monitoring restrictions [22]. An FDA scientific advisory panel voted in favor of approval of volanesorsen in the US, but the FDA submitted a complete response letter to the sponsor failing to approve the drug. While the reasons the FDA failed to approve volanesorsen were not disclosed, the sponsor began testing a more advanced ASO that targets *APOC3* called olezarsen (previously APOCIII-LRx).

Olezarsen is a galactosamine-conjugated APOC-III ASO analog that specifically targets only hepatic APOC-III [28]. A phase 2 dose ranging study in 114 patients with triglycerides levels of 200 mg/dL-500 mg/dL received SC olezarsen or placebo for 6 to 12 months [29]. The baseline triglyceride level of 262 mg/dL was reduced by 23% at the lowest dose (10 mg monthly) and 60% at the highest dose (50 mg monthly). Thrombocytopenia was not observed while the most common adverse reaction was mild injection site reactions. A phase 3 study (BALANCE) is evaluating olezarsen in patients with FCS [22].

ARO-*APOC3* is a small interfering RNA (siRNA) targeting *APOC3* mRNA within the cytoplasm of hepatocytes resulting in prolonged suppression of APOCIII [5]. A phase 1 trial in severe hypertriglyceridemia including some patients with FCS found that ARO-*APOC3* was associated with triglyceride reductions up to 92% [5]. A phase 3, randomized, double-blind, placebo-controlled trial (PALISADE) of ARO-*APOC3* 25 mg or 50 mg given SC every 3 months is enrolling patients with FCS.

Angiopoietin-like protein 3 (ANGPTL3) is a hepatically secreted protein that inhibits lipoprotein and endothelial lipase [30,31]. Loss of ANGPTL3 function decreases triglyceride-rich lipoprotein and HDL-C levels by activation of lipoprotein lipase and endothelial lipase, respectively. ANGPTL3 inhibition also reduces LDL-C levels by an unknown mechanism [31]. Therapeutic strategies for inhibiting the bioactivity of ANGPTL3 include a monoclonal antibody, an ASO, and aRNA silencing agent.

ARO-ANG3 is a siRNA that degrades the mRNA of ANGPTL3 resulting in gene silencing [32]. In an open-label dose-ranging phase I study in 12 healthy volunteers, ARO-ANG3 was given subcutaneously at 100 mg, 200 mg, and 300 mg doses on day 1 and day 29 [33]. Triglycerides were reduced by 62%, 72%, and 67% with the 100 mg, 200 mg, and 300 mg doses, respectively. The average maximum reduction in LDL-C and apolipoprotein B was 50% and 42%, respectively. A phase 2 has also found a 56% reduction in triglyceride levels in patients with mixed dyslipidemia [34]. Clinical trials with ARO-ANG3 are expected to be continued in patients with severe hypertriglyceridemia.

ANGPTL8 is a cofactor of ANGPTL3 efficacy which inhibits lipoprotein lipase. The ANGPTL3/8 complex can inhibit lipoprotein lipase with 100-fold greater potency than ANGPTL3 alone [35]. LY3475766 is a monoclonal antibody that inhibits ANGPTL3/8 complex which can be given SC or intravenously. Single doses of LY3475766 over the range of 100 to 600 mg were given to 48 patients with mixed dyslipidemia [5]. Maximal reductions of 59%, 65% and 70% were seen at 15 days with LY3475766 100 mg, 300 mg, and 600 mg, respectively. LDL-C levels were reduced by a maximum of 17%, 22% and 37%, respectively. There were also dose dependent reductions in cholesterol remnants and increases in HDL-C. Additional studies with LY3475766 are in progress.

Evinacumab is a monoclonal antibody that targets ANGPTL3 which has recently been FDA approved for Homozygous Familial Hypercholesterolemia (HoFH) [36]. The pivotal data with evinacumab in HoFH found the placebo-subtracted decrease in LDL-C at 24 weeks to be 49%. Achievement of ≥ 50% reductions in LDL-C occurred in 56% of evinacumab patients compared to 4.5% with placebo. Its unique mechanism of action which is independent of LDL receptor function is crucial to its effects in HoFH where LDL receptor function is abnormal.

A phase 2 study in 3 small groups of patients with severe hypertriglyceridemia and a history of pancreatitis has been completed [37]. The 3 groups included FCS (n=17), MCS secondary to heterozygous loss of function mutations (n=15), and MCS without genetic mutations (n=19). Evinacumab was associated with a 28% triglyceride reduction in FCS which was no greater than placebo (22%). The triglyceride reduction with evinacumab in MCS with and without genetic mutations was 65% and 82%, respectively. Placebo was associated with an increase in triglycerides in both groups. These data suggest that some lipase lipoprotein activity is necessary for evinacumab to be lower triglycerides. Another phase 2 study designed to evaluate the effectiveness of evinacumab in preventing pancreatitis in severe hypertriglyceridemia was terminated by the sponsor due to slow enrollment. Further development of evinacumab for triglyceride reduction is unlikely.

Vupanorsen is an ASO therapy targeting ANGPTL3 given SC at doses of 60 mg to 160 mg every 2 to 4 weeks [38]. In the TRANSLATE-TIMI 70 study (Targeting ANGPTL3 with an antisense oligonucleotide in adults with dyslipidemia), 286 patients with atherogenic dyslipidemia (non-HDL-C ≥ 100 mg/dL and triglycerides 150 mg/dL-500 mg/dL) treated with statins received 8 different doses of vupanorsen or placebo [39]. Vupanorsen treatment resulted in maximal triglyceride reductions of 57% and non-HDL-C reductions of 28%. However, reductions in LDL-C and apolipoprotein B were both less than 20%. Vupanorsen was also associated with a dose-dependent increase in hepatic fat associated with abnormal liver function tests >3 times the ULN. This signal for hepatotoxicity, especially at higher doses, resulted in the termination of development of vupanorsen by the sponsor. Further study with vupanorsen is not planned.

## Summary

Elevated triglycerides are a known risk for ASCVD, but drug therapy directed at reducing triglyceride levels in the 150 mg/dL to 499 mg/dL range has not reduced ASCVD events more than statin therapy alone. As a result, drug treatment of triglyceride levels <500 mg/dL is currently not recommended. Severely elevated triglyceride

levels (>500 mg/dL) are associated with an increased risk of pancreatitis. The risk of pancreatitis appears to increase especially as triglyceride levels exceed 1000 mg/dL. While the prevalence of severe hypertriglyceridemia is rare, the burden of disease in these patients is high. Several traditional lipid lowering drugs are known to reduce triglyceride levels, but none have been demonstrated to prevent pancreatitis secondary to severe hypertriglyceridemia. Several biologic agents are currently in development for the treatment of severe hypertriglyceridemia including patients with a genetic basis for elevated triglycerides. While there are several promising candidates that have reached testing in phase 3 trials and one agent approved in the Europe for FCS, none of these agents have been approved in the US. Further development of agents that alter the natural progression of severe hypertriglyceridemia remains an important area of research.

## References


1. Virani SS, Morris PB, Agarwala A, Ballantyne CM, Birtcher KK, Kris-Etherton PM, et al. 2021 ACC expert consensus decision pathway on the management of ASCVD risk reduction in patients with persistent hypertriglyceridemia: a report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol. 2021;78(9):960-93.
2. Raposeiras-Roubin S, Rossello X, Oliva B, Fernández-Friera L, Mendiguren JM, Andrés V, et al. Triglycerides and residual atherosclerotic risk. JAm Coll Cardiol. 2021;77(24):3031-41.
3. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2019;73(24):3168-209.
4. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, et al. 2019 ESC/EAS Guidelines for the management of dyslipidemias: lipid modification to reduce cardiovascular risk. Eur Heart J. 2020;41(1):111-88.
5. Gouni-Berthold I, Schwartz J, Berthold HK. Updates in drug treatment of severe hypertriglyceridemia. Curr Atheroscler Rep. 2023;25(10):701-9.
6. Miller M, Stone NJ, Ballantyne C, Bittner V, Criqui MH, Ginsberg HN, et al. Triglycerides and cardiovascular disease: a scientific statement from the American Heart Association. Circulation. 2011;123(20):2292-333.
7. Murphy MJ, Sheng X, Macdonald TM, Wei L. Hypertriglyceridemia and acute pancreatitis. JAMA Intern Med. 2013;173(2):162-4.
8. Linares CL, Pelletier AL, Czernichow S, Vergnaud AC, Bonnefont-Rousselot D, Levy P, et al. Acute pancreatitis in a cohort of 129 patients referred for severe hypertriglyceridemia. Pancreas. 2008;37(1):13-2.
9. Zhang R, Deng L, Jin T, Zhu P, Shi N, Jiang K, et al. Hypertriglyceridemia-associated acute pancreatitis: diagnosis and impact on severity. HPB (Oxford). 2019;21(9):1240-9.
10. Hegele RA, Ginsberg HN, Chapman MJ, Nordestgaard BG, Kuivenhoven JA, Averna M, et al. The polygenic nature of hypertriglyceridemia: implications for definition, diagnosis, and management. Lancet Diabetes Endocrinol. 2014;2(8):655-66.
11. Baass A, Paquette M, Bernard S, Hegele RA. Familial chylomicronemia syndrome: an under-recognized cause of severe hypertriglyceridemia. J Intern Med. 2020;287(4):340-8.
12. Yuan G, Al-Shali KZ, Hegele RA. Hypertriglyceridemia: its etiology, effects, and treatment. CMAJ. 2007;176(8):1113-20.
13. Oh RC, Trivette TC, Westerfield KL. Management of hypertriglyceridemia: common questions and answers. Am Fam Physician. 2020;102(6):347-54.
14. Kim NH, Kim SG. Fibrates revisited: potential role in cardiovascular risk reduction. Diabetes Metab J. 2020;44(2):213-21.
15. Tricor (fenofibrate) package insert. North Chicago IL, Abbvie Inc. 2018.
16. Athyros VG, Giouleme OI, Nikolaidis NL, Vasiliadis TV, Bouloukos VI, Kontopoulos AG, et al. Long-term follow-up of patients with acute hypertriglyceridemia-induced pancreatitis. J Clin Gastroenterol. 2002;34(4):472-5.
17. Berglund L, Brunzell JD, Goldberg AC, Goldberg IJ, Stalenhoef A. Treatment options for hypertriglyceridemia: from risk reduction to pancreatitis. Best Pract Res Clin Endocrinol Metab. 2014;28(3):423-37.
18. Goldberg AC. Clinical trial experience with extended-release niacin (niaspan): dose-escalation study. Am J Cardiol. 1998;82(12A):35U-38U;discussion 39U-41U.
19. Koski RR. Omega-3-acid ethyl esters (Lovaza) for severe hypertriglyceridemia. P T. 2008;33(5):271-303.
20. Bays HE, Ballantyne CM, Kastelein JJ, Isaacsohn JL, Braeckman RA, Soni PN. Eicosapentaenoic acid ethyl ester (AMR101) therapy in patients with very high triglyceride levels (from the multicenter, placebo-controlled, randomized, double-blind, 12-week study with an open-label extension [MARINE] trial). Am J Cardiol. 2011;108(5):682-90.
21. Hilleman DE, Wiggins BS, Bottorff MB. Critical differences between dietary supplement and prescription omega-3 fatty acids: A narrative review. Adv Ther. 2020;37(2):656-70.
22. Warden BA, Duell PB. Volanesorsen for treatment of patients with familial chylomicronemia syndrome. Drugs Today (Barc). 2018;54(12):721-35.
23. Witztum JL, Gaudet D, Freedman SD, Alexander VJ, Digenio A, Williams KR, et al. Volanesorsen and triglyceride levels in familial chylomicronemia syndrome. N Engl J Med. 2019;381(6):531-42.
24. Gouni-Berthold I, Alexander VJ, Yang Q, Hurh E, Steinhagen-Thiessen E, Moriarty PM, et al. Efficacy and safety of volanesorsen in patients with multifactorial chylomicronemia (COMPASS): a multicentre, double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Diabetes Endocrinol. 2021;9(5):264-75.
25. Witztum JL, Gaudet D, Arca M, Jones A, Soran H, GouniBerthold I, et al. Volanesorsen and triglyceride levels in familial chylomicronemia syndrome: Long-term efficacy and safety data from patients in an open-label extension trial. J Clin Lipidol. 2023;17(3):342-55.
26. Davidson M, Stevenson M, Hsieh A, Ahmad Z, Lennep JRV, Crowson C, et al. The burden of familial chylomicronemia syndrome: Results from the global IN-FOCUS study. J Clin Lipidol. 2018;12(4):898-907.e2.
27. Arca M, Hsieh A, Soran H, Rosenblit P, O'Dea L, Stevenson M. The effect of volanesorsen treatment on the burden associated with familial chylomicronemia syndrome: the results of the ReFOCUS study. Expert Rev Cardiovasc Ther. 2018;16(7):537-46.
28. Hegele RA. Apolipoprotein C-III inhibition to lower triglycerides: one ring to rule them all? Eur Heart J. 2022;43(14):1413-5.
29. Tardif JC, Karwatowska-Prokopczuk E, Amour ES, Ballantyne CM, Shapiro MD, Moriarty PM, et al. Apolipoprotein C-III reduction in subjects with moderate hypertriglyceridemia and at high cardiovascular risk. Eur Heart J. 2022;43(14):1401-12.
30. Backes JM, Hilleman DE. New and emerging lipid-lowering therapy. Future Cardiol. 2021;17(8):1407-20.
31. Stitziel NO, Khera AV, Wang X, Bierhals AJ, Vourakis AC, Sperry AE, et al. ANGPTL3 deficiency and protection against coronary artery disease. J Am Coll Cardiol. 2017;69:2054-63.
32. Nurmohamed NS, Dallinga-Thie GM, Stroes ESG. Targeting apoC-III and ANGPTL3 in the treatment of hypertriglyceridemia, Expert Rev Cardiovasc Ther. 2020;18(6):355-61.
33. Watts GF, Schwabe C, Scott R, Gladding PA, Sullivan D, Baker J, et al. RNA interference targeting ANGPTL3 for triglyceride and cholesterol lowering: phase 1 basket trial cohorts. Nat Med. 2023;29:2216-23.
34. Watts GF, Gaudet D, Altamirano D, Hegele RA, Ballantyne CM, Nicholls SJ, et al. ARO-ANG3, an investigational RNAi therapeutic, silences the expression of ANGPTL3 and decreases atherogenic lipoproteins in patients with mixed dyslipidemia: ARCHES-2

study results. 2023;148(suppl 1):Abstract 17120.

35. Chen YQ, Pottanat TG, Siegel RW, Ehsani M, Qian YW, Zhen EY, et al. Angiopoietin-like protein 8 differentially regulates ANGPTL3 and ANGPTL4 during postprandial partitioning of fatty acids. J Lipid Res. 2020;61(8):1203-20.

36. Sosnowska B, Adach W, Surma S, Rosenson RS, Banach M. Evinacumab, an ANGPTL3 inhibitor, in the treatment of dyslipidemia. J Clin Med. 2022;12(1):168.

37. Rosenson RS, Gaudet D, Ballantyne CM, Baum SJ, Bergeron J, Kershaw EE, et al. Evinacumab in severe hypertriglyceridemia with or without lipoprotein lipase pathway mutations: a phase 2 randomized trial. Nat Med. 2023;29(3):729-37.

38. Gaudet D, Karwatowska-Prokopczuk E, Baum SJ, Hurh E, Kingsbury J, Bartlett VJ, et al. Vupanorsen, an N-acetylgalactosamine-conjugated antisense drug to ANGPTL3 mRNA, lowers triglycerides and atherogenic lipoproteins in patients with diabetes, hepatic steatosis, and hypertriglyceridemia. Eur Heart J. 2020;41(40);3936-45.

39. Bergmark BA, Marston NA, Bramson CR, Curto M, Ramos V, Jevne A, et al. Effect of vupanorsen on non-high-density lipoprotein cholesterol levels in statin-treated patients with elevated cholesterol: TRANSLATE-TIMI 70. Circulation. 2022;145(18):1377-86.