HHS Public Access

Author manuscript

Curr Opin Lipidol. Author manuscript; available in PMC 2021 December 01.

Published in final edited form as:

Curr Opin Lipidol. 2020 December ; 31(6): 331–339. doi:10.1097/MOL.0000000000000710.

Hypertriglyceridemia - new approaches in management and treatment

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Abstract

Purpose of review: Hypertriglyceridemia (HTG), a form of dyslipidemia characterized by elevated plasma of triglycerides (TG), is associated with an increased risk for acute pancreatitis. Moreover, HTG has recently been shown to be linked to the development of atherosclerotic cardiovascular disease (ASCVD); therefore, there is a great interest in better understanding the pathophysiology of HTG and improving its clinical management. In this review, we briefly describe TG metabolism, recent guidelines for the clinical management of HTG, and provide an overview of the current and potential new therapies for HTG.

Recent findings: Screening patients for HTG is valuable for not only identifying patients with extreme TG elevations, who are at risk for pancreatitis, but also for managing ASCVD risk in patients with more moderate forms of HTG. Therefore, the most recent USA guidelines for cardiovascular diseases recommend using TG as a risk enhancer test, leading to a more aggressive treatment of patients with intermediate risk. Currently there are several available approaches for reducing plasma TG, which include lifestyle changes, fibrates and omega-3 fatty acid treatment. The addition of eicosapentaenoic acid (EPA) on top of statins has recently been shown to significantly reduce ASCVD events. Nevertheless, there is an unmet need for more effective treatment options. Several new therapies based on newly identified targets in TG metabolism, such as apolipoprotein C-III and angiopoietin-like 3 protein, are currently under development.

Summary: The clinical management of HTG is important in the prevention and treatment of acute pancreatitis and also impacts on how ASCVD risk is managed. More work needs to be done to establish the mechanism for the ability of how EPA lowers ASCVD and how to best integrate it with other lipid-lowering therapies. The efficacy and safety of the novel therapies for HTG should be established soon in the ongoing late-stage clinical trials.

Keywords

cardiovascular diseases; hypertriglyceridemia; management; novel therapies; triglycerides

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Introduction

Hypertriglyceridemia (HTG) is a common lipid disorder characterized by elevated levels of plasma triglycerides (TG) carried on apolipoprotein B (apoB) containing lipoproteins, which primarily include chylomicrons (CM), very low-density lipoproteins (VLDL) and remnant lipoproteins. It can develop from primary genetic disorders or more commonly from a wide variety of secondary causes, such as metabolic syndrome, obesity, iatrogenic drug use, and type 2 diabetes, all of which can disturb TG-rich lipoproteins (TRL) metabolism. The risk of acute pancreatitis is a relatively common problem, which can have significant morbidity and mortality. It typically occurs in patients with marked increases in TG, typically over 1000 mg/dL (TG>11.3 mmol/L) but can also develop at lower TG levels. Moreover, it has been shown in several Mendelian randomization and GWAS studies that genes associated with HTG are causally linked to increased atherosclerotic cardiovascular disease (ASCVD) risk [1–3]. The findings of recent multivariable Mendelian randomization analyses [4] suggest that TG-rich remnant particles have approximately the same or perhaps a greater effect on the risk of cardiovascular disease (CVD) as low-density lipoproteins (LDL), which confirms earlier work from the Copenhagen Heart Study [1]. Therefore, there has been a renewed interest in TG metabolism and recent efforts have focused on developing new treatment options for HTG, which we will cover in this review.

Metabolism of triglyceride-rich lipoproteins

There are two main pathways by which TRL are metabolised (Fig. 1) that depend on the source of TG, namely the exogenous pathway (dietary TG source) or endogenous pathway (hepatic TG source) [5]. The exogenous pathway starts in the small intestine and ends in the liver. In this pathway dietary lipids are absorbed in the intestine and packaged into CM. CM enter the circulation by way of the lymphatics and then undergo hydrolysis by lipases that convert TG to free fatty acids (FFA) and glycerol, which then enter either peripheral tissues for energy generation or adipocytes for energy storage. CM are converted to remnant particles by this process and are mostly taken up by the liver. In the endogenous pathway, the liver synthesizes TG from glycerol and FFA that are derived from the following three main sources: adipocytes, CM remnants and dietary fat directly taken up from the intestine through the portal vein. It has been determined that the fasting hepatic *de novo lipogenesis* can be up to ~10% in healthy adults and significantly up to 22% in patients with insulin resistance and nonalcoholic fatty liver disease [6]. TG are then released by the liver when they secrete VLDL into the plasma. Like CM, VLDL can then undergo lipolysis and produce remnant particles, or undergo more complete lipolysis and be converted into LDL. LDL are also removed by the liver by the LDL receptor but excess of LDL can be deposited into vessels where they can trigger atherosclerosis.

The main enzyme involved in the lipolysis of TG on CM and VLDL is lipoprotein lipase (LPL) [5, 7]. LPL is highly regulated and for its proper function requires several positive and negative regulators to insure that FFA generated from lipolysis are being delivered to the right tissues during the fasting or fed state [5]. A crucial protein that is necessary for LPL activation is apolipoprotein C-II (apoC-II). In contrast, a closely related protein, apolipoprotein C-III (apoC-III), can inhibit LPL and appears to also interfere with hepatic

uptake of remnat lipoproteins. Angiopoietin-like 3 (ANGPTL3) protein is another key inhibitor of LPL [8].

Hypertriglyceridemia

HTG is usually defined as an increase of plasma TG more than 150 mg/dL (1.7 mmol/L) in the fasting state or as >175 mg/dL (>2.0 mmol/L) in the fed state. Patients with fasting or non-fasting plasma TG between 150 – 499 mg/dL (1.7 mmol/L – 5.6 mmol/L) are usually classified as having moderate HTG, whereas in severe HTG plasma TG are ≥500 mg/dL (≥5.6 mmol/L) [9, 10].

Patients with elevated TG are most likely to have a polygenic determinant of HTG. Severe HTG usually reflects the accumulation of CM and/or CM and VLDL and their remnants. Secondary causes, such as e.g. type 2 diabetes and hypothyroidism, are also a common cause of HTG [11, 12]. It is also important to diagnose patients with Familial Chylomicronemia Syndrome (FCS), which is a rare monogenic disorder causing extremely high levels of plasma TG [13]. FCS is the third most common cause of pancreatitis with an overall associated mortality of about 5% to 6% per episode [14]. In addition, severe HTG has been shown to have many other adverse impacts on the normal life of these patients [15, 16].

Management of hypertriglyceridemia

In the 2018-MultiSociety Guideline on the Management of Blood Cholesterol, there are four general recommendations for the clinical management of HTG [9, 10]. The 1st recommendation, class I, focuses on identifying people ≥20 years old who have moderate HTG and advises to address and treat lifestyle factors, secondary factors and medications raising TG by nonpharmacological means where possible. The 2nd recommendation, class IIa, is for adults 40 – 75 years old with a moderate or severe HTG with an ASCVD risk of ≥7.5% for whom the ASCVD risk assessment should be reevaluated after lifestyle and secondary factors are addressed. If TG≥175 mg/dL (≥2.0 mmol/L) are persistent after addressing these other factors, a statin treatment (Table 1) should be considered for reducing ASCVD risk. These patients may not have a particularly elevated LDL-cholesterol (LDL-C) but appear to have a pro-atherogenic lipoprotein phenotype characterized by increased small dense LDL and remnant lipoproteins and thus may benefit from statin therapy [17, 18]. The 3rd recommendation, class IIa, is for adults 40 – 75 years old with a severe HTG and with an ASCVD risk of ≥7.5%. Most patients with severe HTG have multiple ASCVD risk factors and an enhaced risk for developing ASCVD, making it advisable to address any reversible causes of high TG and to consider the use of statin therapy. The last 4th recommendation, class IIa, is for patients with severe HTG, especially those with TG≥1000 mg/dL (≥11.3 mmol/L). To reduce their risk for acute pancreatitis, reduction of TG is necessecary and can be achieved by addressing and eliminating the underlying factors. When addressing secondary causes of HTG in patients with high risk for acute pancreatitis is not sufficiently effective, it is recommended that patients be put on a very-low-fat diet [19] (Table 1). It is generally recommended that the fat intake should be reduced to 15 to 20 g per day (10% – 15% of total daily energy intake). Carbohydrate and alcohol consumption should also be

limited. If there is still a concern for acute pancreatitis, taking fibrates (Table 1) and omega-3 fatty acids (Table 2) might be beneficial for patients because although statins are known to reduce CVD events they typically only have a limited effect in reducing TG. Niacin (Table 1) is another drug that could be considered on top of statins, although it is not explicitly recommended [9] and recent studies have failed to show that niacin on top of statins reduces CVD events [20, 21].

The recent 2019 ESC/EAS guidelines for the management of dyslipidemias [22] are similar to the 2018 AHA/ACC guidelines [9] and recommend considering the use of TG-loweing drugs in high-risk patients with TG>200 mg/dL (>2.3 mmol/L) when lifestyle measures fail to lower TG levels. Possible pharmacological interventions to consider include statins, fibrates, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, and long-chain omega-3 polyunsaturated fatty acids (PUFA).

Marine-derived omega-3 fatty acids in triglyceride management

Fish oils are among the most well recognized health supplements in the USA and there has been much recent progress on their use for HTG [23]. The main active ingredient in fish oils is PUFA, i.e. eicosapentaenoic acid (EPA; 20:5 omega-3) and docosahexaenoic acid (DHA; 22:6 omega-3) [24, 25]. In normolipidemic to borderline hyperlipidemic healthy individuals, 1–5 g/day consumption of EPA/DHA supplements typically results in a variable TG reduction ranging between 4–51% [26]. In addition, intake of omega-3 PUFA decreases postprandial TG levels in both healthy subjects and patients with familial hypercholesterolemia [27, 28].

Most omega-3 PUFA clinical trials have used a mixture of EPA and DHA at various ratios, and a recent study showed that omega-3 PUFA supplements with different EPA/DHA ratios (2.3 vs. 0.3) had nearly identical effects on decreasing TG, VLDL particle number, and TRL subfractions [29]. This finding is consistent with previous studies that used purified EPA and DHA [30, 31]; however, divergent effects of EPA and DHA on other lipid paramaters, such as LDL-C and HDL-cholesterol (HDL-C), have been described [32]. Some of the proposed mechanisms of omega-3 PUFA effects on TG metabolism include decreased hepatic lipogenesis through down-regulating sterol receptor element binding protein-1c (SREBP-1c) transcription factor, increased hepatic fatty acid β-oxidation through activation of peroxisome proliferator-activated receptors alpha (PPARα), and accelerated VLDL clearance through stimulating LPL activity and apoB degradation [33–35].

The most recent recommendations from the American Heart Association concluded that omega-3 PUFA at high doses of 4 g/d (>3 g/d total EPA+DHA) are effective in reducing TG in hyperlipidemic individuals [36]. There are two major types of prescription highly purified omega-3 PUFA: a mixture of EPA and DHA, such as Omacor/Lovaza, Omtryg, and Epanova, and EPA only formulation, such as Vascepa and Epadel (approved only in Japan) (Table 2). The first randomized clinical trial showing the CVD benefit of omega-3 PUFA when added to statins was the JELIS study. In this study, highly purified EPA ethyl ester (Epadel; 1.8 g/day) reduced the risk of major coronary events in hypercholesterolemic patients on a statin compared to those receiving statin monotherapy [37]. More recently, the CHERRY study that used Epadel (1.8 g/day) showed that addition of EPA to high dose statin

treatment significantly reduced coronary plaque volume, suggesting that EPA therapy may reduce the residual risk that remains in secondary prevention patients being treated with statins [38]. The RESPECT-EPA study (UMIN ID No.: UMIN000012069) is currently examining the use of Epadel (1.8 g/day) on the incidence of CVD events and is expected to be reported in 2022.

The REDUCE-IT study is the most recently completed large ASCVD outcome study of an EPA-only prescription (Vascepa) (Table 3). At a high dose of 4 g/day, it was found to lower TG from baseline by 45% and double the reduction in ASCVD events for patients on statins [39]. In contrast, a low dose of prescription omega-3 PUFA mixture (1 g/day) failed to show benefit in over 40,000 patients with respect to primary prevention in both ASCEND and VITAL studies [40, 41]. Another higher dose (4 g/day) study called STRENGTH that used an omega-3 PUFA mixture of EPA and DHA (Epanova) has been halted because of a lack of any apparent ASCVD benefits in patients with mixed dyslipidemia [42]. Thus, at this point it remains unclear whether the lack of CVD health benefits from some omega-3 PUFA clinical trials may be attributable to a low dose or to a low ratio of EPA to DHA. DHA, but not EPA, has been shown to increase total LDL-C levels and small dense LDL [43, 44]. In addition, it does not appear that the benefit from EPA in the REDUCE-IT trial was due to TG lowering and may be due to some other mechanism, since the observed benefits were similar across baseline TG levels.

Therapies for severe hypertriglyceridemia

A newly approved drug for the treatment of FCS that is currently available in the European Union is Waylivra (Volanesorsen) from Akcea Therapeutics [45]. Waylivra is an antisense oligonucleotide (ASO) inhibitor of apoC-III designed to reduce the production of apoC-III [46]. In the APPROACH trial, the mean TG levels decreased by 77% in Waylivra-treated patients versus an 18% increase in patients on placebo and the levels of apoC-III decreased by an average of 84% from baseline after three months in the active treatment group [46]. It has been shown that patients with FCS may develop significant spontaneous fluctuations in platelet blood count leading to thrombocytopenia or thrombocytosis [47]. Results from the Waylivra trial showed that the drug can lead to clinically significant thrombocytopenia in humans [46], which was one of the main reasons that the drug was not approved in the US.

There are also several other therapies under development that show promise for severe HTG [12, 48] (Table 1). Akcea Therapeutics has two emerging ASO drugs named AKCEA-APOCIII-LRx and AKCEA-ANGPTL3-LRx that are targetted against apoC-III and ANGPTL3, respectively. AKCEA-APOCIII-LRx is a second-generation ASO that contains a triantennary N-acetylgalactosamine ($GalNAc_3$) moiety targeted to hepatocytes to enhance drug's potency [49], thereby also potentially limiting its off target toxicity like thrombocytopenia. Results from a Phase 1/2 clinical trial of AKCEA-APOCIII-LRx [50] showed significant and dose-dependent reductions in apoC-III up to 84% after six weeks of treatment and TG reductions as much as 71% from baseline. Moreover, it was demonstrated that AKCEA-APOCIII-LRx had at least 15 times higher potency in reducing plasma apoC-III and TG than Waylivra, a non-GalNAc ASO. This allowed the use of much lower doses of AKCEA-APOCIII-LRx that improved its safety and tolerability [51], and subjects did not

have significant declines in their platelet count [50]. In regard to ASO treatment for ANGTPL3, six weeks of treatment with AKCEA-ANGPTL3-LRx [49] resulted in a robust, dose-dependent reductions of ANGPTL3, TG, and apoC-III up to 84.5%, 63% and 59%, respectively in a Phase 1/2 study [49].

ARO-APOC3 and ARO-ANGPTL3, which are under a development by Arrowhead Pharmaceuticals, are small interfering ribonucleic acid (siRNA) candidates against either APOC3 mRNA or ANGPTL3 mRNA [52]. These therapies trigger the RNA interference mechanism to induce rapid, deep, and durable gene specific silencing while also avoiding off-target effects. Results from the phase 1/2a study of patients taking ARO-APOC3 showed that the mean maximum reduction in plasma apoC-III was up to 94% and for TG it was 95%. It has been suggested that this type of therapy might be particularly well suited for populations with therapy adherence issues since this drug is administered quarterly or at 6 month intervals [53]. Patients given ARO-ANGPTL3 in a Phase 1/2a had a mean maximum decrease of ANGPTL3 of 83% and of TG – 79%. Both candidates had a high level of pharmacologic activity with good safety and tolerability, and the most common adverse events reported were headache, respiratory tract infections, and local injection site reactions [52]. Results from these clinical trials are encouraging and show that siRNA-based treatments may be an effective approach for severe HTG.

Pemafibrate is a highly potent and selective PPARα that significantly reduces TG, apoC-III, and remnant cholesterol while increasing HDL-C [54–56]. Under the name of Parmodia, it received its first global approval on 3 July 2017 for the treatment of hyperlipidemia in Japan [54]. It is being currently investigated for FCS in two randomized, placebo-controlled phase 3 trials [56]. Data from the PROVIDE study showed that pemafibrate treatment significantly reduced TG levels at week 52 by approximately half and was well tolerated in people with type 2 diabetes and HTG [57].

Monocloncal antibodies against ANGPTL3, like evinacumab [58] or against apoC-III, like STT505/STT5058 [59] are other promising approaches being investigated. These antibodies bind to and neutralize the effect of these proteins on the inhibition of lipolysis and thus lower TG levels. Finally, apoC-II-mimetic peptides [11, 60–64] could be a potential new treatment for apoC-II deficiency and other causes of HTG. These peptides have been shown to decrease plasma TG by 80% within a few hours in both apoC-II-deficient mice and h*APOC3*-transgenic (Tg) mice [64]. There was also a 80% reduction in plasma apoC-III and 65% reduction in apoB in h*APOC3*-Tg mice treated with these peptides [64]. The advantage of this strategy is that apoC-II mimetic peptides both directly activate LPL [60–64] and also antagonize apoC-III by causing its displacement from TRL, leading to increase apoC-III renal clearance [11, 64] and an increase in the hepatic uptake of TRL [62].

Conclusions

HTG is typically a multifactorial disorder; therefore, the clinical management of these patients can be challenging. There is a need for new approaches to improve screening, monitoring and treatment of patients with HTG for not only preventing pancreatitis but also for reducing ASCVD risk. Besides the new omega-3 PUFA therapies that utilize pure EPA

that have been shown to lower TG and reduce ASCVD risk when used on top of statins, new drugs are also being actively investigated. More research, however, is needed to better understand the mechanism for the CVD benefit from TG reduction and for identifying which patients would gain the most from such therapies.

Acknowledgments

Financial support

Research was supported by the Intramural Research Program of the NHLBI at the National Institutes of Health. A.W. and A.T.R. have a research grant HL-CR-16-005 with Corvidia Therapeutics, Inc., Waltham, MA, USA. Z.-H.Y. and A.T.R. acknowledge a research grant HL-CR-18-004 with Nippon Suisan Kaisha, Ltd., Tokyo, Japan.

Conflicts of interest

A.W. and A.T.R. have a research grant HL-CR-16-005 with Corvidia Therapeutics, Inc., Waltham, MA, USA and are co-inventors on US patent application PCT/US2018/014532, submitted by Corvidia Therapeutics Inc. that covers composition and use of apoC-II mimetic peptides for the treatment of HTG. A.T.R. is also a co-inventor on US patent #8,936,787 held by the National Institutes of Health that covers composition and use of 18A-CII mimetic peptide. Z.-H.Y. declares no conflict of interest.

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Key points

- Patients with HTG are at increased risk for life-threating acute pancreatitis and ACSVD.
- Recent USA guidelines for management of HTG stress the importance of identifying patients with elevated plasma TG.
- The most effective currently available treatments for HTG are fat-restricted diets, healthy life style schanges, fibrates, and omega-3 PUFA.
- Highly purified EPA may be superior to EPA/DHA mixture medicine for ASCVD risk reduction.
- Novel HTG therapies based on newly identified targets in TG metabolism are under development and show promise in early stage clinical trials.

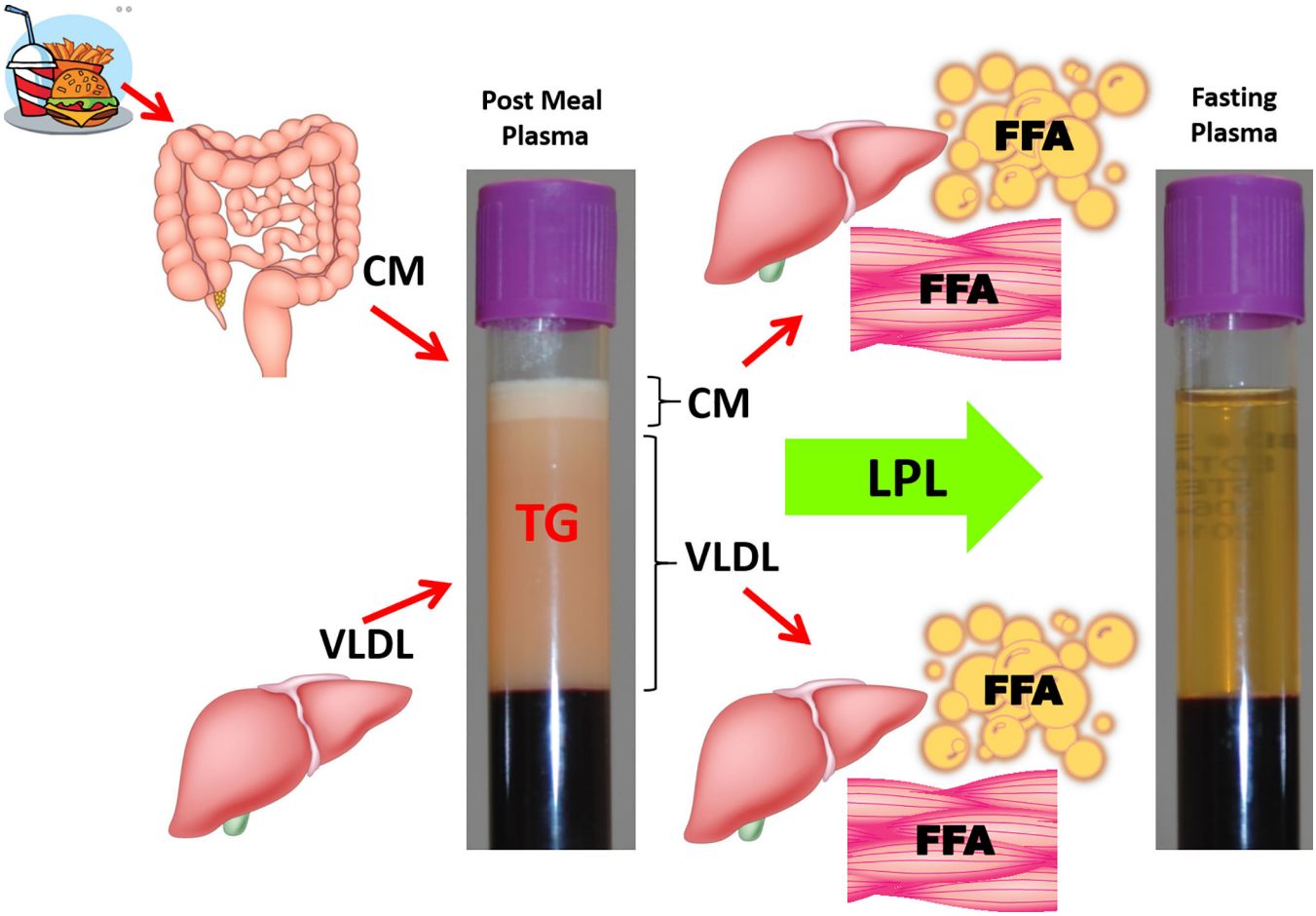

Fig. 1. Two Routes of Triglyceride-Rich Lipoproteins Metabolism: the exogenous and endogenous pathways.

The exogenous route starts with the dietary triglycerides (TG), which are absorbed in the intestine and are secreted in a form of chylomicron lipoproteins (CM) to plasma. CM once hydrolysed by the lipoprotein lipase (LPL) and depleted of TG are removed by the liver and free fatty acids (FFA) generated from the lipolysis are taken up either by the peripheral tissues for energy production or by adipocytes for storage. The endogenous route starts in the liver where TG-rich very low-density lipoproteins (VLDL) are generated. After VLDL is secreted into plasma, LPL converts them into remnant particles, which are then either removed by the liver or undergo further lipolysis and are converted to low-density lipoproteins (LDL). FFA generated from this metabolism are deposited in peripheral, muscle and/or adipose tissue.

Table 1.

Current and Potential New Therapies for Hypertriglyceridemia

Agent	Mechanism of action and effect on lipid metabolism	Stage	Reference
Available therapies			
Healthy lifestyle	Healthy low-fat diet (weight loss), physical activity, alcohol abstinence to improve the metabolism of lipids and reduce plasma TG	-	[9, 19]
Statins	Increase catabolism of CM remnants but have only modest effect on TG	-	[65]
Ezetimibe + simvastatin	Combined with statins lowers plasma cholesterol and production of TRL	-	[66]
Fibrates	Activate PPAR-α receptor; reduce hepatic synthesis of TRL	-	[67]
Niacin	Increases hepatic TRL uptake; reduces hepatic TRL production	-	[68]
Omega-3 PUFA	Increases clearance of TRL, inhibits hepatic TRL synthesis	-	Table 2
Volanesorsen (Waylivra)	ASO against apoC-III; inhibits the production of apoC-III, reduces plasma apoC-III, TG, and hepatic TRL production, and increases TRL catabolism and HDL-C	Approved in EU only	[45, 46]
Therapies in development			
Pemafibrate (Parmodia*)	Selective PPARα modulator; reduces plasma TG and increases HDL-C	Phase 3	[54–57]
AKCEA-APOCIII-LR$_X$	ASO against apoC-III; inhibits the production of apoC-III, reduces plasma apoC-III, TG, and hepatic TRL production, and increases TRL catabolism and HDL-C	Phase 3 planned	[50]
AKCEA-ANGPTL3-LR$_X$ (ISIS 703802)	ASO against ANGPTL3, inhibits the production of ANGPTL3, lowers plasma ANGPTL3 apoB-containing particles, TG, and LDL-C	Phase 2	[49]
Evinacumab	mAb against ANGPTL3; lowers apoB-containing particles and plasma TG, LDL-C and HDL-C	Phase 2	[58]
ARO-APOC3	siRNA against apoC-III; inhibits the expression of APOC3 mRNA, thereby affecting the production of apoC-III, lowers plasma apoC-III and TG	Phase 1/2a	[52]
ARO-ANGPTL3	siRNA against ANGPTL3; inhibits the expression of ANGPTL3 mRNA, thereby affecting the production of ANGPTL3, lowers plasma ANGPTL3, TG and LDL-C	Phase 1/2a	[52]
STT505/STT5058	mAB against apoC-III; lowers circulating apoC-III and TG levels and promotes TRL clearance	Pre-clinical testing	[59]
D6PV (COR-003)	An apoC-II mimetic-apoC-III antagonist peptide; activates LPL and displaces apoC-III from TRL, reduces plasma apoC-II and TG	Pre-clinical testing	[64, 69]

*Under this name pemafibrate received its first global approval on 3 July 2017 for the treatment of hyperlipidemia in Japan. It is being investigated in the treatment of severe HTG in two randomized, placebo-controlled phase 3 trials [54].

ANGPTL3: angiopoietin-like 3 protein; apoB: apolipoprotein B; apoC-II: apolipoprotein C-II; apoC-III: apolipoprotein C-III; ASO: antisense oligonucleotides; CM: chylomicrons; EU: European Union; HDL-C: high-density lipoproteins cholesterol; LDL-C: low-density liporpoteins cholesterol; LPL: lipoprotein lipase; mAb: monoclonal antibodies; PPARα: peroxisome proliferator-activated receptors alfa; PUFA: polyunsaturated fatty acid; siRNA: small interfering ribonucleic acid; TG: triglycerides; TRL: triglyceride-rich lipoproteins; USA: the United States of America

Table 2.

FDA-approved Prescription Omega-3 PUFA Products

Omega-3 PUFA type	Trade name (manufacture)	Years approved	Generic Name	Dosage
EPA-only	Vascepa (Amarin Pharma Inc.)	2012	Icosapent Ethyl	4.0 g/day
EPA+DHA	Omacor/Lovaza (GlaxoSmithKline LLC.)	2004	Omega-3-acid ethyl esters	4.0 g/day
	Omtryg (Trygg Pharma, Inc.)	2014	Omega-3-acid ethyl esters	4.8 g/day
	Epanova (AstraZeneca Pharmaceuticals LP.)	2014	Omega-3-carboxylic acids	2 or 4 g/day

PUFA: polyunsaturated fatty acid; EPA: eicosapentaenoic acid; DHA: docosahexaenoic acid

Table 3.

Recent CVD Outcome Clinical Trials Using Prescription Omega-3 PUFA Products

Omega-3 PUFA type	Trial (Country; Completion date)	No. Age (years)	Duration	Formulation Dose	Major findings
EPA-only	CHERRY (Japan; 2013)	193; 57–78	6–8 months	Ethyl icosapentate (Epadel) 1.8 g/day	Addition of middle-dose EPA to high-dose statin reduced coronary plaque volume compared to statin therapy alone.
	REDUCE-IT (USA; 2019)	8179; ≥45	5 years	Icosapent Ethyl; (Vascepa) 4 g/day	High-dose EPA lowered ischemic event rates beyond statin therapy in at-risk patients with hypertriglyceridemia.
	RESPECT-EPA (Japan; 2022)	3900; 20–79	5 years	Ethyl icosapentate (Epadel) 1.8 g/day	N/A (ongoing study)
EPA+DHA	ASCEND (UK; 2018)	15,480; ≥40	7.4 years	Omega-3-acid ethyl esters (Lovaza) 1.0 g/day	Low-dose EPA+DHA showed no difference in the risk of vascular events compared to placebo in patients with diabetes without CVD
	VITAL (USA; 2019)	25,871; Men ≥50 Women ≥55	5.3 years	Omega-3-acid ethyl esters (Omacor) 1.0 g/day	Low-dose EPA+DHA did not lower major CVD events incidence and cancer compared to placebo in a racially and ethnically diverse population.
	STENGHTH (USA, 2020)	13,086; 18–99 (>40 if diabetes)	5 years	Omega-3-acid ethyl esters (Epanova) 4.0 g/day	High-dose EPA+DHA failed to show apparent benefit in at-risk patients with mixed dyslipidemia, resulting in trial discontinuity.

PUFA: polyunsaturated fatty acid; EPA: eicosapentaenoic Acid; DHA: docosahexaenoic acid; CVD: cardiovascular disease; CHERRY: Coronary Plaque Regression Evaluated by Integrated Backscatter Intravascular Ultrasonography; REDUCE-IT: Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial; RESPECT-EPA: Randomized trial for Evaluation in Secondary Prevention Efficacy of Combination Therapy-Statin and Eicosapentaenoic Acid; ASCEND: A Study of Cardiovascular Events in Diabetes; VITAL: VITamin D and OmegA-3 TriaL; STENGHTH: A Long-Term Outcomes Study to Assess STatin Residual Risk Reduction With EpaNova in HiGh Cardiovascular Risk PatienTs With Hypertriglyceridemia; N/A: not available.