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CLINICAL REVIEW
Clinical update

Clinical review on triglycerides

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Hypertriglyceridaemia is a common clinical problem. Epidemiologic and genetic studies have established that triglyceride-rich lipoproteins (TRL) and their remnants as important contributors to ASCVD while severe hypertriglyceridaemia raises risk of pancreatitis. While low-density lipoprotein is the primary treatment target for lipid lowering therapy, secondary targets that reflect the contribution of TRL such as apoB and non-HDL-C are recommended in the current guidelines. Reduction of severely elevated triglycerides is important to avert or reduce the risk of pancreatitis. Here we discuss interventions for hypertriglyceridaemia, including diet and lifestyle, established treatments such as fibrates and omega-3 fatty acid preparations and emerging therapies, including various biological agents.

Keywords Triglycerides • Review • Lipoproteins • Treatment • Hypertriglyceridaemia

Recent epidemiologic and genetic studies establish triglyceride (TG)-rich lipoproteins (TRL) and their remnants as important contributors to atherosclerotic cardiovascular disease (ASCVD). In addition, hypertriglyceridaemia (HTG) is a frequent cause of pancreatitis. This review article summarizes the current understanding of the TG metabolism from a clinical perspective, the current data on TRL for risk stratification and as treatment targets and discusses established and emerging treatment strategies.

Epidemiology

Hypertriglyceridaemia is a very common problem in clinical practice. Its prevalence is ∼10% in the adult population with considerable interregional variation.[1–5] The prevalence of mild-to-moderate HTG parallels that of obesity and Type 2 diabetes; its increase is, therefore, unsurprising over the last few decades.[5] Severe HTG, defined as plasma TG concentration >10 mmol/L (>885 mg/dL) is less common, with prevalence ranging from 0.10 to 0.20%, while very severe HTG, defined at TG >20 mmol/L (>1770 mg/dL) is rarer still (prevalence 0.014%).[1,6] An upper value for 'normal' fasting TG of 1.7 mmol/L (150 mg/dL) is sometimes defined; when considering non-fasting TG concentration, determining HTG prevalence is more difficult since there is no accepted cut-point. However, in normolipidaemic subjects, post-prandial TG values rarely exceed 4.6 mmol/L (400 mg/dL) even post-fat challenge.[7]

Primary vs. secondary hypertriglyceridaemia

Quantifying the abnormal lipoprotein species in patients with elevated TG, as seen in the Fredrickson or WHO classification of hyperlipidaemias, is technically complicated. For this reason, the general term 'HTG' is usually sufficient for clinical purposes. The causes of primary HTG are listed in *Table 1*. Primary severe HTG has both monogenic and polygenic determinants. A tiny subset of these patients (perhaps 2%) has monogenic chylomicronaemia or familial chylomicronaemia syndrome (FCS, former Type 1), a rare form of monogenic HTG with estimated prevalence of 1–10 in a million. Definitive diagnosis of this autosomal recessive disorder requires molecular detection of rare, biallelic (homozygous or compound heterozygous) variants in one of five genes: *LPL* (accounting for 80% of cases), *APOC2*, *APOA5*, *LMF1*, and *GPIHBP1*. The roles of these gene products in lipolysis are shown in *Figure 1*. Genetic assessment has superseded biochemical assays of plasma lipolytic activity as the gold standard for diagnosis.

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Table 1 Primary causes of hypertriglyceridaemia

A. Severe HTG (TG >10 mmol/L)
Monogenic chylomicronaemia (formerly HLP Type 1 or familial chylomicronaemia syndrome)
Lipoprotein lipase deficiency (Bi-allelic *LPL* gene mutations)
Apo C-II deficiency (Bi-allelic *APOC2* gene mutations)
Apo A-V deficiency (Bi-allelic *APOA5* gene mutations)
Lipase maturation factor 1 deficiency (Bi-allelic *LMF1* gene mutations)
GPIHBP1 deficiency (Bi-allelic *GPIHBP1* gene mutations)
Multifactorial or polygenic chylomicronaemia (formerly HLP Type 5 or mixed hyperlipidaemia)
Complex genetic susceptibility, including
Heterozygous rare large-effect gene variants for monogenic chylomicronaemia (see above); and/or
Accumulated common small-effect TG-raising polymorphisms (e.g. numerous GWAS loci including *APOA1-C3-A4-A5*; *TRIB1*, *LPL*, *MLXIPL*, *GCKR*, *FADS1-2-3*, *NCAN*, *APOB*, *PLTP*, *ANGPTL3*)
Other
Transient infantile HTG (glycerol-3-phosphate dehydrogenase 1 deficiency) from bi-allelic *GPD1* gene mutations
B. Mild-to-moderate HTG (TG 2.0–9.9 mmol/L)
Multifactorial or polygenic HTG (formerly HLP Type 4 or familial HTG)
Complex genetic susceptibility (see above)
Dysbetalipoproteinaemia (formerly HLP Type 3 or dysbetalipoproteinaemia)
Complex genetic susceptibility (see above), plus
APOE E2/E2 homozygosity or
APOE dominant rare variant heterozygosity
Combined hyperlipoproteinaemia (formerly HLP Type 2B or familial combined hyperlipidaemia)
Complex genetic susceptibility (see above), plus
Accumulation of common small effect LDL-C-raising polymorphisms

Most remaining cases of severe HTG are strongly polygenic in nature,[1] which includes contributions from rare heterozygous variants in the above five canonical FCS genes and/or accumulated common variants associated with elevated TG levels identified in genome-wide association studies. Sometimes referred to as multifactorial HTG (former Type 5), certain secondary factors (*Table 2*) can further force the expression of severely elevated TG levels.

Mild-to-moderate HTG is similarly highly polygenic in nature (*Table 1*). Simple HTG (former Type 4) resembles severe HTG but with a lower burden of genetic determinants. Dysbetalipoproteinaemia (former Type 3) also has a polygenic foundation, but with the additional genetic 'hit' of homozygosity for the binding defective apo E2/E2 isoform or a rare binding defective dominant mutation in *APOE*. Combined hyperlipidaemia (former Type 2B) similarly has polygenic susceptibility to HTG, but some patients, in addition, have polygenic susceptibility to elevated low-density lipoprotein (LDL) cholesterol (C). Finally, there are numerous secondary factors of HTG (*Table 2*), which may in some patients be sufficient to cause expression of HTG, but frequently interact with polygenic susceptibility: the resulting phenotype is related to the cumulative burden of underlying genetic risk plus intensity of the secondary factor.

Genetic hypotriglyceridaemia

Some rare heterozygous loss-of-function (LOF) variants are associated with reduced TG levels. These patients show protection from ASCVD providing important evidence for a causal role of TG for ASCVD. For instance, rare heterozygous LOF variants in *APOC3* encoding apo C-III are associated with ~50% reduced TG levels and significantly increased clearance of very-low-density lipoprotein (VLDL).[8,9] Furthermore, individuals who are homozygous for *APOC3* LOF variants have very-low-fasting TG levels, with no rise after a fat load.[9] Such LOF variants of *APOC3* are also associated with reduced ASCVD risk.[10] Similarly, heterozygous LOF variants in *ANGPTL3*[11] and *ANGPTL4*[12] genes are associated with reductions both in plasma TG and ASCVD risk. These hypotriglyceridaemic states contrast with mild HTG and increased ASCVD risk seen with heterozygous LOF mutations in *APOA5*.[11]

Normal triglyceride-rich lipoprotein metabolism

Triglyceride-rich lipoproteins—i.e. chylomicrons and VLDL—are spherical complexes comprised of core lipids [TG and cholesterol esters (CE)] with surface apolipoproteins, phospholipids (PL), and free cholesterol (FC). Exogenous (dietary) TG is transported in intestinally derived chylomicrons, while TG of endogenous origin circulates in hepatically derived VLDL. An overview of the normal production and catabolism of TRL is shown in *Figure 1*.[13]

Triglyceride-rich lipoproteins metabolism in disease states

At any level of chylomicron and VLDL secretion, the efficiency of both lipoprotein lipase (LPL)-mediated lipolysis and hepatic uptake of

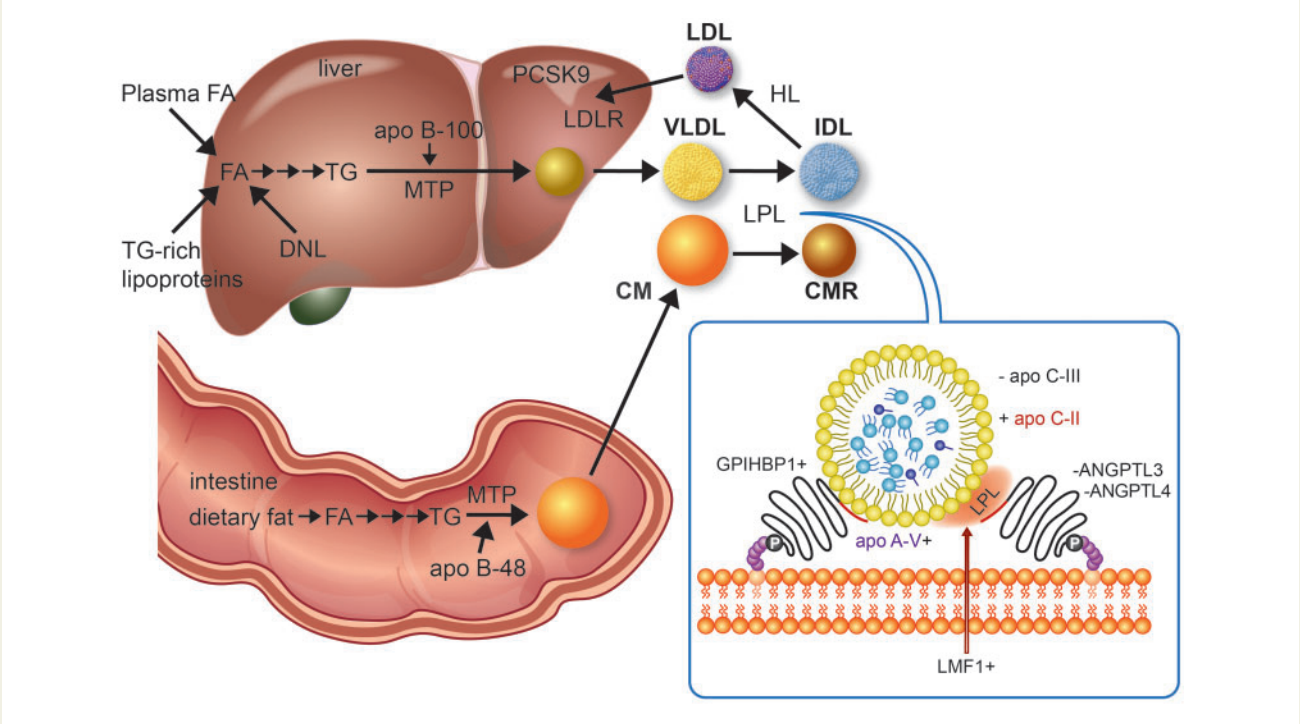


Figure 1 Overview of triglyceride-rich lipoprotein metabolism focused on disease genes and drug targets. Triglyceride-rich lipoprotein assembly begins with triglyceride synthesis, which derive from fatty acids in the intestine from the diet or in the liver taken up from plasma, fatty acids released from lysosomes after breakdown of endocytosed triglyceride-rich lipoproteins, and fatty acids generated from glucose by *de novo* lipogenesis. A series of enzymes, culminating in tissue-specific isoforms of diacylglycerol acyltransferase in intestine and liver, produce triglyceride. Microsomal triglyceride transfer protein unites triglyceride, cholesterol, and phospholipids, with tissue-specific isoforms of apolipoprotein (apo) B, i.e. small B-48, shortened as a result of RNA editing in enterocytes and full-length B-100 in hepatocytes, forming chylomicrons and very-low-density lipoprotein, respectively. Chylomicrons formation also requires Sar1 homolog B GTPase (*SAR1B* gene product, not shown). Chylomicrons enter plasma indirectly through lymphatics while very-low-density lipoprotein is secreted directly into the circulation. Hydrolysis of circulating chylomicrons and very-low-density lipoprotein by lipoprotein lipase releases free fatty acids and produce chylomicron remnant clearance and intermediate-density lipoprotein particles, respectively. Chylomicrons remnant clearance by the liver (not shown) requires apo E, as apo B-48 does not have the low-density lipoprotein receptor binding domain. Intermediate-density lipoprotein can also be removed by the liver (not shown) with apo B-100 and apo E both acting as ligands for the low-density lipoprotein receptor. Intermediate-density lipoprotein can be further lipolyzed by lipoprotein lipase and also remodelled by hepatic lipase to generate low-density lipoprotein, which is cleared by the low-density lipoprotein receptor, whose activity is reduced by proprotein convertase subtilisin kexin 9. The inset depicts lipoprotein lipase activity on a triglyceride-rich lipoprotein particle as well as several interacting proteins at the endothelial surface that affect lipoprotein lipase activity. A plus sign indicates enhancement or stimulation of lipolysis, whereas a minus sign indicates inhibition. Lipase maturation factor 1 (LMF1) is a chaperone protein that ensures that lipoprotein lipase attains functionality and is properly secreted from adipose cells or myocytes. Glycosylphosphatidylinositol-anchored high-density lipoprotein binding protein-1 (GPIHBP1) is necessary for transcytosis of lipoprotein lipase across the endothelium of capillaries in adipose and muscle tissues as well as tethering lipoprotein lipase to the endothelium, thereby stabilizing it. Apo C-II activates lipoprotein lipase, while apo A-V is a stabilizing cofactor. Lipolysis is reduced by apo C-III, which is a component of triglyceride-rich lipoproteins, and by angiopoietin-like proteins 3 and 4 (ANGPTL3 and ANGPTL4), which both operate near the endothelium. Volanesorsen and AKCEA-APOCIII-LRx reduce triglyceride by targeting apo C-III, while evinacumab and IONIS-ANGPTL3-LRx lower triglyceride by targeting ANGPTL3. Peroxisome proliferator-activated receptors (not shown), particularly alpha and delta types, form a regulatory network that influences several of the above target molecules. Adapted from Ref.[13]

remnant particles will determine the circulating levels of fasting and postprandial TG. Lipoprotein lipase-mediated lipolysis of newly secreted TRLs is a saturable process, and as secretion rates and plasma TG levels rise, lipolysis falls.[14] In general, increased VLDL production is the commonest initiating factor for HTG. For any rate of TRL secretion, the inherited capacity of the LPL pathway will also modulate the steady-state level.

Many individuals with HTG also have insulin resistance, obesity, and Type 2 diabetes mellitus, encompassed by the term 'metabolic syndrome'. This milieu drives increased VLDL secretion, which is particularly enhanced when FA and insulin are in excess.[15] Insulin resistance with increased circulating FAs and decreased insulin signalling can also lead to increased chylomicron secretion.[15] Furthermore, hyperglycaemia stimulates, while glucagon-like peptide 1 inhibits chylomicron secretion. Also, apo C-III inhibits removal of remnants; thus in states of increased VLDL secretion, when apo C-III is elevated, uptake of remnant particles will be reduced, compounding the dyslipidaemia.[16]

Table 2 Secondary causes of hypertriglyceridaemia

Diet with high positive energy-intake balance and high fat or high glycaemic index
Increased alcohol consumption (HTG risk increases with > 2 and > 1 drink(s) per day in men and women, respectively)
Obesity
Metabolic syndrome
Insulin resistance
Diabetes mellitus (predominantly Type 2)
Hypothyroidism
Renal disease (proteinuria, uraemia, or glomerulonephritis)
Pregnancy (particularly in the third trimester)
Paraproteinaemia
Systemic lupus erythematosis
Medications, including corticosteroids, oral oestrogen, tamoxifen, thiazides, non-cardioselective beta-blockers and bile acid sequestrants, cyclophosphamide, L-asparaginase, protease inhibitors, and second-generation antipsychotic agents (such as clozapine and olanzapine)

Triglyceride-rich lipoproteins and risk of atherosclerotic cardiovascular disease

Serum TRL are consistently associated with ASCVD risk, probably independent of other metabolic disturbances.[17] For example, in large cohort studies from Copenhagen, non-fasting TG of 6.6 vs. 0.8 mmol/L was associated with a five-, three-, and two-fold increased adjusted risk for myocardial infarction, ischaemic stroke, and all-cause mortality, respectively.[18,19] The Copenhagen General Population Study showed that TG adds important information for primary ASCVD prevention. Individuals aged 40–65 years and free of ASCVD and diabetes with TG >3.0 mmol/L (264 mg/dL) showed a similar risk of ASCVD compared to statin eligible individuals (defined according to the 2016 ESC/EAS guidelines) These data suggest an important opportunity for clinical studies in this population because 80% of ASCVD events occur in individuals who are not eligible for prophylactic statin therapy according to the 2016 ESC/EAS guidelines.[20] Triglyceride levels also independently predict long- and short-term ASCVD risk in patients post an acute coronary syndrome, who are treated with a statin and therefore represent a potential target in secondary prevention.[21]

A causal relationship between TRL and ASCVD is supported by Mendelian randomization studies and in conditions as dysbetalipoproteinaemia, which is typically seen in some patients homozygous for the E2 allele (<1% of Europeans)[18,21,22]; lipoproteins with this form of apo E bind defectively cell surface receptors. However, the extent of the association of serum TG with ASCVD differs between studies and was sometimes lost in multivariate analyses.[22] Indeed, not all TG particles are atherogenic. Large TRL particles such as nascent chylomicrons are unable to penetrate the vessel wall.[23] Although circulating levels of TRLs predict increased ASCVD risk, it is less clear whether TG themselves contribute to atherogenesis. In contrast to cholesterol that accumulates in intimal foam cells and atherosclerotic plaques, TG is degraded by most cells. However, CE-enriched smaller TRLs ('remnants') promote atherogenesis via infiltration into the vessel wall and pro-inflammatory and pro-thrombotic pathways. In addition, elevated TG is frequently associated with pathological high-density lipoprotein (HDL) particles that may contribute to ASCVD risk.[2]

The correlation of plasma TG with ASCVD risk in epidemiological studies is attenuated or lost after adjusting for non-high-density lipoprotein cholesterol (non-HDL-C) or apo B. Most circulating TG is carried by VLDL particles and their remnants, which contain apo B. All TRL particles, as well as LDL particles, contain a single apo B molecule. An estimate for all apo B-containing lipoproteins is non-HDL-C (calculated as TC - HDL-C). A recent Mendelian randomization study found that all apoB-containing lipoproteins have a similar effect on ASCVD risk.[24] Atherosclerotic cardiovascular disease risk mediated by TRLs appears to be determined by the circulating concentration of apoB-containing particles rather than their TG content and that the clinical benefit of lowering TG correlates with the reduction in apoB, rather than the change in plasma TG concentration.

Triglyceride and risk of pancreatitis

Severe HTG may lead to acute pancreatitis and HTG is believed to be causative in 1–10% of episodes of acute pancreatitis.[25,26] It is, however, unclear whether all TRLs carry the same risk or whether chylomicrons and chylomicron remnants carry a greater risk than VLDL and VLDL-remnants. From a clinical perspective, this may not be very relevant, since a mixture of TRLs is present in most cases of severe HTG.

Mild-to-moderate HTG is associated with low-grade inflammation and higher risk of acute pancreatitis. While for many years it was thought that only severe HTG is associated with acute pancreatitis, newer data indicate that pancreatitis risk increases at moderately elevated TG concentrations in a dose-dependent manner.[27] Thus, the risk is elevated [hazard ratio (HR) 2.4] at TG levels between 2.0 and 3.0 mmol/L (177–265 mg/dL) but is still very low in absolute terms (5.5 events per 10 000 patient-years). Even so, the majority of subjects with TG >10 mmol/L (885 mg/dL) will never experience pancreatitis. Cohort studies indicate that acute pancreatitis may occur in 3% of those with TG concentrations between 10 and 20 mmol/L (885–1770 mg/dL) and 15% of those with levels >20 mmol/L (1770 mg/dL), although higher rates were reported in some selected groups. For example, in a German cohort, 19% of those with TG >1000 mg/dL (>11.3 mmol/L) had pancreatitis.[26,28] However, pancreatitis risk is highest in rare patients with monogenic chylomicronaemia, in which chylomicrons are indeed the predominant species, with low to undetectable levels of remnants and downstream lipoproteins due to severely impaired lipolytic machinery.[6,14,29,30]

While TG >10 mmol/L (885 mg/dL) may be sufficient to precipitate acute pancreatitis without additional factors, in many patients, especially those experiencing pancreatitis at relatively low TG levels, additional factors such as alcohol consumption, gallstone disease or certain medications are present. These factors either contribute to

Table 3 Approximate effect size of lifestyle changes on serum triglycerides

Intervention	Lowering of triglycerides	PMID
Alcohol abstinence	Variable response	6736783
	Up to 80% in subjects with high TG and excess intake	4359737
Weight loss	Approximately 8 mg/dL (0.1 mM/L) per kg weight loss	27324830 1386186
Aerobic exercise	10–20%	17533202
n3-PUFA (e.g. fish, flaxseed)	10–15%	16287956

PMID is the PubMed identifier of the respective literature.

HTG or may directly cause acute pancreatitis. The mechanism behind HTG-associated pancreatitis is incompletely understood. Changes in the micro-environment especially changes in local pH due to very high concentrations of free fatty acids have long been postulated as the main factor.[31] Genetic factors such as polymorphisms in the cystic fibrosis transmembrane conductance regulator or the presence of the *APOE* E4 allele may also play a role.[32,33] A recent analysis from Denmark in >115 000 individuals indicates that the inflammation associated with HTG may contribute to the development of acute pancreatitis.[34]

Diagnosis of hypertriglyceridaemia

One reason for variability and heterogeneity of TG measurements is the post-prandial regulation of TG-rich lipoproteins.[35] Atherosclerosis has been suggested to be a 'post-prandial disease', with non-fasting TG contributing to atherogenesis.[36,37] However, an oral fat tolerance test to assess post-prandial TG kinetics did not improve risk prediction in patients with coronary artery disease compared with fasting TG; indeed post-prandial TG increase is highly correlated with fasting TG concentrations.[37] Thus, a fat tolerance test provides no additional clinical information.

In general, non-HDL-C and apoB concentrations are highly correlated with each other and somewhat less with LDL-C. However, in individuals with HTG, the calculated or directly measured LDL-C level may underestimate ASCVD risk. For general risk screening, non-fasting blood samples have similar prognostic value as fasting and are recommended in order to improve patient compliance and because of practical reasons. However, non-fasting samples contain higher TG levels. When assessing patients with elevated TG, e.g. in metabolic syndrome or diabetes, calculated LDL-C should be interpreted with caution; fasting samples remain the method of choice. In a joint statement, the European Atherosclerosis Society and the European Federation of Clinical Chemistry and Laboratory Medicine recommend repeating a fasting sample when non-fasting TG >5 mmol/L (440 mg/dL).[38] For non-fasting samples, TG ≥2 mmol/L (175 mg/dL) should be flagged as abnormal, for fasting samples, abnormal concentrations correspond to TG ≥1.7 mmol/L (150 mg/dL).[38]

Therapy—lifestyle

The most important principle for treating individuals with HTG is to manage lifestyle factors associated with elevated TG.[39,40] These include obesity and metabolic syndrome resulting from physical inactivity and diets with high positive energy-intake balance due to high-fat or high-glycaemic index and, importantly, alcohol consumption. Medications that raise TG include corticosteroids, thiazides, non-selective beta-blockers, oestrogen, tamoxifen, bile acid sequestrants, cyclophosphamide, antiretroviral drugs, and second-generation antipsychotic agents. Additional contributors to secondary HTG are renal disease (uraemia or glomerulonephritis), pregnancy (particularly in the third trimester), paraproteinaemia, and systemic lupus erythematosus.[40]

The first practical step of lifestyle modification relates to alcohol consumption, which should be avoided in any form and quantity by individuals with high TG. Also, because of many additional beneficial metabolic and health effects, an increase of physical activity is another cornerstone of lifestyle recommendations. With regard to diet, the most important principle is to reduce net caloric intake. With regard to specific dietary recommendations, refined carbohydrate-rich foods as well as sucrose and fructose increase TG much more compared to fibre-rich, low glycaemic index foods.[41] As much as possible, saturated fat should be replaced by mono- or polyunsaturated fats that improve insulin sensitivity. Trans-fatty acids should be avoided. Diets rich in saturated fatty acids (tropical oils, fatty or processed meat, sweets, cream, and butter) should be replaced (e.g. with vegetables, wholegrain foods, and fish) and with monounsaturated fat (extra virgin olive oil) and polyunsaturated fat (non-tropical vegetable oils). However, randomized control trial evidence for these specific dietary recommendations is lacking.[39] The approximate effect size of lifestyle changes on serum TG is depicted in *Table 3*.

For patients with severe HTG and fasting chylomicronaemia, total dietary fat should be reduced as much as possible, i.e. <30 g/day. Medium-chain TGs (6- to 12-carbon backbone), which are directly transported and metabolized in the liver following portal vein transit, thereby bypassing chylomicrons formation, can also be considered for selected cases.

Therapy—approved pharmacologic treatments

All commonly available lipid-lowering drugs such as statins, ezetimibe, PCSK9 inhibitors, fibrates, omega-3-fatty acids, and niacin affect TG levels. The effect of LDL-lowering drugs such as statins, ezetimibe and PCSK9 inhibitors on TG levels is usually modest (5–15%), while fibrates, omega-3-fatty acids, and niacin have more profound effects (25–45%). Seminal randomized cardiovascular outcome studies with TG-lowering drugs are summarized in *Table 4*.

Clinically, there are two distinct aspects to TG reduction: (i) modifying lipid levels to decrease ASCVD risk; and (ii) reducing TG to decrease the risk for acute pancreatitis. Although LDL-lowering drugs

Table 4 Randomized cardiovascular outcome studies with triglyceride-lowering drugs

Trial	Treatment	Population	*n*	Endpoint	Statin	*P* < 0.05	PMID
Fibrates							
WHO	Clofibrate	High cholesterol, no CHD	5331	Non-fatal MI + CHD death	No	Yes	361054
CDP	Clofibrate	CHD	3892	Non-fatal MI + CHD death	No	No	1088963
HHS	Gemfibrozil	High cholesterol, no CHD	4081	MI + CHD death	No	Yes	3313041
VA-HIT	Gemfibrozil	Low HDL, CHD	2531	Non-fatal MI + CHD death	No	Yes	10438259
BIP	Bezafibrate	Previous MI or angina	3090	MI + sudden death	No	No	10880410
FIELD	Fenofibrate	T2DM/CVD	9795	Non-fatal MI + CHD death	No	No	16310551
ACCORD	Fenofibrate	T2DM/CVD	5518	MI + stroke + CV death	Yes	No	20228404
Niacin							
CDP	IR-Niacin	CHD	3980	Non-fatal MI + CHD death	No	No	1088963
AIM-HIGH	ER-Niacin	Dyslipidaemia + CHD	3414	MI + stroke + CAD death + revascularization	Yes	No	22085343
HPS2-THRIVE	ER-Niacin + Laropiprant	CHD, PAD, or DM	25 673	MI + stroke + CAD death + revascularization	Yes	No	25014686
High-dose omega-3-fatty acids							
JELIS (open label in Japan)	Icosapent ethyl 1.8 g	High cholesterol	18 645	MI + stroke + sudden cardiac death + angina+ revascularization + PCI + CABG	Yes	Yes	17398308
REDUCE-IT	Icosapent ethyl 4 g	High TG + ASCVD or high-risk DM	8179	MI + stroke + CVD death + angina + revascularization	Yes	Yes	30415628

The main inclusion criteria are listed under 'Population'. 'Endpoint' lists the primary endpoint. 'Statin' indicates whether the triglyceride-lowering drug was tested on a statin background medication. 'PMID' is the PubMed identifier of the primary publication of the trial.
ASCVD, atherosclerotic cardiovascular disease; CAD, coronary artery disease; CHD, coronary heart disease; CVD, cardiovascular disease; ER, extended release; HTG, hypertriglyceridaemia; IR, immediate release; MI, myocardial infarction; PCI, percutaneous coronary angioplasty; TG, triglyceride.

Table 5 Treatment options for hypertriglyceridaemia associated acute pancreatitis

Option	Theoretical basis	Comment
Replete fluids with saline; avoid IV glucose	Glucose may stimulate VLDL production in the liver and thus worsen hypertriglyceridaemia.	Patients with acute pancreatitis are often hypovolemic (third spacing) and may require large amounts of fluids; this may make complete avoidance of iv glucose difficult.
Insulin	Insulin blocks the release of free fatty acids, which may lead to a decreased production of VLDL from the liver.	No randomized, controlled trials available; insulin should only be administered in uncontrolled Type 2 diabetes or in patients with Type 1 diabetes with diabetic ketoacidosis (in which severe hypertriglyceridaemia is not uncommon).
Heparin	Heparin releases LPL from the endothelium and may thus help catabolize TRL lipoproteins.	No randomized, controlled trials available, but if no contraindications are present, then iv-heparin should be considered; in the non-acute setting heparin is used to evaluate LPL activity and results in triglyceride reduction; effect may also depend on the underlying cause of hypertriglyceridaemia (no effect if LPL is deficient or malfunctioning).
Plasmapheresis	The procedure acutely decreases the concentration of TRL by 50–70%, but rebound is rapid unless the underlying cause of HTG is managed.	Reserved for severe HTG in pregnancy; not recommended in most cases of HTG-associated pancreatitis.
Fibrates, omega-3 fatty acids, niacin	May decrease TG levels by up to 70% in chronic HTG.	No role in the acute setting; fibrate and/or high dose omega-3 fatty acids should be considered after the acute episode to prevent recurrence (besides lifestyle modification).
Statins, Ezetimibe, and PCSK9-inhibitors	May decrease TG levels by 5–15% in chronic HTG.	No role in the acute setting; depending on the overall cardiovascular risk LDL-C (non-HDL-C) lowering should be considered after the acute episode.

HDL-C, high-density lipoprotein cholesterol; HTG, hypertriglyceridaemia; LDL-C, low-density lipoprotein cholesterol; LPL, lipoprotein lipase; TG, triglyceride.

have only moderate effects on TG levels, they reduce ASCVD risk in patients with and without HTG.[42] Therefore, depending on the absolute risk, specific LDL-C and non-HDL-C goals should be achieved.[40]

Once the LDL-C goal is achieved, it must be decided, whether residual TG-associated risk for acute pancreatitis and/or ASCVD is sufficiently high to justify initiation of specific TG-lowering drugs, such as fibrates, omega-3-fatty-acids, or niacin. There is a lack of convincing outcomes evidence for ASCVD reduction when these medications are added to statin therapy. There are also no high-quality trial data demonstrating that acute pancreatitis risk decreases with specific TG-lowering therapy.

Fibrates can reduce TG by up to 70%, albeit with marked interindividual variation. As monotherapy, fibrates likely reduce ASCVD risk.[43–45] But when used in combination with statins no further risk reduction was observed,[46] although subgroup analyses indicate that patients with HTG and low HDL-C may benefit from such combination therapy.[47] It is currently unclear whether the failure to show benefit relates to true failure or methodological issues with study design and enrolment criteria. An ongoing ASCVD outcome trial using the new agent, pemafibrate, will probably report in 2021.[48,49] Many lipid clinics in the USA and Canada consider fibrate therapy in patients with elevated ASCVD risk and persistent TG concentrations >200 mg/dL despite reaching LDL-C goal and despite lifestyle modifications.

High doses of omega-3-fatty acids (>2 g/day) can variably decrease TG levels; at lower doses (1 g/day) these agents have generally failed to show reduced ASCVD.[50,51] A recently published study, REDUCE-IT, which evaluated the effect of 4 g icosapent ethyl (Vascepa) in high-risk patients with elevated TG levels on background statin therapy, is interesting and informative in this regard. In >9000 high-risk patients, a dramatic risk reduction (HR 0.75) for ASCVD events was observed over a period of 4.9 years.[52] It is currently unclear whether the observed benefit relates to the particular omega-3 fatty acid formulation used (icosapent ethyl), the high daily dose of 4 g, the carefully selected study population, or a possible deleterious effect of the mineral oil comparator used as placebo. In addition, the strongly positive outcomes seemed to be mediated by factors other than TG reduction, since benefit was seen independent of baseline TG level. Another study using high-dose omega-3 fatty acids is ongoing[53]; once results are reported—likely in 2021—the role of omega-3 fatty acids in treating patients with elevated TG will become clearer.

Therapy of acute pancreatitis associated with high triglyceride

Initial diagnostic and therapeutic steps should be the same as in other causes of acute pancreatitis. A TG level should be determined in all cases of acute pancreatitis as severe HTG may contribute even when the primary cause is obvious (e.g. alcohol). Initially, IV glucose should be avoided as this may further increase TG levels.

Heparin and insulin have been used in TG-associated pancreatitis without clear evidence of benefit and mostly based on case reports

or small case series. Heparin releases endothelial bound LPL and may reduce TG levels.[54] Thus, if there is no contraindication some lipid clinics recommend the use of heparin in this situation. Insulin would be appropriate and indeed recommended in patients with uncontrolled Type 2 diabetes or in patients with Type 1 diabetes with diabetic ketoacidosis, in whom severe HTG is not uncommon.[55] However, in non-diabetics, the use of insulin, with glucose, has not been proven to be efficacious.

Plasmapheresis acutely decreases TG levels by 50–80% and may thus theoretically eliminate the causal factor in HTG-induced pancreatitis.[26,56] However, a recent case series of 22 cases of acute pancreatitis with mean TG levels of 45 mmol/L showed comparable TG reductions—about 70% within 48 h—using conservative management alone, without plasmapheresis.[57] Randomized, controlled studies evaluating the value of plasmapheresis vs. conservative management are desirable. Case series show great variability in triggers for the use plasmapheresis, e.g. severity of both HTG and pancreatitis, as well as in timing and frequency of plasmapheresis, and the anti-coagulant used.[26] Currently, very-low-grade evidence suggests plasmapheresis might rarely be considered in certain situations, such as pregnancy, when TG >11.3 mmol/L (1000 mg/dL) and acute pancreatitis risk is imminent. TG levels rebound rapidly after plasmapheresis if the root cause is not properly managed. Treatment options for HTG-associated acute pancreatitis are summarized in *Table 5*.

Novel and emerging treatments for triglycerides

New fibrate and omega-3 preparation

Pemafibrate (K-877, Kowa), a selective PPAR modulator that reduces TG levels by 35–45%, is being evaluated in PROMINENT (Pemafibrate to Reduce Cardiovascular OutcoMes by Reducing Triglycerides IN patiENts With diabeTes), a Phase 3 ASCVD outcomes study of ~10 000 patients with Type 2 diabetes and HTG (NCT03071692)[48] *Table 6*. STRENGTH (Statin Residual Risk Reduction with EpaNova in High Cardiovascular Risk Patients with Hypertriglyceridaemia; clinicaltrials.gov: NCT02104817) is a current Phase 3 trial of >13 000 patients[53] evaluating ASCVD outcomes of 4 g daily of omega-3 carboxylic acids containing eicosapentaenoic acid and docosahexaenoic acid (Epanova, AstraZeneca).

Treatments to reduce apolipoprotein C-III

Apo C-III is expressed both intestinally and hepatically, circulates with TG-rich lipoproteins, has net deleterious effects on lipoprotein metabolism[58–63] and is a genetically validated target to reduce ASCVD risk.[8–10,64–66] Volanesorsen (Waylivra; ISIS 304801 or IONIS-APOCIII$_{Rx}$; Ionis/Akcea), a subcutaneously injected second-generation 2'-O-methoxyethyl chimeric antisense inhibitor, impairs translation of apolipoprotein (apo) C-III mRNA.[58,67] In a Phase 2 trial of volanesorsen, 300 mg given weekly to HTG patients (NCT01529424), TG levels were reduced by 80%.[68] This correlated with >80% reductions in apo C-III, favourable changes across multiple lipoprotein species, unchanged LDL-C and improved carbohydrate metabolism.[69–71] In three patients with FCS, volanesorsen-reduced TG levels by up to 86%,[72] through a mechanism independent of LPL activity.[73]

APPROACH (NCT02211209) was a 52-week Phase 3 trial of 66 FCS patients with fasting TG ≥8.4 mmol/L randomized to receive weekly subcutaneous volanesorsen 300 mg or placebo.[29] In volanesorsen- and placebo-treated patients, TG decreased by 77% and increased by 18%, respectively ($P < 0.0001$).[74] Two-thirds of patients on volanesorsen had injection-site reactions. Reduced platelet counts below 100 000 per microliter was a common adverse event in the volanesorsen group (15 of 33 patients, two patients with levels < 25 000 per microliter).[74] The drug-induced thrombocytopenia, possibly related to the antisense formulation, led to five early terminations of volanesorsen.[75] COMPASS (NCT02300233) was a 26-week Phase 3 trial of 113 patients with fasting TG ≥5.7 mmol/L who were randomized in a 2:1 ratio to receive volanesorsen 300 mg weekly or placebo. In volanesorsen- and placebo-treated patients, TG decreased by 72% and increased by 1%, respectively ($P < 0.0001$). Site reactions were seen with one-quarter of volanesorsen injections. There was one treatment-related case of serum sickness, but no thrombocytopenia occurrences. In COMPASS and APPROACH studies combined, nine and one pancreatitis events occurred in placebo and volanesorsen groups, respectively ($P = 0.0185$). Quality of life analysis showed reduction of pancreatitis-related symptoms.[76]

The US Food and Drug Administration did not approve volanesorsen for FCS, while the European Medicines Agency recommended conditional marketing authorization. While the mechanism underlying the thrombocytopenia remains unclear, a next-generation N-acetylgalactosamine (GalNac)-conjugated allele-specific oligonucleotide (ASO) targeting apo C-III (AKCEA-APOCIII-L$_{Rx}$) may mitigate this risk; this is being developed by Akcea and Novartis. In a double-blind, placebo-controlled, dose-escalation phase 1/2a trial in healthy volunteers with mild HTG, multiple doses of AKCEA-APOCIII-L$_{Rx}$ resulted in mean TG reductions of 65%, with other favourable changes in the lipid profile, and no safety signals. Drug development is focused on patients with ASCVD risk rather than FCS.

Treatments to reduce angiopoietin-like protein 3

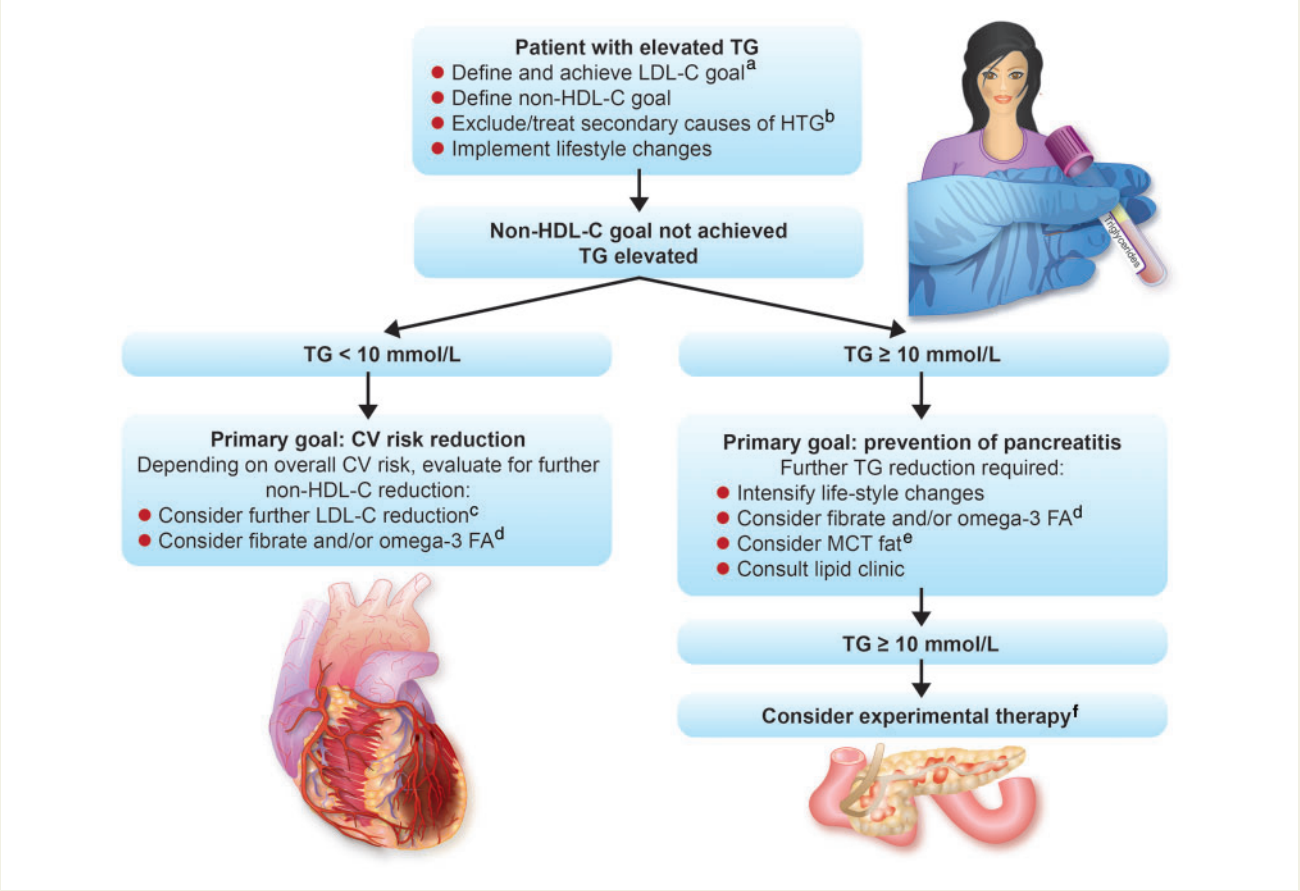
ANGPTL3 is a genetically validated target for HTG to reduce ASCVD risk.[11,77–79] The monoclonal antibody evinacumab and ASO IONIS-ANGPTL3-L$_{Rx}$ reduce angiopoietin-like protein 3 (ANGPTL3), a liver-derived protein that regulates lipid metabolism through incompletely defined mechanisms. Anti-ANGPTL3 therapies reduce both severely elevated TG and severely elevated LDL-C (familial hypercholesterolaemia). In dose-finding studies, evinacumab reduced both TG and LDL-C by up to 75% and 23%, respectively; the latter effect appears to be independent of the LDL receptor pathway.[80] Among homozygous familial hypercholesterolaemia patients, evinacumab reduced LDL-C, TG and HDL-C by 49%, 47%, and 36%, respectively.[81]

IONIS-ANGPTL3-L$_{Rx}$ is a GalNac-modified ASO that targets ANGPTL3.[82] In a dose-finding study in HTG patients, IONIS-ANGPTL3-L$_{Rx}$ reduced TG and LDL-C by up to 63.1% and 32.9%, respectively.[82] In contrast to evinacumab, which acts mainly in the plasma space to bind mature formed ANGPTL3, IONIS-ANGPTL3-L$_{Rx}$ ASO acts primarily within hepatocytes to block production of

Table 6 **Emerging treatments for hypertriglyceridaemia**

Name	Company	Target	Mechanism of action	Indication	Stage	Biochemical effect	Current or possible use in 5 years
Icosapent ethyl	Amarin	Unclear	Not fully defined	Elevated TG	Phase 3 CVOT completed (REDUCE-IT)	Reduces TG	Add-on therapy to statin for ASCVD risk reduction
Epanova	AstraZeneca	Unclear	Not fully defined; omega-3 carboxylic acids containing EPA and DHA	Elevated TG	CVOT in progress (STRENGTH)	Reduces TG	Possible add-on therapy to statin for ASCVD risk reduction
Pemafibrate	Kowa	PPAR	Selective PPAR modulator	Elevated TG	CVOT in progress (PROMINENT)	Reduces TG, increases HDL-C	Possible add-on therapy to statin for ASCVD risk reduction
Volanesorsen (Waylivra)	Akcea	APOC3	First-generation anti-APOC3 ASO	FCS	Approved in Europe but not North America	Reduces TG, increases HDL-C	Possible special access for high-risk patients
AKCEA-APOCIII-L_{Rx}	Akcea/Novartis	APOC3	N-acetylgalactosamine (GalNac)-conjugated anti-APOC3 ASO	ASCVD	Phase 3 CVOT planned	Reduces TG, increases HDL-C	Possible add-on therapy to statin for ASCVD risk reduction; potential off label use for FCS
Evinacumab	Regeneron	ANGPTL3	Anti-ANGPTL3 antibody	FH; severe HTG; FCS	Phase 2–3	Reduces TG, LDL-C, and HDL-C	FCS; HoFH; refractory severe hyperlipidaemia
IONIS-ANGPTL3-L_{Rx}	Akcea-Ionis	ANGPTL3	N-acetylgalactosamine (GalNac)-conjugated anti-ANGPTL3 ASO	FH; severe HTG; FCS	Phase 2–3	Reduces TG, LDL-C, and HDL-C	FCS; HoFH; refractory severe hyperlipidaemia
Alipogene tiparvovec(Glybera)	uniQure	LPL	LPL gene therapy	FCS	Approved; but no longer marketed	Reduces TG	No obvious path forward; indication limited to FCS due to bi-allelic *LPL* gene mutations

ANGPTL3, angiopoietin like 3; APOC3, apolipoprotein C-III; ASCVD, atherosclerotic cardiovascular disease; ASO, antisense oligonucleotide; CVOT, cardiovascular outcomes trial; DGAT, diacylglycerol acyltransferase; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; FCS, familial chylomicronaemia syndrome; FH, familial hypercholesterolaemia; HDL-C, high-density lipoprotein cholesterol, HoFH, homozygous FH; HTG, hypertriglyceridemia; LCAT, lecithin cholesterol acyl transferase; LDL-C, low-density lipoprotein cholesterol; LDLR, LDL receptor; LIPA, lysosomal acid lipase; Lp(a), lipoprotein(a); LPL, lipoprotein lipase; PPAR, peroxisome proliferator-activated receptor; PROMINENT, Pemafibrate to Reduce Cardiovascular OutcoMes by Reducing Triglycerides IN patiENts With diabeTes; STRENGTH, Statin Residual Risk Reduction with EpaNova in High Cardiovascular Risk Patients with Hypertriglyceridaemia; TG, triglyceride.



Take home figure Treatment algorithm for patients with elevated fasting triglycerides. [a]Low-density lipoprotein cholesterol goal depends on absolute cardiovascular risk. [b]Potential secondary causes for hypertriglyceridaemia are listed in *Table 2*. [c]Further low-density lipoprotein cholesterol reduction will also help in achieving non-high-density lipoprotein cholesterol goals. [d]Omega-3-FA, omega-3 fatty acids. [e]MCT, fats containing medium-chain fatty acids. [f]Experimental therapies are listed in *Table 6*.

hepatic ANGPTL3. In murine models, it reduced hepatic TG content, which differentiates it from anti-ANGPTL3 antibodies.[83] A Phase 2 trial of IONIS-ANGPTL3-L_{Rx} in patients with Type 2 diabetes, hepatosteatosis, and TG >2.3 mmol/L is underway (NCT03371355).

Lipoprotein lipase gene therapy

Alipogene tiparvovec (Glybera; uniQure, Lexington, MA, USA) gene therapy for LPL deficiency was available in Europe until 2017, when the sponsor declined to renew market authorization. Spinal anaesthesia was needed for intramuscular injections of the adeno-associated virus subtype 1 vector carrying hyperfunctional *LPL* p.S447X; TG normalized within 12 weeks.[84–86] Unfortunately, TG drifted back to baseline levels within 6 months, although a few exceptional cases experienced sustained benefits.[84–87]

Diacylglycerol acyltransferase inhibition

Pradigastat (Novartis) and AZD7687 (AstraZeneca) are oral inhibitors of intestinal DGAT1, which governs dietary fat absorption and TG synthesis.[58] DGAT1 is not a genetically validated target for either severe HTG or ASCVD risk. Gastrointestinal adverse effects were common with AZD7687.[88] In six FCS patients, pradigastat reduced fasting TG by 70%.[89] In obese patients with milder dyslipidaemia, pradigastat improved TG and other metabolic traits.[90] Dosage reduction and fat restriction mitigated diarrhoea and nausea, but frequent side effects have halted development.[90]

Treatments targeting apolipoproteins C-II and A-V and angiopoietin-like protein 4

Apo C-II is a cofactor for LPL[91,92] and complete apo C-II deficiency accounts for ~2% of all FCS cases.[93] These ultra-rare patients, who are at high risk for acute pancreatitis, might benefit from an infused apo C-II peptide.[94] However, apo C-II has not been genetically validated as a target for ASCVD.[91] In contrast, apo A-V, which promotes LPL activity through partially defined mechanisms, is a strong genetically validated target for ASCVD.[95,96] Boosting apo A-V levels might be beneficial for ASCVD prevention and also for the subset of FCS patients with complete apo A-V deficiency.[93,95] Finally, angiopoietin-like protein 4 (ANGPTL4) regulates LPL activity, analogous to ANGPTL3, but its mechanism is incompletely defined.[91,97,98] Genetically attenuated *ANGPTL4* is associated with favourable lipid and glycaemia profiles, and with reduced ASCVD risk.[12,99] Rodents

given an anti-ANGPTL4 antibody developed mesenteric adenitis, providing a cautionary note about pursuing this target in humans.[99]

Open questions

Importantly, the efficacy and the safety of the emerging treatments for HTG depicted in *Table 6* need to be assessed in outcome trials. Such trials will help to better understand whether the clinical effect of TG-lowering correlates with ApoB reduction and the importance of TG lowering in patients with well-controlled (very low) LDL-C. We need better understanding of the potentially heterogeneous pathology of different TG-rich particles and their metabolism, e.g. the importance of increased TG production vs. reduced catabolism. Since lifestyle measures are of outmost importance for the management of HTG patients, novel approaches are wanted to improve implementation, monitoring, and adherence. To this end, point of care analytical devices such as a recently reported miniaturized electrochemical TG analyzer that can be used in a smartphone may provide important options for future research and patient care.[100]

Summary

Epidemiologic and genetic studies establish TRL and their remnants as important contributors to ASCVD. In addition to LDL-C, the primary treatment target for lipid-lowering therapy, secondary targets that reflect the contribution of TRL such as apoB and non-HDL-C are recommended in the current guidelines.

The first step of treatment is the implementation of lifestyle interventions. Secondly, LDL-C lowering with statins is recommended to reduce vascular risk; this is independent of statin-associated lowering of TRL themselves. Previous trials with fibrates, niacin, and CETP inhibitors did not provide conclusive evidence of ASCVD reduction in patients with optimal cholesterol-lowering. However, recent and ongoing studies show the importance of TRL for the residual risk in ASCVD patients on statin. Novel and emerging data, e.g. on omega-3 fatty acids (high-dose icosapent ethyl) and the selective PPAR modulator pemafibrate may identify patients who will benefit from TRL lowering. Based on enhanced understanding of the molecular pathways of TRL, novel treatment targets have emerged that are in clinical testing. These include apo C-III antisense inhibitor (volanesorsen), inhibitors of angiopoietin-like protein 3 (evinacumab; ASO IONIS-ANGPTL3-L_{Rx}), inhibitors of intestinal diacylglycerol acyltransferase (pradigastat) and treatments targeting apo C-II and A-V, and angiopoietin-like protein 4.

In summary, TRL have emerged as important markers of residual risk and as treatment targets. Several ongoing trials will report the efficacy of novel pharmacologic strategies to lower serum TGs. We speculate that treating of TRL in specific patient populations will become an essential part of lipid-directed treatment in addition to the lowering of LDL-C in the future.

Conflict of interest: U.L.: lectures/consulting for Amgen, Boehringer-Ingelheim, Novartis, Pfizer, Regeneron, Sanofi, and Servier. K.G.P.: lectures/consulting for Aegerion, Akcea, Amgen, Amryt, Berlin-Chemie, Boehringer-Ingelheim, MSD, Novartis, Pfizer, Regeneron, and Sanofi. H.G.: grant from Medimmune/Axtrazeneca; consulting for Sanofi, Regeneron, Amgen, Resverlogix, Janssen, Pfizer, Silence Therapeutics, Merck, Kowa, and Akcea. R.A.H.: consulting for Acasti, Akcea/Ionis, Amgen, HLS Therapeutics, and Sanofi.

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