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New approaches to triglyceride reduction: Is there any hope left?

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ABSTRACT

Triglycerides play a crucial role in the efficient storage of energy in the body. Mild and moderate hypertriglyceridemia (HTG) is a heterogeneous disorder with significant association with atherosclerotic cardiovascular disease (ASCVD), including myocardial infarction, ischemic stroke, and peripheral artery disease and represents an important component of the residual ASCVD risk in statin treated patients despite optimal low-density lipoprotein cholesterol reduction. Individuals with severe HTG (>1,000 mg/dL) rarely develop atherosclerosis but have an incremental incidence of acute pancreatitis with significant morbidity and mortality. HTG can occur from a combination of genetic (both mono and polygenic) and environmental factors including poor diet, low physical activity, obesity, medications, and diseases like insulin resistance and other endocrine pathologies. HTG represents a potential target for ASCVD risk and pancreatitis risk reduction, however data on ASCVD reduction by treating HTG is still lacking and HTG-associated acute pancreatitis occurs too rarely to effectively demonstrate treatment benefit. In this review, we address the key aspects of HTG pathophysiology and examine the mechanisms and background of current and emerging therapies in the management of HTG.

1. Introduction - Triglyceride Pathophysiology, Metabolism, and Genomics

Triglycerides (TG) are a major component of dietary fat. The macromolecule is composed of a glycerol backbone with three fatty acid (FA) chains. TG are insoluble in plasma and are transported by chylomicrons (CM), very low-density lipoprotein (VLDL), and VLDL-remnants, which are collectively referred to as "TG rich lipoproteins" (TRL) [1]. When ingested, TG undergo hydrolysis by intestinal lipases in the gut, forming FA and monoglycerides [2]. Monoglycerides undergo esterification in enterocytes to reform TG in a reaction catalyzed by diacylglycerol acyltransferase [3]. Cholesterol is esterified with FA by

Abbreviations: AP, acute pancreatitis; Apo, apolipoprotein; ASCVD, atherosclerotic cardiovascular disease; CHD, coronary heart disease; CVD, cardiovascular disease; CM, chylomicrons; CMr, chylomicron remnants; FA, fatty acids; FCS, familial chylomicronemia syndrome; FFA, free fatty acids; HDL-C, high density lipoprotein cholesterol; HTG, hypertriglyceridemia; IDL, intermediate-density lipoprotein; LDL, low density lipoprotein; LDL-C, low density lipoprotein cholesterol; LPL, lipoprotein lipase; MCS, multifactorial chylomicronemia syndrome; MI, myocardial infarction; RC, remnant cholesterol; TG, triglycerides; TRL, triglyceride rich lipoprotein; VLDL, very low-density lipoprotein.

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acyl-coenzyme A:cholesterol acyltransferase [4]. Together, with phospholipids, cholesterol esters, and a variety of apoproteins, the TG are packed into nascent chylomicrons (CM) using apolipoprotein B48 as a scaffold by microsomal TG transfer protein [5]. CM enter the bloodstream, delivering FA to muscle and adipose tissue subsequent to lipolysis by lipoprotein lipase (LPL), which is expressed on the endothelial surface of capillaries in adipose, skeletal, and cardiac muscle tissue. During TG lipolysis, the CM particle is converted into a smaller CM remnant (CMr) [2]. CM and their remnants are cleared from the circulation via hepatocyte receptors and low-density lipoprotein (LDL) receptor related protein 1 [6,7]. CM bind to the latter receptor via apoprotein E. The liver oxidizes the FA in TG via the beta-oxidation pathway or packages them back into VLDL, which are then secreted into the bloodstream [2,8].

Endogenous TRL production begins in hepatocytes via the incorporation of cholesterol, FA, and TG with apolipoprotein B100 by a process that recapitulates intestinal CM production mediated by microsomal TG transfer protein. Hepatic cholesterol concentrations are kept relatively constant, but TG availability varies depending upon recovery from CMr, FA delivery from peripheral sources, and *de novo* lipogenesis [2]. Carbohydrates can be converted into FA; when there is excess carbohydrate available, large amounts of pyruvate are converted to acetyl-CoA, which is used to synthesize both FA and cholesterol. During lipogenesis, FA undergo esterification with glycerol-3-phosphate, which can be released into the bloodstream within the core of VLDL particles. LPL hydrolyzes VLDL, releasing FA for uptake by extrahepatic tissues, such as skeletal muscle and adipose tissue [9]. VLDL particles undergo lipolysis, become smaller in size and increase in density, as TG are depleted and cholesterol is added [10]. Remnant cholesterol (RC) is defined as the amount of cholesterol carried by TRL [11]. The lipoprotein particles form smaller VLDLs and then intermediate-density lipoprotein (IDL) particles (the precursor to LDL particles). VLDL can be cleared by VLDL receptors, LDL receptor related protein 1, and heparan sulfates, while IDLs can be cleared by both LDL receptors and LDL receptor related protein 1 [6,7] (Fig. 1). Given the multiple factors involved in the normal circulation from substrate to lipoprotein clearance, there are multiple points where this process can go awry.

Similar to LDL particles, TRLs become entrapped by glycosaminoglycans within the intima of blood vessels (Fig. 2). Here, macrophages scavenge them, leading to the formation of foam cells and the promulgation of inflammation [12]. Evidence suggests that free fatty acids, released from TG and TRL in the subendothelial space, have pro-inflammatory properties and contribute to atherosclerosis development [12,13]. Remnants further stimulate the expression of pro-inflammatory cytokines and exert direct cytotoxic effects on the endothelium [14,15]. This inflammation within the subendothelial space triggers the formation of a pro-oxidative, pro-atherogenic substrate. In most people, remnant lipoproteins (and TRL in general) are highly heterogeneous. Thus, defining which features confer atherogenicity is challenging [16].

Genome-wide association studies have been performed to screen for genetic causes of hypertriglyceridemia (HTG) [17]. Monogenic

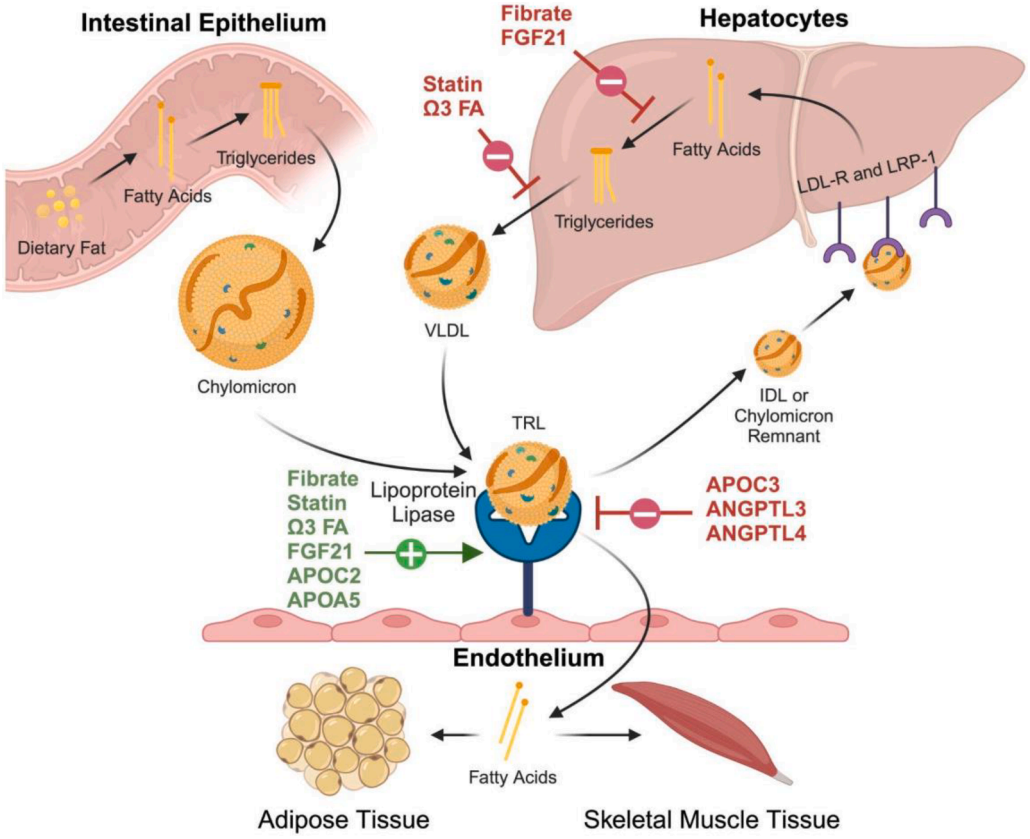


Fig. 1. Absorption, transport, and metabolism of triglycerides.
ANGPTL=angiopoietin-like; APO=apolipoprotein; FA=fatty acid; FGF21=fibroblast growth factor 21; W3= omega3; IDL=intermediate density lipoprotein; LDL-R=low density lipoprotein receptor; LRP-1=low density lipoprotein receptor-related protein 1; TRL=triglycerides rich lipoprotein; VLDL=very low density lipoprotein. Created with biorender.com.

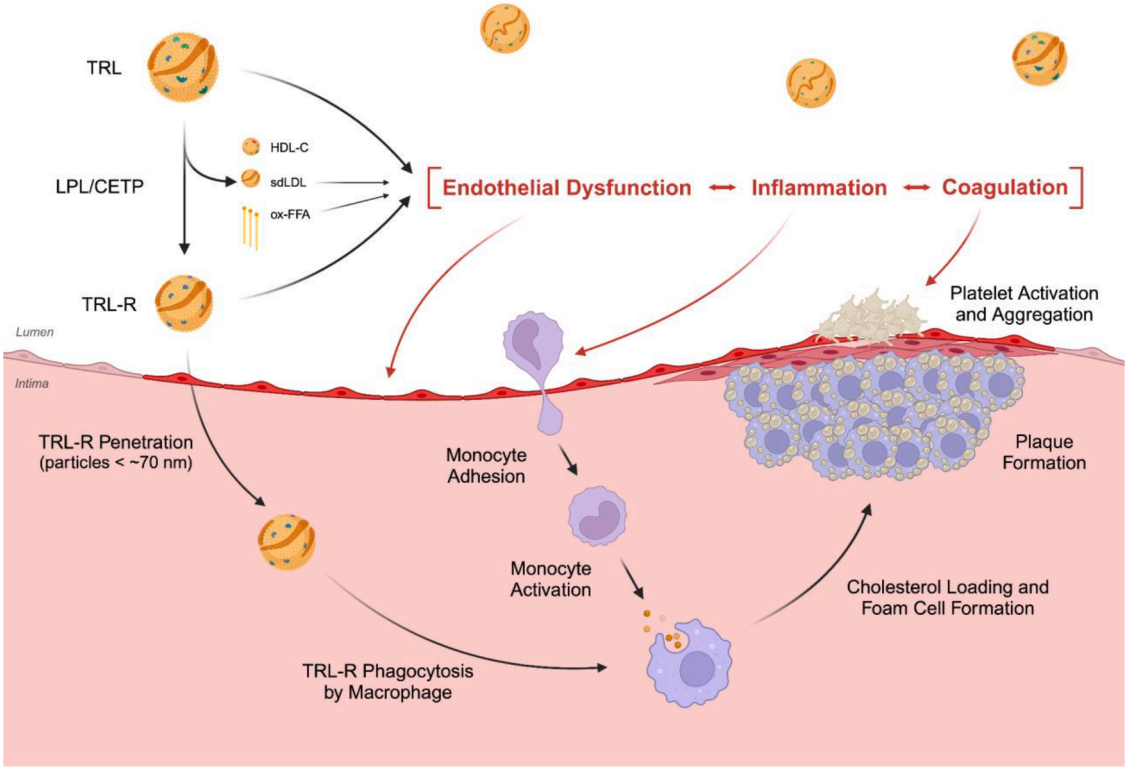


Fig. 2. Pathophysiology of triglyceride pro-atherogenic effects.
CETP: cholesterol ester transfer protein, HDL-C: high-density lipoprotein cholesterol, LPL: lipoprotein lipase, ox-FFA: oxidated free fatty acid, sdLDL: small dense low-density lipoprotein, TRL: triglyceride-rich lipoprotein, TRL-R: triglyceride-rich lipoprotein remnant. Created with biorender.com.

mutations are very rare (approximately 2 % of HTG), whereas polygenic mutations that interact with nongenetic factors constitute most of the genetic drivers of HTG [17]. The spectrum of genetic variations results in a wide range of phenotypic expression of serum TG levels with familial chylomicronemia syndrome (FCS) and multifactorial chylomicronemia syndrome (MCS) at the higher end of the HTG spectrum.

2. Hypertriglyceridemia

2.1. Definition

Normal TG are generally defined as fasting serum levels <150 mg/dL with HTG generally defined as levels >150 mg/dL. The American College of Cardiology (ACC) and American Heart Association (AHA) define moderate and severe HTG (fasting or non fasting) as 175 to 499 mg/dL (2.5 to 5.6 mmol/L), and as a fasting value of >500 mg/dL (>5.65 mmol/L), respectively [18,19]. The European Society of Cardiology Guidelines define mild to moderate HTG as 175 to 885 mg/dL (2.0 to 9.9 mmol/L), severe HTG as >886 mg/dL (>10 mmol/L), and very severe as >1,770 mg/dL (>20 mmol/L)[20]. HTG is pathogenic and is associated with an increased risk for atherosclerotic cardiovascular disease (ASCVD), acute pancreatitis (particularly when >1,000 mg/dl), insulin resistance, and visceral organ steatosis [21].

2.2. Hypertriglyceridemia and Coronary Plaque

Triglycerides have been linked to atherosclerotic pathogenesis via vascular endothelium dysfunction. While large chylomicrons and VLDL fail to cross the endothelial barrier, TRL (such as VLDL-remnants and CMr) can accumulate in the arterial endothelium and become trapped in the subendothelial glycoprotein matrix [22]. There, unlike LDL, they do not require oxidation to be taken up by macrophages which then stimulate formation of foam cells. These foam cells promote fatty streak formation, the precursor to atherosclerotic plaque [15]. TRL are larger than LDL and carry up to 40 times more cholesterol per particle, which may render them more atherogenic than LDL. Free FA (FFA) also induce oxidative stress and inflammation, which can impact insulin signaling and lead to insulin resistance. Additionally, FFA activation of renin-angiotensin system increases endothelin-1 levels, causing vasoconstriction, and triggers apoptotic pathways, resulting in endothelial cell apoptosis [16]. CM and VLDL-remnants amplify the inflammatory response eliciting arterial wall inflammation by increasing interleukin and cytokine release [17].

Numerous studies have focused on the interaction between HTG and coronary plaque. In asymptomatic individuals, the Multi-Ethnic Study of Atherosclerosis (MESA) study showed no association between HTG and coronary artery calcium in an intermediate risk population, though patients with TG >400 mg/dL were excluded [23]. *Raposeiras-Rubin et al* analyzed data from the Progression of Early Subclinical Atherosclerosis (PESA) study and found no correlation between TG level and CAC but TG levels ≥150 mg/dl showed an association with subclinical non-coronary atherosclerosis (odds ratio [OR]: 1.35; 95 % confidence interval [CI]: 1.08 to 1.68; p = 0.008) and with the presence of arterial inflammation (OR: 2.09; 95 % CI: 1.29 to 3.40; p = 0.003) [24]. This prospective cohort study included 3,754 middle-aged individuals (mean age 46, 39 % female, 0.3 % with diabetes, 20 % smoking) without prior

ASCVD, not on statin therapy, with low to moderate cardiovascular risk and evaluated subclinical atherosclerosis by 2-D vascular ultrasound, CAC and fluorine-18 fluorodeoxyglucose uptake on positron emission tomography.

In symptomatic patients, a single-center retrospective study of 2,096 patients who underwent percutaneous coronary intervention guided by optical coherence tomography showed higher TG levels were associated with higher prevalence of plaque vulnerability markers [25]. *Matsuo et al*, using intravascular ultrasound (IVUS) in 40 male patients on statin therapy with stable angina, found RC levels, and not low-density lipoprotein cholesterol (LDL-C), to highly correlate with plaque necrosis [26]. *Koide et al*, conducted a single center prospective study of 935 patients (55 % male, 34 % on statin therapy) who underwent coronary computed tomography angiography (CCTA) for suspected coronary artery disease (CAD), also demonstrated that higher serum TG/high density lipoprotein cholesterol (HDL-C) ratios, but not LDL-C, were associated with high-risk coronary plaque (defined by positive remodeling, spotty calcification, and low-density attenuation plaque) [27]. The relationship between TG/HDL-C ratio with metabolic syndrome, insulin resistance and cholesterol remnants has been established,[28] supporting the role of TRL in plaque vulnerability. Moreover, a study by *Lin et al* retrospectively evaluated 587 patients (mean age 61, 53 % male, 13 % diabetes, 32 % on statin therapy) who underwent a clinically indicated CCTA with a lipid profile within 3 months from the study. Authors found that RC were associated with plaque burden in univariate (OR 1.29 [95 % CI 1.08-1.52], p=0.01) and multivariate analysis in the subset of patients with with optimal LDL-C levels (OR 3.87, 95 %CI 1.34–7.55 per 1 mmol/L increase, p=0.004) [29]. Authors found no association between TG and total atherosclerotic burden. Altogether, findings suggest that it is likely that elevated TG are a marker of increased levels of RC, and that is the latter which causes atherosclerosis.

2.3. Hypertriglyceridemia and ASCVD Risk

Although clinical practice has primarily focused on LDL-C lowering methods to prevent ASCVD, emerging data in the past two decades has broadened the focus to include TG and their impact on ASCVD [30]. Even though normal TG levels have been defined as <150 mg/dL, *Aberra et al* analyzed 5,792 study participants, aged 40-65 years, free of CVD from the Atherosclerosis Risk in Communities and Framingham Offspring studies and found that regardless of the method of measurement, higher TGs were associated with increased CVD risk, even at levels previously considered "optimal" (<150 mg/dL) [31]. The prospective Copenhagen General Population Study, including 58,547 participants in Denmark, reported incidence rates of major adverse cardiovascular event (MACE) and myocardial infarction (MI) in patients with TG levels between 352-439 mg/dL (4.0-4.99 mmol/L) of 7.9 (95 % CI 6.0 to 10.3) and of 4.3 (95 % CI 3.0 to 6.2) per 1000 person-years, respectively, compared to individuals with TG levels <88 mg/dL (<1.0 mmol/L) who had incidence rates of 2.2 (95 % CI 1.9-2.5) and 0.6 (95 % CI 0.5-0.8) per 1000 person-years [32].

A study performed by *Jorgensen et al* including participants within the Copenhagen General Population Study, Copenhagen City Heart Study, and Copenhagen Ischemic Heart Disease Study, showed that higher levels of TG and TRL increased the risk of MI (OR 1.87; 95 % CI 1.25-2.81) regardless of age, sex, smoking, hypertension and diabetes [23]. Data from the PREDIMED (Prevencion con Dieta Mediterranea) population trial with 6,901 individuals (mean age 67, 43 % male and 48 % with diabetes, on statin 41 %) showed that levels of triglycerides (HR 1.04; 95 % CI 1.02-1.06, per 10 mg/dl; p<0.001) and RC (HR 1.21; 95 % CI 1.10-1.33, per 10 mg/dl; p<0.001), but not LDL-C or HDL-C, were associated with cardiovascular outcomes independent of other risk factors [33]. Moreover, among patients on statins, reaching a TG target <150 mg/dL reduced the risk of recurrent cardiovascular events (including recurrent cardiovascular death or MI) compared to TG levels >150 mg/dL, with HR of 0.73 (95 % CI 0.62-0.87; P <0.001) regardless of LDL-C level [34–36]. Lastly, a study from the Korean National Health Insurance Service database across 15.6 million participants (aged 118-99) with follow-up over 8.8 years showed a clear log-linear association between TG and CVD mortality down to 50 mg/dL. Each two-fold increase in TG was associated with a 1.10-fold (overall CVD), 1.22-fold (ischemic heart disease), 1.24 (acute MI), and 1.10-fold (ischemic stroke) higher associated cardiovascular mortality; the effect of TG on CVD was apparent even in participants with LDL-C < 100 mg/dl [37,38]. Interestingly, genetic variants leading to hypotriglyceridemia have been linked to a reduced risk of ischemic heart disease (HR 0.40; 95 % CI 0.31-0.52) [39].

In a cohort of primary prevention subjects from the Jackson Heart Study and a random sample from the Framingham Offspring Cohort Study, RC were associated with predictive of CAD independently of traditional cardiovascular risk factors [25]. In particular, data from the Copenhagen General Population Study, showed that Moreover, RC ≥30mg/dL were typically associated with increased ASCVD risk [27]. Recent studies reported a causal association between RC and CAD [40]. Furthermore, elevated RC levels were associated with an increase in all-cause mortality in large Danish populations both with and without CAD [35,36].

Peripheral vascular disease is another common manifestation of ASCVD and has been linked to CVD mortality. In a large retrospective analysis of a medical claims database, among patients on statin therapy, those with HTG had higher rates of peripheral revascularization compared to patients with TG <150 mg/dL (HR 1.37 95 %, CI 1.35 - 1.64) [41]. Moreover, a meta-analysis including 61 prospective cohort studies reported a higher risk of CVD and all-cause mortality by 13 % and 12 % (P<0.001) per 88 mg/dL (1 mmol/L) TG increase. This relationship could be linked to TG's roles in promoting inflammation, oxidative stress, and endothelial dysfunction [19].

Emerging data have shown a modest association between elevated TG and ischemic stroke. In a large prospective cohort study in China, 267,500 individuals were followed over 6 to 19 years. For every 1 mmol/L increase in serum TG, the adjusted HR was 1.07 (95 %CI 1.05-1.09) [42]. Another prospective study in China with 42,005 participants showed that high TG levels were associated with an increased risk of stroke (HR 1.06, 95 %CI 1.00-1.12) after adjusting for age, body mass index, blood pressure, and other comorbidities [43].

Support for a causal role of HTG in atherosclerotic disease is also provided by genome-wide association and Mendelian randomization studies [44,45]. A mendelian randomization meta-analysis with 17 studies including 62,199 participants and 12,099 CHD events found that for triglycerides, the unrestricted allele score (67 single nucleotide polymorphisms [SNPs]) and the restricted allele score (27 SNPs) were both associated with CHD (OR: 1.62; 95 % CI: 1.24, 2.11 and 1.61; 95 % CI: 1.00, 2.59, respectively) per 1-log unit increment. The interplay among three apolipoprotein A5 (APOA5) variants and TG levels were explored in a Mendelian genomic study. A doubling of non-fasting TG levels and calculated RC levels were associated with an increase of 1.9- and 2.2-fold causal risk for MI, respectively [23]. Another Mendelian randomization study by *Thomsen et al*, reported that genetic variants in LPL resulted in reduced non-fasting TG levels and that an increasing

number of triglyceride-decreasing LPL alleles correspond to a reduction of non-fasting TG levels and RC (by 31 % and 23 %, respectively), with a 15 % increase in HDL-C. A higher number of triglyceride-decreasing LPL alleles was also associated with increased survival (p=0.004) [46].

A Mendelian randomized study by *Ferrence et al* investigated the genetic variants of the LPL gene and the LDL-C–lowering variants in the LDL receptor gene. Both variants were associated with a lower risk of CHD per unit change in apolipoprotein B (apoB) (OR 0.771 [95 % CI, 0.741-0.802], p= 3.9×10^{-38} and OR 0.773 [95 % CI, 0.747-0.801], p = 1.1×10^{-46}, respectively) [47].

The vast majority of available evidence suggests a clinical benefit in reducing TG levels, potentially through an absolute reduction in TRL and apoB-containing lipoproteins.

2.4. Hypertriglyceridemia and Acute Pancreatitis

The prevalence of HTG-induced acute pancreatitis (AP) has been reported to be as high as 22 % [48,49]. The estimated global incidence for AP is 34 cases per 100,000 person-years [50]. While severe HTG is a well-recognized cause of AP, mild to moderate HTG has recently been associated with higher risk of acute pancreatitis (HR 2.3; 95 % CI 1.3-4.0), despite an overall low incidence (5.5 events per 10,000 patient-years) [51,52]. Thus, there may be a dose dependent relationship between HTG and AP. The pathophysiology of HTG causing AP is not fully understood but has been suggested that HTG collectively contributes to making the pancreas susceptible to AP. High levels of CM are thought to increase plasma viscosity, which then may lead to impaired blood flow to pancreatic tissue, tissue ischemia and destruction, and ultimately acute pancreatitis [53,54]. Alternatively, there is reason to believe that ambient exposure to pancreatic lipase by CM in the pancreatic microcirculation leads to rapid fatty acid release triggering trypsin activation and pancreatic auto-digestion [31,32]. Furthermore, the breakdown of TRL increases proinflammatory FFA, leading to damage of vascular endothelium and ischemia within the pancreas [55].

It is unclear whether all TRL are equally causative of AP, or if there is variation in the risk between CM and VLDL particles. While HTG may occur under a variety of circumstances and vary according to variable characteristics like obesity, insulin resistance, other medical and other medical conditions, individuals with FCS have persistently low or no LPL activity and significant chylomicronemia. Individuals with FCS have the highest lifetime risk of AP, with an incidence rate reported as high as 75-85 % [56,57]. Unfortunately, pharmacotherapy for this rare condition is not available since all available TG-lowering medicines enhance LPL activity as their primary mechanism.

2.5. Hypertriglyceridemia: Environmental and Genetic

The prevalence of HTG is approximately 25 % in the United States, with a greater prevalence in patients with metabolic syndrome or diabetes [58]. Among statin-treated adults, 31.6 % have TG >150 mg/dL [58]. In Europe, its prevalence is around 10 % in the adult population, with considerable interregional variation [59]. In the United States population, 2 % present as severe hypertriglyceridemia (TG >500 mg/dL) [60]. Causes of HTG include primary factors, involving monogenic and polygenic variants, and secondary factors, which include medications, comorbidities, and lifestyle behaviors such as dietary indiscretion and alcohol intake [17,56,61]. Other disorders related to HTG include chronic liver, kidney, or thyroid disease, and most commonly, type 2 diabetes. Although incidence of HTG is rising in tandem with that of metabolic syndrome, severe HTG tends to require an inherited predisposition (primary factors).

There are many genetic variants associated with primary HTG. A very small percentage of primary HTG patients (estimated to be around 2 % of cases) are due to monogenic variants, which cause autosomal recessive FCS. Individuals with FCS have persistently low or no LPL activity, which results in the inability to hydrolyze FA from CM and VLDL. They have persistently very elevated and severe HTG and chylomicronemia with low apolipoprotein B. FCS is either due to a mutation in LPL (80 % of cases) or mutations in various genes encoding proteins that metabolize TRL [62]. These patients rarely develop atherosclerosis, possibly due to the inability of the massive CM to penetrate the intima, but they suffer from frequent debilitating AP episodes.

The remaining genetic disorders that cause moderate or severe HTG are from the complex interplay between polygenic mutations and nongenetic factors, which are manifest as conditions like familial HTG, familial combined hyperlipidemia, metabolic syndrome, and remnant hyperlipidemia. MCS is the most common form of chylomicronemia and severe HTG with an estimated US prevalence between 1:600 and 1:250 [63]. This usually has a late-onset and presents with eruptive xanthomas, lipemia retinalis, and abdominal pain. MCS has been studied extensively in genomic studies that have identified over 40 loci with common variants associated with elevations in TG [64]. These variants can either act alone or more commonly, in conjunction with other genetic and nongenetic factors that lead to moderate or severe HTG [62,64].

3. Current Treatments for Hypertriglyceridemia

3.1. Lifestyle and Behavioral Modifications

Lifestyle and behavioral modifications can have a significant effect on TG levels in patients with moderate to severe HTG (Table 1) [61]. For patients with FCS, extreme lifestyle modification with nutritionist support is recommended. Physical activity enhances insulin sensitivity, leading to more effective lipolysis. Cardiac rehabilitation and exercise training can lead to a TG reduction of 31 % in patients with CAD and HTG [65]. Weight loss is also associated with a TG lowering effect; weight loss of 5-10 % can lead to a 20 % TG reduction [66–68].

Altering macronutrient intake by replacing trans-fatty acids with polyunsaturated or monounsaturated fats and increasing dietary fiber has shown effectiveness in lowering TG levels [69]. The Mediterranean diet was associated with the lowest TG levels in the Framingham Heart Offspring Study, showing a 12-14 % TG reduction when compared to the control diet [70–72]. The relationship between alcohol consumption and TG levels is complex, but excess alcohol use has been linked to elevated triglycerides, requiring abstinence in severe cases and particularly in FCS.

Table 1
Treatments Currently Available for Hypertriglyceridemia.

Class	Mechanism of action	Reduction in TG (%)
Weight loss of 5-10 %	Reduced dietary intake, enhanced insulin sensitivity	20 %
Mediterranean diet	Reduced dietary intake of unfavorable fats	12 %
Statins	Inhibit HMG-CoA reductase, which limits hepatic cholesterol biosynthesis	20-50 %
Fibrates	Activate peroxisome proliferator-activated receptors and enhance lipid metabolism	30-50 %
Omega-3 fatty acids	Unclear mechanism	20-30 %

TG=triglycerides; HMG-CoA= 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase.

3.2. Statins

Statins are first-line therapy for the primary prevention of ASCVD in those 40 to 75 years old with an LDL-C ≥70 <190 mg/dL and estimated risk ≥7.5 % as per the pooled cohort equation, those with diabetes who are 40 to 75 years old, and those with LDL-C levels over 190 mg/dL (Central 1) [18]. They are also first-line therapy for secondary prevention in those with established ASCVD or in those with subclinical coronary atherosclerosis [73]. Statins lower LDL-C levels and reduce the production of VLDL, leading to a reduction in both apoB and TG [74]. Notably, in patients affected by HTG, statins also induce a dose-dependent reduction in TG levels, ranging from 10 % to 30 %[61], which can increase to 40-45 % in cases of severe HTG [10]. Concordant results were reported in a review of statins, showing a statin-associated TG reduction from 21 % to 52 % in patients with isolated HTG [75].

Statins are first-line therapy for HTG among patients who meet the aforementioned criteria for primary or secondary prevention of ASCVD. Some evidence suggests that there could be a cardioprotective benefit to additional TG lowering, beyond that provided by a statin. A study of the Cardiovascular Health in Ambulatory Care Research Team (CANHEART) cohort analyzed a secondary prevention cohort of 196,717 patients, almost all of which were already on statin therapy [44]. The study revealed that HTG was common, and that it was associated with increased ASCVD risk proportional to the degree of HTG. Moreover, in

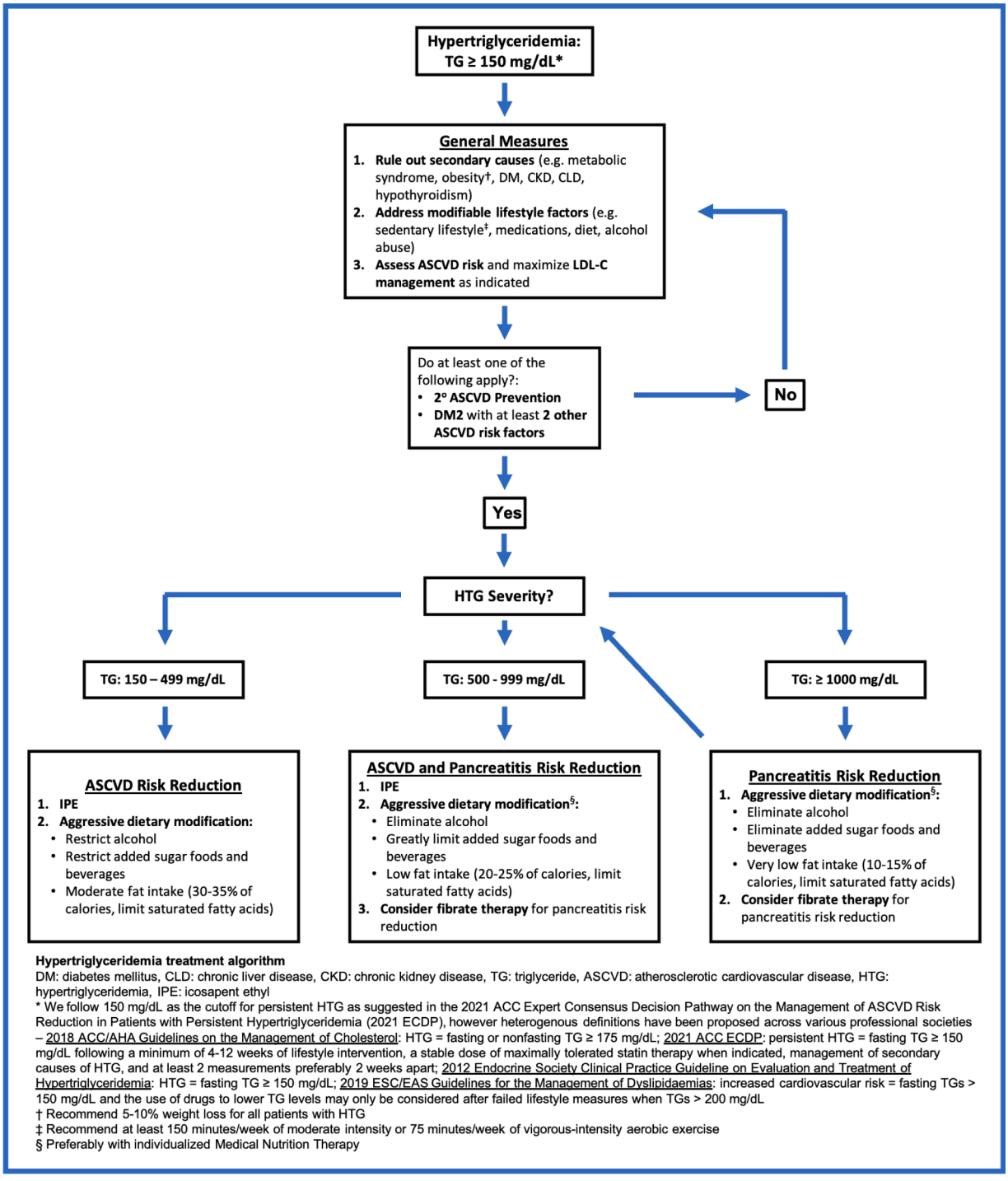
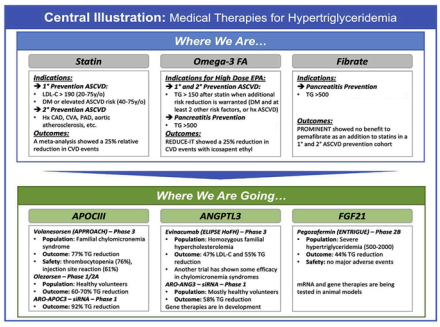


Fig. 3. Suggested HTG treatment algorithm.



Central 1. Illustration. APO=apolipoprotein; ANGPTL=angiopoietin-like proteins; ASCVD=Atherosclerotic Cardiovascular Disease; CAD=coronary artery disease; CVA=cerebral vascular accident; CVD=cardiovascular disease; DM=diabetes mellitus; FA=fatty acid; FGF=fibroblast growth factor; Hx=history; LDL-C=low-density lipoprotein-cholesterol; PAD=peripheral artery disease; TG=triglycerides; HoFH=homozygous familial hypercholesterolemia; siRNA=small interfering RNA; mRNA=messenger RNA.

the Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22) trial[34], patients with low TG (<150 mg/dL) and on statin therapy were at 20 % lower risk of death, MI, and recurrent ACS after adjustment for LDL-C and other covariates as compared to those with TG >150 mg/dL. Therefore, HTG is a marker of residual ASCVD risk after statin therapy, even when LDL-C levels are at goal. These findings lead to the the hypothesis that additional interventions beyond statins, aimed at further lowering TG, could decrease this residual risk [76].

3.3. Omega-3 Fatty Acids

Omega-3 fatty acids are polyunsaturated FA (PUFA), with alpha-linolenic acid (ALA) obtained from plant oils, and eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) procured from fish, other seafood, and fish oil supplements. Omega-3 fatty acids have been an intervention of interest to decrease the residual CVD risk after statin therapy. Epidemiological studies suggested that omega-3 fatty acids are associated with reduced CVD mortality, possibly secondary to their biological effects on plaque stabilization, reduction of inflammation, inhibition of platelet aggregation, and TG reduction [77]. The first major trial for omega-3 supplements in the pre-statin era, Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardio - Prevenzione (GISSI-P), randomized 11,324 patients with a recent MI to 1g daily omega-3, vitamin E both or none (Table 2). It demonstrated a 14 % reduction in death, non-fatal MI, and stroke in those receiving omega-3 (a mix of EPA and DHA) over 4 years of follow up [78–80].

There have been multiple key trials in the post-statin era, though comparison is difficult due to differences in omega-3 doses, formulations (with EPA thought to have more effect than DHA), placebo formulations, and patient populations. In the open-label Japan EPA Lipid Intervention Study (JELIS) trial, 18,645 patients with hypercholesterolemia, with or without CHD, were randomized to 1,800 mg of daily EPA in addition to a statin, versus a statin alone [81]. The trial noted a 19 % relative reduction (p=0.011) in major CVD events over an average follow up period of 4.6 years that was independent of the degree of LDL-C reduction. In subgroup analyses, this was shown to be driven by the secondary prevention cohort, with a significant 19 % relative risk reduction (p=0.048), as the effect on the primary prevention cohort did not reach statistical significance. The Study of Cardiovascular Events in Diabetes (ASCEND) trial, which studied omega-3 fatty acids at a dose of 840 mg per day in 15,480 patients with diabetes without CHD, and the VITAL trial, with a 2 × 2 factorial design which studied 25,871 healthy middle aged adults (men>50, women> 55 years of age) randomized to vitamin D or placebo and omega-3 fatty acids at a dose of 1g per day or placebo, did not show statistically significant effectiveness in the primary prevention of overall CVD events [82,83]. The VITAL trial showed a significant 28 % reduction in total MI (1.1 % vs. 1.5 %, HR 0.72, 95 % CI 0.59-0.90), though the primary outcome of CV death, nonfatal MI, or stroke, was not significant (3.0 % vs. 3.2 %, HR 0.92, 95 % CI 0.80-1.06, p=0.24). Moreover, the nested VITAL-CKD and the VITAL Rhythm, showed no difference in progression/development of CKD among patients with type 2 diabetes or AF development [84,85].

The Long-Term Outcomes Study to Assess Statin Residual Risk with Epanova in High Cardiovascular Risk Patients with Hypertriglyceridemia (STRENGTH) trial sought to examine the effect of omega-3 fatty acids, specifically EPA combined with DHA, in a higher risk patient population [86,87]. This randomized, parallel, double-blind study, included 13,078 statin treated patients (mean age 63, 35 % female, 70 % with diabetes) with CVD or at high risk for CVD and with elevated TG and low HDL-C randomized to omega-3 fatty acids or placebo. The trial was terminated when interim data suggested a low probability of benefit. The primary outcome of cardiovascular death, myocardial infarction, stroke, coronary revascularization, or hospitalization for unstable angina occurred in 12.0 % of the omega-3 group compared with 12.2 % of the placebo group (p=0.84). The Reduction of Cardiovascular Events with Icosa- pent Ethyl–Intervention Trial (REDUCE-IT) trial, however, did show a benefit in patients randomized to icosapent ethyl (IPE) 4g total daily, with a 25 % reduction in CVD events among a population of 8179 statin treated patients (median age 64, 28.8 % female) with elevated fasting TG (135-499 mg/dL) and either CVD (70.7 %) or at high risk for developing CVD (HR=0.75; 95 %CI: 0.68- 0.83; p<0.001) [87]. Notably, the benefit of therapy was independent of TG reduction. The key differences between the REDUCE-IT trial and the STRENGTH trial include different patient populations, with REDUCE-IT having a greater proportion of secondary prevention patients (70.7 % versus 55.9 % in STRENGTH) and higher overall CVD event rates (25.5 % in the placebo group over 4.9 years of follow up versus 12 % over 3.5 years in STRENGTH), different omega-3 formulations (REDUCE-IT had a higher dose and more purified EPA formulation), and different placebos (with REDUCE-IT using mineral oil and STRENGTH using corn oil) [76,88].

3.4. Fibrates

Fibrates activate peroxisome proliferator-activated receptors, increasing the production of apoA-I and apoA-II, while reducing the production of apoB, apoC-III, VLDL, and TG [64]. Fibrates were first tested in the era before widespread use of statins. The Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT) showed that gemfibrozil was associated with a 31 % reduction in TG and a 22 % reduction in CHD death in patients with CHD whose primary lipid abnormality was low HDL-C [65]. A mortality benefit was not appreciated after 6 years of follow up in the Bezafibrate Infarction Prevention Study (BIP), which tested bezafibrate in a population of patients with CHD [66]. The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study evaluated fenofibrate use in a population of diabetic patients without a clear indication for cholesterol-lowering therapy, and also did not show a mortality benefit, though the placebo group was more likely to be treated with alternative lipid lowering agents (primarily statins) [67]. Of note, statin use was overall quite low in these early fibrate trials, which makes them less applicable in the modern era.

Two key trials served to evaluate fibrates in the era of widespread statin use. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) Lipid trial was notable for studying fibrates in a primary and secondary prevention cohort of diabetic patients, all of whom were started on simvastatin at the randomization visit, and it did not show a reduction in mortality or CVD events in the fenofibrate group despite a 16 % reduction in TG compared to placebo [68]. The Pemafibrate to Reduce Cardiovascular Outcomes by Reducing Triglycerides in Patients with Diabetes (PROMINENT) trial, which studied pemafibrate use in

Table 2
Description of major clinical trials on hypertriglyceridemia with ASCVD endpoints.

Name	Published (month/ year)	Intervention	Placebo Composition	Participants	Major Inclusion Criteria	Primary or Secondary Prevention	Length of Trial (Actual Median/ Mean Follow-Up, if Given)	Primary Endpoint	Major Findings (compared to control)	Treatment Composition (per day)
GISSI-P	8/1999	EPA/DHA +/- vitamin E	no placebo	11324	MI within past 3 months	Secondary	3.5 years	cumulative rate of all-cause death, non-fatal MI, and non-fatal stroke	10 % and 15 % RRR of EPA/DHA vs placebo by two-way and four-way analyses, respectively	850–882 mg of EPA/DHA (ratio 1:2), 300 mg vitamin E
JELIS	3/2007	EPA	no placebo	18645	Japanese particupants with total cholesterol > ~250 mg/dL	Mixed	4.6 (mean)	composite: sudden cardiac death, fatal and non-fatal MI, and other non-fatal events including unstable angina pectoris, angioplasty, stenting, or coronary artery bypass grafting	19 % RRR (0.7 % ARR) (P=0.011)	600 mg of EPA, three times a day after meals (to a total of 1800 mg per day)
ASCEND	10/2018	EPA/DHA	olive oil	15480	age ≥ 40 years, DM, and without evidence of CVD	Primary	7.4 (mean)	composite: nonfatal MI or stroke (excluding ICH), TIA, or vascular death excluding ICH	8.9 % vs 9.2 % (rate ratio, 0.97; 95 % CI, 0.87-1.08; P=0.55)	840 mg of marine n−3 fatty acids (460 mg of EPA/ 380 mg of DHA) (fatty acid group)
REDUCE-IT	1/2019	IPE	mineral oil	8179	age ≥ 45 years with CVD or age ≥ 50 with DM and additional risk factors; patients were on statin therapy, with TG 135-499 mg/dL, and LDL-C 41-100 mg/dL	Mixed	4.9 (median)	composite: cardiovascular death, nonfatal MI, nonfatal stroke, coronary revascularization, or unstable angina	17.2 % vs 22.0 % (HR, 0.75; 95 % CI, 0.68-0.83; P<0.001)	4 g IPE
VITAL	4/2020	EPA/DHA + vitamin D	not disclosed	25871	age ≥ 50 (men) or 55 (women) years with no prior history of cancer (except non-melanoma skin cancer), MI, stroke, transient ischemic attack, angina pectoris, coronary-artery bypass grafting, or percutaneous coronary intervention	Primary	5.3 (median)	composite: MI, stroke, and death from cardiovascular causes	3.0 % vs. 3.2 % (HR, 0.92; 95 % CI 0.80-1.06, P=0.24)	840 mg of EPA/ DHA (ratio 1.3:1); 2000 IU/day chlecalciferol
EVAPORATE	10/2020	IPE	mineral oil	80	age 30–85 years with coronary atherosclerosis documented by MDCT (one or more angiographic stenoses with ≥ 20 % narrowing), on statin therapy, and with persistently elevated TG (135–499 mg/dL)	Primary	1.5	change in low-attenuation plaque volume at 18 months between IPE and placebo groups	17 % reduction vs 109 % increase (P=0.0061)	4 g IPE vs 4 g mineral oil
STRENGTH	11/2020	EPA/DHA	corn oil	13078	age ≥ 18 years with established ASCVD; DM with at least 1 additional risk factor: smoking, HTN, hs-CRP ≥ 2, albuminurial; or high-risk primary prevention patients with at least 1 additional risk factor: family history of premature CAD, smoking, hs-CRP ≥ 2 mg/L, CKD, or coronary calcium score > 300 Agatston units	Mixed	3.5 (median)	composite: cardiovascular death, nonfatal MI, nonfatal stroke, coronary revascularization, or unstable angina requiring hospitalization	Terminated - futility (12.0 % vs 12.2 %, HR, 0.99 [95 % CI, 0.90-1.09]; P=0.84)	-

(*continued on next page*)

Table 2 (*continued*)

Name	Published (month/ year)	Intervention	Placebo Composition	Participants	Major Inclusion Criteria	Primary or Secondary Prevention	Length of Trial (Actual Median/ Mean Follow-Up, if Given)	Primary Endpoint	Major Findings (compared to control)	Treatment Composition (per day)
OMEMI	11/2020	EPA/DHA	corn oil	1027	age 70-82 years admitted for MI	Secondary	2	composite: nonfatal MI, unscheduled revascularization, stroke, all-cause death, heart failure hospitalization	21.4 % vs 20.0 % (HR, 1.08; 95 % CI, 0.82-1.41; P=0.60)	930 mg EPA/660 mg DHA, corn oil (56 % linoleic acid, 32 % oleic acid, 10 % palmitic acid)
VA-HIT	6/2001	Gemfibrozil	not defined	2531	men < 74 years old, established CAD, HDL-C < 40 mg/dL, LDL-C < 140 mg/dL, and TG < 300 mg/ dL	Secondary	5.1 (median)	nonfatal MI or death from coronary causes	22 % RRR (4.4 % ARR) in the primary outcome (P=.0006)	1200 mg gemfibrozil
BIP	7/2020	Bezafibrate	not defined	3090	age 45-74 years with previous myocardial infarction or stable angina, total cholesterol of 180-250 mg/dL, HDL-C ≤ 45 mg/dL, TG ≤ 300 mg/dL, and LDL-C ≤ 180 mg/dL	Secondary	16 years (mean)	fatal or nonfatal MI or sudden death	13.6 % vs 15.0 % (P=0.26); post hoc analysis: in patients with TG ≥ 200 mg/dL, reduction in the cumulative probability of the primary end point was 39.5 % (p=0.02)	400 mg bezafibrate
FIELD	11/2005	Fenofibrate	not defined	9795	age 50–75 years, type 2 DM, and not taking statin therapy at study entry	Mixed	5 years	coronary heart disease death or non-fatal MI	11 % RRR (HR, 0.89; 95 % CI, 0.75–1.05, P=0.16)	200 mg fenofibrate
ACCORD	4/2021	Fenofibrate	not defined	5518	DM2, Hgb A1c ≥ 7.5 %, and either age > 40 with evidence of ASCVD or age ≥ 55 years and at least 2 CVD risk factors	Mixed	4.7 (mean)	composite: major cardiovascular event, including nonfatal MI, nonfatal stroke, or death from cardiovascular causes	2.2 % vs 2.4 % (HR, 0.92; 95 % CI, 0.79-1.08; P=0.32)	160 mg fenofibrate
PROMINENT	11/2022	Pemafibrate	not defined	10544	Type 2 DM, TG 200–499 mg/dl, HDL-C ≤ 40 mg/dl, and on moderate-high intensity statin therapy or have LDL-C ≤ 70 mg/ dl within prior 12 months	Mixed	3.4 (median)	composite: nonfatal MI, nonfatal ischemic stroke, hospitalization for unstable angina requiring urgent coronary revascularization, and cardiovascular death	Terminated - futility (hazard ratio, 1.03; 95 % confidence interval, 0.91 to 1.15)	0.2 mg pemafibrate twice daily

CAD: coronary artery disease, CKD: chronic kidney disease, CVD: cardiovascular disease, DHA: docosahexaenoic acid, HDL-C: high-density lipoprotein cholesterol, hs-CRP: high-sensitivity c-reactive protein, ICH: intracranial hemorrhage, IPE: icosapent ethyl, LDL-C: low-density lipoprotein cholesterol, MI: myocardial infarction, RRR: relative risk reduction, TG: triglyceride.

patients with diabetes, HTG, and low HDL-C, put an end to the discussion of fibrate use for ASCVD risk reduction. Among its population of patients, 67 % of which were in the secondary prevention cohort, and 96 % of whom were on a statin, there was no reduction in adverse CVD events associated with the addition of fibrate therapy despite a 26 % reduction in TG and VLDL compared to placebo [69].

3.5. Glucagon-Like Peptide 1 Receptor Agonists (GLP1-RA)

A new set of medications named GLP1-RAs, are now guideline recommend in the management of type 2 DM and overweight status or obesity. They have been shown to reduce the risk of MACE in patients with type 2 DM at high ASCVD risk [89]. Exenatide, liraglutide, and dulaglutide are first generation GLP1-RA. Exenatide was associated with a modest decrease in TG and weight but did not show significant cardiovascular benefits. Conversely, both liraglutide and dulaglutide resulted in a significant reduction in MACE compared to placebo in patients with type 2 DM, and were also associated with a dose-dependent weight loss. No significant changes were documented on TG levels [90–92]. However, in a diabetes population receiving up to liraglutide 1.8 mg weekly, a 60 % reduction in CM secretion and a 33 % reduction in CM synthesis was reported, with no significant effects on VLDL [93]. Semaglutide is a potent long-acting GLP1-RA. In an overweight and obese population, Semaglutide demonstrated a 16 % reduction in TG levels [94]. The SELECT multicenter trial included 17,604 patients (aged $\geq$45 years, BMI $\geq$27 kg/m^2) with established CVD and no history of diabetes (28 % female, 66 % prediabetes, 88 % on statin therapy), who were randomized to semaglutide or placebo. This trial showed that those randomized to semaglutide had lower incidence of cardiovascular death, nonfatal MI, or nonfatal stroke HR 0.80 (95 %CI 0.72-0.90, p<0.001). In addition, semaglutide improved lipid measures, inflammatory markers, and blood pressure. The mean change in TG levels was -18.34 % with semaglutide and -3.2 % with placebo (estimated treatment difference, -15.64 %; 95 %CI -16.68 % to -14.58 %)

Table 3
Description of major clinical trials on hypertriglyceridemia with lipid endpoints.

Name	Published (month/year)	Phase	Intervention	Target	Mechanism	Participants	Major Inclusion Criteria	Primary Endpoint	Major Findings (compared to control)
APPROACH	8/2019	3	Volanesorsen	APOC3	antisense oligonucleotide	66	FCS, TG $\geq$ 750 mg/dL	TG relative to the baseline percentage change, at month 3	ApoC3 - 84 % vs 6.1 % reduction, TG - 77 % vs 18 % reduction; non-HDL-c - 46 % reduction, HDL - 46 % increase, LDL-C - 136 % increase, total ApoB - 20 % increase
COMPASS	5/2021	3	Volanesorsen	APOC3	antisense oligonucleotide	114	HTG (TG $\geq$ 500 mg/dL), BMI $\leq$ 45 kg/m2	% change from baseline in TG at 3 months	TG - 71.2 % vs 0.9 % reduction
BROADEN	11/2022	2/3	Volanesorsen	APOC3	antisense oligonucleotide	40	FPLD, HTG, T2DM	% change from baseline in TG at 3 months	TG - 67 % relative reduction, HFF - 53 % relative reduction
TRANSLATE - TIMI 70	5/2022	2	Vupanorsen	ANGPTL3	antisense oligonucleotide	286	TG $\geq$ 150 mg/dL but $\leq$ 499 mg/dL, non–HDL-c $\geq$ 100 mg/dL, on SOC LLT	% change from bseline Non-HDL-C at 24 weeks	22.0 - 27.7 % reduction in non-HDL-c and 41.3-56.8 % reduction in TG levels, 6.0-15.1 % reduction in ApoB; elevation of liver enzymes $\geq$3 times the upper limit of normal seen in up to 44.4 % of patients; up to 76 % increase in HFF
ELIPSE HoFH	8/2022	3	Evinacumab	ANGPTL3	monoclonal antibody	65	Diagnosis of functional HoFH	% change from baseline calculated LDL-C at week 24	50.4 % reduction in TG (secondary analysis)
(NCT03452228)	3/2023	2	Evinacumab	ANGPTL3	monoclonal antibody	52	TG $\geq$ 1000 mg/dL on more than 1 occasion, all fasting TG values $\geq$ 500 mg/dL (5.6 mmol/L) at screening, prior hospitalization and diagnosis of acute pancreatitis in the past 10 years, on SOC LLT	% change From baseline in TG following 12 weeks of repeated IV doses of evinacumab in actual cohort 3 participants with MCS	27.1 % reduction in TG for cohort 3
ENTRIGUE	6/2024	2	Pegozafermin	FGF21	growth factor analogue	85	TG $\geq$ 500 mg/dL and $\leq$ 2,000 mg/dL	median % change in TGs from baseline to 8 weeks	43.7 % relative reduction in TG

FCS: familial chylomicronemia syndrome, FPLD: familial partial lipodystrophy, HDL-C: high-density lipoprotein cholesterol, HFF: hepatic fat fraction, LDL-C: low-density lipoprotein cholesterol, LLT: lipid lowering therapy, SOC: standard of care, TG: triglyceride.

[95]. The particular mechanism of the outcomes effect and potential contribution of TG lowering still needs to be determined. Lastly, Tirzepatide, a novel GLP1-RA and glucagon inhibitory peptide (GIP) agonist, has been associated with a 20.9 % reduction in weight and a 20.3 % reduction in TG levels [96]. This new group of medications shows promising cardiometabolic effects with lowering of TG but they should not be used in those with history of pancreatitis.

3.5.1. Emerging Treatments for Hypertriglyceridemia

3.5.1.1. Apolipoprotein C3 Inhibition. Apolipoprotein C3 (ApoC3) is a circulating apolipoprotein found on the surface of TRL and is a key regulator of TRL metabolism primarily in the liver and intestine [97]. It inhibits the activation of LPL [98,99]. ApoC3 also inhibits the uptake of TRL via LDL receptor and LDL receptor-related protein-1 [100]. Lastly, intracellularly, ApoC3 promotes TG synthesis and VLDL assembly [101]. It has been proposed that ApoC3 promotes endothelial inflammation [102,103].

3.6. Volanesorsen

Volanesorsen (ISIS 304801) is a second generation 2′-O-(2-methoxyethyl)–modified antisense oligonucleotide (ASO) that inhibits the synthesis of APOC3 in the liver by specifically binding to *APOC3* mRNA and leading to its degradation by RNase H1 [104].

In the multicenter randomized trial, Volanesorsen and Triglyceride Levels in Familial Chylomicronemia Syndrome (APPROACH), 66 patients with FCS received Volanesorsen 300mg/week or placebo (Table 3) [105]. A significant reduction of ApoC3 and TG was documented in the treatment group (84 % and 77 %; P<0.001) compared to the control group (6.1 % and 17 %; P<0.001). The treatment was effective regardless of baseline TG levels or presence of baseline therapy for HTG, with 76 % and 73 % reductions, respectively. Moreover, an increase in LDL-C and apoB was reported (136 % and 20 %, respectively). This translated to an absolute increase from 28 mg/dL to 61 mg/dL in the treatment arm, and was accompanied with a reduction in non-HDL-C of 46 % (from 276 mg/dL to 131 mg/dL) [105].

In terms of safety, thrombocytopenia, was reported in 76 % and 24 % of the treatment and control group, respectively. Additionally, 61 % of patients had at least one injection-site reaction, and consequently, one additional subject dropped out from the treatment arm. Subsequently, the Efficacy and Safety of Volanesorsen in Patients with Multifactorial Chylomicronemia (COMPASS) trial expanded the study population to adults with multifactorial severe HTG or FCS (baseline serum TG >500 mg/dL). In a cohort of 114 patients, a 71.2 % reduction of TG levels was documented in the Volanesorsen group, whereas the control group had a 0.9 % increase in TG level. The development of thrombocytopenia between treatment and placebo groups was reported in 13 % versus 5 %, respectively. Also, injection-site reactions occurred in 24 % versus 0.2 % of the Volanesorsen and placebo groups, respectively [106].

A 2022 meta-analysis of four randomized control trials on volanesorsen documented a reduction of 74 % in TG, 71 % in VLDL-C, and 69 % in apoB48, as well as an increase of 46 % in HDL-C. Volanesorsen was also associated with a 10-fold reduction in the risk of AP [107]. The Assessment of Efficacy and Safety of Volanesorsen for Treatment of Metabolic Complications in Patients with Familial Partial Lipodystrophy (BROADEN) was a multicenter, double-blind, randomized placebo-controlled phase 2/3 trial in patients with familial partial lipodystrophy (FPLD) which reported a reduction in TG level by 67 % more in the treatment group (95 % CI, –104 to–30; P=0.0009). A 53 % relative reduction in hepatic fat fraction in the treatment arm was also noted at 12 months. (observed mean [SD]: 9.7 [7.65] vs. 18.0 [8.89]; P=0.0039) [108]. Thrombocytopenia occurred in 52.6 % of the Volanesorsen group and 11.1 % of the placebo group. A recent fixed-effects meta-analysis on three randomized controlled trials on patients with HTG>500mg/dL reported a significant reduction in the incidence of AP in volanesorsen group compared to placebo (OR 0.18; 95 % CI 0.04-0.82) [105,106,108,109]. TG < 500mg/dL occurred in 84 % of the patients treated with volanesorsen compared to 35 % in the placebo group.

The open-label extension trial of Volanesorsen 300mg/week in patients with FCS (APPROACH-OLE) examined patients from the APPROACH trial, COMPASS trial, and treatment naïve patients not in either index study for up to 104 weeks [110]. The reduction in TG, non-HDL-C, and APOC3 at 3, 6, 12, and 24 months after baseline were comparable to those found in the index study and were also consistent in treatment-naïve patients. Also, consistent with the index studies, the most common adverse event was injection-site reactions (61.8 %); 25 % of patients had significant thrombocytopenia, which led to 10 patients (15 %) being removed from the study.

Given these results, the European Medicines Agency (EMA) allowed conditional marketing authorization for patients with confirmed FCS who are at high risk for AP and in whom there is a suboptimal reduction in TG with other measures [111]. However, the US Food and Drug Administration (FDA) denied approval to Volanesorsen due to concerns for thrombocytopenia and bleeding risk [112,113].

3.7. Olezarsen

Olezarsen (AKCEA-APOCIII-L_{Rx}) is a third-generation ASO that is conjugated to an N-acetyl-galactosamine (Gal-NAc), which increases the first-pass hepatic clearance by specifically binding hepatic asialoglycoprotein receptors and targeting *APOC3* mRNA [114,115]. Preclinical studies have shown a 20-fold improvement in potency as compared to Volanesorsen due to receptor mediated uptake in hepatocytes[116,117], and the addition of Gal-NAc has already shown promise in a multicenter phase 2 clinical trial in patients with elevated lipoprotein(a) [Lp(a)] at lower dosages than prior ASO [118].

In 2016, a phase 1/2a, double blind, randomized, placebo-controlled, dose-escalation study on olezarsen reported a significant reduction of ApoC3 and TG levels (70-80 % and 60-70 %, respectively). No major adverse events were reported; there were no episodes of thrombocytopenia and only one episode of injection site reaction [115]. In 2018, a phase 2, multi-center, dose-ranging, randomized double-blind, placebo-controlled trial randomized 114 subjects to olezarsen 10-50 mg/month or placebo [119]. Notably, patients were receiving standard-of-care preventative therapies for their elevated ASCVD risk. At six months, the treatment arm sustained a mean percent TG reduction of 23 % with 10 mg every 4 weeks, 56 % with 15 mg every 2 weeks, 60 % with 10 mg every week, and 60 % with 50 mg every 4 weeks, compared with an increase of 6 % for the pooled placebo group (p-values ranged from 0.0042 to <0.0001). Olezarsen also led to significant reductions in VLDL-C, non-HDL-C, and apoB, while increasing HDL-C. In the treatment group, 10 % of participants experienced serious adverse events compared to 4 % in the placebo group; none were thought to be drug-related. There were no platelet count reductions to less than 100,000/mL.

Further insights will be gained from several ongoing studies (Table 4). The BALANCE trial (NCT04568434) is a multi-center double-blind study that aims to assess olezarsen's effect on percent change in TG over a 53-week period in 66 patients diagnosed with FCS who have fasting TG ≥880 mg/dL and history of pancreatitis [120]. Two other phase 3, multi-center, randomized, double-blind, placebo-controlled trials (NCT05079919 and NCT05552326) are being done in patients who have fasting TG ≥500 mg/dL and are on standard of care lipid-lowering therapies at baseline [121,122]. A total of 540 and 390 subjects are being recruited for each study and the primary endpoint in both trials is percent change from baseline in fasting TG at 6 months. Lastly, a phase 3, multi-center, placebo-controlled trial (NCT05610280) in 1312 participants with HTG and ASCVD is being undertaken [123]. Subjects must meet one of two inclusion criteria: 1. HTG with fasting TG ≥200 mg/dL and <500 mg/dL with known ASCVD or increased risk for

Table 4
Description of major ongoing clinical trials on hypertriglyceridemia.

Drug	Target	Mechanism	Name	Trial Number	Phase	Participants	Population	Primary Endpoint	Estimated Completion
Olezarsen	APOC3	ASO	-	NCT05579860	1	104	Healthy, adult male or female, 18 to 64 years of age	bioequivalence of olezarsen between 2 subcutaneous (SC) formulations [(autoinjector (AI) and vial] at 2 dose levels	5/2022
Olezarsen	APOC3	ASO	-	NCT05355402	2	152	1. HTG with fasting TG ≥ 150 mg/dL and < 500 mg/dL w/ known or increased risk for ASCVD, or 2. Severe HTG with fasting TG ≥ 500 mg/dL on SOC lipid lowering therapies	% Change From Baseline in Fasting TG at Week 25; CCTA sub study to evaluate plaque progression	12/2023
Olezarsen	APOC3	ASO	BALANCE	NCT04568434	3	66	FCS, TG ≥ 880, prior AP	% Change from Baseline in Fasting TG at 6 Months	10/2023
Olezarsen	APOC3	ASO	-	NCT05079919	3	540	TG ≥ 500, SOC LLT	% Change from Baseline in Fasting TG at 6 Months	2/2025
Olezarsen	APOC3	ASO	-	NCT05185843	3	24	FCS, previously received volanesorsen	safety outcomes, including thrombocytopenia, liver injury, renal injury, and bleeding	6/2025
Olezarsen	APOC3	ASO	-	NCT05610280	3	1312	1. HTG with fasting TG ≥ 200 mg/dL and < 500 mg/dL w/ known or increased risk for ASCVD, or 2. Severe HTG with fasting TG ≥ 500 mg/dL on SOC lipid lowering therapies	% Change From Baseline in Fasting TG at Week 25; CCTA sub study to evaluate plaque progression	6/2025
Olezarsen	APOC3	ASO	-	NCT05552326	3	390	TG ≥ 500, SOC LLT	% Change from Baseline in Fasting TG at 6 Months	7/2025
ARO-APOC3	APOC3	siRNA	SHASTA-2	NCT04720534	2	229	TG ≥ 500 mg/dL and ≤ 4000 mg/dL	% Change From Baseline in Fasting TG at 24 weeks	8/2023
ARO-APOC3	APOC3	siRNA	MUIR	NCT04998201	2	353	TG ≥ 150 mg/dL but ≤ 499 mg/dL, non-HDL-C ≥ 100 mg/dL OR LDL-C ≥ 70 mg/dL	% Change From Baseline in Fasting TG at 24 weeks	8/2023
ARO-APOC3	APOC3	siRNA	PALISADE	NCT05089084	3	72	FCS, TG ≥ 10 mmol/L (≥ 880 mg/dL), on SOC LLT	% Change From Baseline in Fasting TG at 10 months	4/2026
ARO-ANG3	ANGPTL3	siRNA	ARCHES-2	NCT04832971	2	204	TG ≥ 150 mg/dL but ≤ 499 mg/dL, LDL-C ≥ 70 mg/dL OR non-HDL-C ≥ 100 mg/dL, on SOC LLT	% Change From Baseline in Fasting TG at 24 weeks	12/2024
Pegozafermin	FGF21	growth factor analogue	ENTRUST	NCT05852431	3	360	TG ≥ 500 mg/dL and ≤ 2000 mg/dL	% Change From Baseline in Fasting TG at 26 weeks	9/2026

AP: acute pancreatitis, ASO: anti-sense oligonucleotide, ASCVD: atherosclerotic cardiovascular disease, ASO: anti-sense oligonucleotide, CCTA: coronary computed tomography angiography, FCS: familial chylomicronemia syndrome, FPLD: familial partial lipodystrophy, HDL-C: high-density lipoprotein cholesterol, HFF: hepatic fat fraction, HTG: hypertriglyceridemia, siRNA: short interfering RNA.

ASCVD, or 2. Severe HTG with fasting TG ≥500 mg/dL with adherence to standard of care lipid lowering therapies. The primary outcome measure is percent change from baseline in fasting TG at 25 weeks. A coronary tomography angiography sub-analysis is planned to evaluate whether olezarsen use may reduce coronary plaque progression.

Olezarsen presents a promising therapeutic option for patients affected by MCS, FCS, and severe HTG who are at high risk of AP. As such, on February 15th, 2024, the FDA granted Orphan Drug designation to olezarsen for the treatment of FCS [124]. Also, the phase 2 BRIDGE-TIMI 73a (NCT05355402), which examined the safety and efficacy of olezarsen in patients with HTG and high CVD risk, was recently completed and slated as a late-breaking presentation at the American College of Cardiology 73rd Annual Scientific Session and Expo (ACC 2024) [125].

3.8. ARO-APOC3

ARO-APOC3 is a Gal-NAc conjugated short interfering RNA which targets hepatocyte *APOC3* transcription [126]. Phase 1 trials in patients with severe HTG showed 96 % reductions in ApoC3 and 92 % reductions in TG levels in the absence of treatment-related serious or severe adverse events [127]. Consequently, in 2023, Arrowhead Pharmaceuticals received FDA Fast Track designation for reducing HTG in patients with FCS. The phase 2 SHASTA-2 study examining the effect of ARO-APOC3 in patients with severe HTG will be presented as a late-breaking trial at ACC 2024; preliminary reports suggest significant reductions in APOC-3 and TG [128]. At present, ARO-APOC3 is undergoing the phase 2 MUIR study (NCT04998201) in patients with mixed dyslipidemia and phase 3 PALISADE study (NCT05089084) in patients with FCS [129].

3.8.1. Apolipoprotein C2 Inhibition

ApoC2 resides on TRL and has a central role in modulating LPL activity largely through opposing the suppressive effects of ApoC3, and thus, activating LPL [130–133]. Several studies have shown that ApoC2 may be a rate limiting step in LPL-mediate lipolysis and that both low and high circulating levels are associated with HTG [62,134,135]. A

study by Silbernagel et al. examined 3141 subjects over 10 years and found a trend towards an inverse J-shaped relationship between ApoC2 quintiles and CVD mortality [136]. They also used *in vitro* experiments to show that as more exogenous ApoC2 was added, LPL activity increased until very high levels of ApoC2 where function decreased, also following an inverted J-shaped relationship [136]. However, such a non-linear mechanistic relationship between ApoC2 and TG levels and a narrow therapeutic window renders ApoC2 modulation a difficult therapeutic target for pharmacologic management. Furthermore, neither genome-wide association nor Mendelian randomization studies have supported robust causal links between ApoC2 and ASCVD to date [137]. Studies with ApoC2 mimetic drugs have not passed the preclinical phase [138,139].

3.8.1.1. Angiopoietin-Like Protein Inhibition. Lipoprotein Lipase is the central regulator of TG metabolism. LPL activity is upregulated in white adipose tissue (WAT) so TG can be hydrolyzed for FA uptake and downregulated in oxidative tissues (heart and skeletal muscle) when fed, and conversely, LPL function is increased in oxidative tissues while being decreased in WAP when fasting [140]. In addition to ApoC2 and ApoC3, the circulating angiopoietin-like (ANGPTL) proteins (ANGPTL3, ANGPTL4, and ANGPTL8) are key regulators of LPL activity [141,142]. The complex interplay of endocrine and paracrine functions within the ANGPTL family has not been completely elucidated. ANGPTL3 is secreted constitutively throughout the day to inhibit LPL in oxidative tissues and endothelial lipase while fasting, whereas ANGPTL8 and ANGPTL4 are secreted by the liver and adipocytes, respectively, to modulate TG partitioning [141,143]. ANGPTL8 complexes with and stimulates ANGPTL3, so in a fed state when ANGPTL8 is elevated overall LPL function in the skeletal and muscle tissue is decreased. Fasting increases ANGPTL4, which inhibits LPL activity in WAT, and decreases ANGPTL8, which itself increases LPL activity in oxidative tissues while decreasing it in WAT [144]. Modulation of the ANGPTL axis has emerged as a possible target for HTG treatment. ANGPTL3 inhibition by ASO, siRNA, and monoclonal antibodies (mAb) is in development.

3.9. Vupanorsen

Vupanorsen (AKCEA-ANGPTL3-LRx or ISIS 703802) is an Gal-NAc-conjugated ASO. After successful phase 1 and 2a trials in subjects with HTG, type 2 diabetes mellitus, and nonalcoholic fatty liver disease, the phase 2b trial, Effect of vupanorsen on Non-High-Density Lipoprotein Cholesterol Levels in Statin-Treated Patients With Elevated Cholesterol (TRANSLATE-TIMI 70) was conducted [145,146]. The study randomized 286 subjects on statin therapy to placebo or a range of vupanorsen doses who have non-HDL-C $\geq$100 mg/dL and TG 150 to 500 mg/dL to placebo or a range of vupanorsen doses. The treatment arm reported a 22.0-27.7 % reduction in non-HDL-C and 41.3-56.8 % reduction in TG levels, however apoB only saw a 6.0-15.1 % reduction. Vupanorsen appeared to reduce the TG content of VLDL particles rather than decreasing their quantity, suggesting a potential, albeit modest, role in lowering the risk of ASCVD. Regardless, liver enzyme elevations $\geq$3 times the upper limit of normal, which were seen in up to 44.4 % of patients, and dose-dependent increase in hepatic fat fraction of up to 76 % ultimately led to discontinuation of the vupanorsen program [147].

3.10. Evinacumab

Evinacumab is a fully human mAb directed against ANGPTL3. The phase 3 ELIPSE HoFH trial (NCT03399786) showed significant LDL-C reduction with evinacumab versus placebo (49.0 % reduction) in patients with homozygous familial hypercholesterolemia (HoFH) on maximal baseline lipid lowering therapies, and this led to FDA approval with orphan drug status for adjunct LDL-C lowering in this population [148]. In several studies including the ELIPSE HoFH trial and a double-blind, placebo-controlled, phase 2 trial in patients with or without heterozygous familial hypercholesterolemia (HeFH), evinacumab also induced significant reductions in TG (up to 61.5 %); hence, evinacumab is being considered for the management of severe HTG [149–152]. In March of 2023, a phase 2 trial in subjects with severe HTG failed to achieve significance in the prespecified primary endpoint of percent change in mean TG. This was attributed to the lack of normal distribution of TG; however, a post-hoc analysis of median TG levels suggested significant reductions in fasting TGs with evinacumab in patients with normal LPL function [153]. Specifically, the cohort of patients with FCS with bi-allelic loss of function (LOF) LPL mutations did not show a significant TG reduction in the treatment versus control arm (−27.7 % versus −22.9 %, p=0.9495), whereas the response in the cohorts with MCS with and without heterozygous LPL mutations was significant (–64.8 % versus +9.4 %, p=0.0076; and –81.7 % versus +80.9 %, p=0.0418, respectively).

3.11. ARO-ANG3

ARO-ANG3 is a subcutaneously administered Gal-NAc-conjugated double-stranded small interfering RNA, and results from the first in-human proof-of-concept phase 1 trial, AROANG001, were published in September of 2023 [154]. No major adverse events or significant thrombocytopenia were reported. ARO-ANG3 elicited up to a 92.7 % reduction from baseline in serum ANGPTL3 concentrations. There were concomitant reductions in serum TG (up to 58.58 %), LDL-C (up to 24.23 %), and non-HDL-C (26.2 %). The phase 2 trial of ARO-ANG3 in adults with mixed dyslipidemia, ARCHES-2 (NCT04832971), is ongoing [155].

Studies evaluating the effects of GalNAc conjugated ASO and siRNA drugs targeting ANGPTL4 and ANGPTL8 on TG and ASCVD are in progress [140,156,157,158]. Preclinical knockout studies in ANGPTL4 have shown adverse events in mice, leading to safety concerns [159].

3.11.1. Fibroblast Growth Factor Analogues

3.11.1.1. Pegozafermin. Fibroblast growth factor 21 (FGF21) is a stress hormone, which regulates lipid and glucose metabolism, and has pleiotropic effects within the liver that are relevant to TG partitioning and flux. It has roles in FFA oxidation, down-regulation of de novo lipogenesis, TG secretion in the liver, TRL turnover, and up-regulation of LDL-receptor expression [160,161]. Pegozafermin is a glycopyegylated recombinant analog of human FGF21 that has been shown to improve lipid profiles, including reductions in TG in diabetic patients and those with nonalcoholic steatohepatitis. Recently, the phase 2b trial, The FGF21 Analog pegozafermin in Severe Hypertriglyceridemia (ENTRIGUE) was conducted among patients with severe HTG (fasting TG $\geq$ 500 mg/dL and $\leq$2,000 mg/dL) across both a main cohort who were not on concurrent fibrate therapy and a fibrate expansion cohort [162]. After 8 weeks of treatment, the pegozafermin group experienced a significant TG reduction (43.7 %) compared to the placebo group (95 %CI -57.1 %, -30.3 %; p<0.001). The effect was consistent across the 55 % of patients on baseline lipid modifying agents, including statins (45 %), prescription O3FA (14 %), and fibrates (7 %). Furthermore, the study revealed incremental reductions in non-HDL-C (−18.3 % vs −0.6 %; 95 % CI: −30.7 %, −5.1 %; p=0.007, respectively), ApoC3 (–41.9 % vs –8.9 %; 95 % CI: −44.7 %, −18.0 %; p<0.001), and liver fat (−42.2 % vs −8.3 %; 95 % CI: −60.9 %, −8.7 %; p=0.012) in the pooled pegozafermin group as compared to placebo with an overall acceptable safety profile. Taken together, these findings suggest FGF21 analogs like pegozafermin may be promising therapies for robust management of HTG and ASCVD reduction. A phase 3 trial, ENTRUST (NCT05852431) in patients with severe HTG, which will evaluate pegozafermin versus placebo over 26 weeks, is currently recruiting [163].

4. Conclusions

Hypertriglyceridemia is common and clearly pathological even at levels below the definition of optimal and associated with increased ASCVD risk in both primary and secondary risk populations where it represents a significant component of the residual risk. HTG significantly amplifies the risk of ASCVD and can cause AP in particular in those with severe HTG. Guidelines recognize HTG as a risk-amplifying factor and advocate for a systematic and stepwise approach for TG reduction from those with mild to severe HTG (See Fig. 3 for a suggested algorithm). While trials aimed at decreasing ASCVD by reducing HTG have yielded negative results, in recent years, clinicians, researchers, and the pharmaceutical industry have shown increasing interest in developing novel pharmacological agents for HTG treatment. Emerging therapeutics targeting ApoC3 and ANGPTL3 have demonstrated promising safety profiles, tolerability, and efficacy in lowering TG and TRL. These treatments offer hope for further ASCVD risk reduction in patients with HTG, and numerous clinical trials evaluating these therapies are ongoing with therapies that decrease TRL and apoB being more likely to yield improvement in ASCVD outcomes.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Leandro Slipczuk reports a relationship with Amgen Inc that includes: funding grants. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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