Hypertriglyceridaemia: an update

Anthony S Wierzbicki ,[1] Eun Ji Kim,[1] Oluwayemisi Esan,[1] Radha Ramachandran[2]

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/jclinpath-2021-207719).

[1]Chemical Pathology, Guy's and St Thomas' NHS Foundation Trust, London, UK
[2]Metabolic Medicine, Guy's and St Thomas' NHS Foundation Trust, London, UK

Correspondence to
Dr Anthony S Wierzbicki, Chemical Pathology, Guy's and St Thomas' NHS Foundation Trust, London SE1 7EH, UK; anthony.wierzbicki@kcl.ac.uk

Received 26 August 2021
Accepted 2 June 2022
Published Online First 16 June 2022

ABSTRACT

Triglycerides (TGs) form part of the standard lipid profile. Elevations in TGs are associated with increased cardiovascular disease risk through triglyceride-rich lipoprotein particles found as part of non-HDL cholesterol. Many elevations of TGs are secondary to other causes, but primary hypertriglyceridaemia syndromes need to be identified. The genetic causes of hypertriglyceridaemia range from familial combined hyperlipidaemia through the autosomal recessive remnant hyperlipidaemia (related to apolipoprotein E variants) and familial chylomicronaemia syndromes. Patients with primary hypertriglyceridaemia >10 mmol/L require characterisation and specific intervention. Simple lipid profiles do not provide adequate information for detailed diagnosis and additional assays such as apolipoprotein (apo)B_{100}, apoE genotype and next-generation sequencing may be useful. Management of raised TGs includes optimising diet, reducing exacerbating factors as well as lipid-lowering medications such as statins, fibrates, niacin and omega-3 fatty acids. Novel medications for orphan disease indications such as familial chylomicronaemia syndrome include volanesorsen, evinacumab and other antisense therapeutics. Extreme hypertriglyceridaemia syndromes, especially chylomicronaemia syndromes, which can be exposed by pregnancy or other factors are a medical emergency and require admission and specialist management sometimes including plasma exchange.

INTRODUCTION

Triglycerides (TGs) show a complex relationship with glucose metabolism and CVD and are affected by processes, which control energy metabolism. The epidemiology, investigation and management of patients with raised TGs have moved on since this topic was last reviewed in 2009.[1] This article presents a short update on these topics

METABOLISM OF TRIGLYCERIDE-RICH LIPOPROTEINS

Biologically, TGs are the main energy source for metabolism and are stored in adipose tissue. A detailed discussion is beyond the scope of this article, but reviews exist on liver, muscle and general metabolism of triglycerides.[2–4] Triglycerides are synthesised by enterocytes in the gut postprandially (exogenous pathway) and by hepatocytes in the liver (endogenous pathway)[5] (online supplemental figure 1). Enterocytes secrete chylomicron (CM) particles containing a short form (48%) of apolipoprotein (apo) B ($apoB_{48}$), while hepatocytes secrete very low-density lipoprotein (VLDL) with full length apoB ($apoB_{100}$). Secretion of hepatic triglyceride-rich lipoproteins (TGRL) is complex as hepatocytes secrete 2 forms of VLDL, which are metabolised differently.[2 6] These particles can be further modified to form atherogenic small dense particles.[7]

DEFINITION OF HYPERTRIGLYCERIDAEMIA

Hypertriglyceridaemia is categorised using the National Cholesterol Education Program consensus with TG >2.3 mmol/L (200 mg/dL) defined as abnormal (table 1).[8] The stricter criterion of >1.7 mmol/L (150 mg/dL) was introduced based on the detection of small dense LDL in Caucasian patients. Elevated TGs are found in 30% of individuals and prevalence increases with age.[9] This definition was based on consensus and does not map easily onto centiles of the triglyceride distribution. In the community, the 99th centile is TG >5.7 mmol/L in men and >3.7 mmol/L in women[10] and elevated TGs are common in lipid clinics.[5 8 11]

EPIDEMIOLOGY OF TRIGLYCERIDES

The relationship of TG with CVD risk has proved difficult to establish given the inverse relationship between TG and high-density lipoprotein cholesterol (HDL-C). The lower variance in HDL-C compared with TG leads to HDL-C being prioritised for CVD risk calculators. The Munster Heart Study (PROCAM)[12] and other cohorts[13] identified TG as a CVD risk factor after correcting for HDL-C. Meta-analyses have confirmed the relationship between TG and CVD risk.[14 15] The clearest relationship with CVD is seen with the cholesterol content of TGRL and other particles—non-HDL-C (the difference between total cholesterol and HDL-C).[15] Non-HDL-C shows greater predictive capacity than LDL-C and correlates strongly with apoB or particle number.[16 17] Many CVD guidelines have adopted non-HDL-C[18–20] as a secondary target after LDL-C while some also add apoB levels as a further criterion.[19 21] While current treatment strategies focus on optimising LDL-C levels, the role of TGs in identifying excess residual risk is increasingly recognised.[5 22 23]

High TGs, reduced HDL-C and atherogenic sdLDL (the atherogenic triad) form part of the metabolic insulin resistance syndrome (M-IRS).[5 7] This is defined as (population-specific[24]) central obesity, allied with 2 from 4 of raised TG (>1.7 mmol/L), reduced HDL-C (<1.0 mmol/L), hypertension and dysglycaemia.[25] The number of M-IRS risk factors shows an approximately linear association with CVD but a power relationship for diabetes.[26]

Elevated TG levels are also associated with increased risk of pancreatitis. The relative risk compared with TG <1.0 mmol/L is 2.9 (95% CI 1.6 to 5.7)-fold at 3–4 mmol/L[27] increasing to 360-fold in patients with TG >20 mmol/L and

Linked

► http://dx.doi.org/10.1136/jcp-2022-208513

Check for updates

To cite: Wierzbicki AS, Kim EJ, Esan O, *et al. J Clin Pathol* 2022;**75**:798–806.

Table 1 Definitions of hypertriglyceridaemia in National Cholesterol Education Program[152] correlated against Fredrickson-defined hyperlipidaemia class, predominant lipoprotein fractions and approximate prevalence in the National Health and Nutrition Examination Study (NHANES)[9] and Very Large Database of Lipids study of specialised lipid sample requests[11]

Category	Definition (mmol/L; mg/dL)	Fredrickson class	Prevalence in general population (%)	Prevalence in lipid clinics (%)
Normal	<1.7 (150)	2A LDL	67	59.9
Borderline	1.7–2.2 (150-200)	2A LDL	15	3.9
Raised	2.3–5.5 (200-500)	2B LDL >VLDL	16.5	10.3
High	5.6–10.9 (500–1000)	3 or 4 IDL and VLDL	1.5	1.7
Severe	11.0–19.9 (1000–1800)	4 Excess VLDL		24.1
Extreme	>20–22 (>1800–2000)	5 VLDL and CM	NA	0.13
	>20–22 (>1800–2000)	1 CM and CM remnants	1 in 10^6	NA

CM, chylomicron; IDL, intermediate density lipoprotein; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein.

chylomicronemia syndromes.[28] There is a case for characterising and treating any patient with TG >10 mmol/L by analogy to severe hypercholesterolaemia with cholesterol >9 mmol/L.[29] Most hospital admissions seem to occur with TG >35 mmol/L,[30] but interactions occur between TGs, inflammation and other factors.[31 32]

TRIGLYCERIDE-RELATED LABORATORY TECHNIQUES

Triglycerides can be measured in fasting and postprandial states.[32–35] Usually, these two measures are well correlated and 8–12-hour fasting is not required except in severe cases or when insulin resistance/diabetes is present.[33 35] The standard assays measure glycerol released after hydrolysis of triglycerides.[36] Patients with some inherited errors of glycolysis or those receiving intravenous fat emulsions, which contain glycerol can have pseudo-hypertriglyceridaemia.[37] While TGs are usually measured in plasma or serum, they can be used in the diagnosis of chylothorax either by a significant discrepancy of lipids and apoB from plasma levels or by TG >1 mmol/L with cholesterol <5 mmol/L.[38] Combinations of lipids and apoB levels are used in the diagnosis of familial chylomicronaemia syndrome (FCS) (ie, TG >10 mmol/L; TG/cholesterol ratio >2.2 (in mmoL/L) and apoB <1 g/L) and to identify patients likely to have apoE variants.[39–41] Automated analysers also detect CM particles through the lipaemia index[42] and ideally all specimens with a high lipaemic index should have TG measured. Elevated indices indicate TG interference with some assays e.g. plasma sodium or liver transaminases.[42]

A detailed discussion of analytical methods is beyond the scope of this article, but details of assays can be found in reference texts.[43] The reference methods of lipid centrifugation identify CM and VLDL fractions as well as LDL and report TG or cholesterol contents.[36] These may be superseded by fast protein liquid chromatography[44] as problems with recovery of 'sticky' CMs occur with centrifuge assays exist.[45] Similarly, antibody-based techniques for quantitation of apolipoproteins within TGRLs or other particles may be superseded by ultraperformance liquid chromatography mass spectrometry methods.[46 47]

Lipid electrophoresis can distinguish CM (origin band), VLDL (pre-beta) and LDL (beta) fractions (online supplemental figure 2) but is a dated slow assay. Its conclusions can be achieved more speedily using automated profiles (lipids and apoB) which can be interpreted using an algorithm[48] (online supplemental figure 3). Assays for $apoB_{100}$ distinguish VLDL from CMs while $apoB_{48}$ is used in research as it is not standardised.

More detailed profiles of TGRLs and their subfractions can be obtained using gradient ultracentrifugation techniques, size separation through graduated gels or by magnetic resonance profiling of lipid particles.[36 49 50] They are mostly used in research as they add little to standard profiles and show poor intermethod agreement.[36 50]

Genetic techniques and triglycerides

Genetic techniques have long been used in the investigation of lipid disorders, but few have made the transition from research to the laboratory except in rare disorders.[51 52] Specific genetic panels are used to identify patients with chylomicronaemia syndromes (see below) and polygenic risk score panels have been devised but not yet widely adopted. The most common genetic marker used in lipid clinics identifies common coding single nucleotide polymorphisms in the apolipoprotein E (apoE) gene, which result in altered amino acid charges.[53] Different isoforms can be separated on ampholyte isoelectric focusing gels (phenotyping) or identified by genetic techniques.[54] ApoE acts a marker of macrophage function and apoE deficient mice are a long-established model of atherosclerosis.[53] Homozygosity for apoE2 in remnant hyperlipidaemia (familial dyslipoproteinaemia; Fredrickson type 3) is associated with excess intermediate density lipoprotein (IDL), remnant hyperlipidaemia, reduced LDL-C (online supplemental figure 4).[55] Many individuals with apoE2/E2 do not develop lipid abnormalities or CVD so secondary genetic or environmental factor are likely to be necessary.[56 57] Homozygosity for apoE2 allied with remnant hyperlipidaemia is associated with an 8–9-fold increased risk of CVD.[13 56] Large epidemiological studies show no clear association with CVD for apoE but a dose proportional association for apoE4 with an 8%–12% excess risk per allele (figure 1).[55] However, apoE4

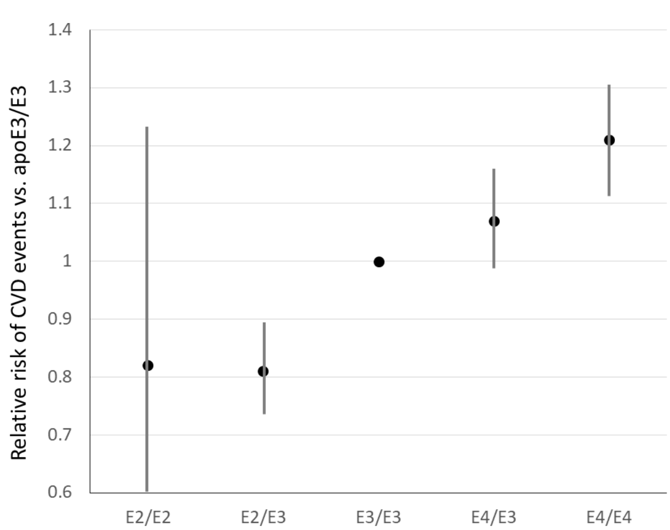

Figure 1 Relative risk of cardiovascular disease (CVD) events associated with different apolipoprotein E genotypes. Data provided for genotypes with 95% CIs. Data from Bennet *et al*.[55]

also associates with the function of brain-associated macrophage lineage cells (microglia) and a dose proportional risk (heterozygote OR 4–6; homozygote OR 8–12) for Alzheimer's disease.[58] This translates to an earlier onset of disease of 2.5 years per apoE4 allele. However, apoE4 shows only a sensitivity of 57% and specificity of 67% for Alzheimer's disease.[58]

Influence of TGs on calculating LDL-C

Most laboratories do not measure LDL-C but calculate its level using the Friedewald equation.[36 59] This method assumes a fixed TG proportion in TGRLs (ie, divide TG by 2.2 (mmol/L) or by 5 (mg/dL) and so requires fasting samples (ideally >12 hours). It shows negative bias in reporting LDL-C with TG >2.0 mmol/L becoming severe at TG >4.5 mmol/L,[45] which is increased with aggressive lipid-lowering therapies as these change the relative loading of TGs and cholesterol in TGRLs.[60] Quantification of LDL-C can be improved using direct LDL assays, but these are not reliably free of interference by TGRLs.[36] Improved methods of calculating LDL-C in fasting samples have been derived[36] either as tables[61] or in a new equation valid up to TG of 8 mmol/L[45] but remain to be fully validated in populations with rare dyslipidaemias or on lipid-lowering therapies.[62]

LDL-C=TC/0.948–HDL-C/0.972–((TG/8.26)+(TGxN-HDL-C/2140)–(TGxTG/21400))–9.44 in mg/dL[45]

CLINICAL ASPECTS OF HYPERTRIGLYCERIDAEMIA

Physical and pathological signs

The skin is a major organ for lipid metabolism.[63] Severe hypertriglyceridaemia is associated with deposition of lipids in the skin.[64] These occur commonly in the thin skin around the eyelids as xanthelasma. Deposits in the dermis visible in skin creases, for example, palmar striae are typical of remnant hyperlipidaemias. Severe cases result in epidermal as well as dermal lipid deposition—tuberose xanthomata on the knees, elbows and occasionally palms. Greater levels of TGs and VLDL are associated with epidermal TG and cholesterol deposition especially on the abdomen, elbows, knees and pressure points (Koebner phenomenon). Eruptive xanthomata are filled with yellow lipid deposits but fade to pink as they resolve.

Primary versus secondary hypertriglyceridaemia

A distinction is made between primary and secondary hypertriglyceridaemias. The common secondary causes are poorly controlled diabetes, excess alcoholic consumption and various medications or endocrine disease (table 2). Many cases arise from interaction of genetic factors with environmental and secondary causes such as non-alcoholic fatty liver disease. Secondary causes need treatment alongside lipid-lowering therapies. Lipodystrophy or mitochondrial myopathies require disease-specific management and some lipid-lowering therapies may not be appropriate.[65]

GENETIC LIPID SYNDROMES

A number of genetic aetiologies are associated with hypertriglyceridaemia[66] ranging from common disorders such as familial combined hyperlipidaemia (FCHL), uncommon such as remnant hyperlipidaemia or rare ones such as monogenic dyslipidaemias.[67]

Familial combined hyperlipidaemia

FCHL has a frequency of 0.48%–11.4% depending on the criteria used.[68] It may show an 'autosomal dominant' pattern inheritance but is actually caused by polygenic inheritance of a group of genes exacerbated by environmentally determined factors leading to a variable lipid profile and often premature CVD.[69 70] The diagnosis is based on the lipid profile, family history and exclusion of secondary causes though diagnostic nomograms based on TG and apoB have been proposed in some populations.[71] Unlike familial hypercholesterolaemia (FH), FCHL is not a classical genetic disorder of coding proteins. It is most probably caused by an adiposopathy characterised by poor adipocyte retention of TGs and enhanced release of free fatty acids.[72 73] The phenotype is exacerbated by the lipid genes located on chromosome 11 and those associated with endoplasmic reticulum VLDL handing (eg, uncoupling stimulating factor-1).[74] This hyperlipidaemia is often treated with fibrate-statin combination therapy though no specific trials exist for this indication.

Remnant hyperlipidaemia

Remnant hyperlipidaemias are associated with polymorphisms in apoE.[75] Homozygosity for apoE2 (familial dysbetalipoproteinaemia) leads to reduced clearance of IDL by the apoE-binding domain of the LDL receptor. Only 1% of individuals carrying apoE2/E2 develop remnant hyperlipidaemia suggesting an interaction with environmental or (as yet uncharacterized) genetic factors as apoE2 explains 35% of the variance.[76] It is associated with 7–9-fold excess of CVD distributed across all vascular beds.[13 56] Dermal skin crease lipid deposits may be

Table 2 Principal causes of secondary hypertriglyceridaemia

Lifestyle factors	Principal diseases	Medications
Pregnancy (physiological in third trimester)	Diabetes (uncontrolled)	Glucorticoids
	Insulin resistance/obesity	Retinoids
Alcohol excess	Chronic renal failure	Oncologics (bexarotene; PD1 antagonists)
Carbohydrate excess	Cushing's syndrome	Anti-psychotics
Glucose-containing drinks	Growth hormone deficiency	HIV protease inhibitors and non-nucleoside analogues
Caffeine excess	Lipodystrophy	Ciclosporin
Adrenergic drugs of abuse	Metabolic disease and mitochondrial myopathy	Tamoxifen
	Glycogen storage disease	High-dose beta-blockers
	Bone marrow disease (paraproteinaemia)	High dose thiazide diuretics
	Infection/extreme inflammation for example, pancreatitis	Amiodarone
	Systemic lupus erythematosus	Interferon

Many of these causes interact with polygenic risk factors for hypertriglyceridaemia in susceptible individuals.

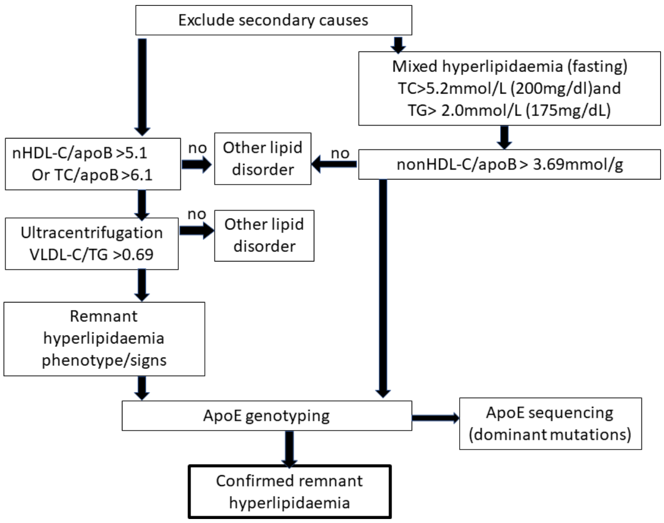

Figure 2 Clinical algorithms to identify patients requiring apolipoprotein E genotyping based on simple lipid profiles including total cholesterol (TC), triglycerides (TG), non-high-density lipoprotein cholesterol (nonHDL-C) and apolipoprotein B (apoB)[40] and those also providing ultracentrifuge-derived beta quantification of very low-density lipoprotein-cholesterol (VLDL-C).[39]

visible and in extreme cases planar palmar xanthomata develop. ApoE genotype or phenotype assays are specialist tests so algorithms to improve clinical diagnosis or to guide requesting exist (figure 2).[39 40] This hyperlipidaemia is commonly treated with fibrate-statin combination therapy to enhance clearance of IDL though no specific trials exist for this indication.

Familial chylomicronaemia syndrome

FCS is a rare cause of severe TG elevation with a frequency of 1 in 1 000 000.[77] It is caused by homozygosity in loss of function of genes associated with the lipolytic pathway—

specifically LPL and its controlling cofactors (apoC2; apoA5; lipid maturation factor-1 and a cell surface receptor for LPL adducted to CM or VLDL—glycosyl-phospho-inositol-HDL-binding protein-1 (GPIHBP1). Persistence of CM in the general circulation is associated with free fatty acid toxicity and allied with their pro-inflammatory properties promotes pancreatitis.[78] In contrast, VLDL particles seem to have a lower inflammatory potential, so many patients with FCS have TG in the range 5–30 mmol/L while extreme TG levels >50 mmol/L are more typical of patients with excess VLDL. The risk of pancreatitis is associated exponentially with TGs[28] but the threshold for presentation with pancreatitis seems to be 35 mmol/L.[30] A consensus statement has suggested a scoring system for diagnosis of FCS, which can be used to guide genetic testing (table 3).[79 80] A monogenic cause has been found in 75% of patients with clinical presentations of FCS, but 25% of identical severe phenotype seems to have a polygenic cause.

Multigenic chylomicronaemia syndrome

A spectrum of severity exists in chylomicronaemia syndromes ranging from polygenic through rare variants to monogenic FCS.[81–83] Patients with severe recurrent disease or extreme TG levels more commonly have monogenic causes, but polygenic causes occur in many cases and predominate at lower degrees of severity and hypertriglyceridaemia.[84] In epidemiological studies of patients with high TG levels with multifactorial chylomicronaemia syndrome (MCS), heterozygosity for rare pathogenic variants is associated with a more severe phenotype than polygenic disease.[81] Polygenic risk scores for high TGs for have been proposed but have not been widely validated.[76 84] These effects are exacerbated not only by environmental risk factors,[85 86] such as viral infections, smoking, gallstones or alcohol, but also by diabetes and autoimmune syndromes (IgG4 disease)[87] or genes directly associated with pancreatitis.[86] Polymorphisms also interact with environmental factors, for example, a carbohydrate responsive element binding protein polymorphism interacts with sugary drink consumption affecting TG levels.[88]

Severe TG syndromes are commonly associated with pancreatitis rather than CVD events but apoA5 variants are independently associated with CVD.[89] A small proportion of chylomicronaemia syndromes has an autoimmune cause with antibodies to LPL pathway proteins (including GPIHBP1, apoA5 and apoC2), and these may merit treatment with immune modulating drugs such as rituximab if such autoantibodies are found.[90]

Table 3 Points scoring system for familial chylomicronaemia syndrome[79 80]

Parameter	Points
Fasting TG >10 mmol/L (at least 3 times; measured 1 month apart)	+5
Fasting TG >20 mmol/L (at least once)	+1
Previous TG <2 mmol/L	−5
No secondary factors (except pregnancy or oestrogen therapy) Exclude alcohol, diabetes, metabolic syndrome, hypothyroidism, corticosteroids and additional drugs	+2
History of pancreatitis	+1
Unexplained recurrent abdominal pain	+1
No history of FCHL	+1
TG response to drug therapy <20%	+1
Age of onset	
<10 years	+3
<20 years	+2
<40 years	+1

FCS likely >10 pts; FCS unlikely <9 pts; FCS very unlikely <8 pts.
AUROC 0.91; Sensitivity 88%; Specificity 85%.
FCHL, familial combined hyperlipidaemia; FCS, familial chylomicronaemia syndrome; TG, triglycerides.

TREATMENT OF HYPERTRIGLYCERIDAEMIA

Dietary interventions

High-fat diets increase postprandial triglycerides, including both CMs and VLDL,[91] but most VLDL-TG is derived from adipose tissue fatty acid recycling,[92] and the major effects are mediated by insulin action in the liver.[93] As the production of TGs is related to dietary factors, the amount of calories, carbohydrate and their glycaemic index will affect TG levels, modify HbA_{1c} and weight.[94] Alcohol contributes to higher TGs both through its actions in contributing free fatty acid precursors, action on cholesterol ester transfer protein and possibly by inhibiting LPL.[95 96] Catecholamines regulate lipolysis. Epinephrine analogues including cocaine or amphetamines have significant effects on TG levels.[97] A non-linear effect in normotriglyceridaemic individuals is seen with coffee with a reduction switching to an increase in those exceeding six cups per day.[98] This threshold is likely to be reduced in those who smoke[98 99] or have higher baseline TGs. A different relationship is seen with (green) tea as lower TG levels are found.

Medium chain triglyceride (MCT) oil has long been used in the management of chylomicronemia, but data on its efficacy in patients with high TG are limited. In normotriglyceridaemic individuals, MCT oil use reduces TG by 10%,[100] but case reports in chylomicronaemia show up to 90% reductions.[101]

Insulin resistance and metabolic syndrome

Insulin resistance is associated with changes in lipid profiles and excess peripheral lipolysis due to the reduced sensitivity of adipose tissue to insulin with increased free fatty acid flux to the liver leading to VLDL synthesis and lipogenesis causing a fatty liver and excess plasma VLDL and TGRLs. Treatment of insulin resistance can reduce TGs by 10%–25%.[102] Weight loss is key to improving the metabolic syndrome. Among drug therapies, metformin, pioglitazone, glucagon-like peptide 1 (GLP1) agonists or dipeptidyl peptidase-1 antagonists (which prevent GLP1 degradation) have all been shown to improve NAFLD, insulin resistance and in many cases TG levels. However, GLP-1 agonist therapies are associated with an increase in risk of pancreatitis and so have to be used with caution in patients with severe hypertriglyceridaemia.

Statins

Statins inhibit 2-hydroxymethylglutarylCoA reductase causing upregulation of hepatocyte LDL receptors. The LDL receptor can clear TGRLs through binding apoE and LDL by binding $apoB_{100}$.[103] Statins reduce TGs in proportion to baseline TG levels and to the LDL-lowering potency and dose of the statin.[104] They are first-line drugs in the treatment of CVD and reduce CVD events by 21% per 1 mmol/L LDL-C reduction.[105] Statins have anti-inflammatory actions through inhibition of isoprenoid synthesis[106 107] and reduced the incidence of pancreatitis in clinical trials in a post hoc analysis of patients with limited, if any, hypertriglyceridaemia.[108]

Fibrates and peroxisomal proliferator activator receptor agonists

Fibrates are peroxisomal proliferator activator receptor-alpha (PPAR-α) agonists.[109 110] This nuclear receptor gene family can function as homodimers or heterodimers with the retinoid-X receptor[109] (online supplemental figure 5). This network of receptors with (likely) fatty acid derived ligands can modulate lipids (PPAR-α), glucose (PPAR-γ), bile acids (farnesoid-X receptor) and inflammation (glucocorticcoids). Drugs tend to be selective and not specific for receptor subsets in this network. Fibrates increase synthesis of LPL, inhibit apoC3 (an inhibitor of TGRL clearance by the LDL receptor) and may increase apoA1 synthesis and HDL-C. Adverse effects include increased risk of gallstones and creatinine. Unlike other fibrates, emfibrozil inhibits statin metabolism increasing the risk of myositis/rhabdomyolyisis.[111] Fibrates reduce TGs in proportion to baseline levels with reductions of 40% occurring at TG 3–5 mmol/L. While effective in MCS, they show reduced or no efficacy in FCS. No specific trial data exist for fibrates in pancreatitis, but meta-analyses from other CVD trials suggest either deleterious or beneficial effects. Fibrates have a third-line status for treatment of CVD as they not only reduce non-fatal CVD events[112] but also improve microvascular endpoints in diabetes such as retinopathy or nephropathy.[113]

Niacin

Niacin has a complex mechanism of action.[114] It inhibits TGRL production by inhibiting diacylglycerol transferase-1 to interfere with lipid particle loading and increases HDL-C by inhibiting the HDL-apoA1 holoparticle receptor. Its action in inhibiting peripheral lipolysis mediated by the GP109A receptor (mimicked by nicotinamide) is not essential to its activity. Its adverse effects include severe facial flushing mediated by prostaglandin (PG) D2 and PGE2 but also causes significant dysglycaemia.[115] Niacin reduces TGs to a similar extent to fibrates and reduces CVD events in monotherapy but does not add to statins in combination therapy.[23 116] Its use is now not recommended in many guidelines.

Omega-3 fatty acids

Omega-3 fatty acids reduce TGs related to dose and baseline TG levels with a maximum reduction of 40% at TG=8 mmol/L[117] by reducing production rates of CM and VLDL[118] mediated by the free fatty acid receptor-4 and have anti-inflammatory actions.[119 120] At low doses, their effects on CVD outcomes are minimal[121] but higher doses, particularly of eicosapentaenoic acid (EPA), seem to be associated with lipid-independent effects in reducing CVD events.[23 122] High doses of EPA are associated with reductions in CVD events but increase rates of atrial fibrillation and gastrointestinal adverse events. High dose mixed omega-3 fatty acids may exacerbate hypertriglyceridaemia in extreme cases (eg, chylomicronaemia) but may be used in special circumstances (eg, pregnancy) (see below).

Orphan indication drugs

A number of orphan indication medications have been developed for use in FCS.[123] Initially, drugs targeting CM and VLDL synthesis were considered. One patient with FCS was treated with lomitapide, a microsomal transfer protein inhibitor, for 13 years with a reduction in TGs and pancreatitis but later developed hepatic fibrosis.[124] Newer therapies target improving clearance of TGRLs by increasing the apoE/apoC3 ratio[125] by inhibiting apoC3 or by targeting other modulators of the LPL pathway such as angiopoetin-like peptides. Volanesorsen, an antisense oligonucleotide (ASO) apoC3 inhibitor, reduces TGs by 70%–80%.[126 127] Postlicensing registry studies suggest a 30%–50% reduction in pancreatitis events and admissions in FCS based on secondary (safety) endpoints.[128 129] This ASO is associated with injection site reactions and thrombocytopaenia. Regular platelet monitoring is required and most cases of thrombocytopaenia are treated with dose interruption. Newer formulations in development such as ApoC3LRx based on N-acetyl galactosamine (Gal-NAc) modified ASO technology seem to have less adverse effects.[130] An alternative strategy is to target ANGPTL3 either though an antibody (evinacumab) or using ASO or siRNA technologies. Early studies suggest that this is more effective in MCS than FCS unlike volanesorsen, which seems equally effective in both.[131] Other approaches rely on upregulating apoC2 function—an activator of LPL.[132]

Novel medications

Gene therapy has been investigated in patients with FCS. Alipogene tiparvovec, an adeno-associated virus-1 vector containing an increased function variant LPL S447X, transiently decreased TGs but reduced pancreatitis events by 30%–50% by reducing CM production.[133] It was discontinued for commercial reasons.

New therapies in development include further trials of derivatives of EPA, a new more PPAR-α-specific fibrate- pemafibrate, which does not seem to affect creatinine metabolism, and a ANGPTL3 inhibitor—vupanorsen. The high TG/low HDL-C subgroup in the Action to Control Cardiovascular Risk in Diabetes trial showed benefit of adding fenofibrate to statin therapy on CVD outcomes in patients with type 2 diabetes (T2DM) in contrast to the overall results, which have discouraged the use

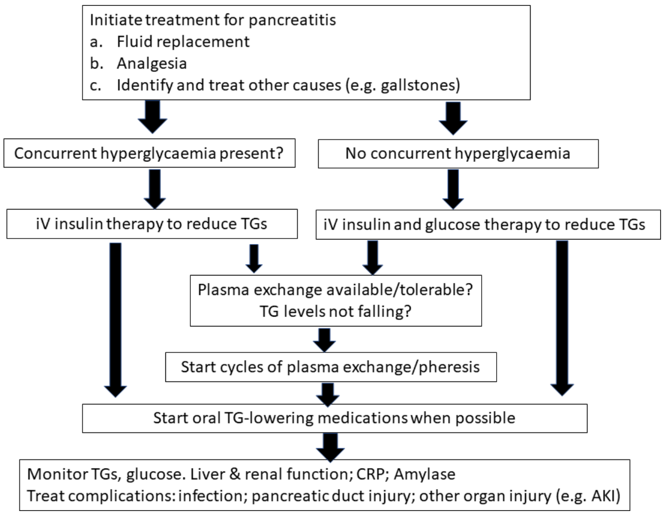

Figure 3 A scheme to manage acute pancreatitis induced by hypertriglyceridaemia. AKI, acute kidney injury; CRP, C-reactive protein; TG, triglyceride.

of combination therapy.[134] However, recently the Pemafibrate to Reduce Cardiovascular OutcoMes by Reducing Triglycerides IN patiENts With diabeTes (PROMINENT) trial[135] in secondary prevention or high-risk individuals with T2DM with residual dyslipidaemia (high TG; low HDL-C) was discontinued due to futility for CVD endpoints though combination therapy was safe. The development of vupanorsen was discontinued despite efficacy in reducing triglycerides.[136 137]

Triglyceride emergencies

Extreme hypertriglyceridaemia is a medical emergency.[138 139] The risk of pancreatitis increases up to 200-fold at TG >20 mmol/L.[28] In clinical practice, most admissions for TG-associated pancreatitis seem to occur with TG >35 mmol/L.[30] Admissions are precipitated by infections (often viral), gallstones or alcohol intake and only 5%–10% are due to hypertriglyceridaemia alone.[140 141] On admission patients need to be assessed through standard pancreatitis protocols and managed nil-by-mouth with fluids and pain relief (figure 3).[138 139 142 143] Fasting TGs halve approximately every 24–48 hours and TG <5.65 mmol/L (500 mg/dL) is often used to define resolution.[144] Insulin therapy (allied with heparin) is used to manage TGs with hyperglycaemia in patients with diabetes.[139] Supportive management allied to fasting is superior to combined insulin-dextrose therapy.[139 144] If TGs do not fall at the predicted rate, then plasma exchange or plasmapheresis may be used to reduce TGs by 60%–65%.[139 143] In a series of five observational studies totaling 59 patients with FCS where 10% died, plasmapheresis was associated with a 77%–100% complete recovery rate.[141] Plasma exchange or plasmapheresis are more frequently required if patients are on extracorporeal membrane oxygenation as CMs and large TG block the oxygenation membrane.[145] Apheresis is ineffective.

Triglycerides and pregnancy

A physiological increase in TGs occurs in the third trimester of pregnancy[146] rising from 1.5 mmol/L to 4 mmol/L,[147] especially in patients with gestational diabetes.[148] Individuals with latent hypertriglyceridaemia may be uncovered by pregnancy and require management by specialist medical obstetricians allied with lipid specialists. Most drug therapies are contraindicated in pregnancy. Management consists of minimising TGs with dietary fat restriction (often less than 10 gm /day).[149 150] Drug intervention with MCT oil and/or omega-3 fatty acids is suggested at TG >10 mmol/L.[150] Any hyperglycaemia needs to be managed aggressively with metformin and, if necessary, insulin. Intermittent plasma exchange or plasmapheresis may be required to keep TG <20 mmol/L.[151] Labour is usually induced at 35–36 weeks.

CONCLUSION

Hypertriglyceridaemia is a common finding that often confuses both primary and secondary care. Detailed investigations are available for raised TGs but are relatively underused. Analogous to cholesterol >9 mmol/L any primary hypertriglyceridaemia >10 mmol/L should be characterised and treated.[29] Extreme hypertriglyceridaemia associated with pancreatitis and/or pregnancy is a lipid emergency and requires urgent secondary care management.

Handling editor Patrick J Twomey.

Contributors ASW wrote the initial draft of the manuscript. EJK, OE and RR revised the manuscript and approved the final version.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests ASW is a site clinical investigator for clinical trials of drugs in management of familial chylomicronaemia syndrome and high triglycerides including Akcea (volanesorsen; apoC3LRx), Arrowhead (Aro-apoC3) and Regeneron (evinacumab).

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Commissioned; externally peer reviewed.

ORCID iD
Anthony S Wierzbicki http://orcid.org/0000-0003-2756-372X

REFERENCES

1 Ferns G, Keti V, Griffin B. Investigation and management of hypertriglyceridaemia. *J Clin Pathol* 2008;61:1174–83.
2 Fisher EA. The degradation of apolipoprotein B100: multiple opportunities to regulate VLDL triglyceride production by different proteolytic pathways. *Biochim Biophys Acta* 2012;1821:778–81.
3 Hassing HC, Surendran RP, Mooij HL, *et al*. Pathophysiology of hypertriglyceridemia. *Biochim Biophys Acta* 1821;2012:826–32.
4 Xiao C, Lewis GF. Regulation of chylomicron production in humans. *Biochim Biophys Acta* 2012;1821:736–46.
5 Chapman MJ, Ginsberg HN, Amarenco P, *et al*. Triglyceride-Rich lipoproteins and high-density lipoprotein cholesterol in patients at high risk of cardiovascular disease: evidence and guidance for management. *Eur Heart J* 2011;32:1345–61.
6 Björnson E, Packard CJ, Adiels M, *et al*. Apolipoprotein B48 metabolism in chylomicrons and very low-density lipoproteins and its role in triglyceride transport in normo- and hypertriglyceridemic human subjects. *J Intern Med* 2020;288:422–38.
7 Mikhailidis DP, Elisaf M, Rizzo M, *et al*. "European panel on low density lipoprotein (LDL) subclasses": a statement on the pathophysiology, atherogenicity and clinical significance of LDL subclasses. *Curr Vasc Pharmacol* 2011;9:533–71.
8 Grundy SM, Cleeman JI, Merz CNB, *et al*. Implications of recent clinical trials for the National cholesterol education program adult treatment panel III guidelines. *Circulation* 2004;110:227–39.
9 Christian JB, Bourgeois N, Snipes R, *et al*. Prevalence of severe (500 to 2,000 mg/dl) hypertriglyceridemia in United States adults. *Am J Cardiol* 2011;107:891–7.
10 Hughes D, Crowley J, O'Shea P, *et al*. Lipid reference values in an Irish population. *Ir J Med Sci* 2021;190:117–27.
11 Sathiyakumar V, Pallazola VA, Park J, *et al*. Modern prevalence of the Fredrickson-Levy-Lees dyslipidemias: findings from the very large database of lipids and national health and nutrition examination survey. *Arch Med Sci* 2020;16:1279–87.

12 Assmann G, Cullen P, Schulte H. The Münster heart study (PROCAM). Results of follow-up at 8 years. *Eur Heart J* 1998;19 Suppl A:A2–11.
13 Hopkins PN, Wu LL, Hunt SC, *et al*. Plasma triglycerides and type III hyperlipidemia are independently associated with premature familial coronary artery disease. *J Am Coll Cardiol* 2005;45:1003–12.
14 Sarwar N, Danesh J, Eiriksdottir G, *et al*. Triglycerides and the risk of coronary heart disease: 10,158 incident cases among 262,525 participants in 29 Western prospective studies. *Circulation* 2007;115:450–8.
15 Emerging Risk Factors Collaboration, Di Angelantonio E, Sarwar N, *et al*. Major lipids, apolipoproteins, and risk of vascular disease. *JAMA* 2009;302:1993–2000.
16 Sniderman AD, Thanassoulis G, Glavinovic T, *et al*. Apolipoprotein B particles and cardiovascular disease: a narrative review. *JAMA Cardiol* 2019;4:1287–95.
17 Emerging Risk Factors Collaboration, Di Angelantonio E, Gao P, *et al*. Lipid-related markers and cardiovascular disease prediction. *JAMA* 2012;307:2499–506.
18 Grundy SM, Stone NJ, Bailey AL, *et al*. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American heart association Task force on clinical practice guidelines. *Circulation* 2019;139:e1082–143.
19 Mach F, Baigent C, Catapano AL, *et al*. 2019 ESC/EAS guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J* 2020;41:111–88.
20 Rabar S, Harker M, O'Flynn N, *et al*. Lipid modification and cardiovascular risk assessment for the primary and secondary prevention of cardiovascular disease: summary of updated NICE guidance. *BMJ* 2014;349:g4356.
21 Visseren FLJ, Mach F, Smulders YM, *et al*. 2021 ESC guidelines on cardiovascular disease prevention in clinical practice. *Eur Heart J* 2021;42:3227–337.
22 Chait A, Ginsberg HN, Vaisar T, *et al*. Remnants of the triglyceride-rich lipoproteins, diabetes, and cardiovascular disease. *Diabetes* 2020;69:508–16.
23 Marston NA, Giugliano RP, Im K. Association between triglyceride lowering and reduction of cardiovascular risk across multiple lipid-lowering therapeutic classes: a systematic review and meta-regression analysis of randomized controlled trials. *Circulation* 2019;140:1308–17.
24 Sumner AE, Cowie CC. Ethnic differences in the ability of triglyceride levels to identify insulin resistance. *Atherosclerosis* 2008;196:696–703.
25 Alberti KGMM, Eckel RH, Grundy SM, *et al*. Harmonizing the metabolic syndrome: a joint interim statement of the International diabetes Federation Task force on epidemiology and prevention; National heart, lung, and blood Institute; American heart association; world heart Federation; international atherosclerosis Society; and international association for the study of obesity. *Circulation* 2009;120:1640–5.
26 Sattar N, Gaw A, Scherbakova O, *et al*. Metabolic syndrome with and without C-reactive protein as a predictor of coronary heart disease and diabetes in the West of Scotland coronary prevention study. *Circulation* 2003;108:414–9.
27 Pedersen SB, Langsted A, Nordestgaard BG. Nonfasting mild-to-moderate hypertriglyceridemia and risk of acute pancreatitis. *JAMA Intern Med* 2016;176:1834–42.
28 Gaudet D, de Wal J, Tremblay K, *et al*. Review of the clinical development of alipogene tiparvovec gene therapy for lipoprotein lipase deficiency. *Atheroscler Suppl* 2010;11:55–60.
29 Garg A, Garg V, Hegele RA, *et al*. Practical definitions of severe versus familial hypercholesterolaemia and hypertriglyceridaemia for adult clinical practice. *Lancet Diabetes Endocrinol* 2019;7:880–6.
30 Lloret Linares C, Pelletier AL, Czernichow S, *et al*. Acute pancreatitis in a cohort of 129 patients referred for severe hypertriglyceridemia. *Pancreas* 2008;37:13–2.
31 Hansen SEJ, Madsen CM, Varbo A, *et al*. Low-Grade inflammation in the association between mild-to-moderate hypertriglyceridemia and risk of acute pancreatitis: a study of more than 115000 individuals from the general population. *Clin Chem* 2019;65:321–32.
32 Wilson PWF, Jacobson TA, Martin SS, *et al*. Lipid measurements in the management of cardiovascular diseases: practical recommendations a scientific statement from the National lipid association writing group. *J Clin Lipidol* 2021;15:629–48.
33 Kolovou GD, Watts GF, Mikhailidis DP, *et al*. Postprandial hypertriglyceridaemia revisited in the era of Non-Fasting lipid profile testing: a 2019 expert panel statement, narrative review. *Curr Vasc Pharmacol* 2019;17:515–37.
34 Lambert JE, Parks EJ. Postprandial metabolism of meal triglyceride in humans. *Biochim Biophys Acta* 2012;1821:721–6.
35 Nordestgaard BG. A Test in Context: Lipid Profile, Fasting Versus Nonfasting. *J Am Coll Cardiol* 2017;70:1637–46.
36 Nordestgaard BG, Langlois MR, Langsted A, *et al*. Quantifying atherogenic lipoproteins for lipid-lowering strategies: consensus-based recommendations from EAS and EFLM. *Atherosclerosis* 2020;294:46–61.
37 Johnson-Arbor K, Salinger L, Luczycki S. Prolonged laboratory interference after administration of intravenous lipid emulsion therapy. *J Med Toxicol* 2015;11:223–6.
38 Vadala R, Talwar D, Talwar D. Recurrent non-traumatic idiopathic chylothorax: a diagnostic dilemma with therapeutic challenge. *Respirol Case Rep* 2020;8:e00637.
39 Boot CS, Middling E, Allen J, *et al*. Evaluation of the non-HDL cholesterol to apolipoprotein B ratio as a screening test for dysbetalipoproteinemia. *Clin Chem* 2019;65:313–20.
40 Paquette M, Bernard S, Blank D, *et al*. A simplified diagnosis algorithm for dysbetalipoproteinemia. *J Clin Lipidol* 2020;14:431–7.
41 Varghese B, Park J, Chew E, *et al*. Importance of the triglyceride level in identifying patients with a type III hyperlipoproteinemia phenotype using the ApoB algorithm. *J Clin Lipidol* 2021;15:104–15.
42 Hunsaker JJH, Wyness SP, Needham LL, *et al*. Evaluation of L-index interference limits on Roche Cobas c502 and c702 immunoturbidimetric assays using endogenously lipemic specimens and Intralipid spiking. *Clin Biochem* 2019;70:18–23.
43 Rifai N, Warnick GR, Dominiczak MH. *Handbook of lipoprotein testing*. 2nd ed. Washington DC; USA: American Association of Clinical Chemistry Press, 2000.
44 Han S, Flattery AM, McLaren D, *et al*. Comparison of lipoprotein separation and lipid analysis methodologies for human and cynomolgus monkey plasma samples. *J Cardiovasc Transl Res* 2012;5:75–83.
45 Sampson M, Ling C, Sun Q, *et al*. A new equation for calculation of low-density lipoprotein cholesterol in patients with Normolipidemia and/or hypertriglyceridemia. *JAMA Cardiol* 2020;5:540–8.
46 Lassman ME, McLaughlin TM, Somers EP, *et al*. A rapid method for cross-species quantitation of apolipoproteins A1, B48 and B100 in plasma by ultra-performance liquid chromatography/tandem mass spectrometry. *Rapid Commun Mass Spectrom* 2012;26:101–8.
47 Lassman ME, McLaughlin TM, Zhou H, *et al*. Simultaneous quantitation and size characterization of apolipoprotein(a) by ultra-performance liquid chromatography/mass spectrometry. *Rapid Commun Mass Spectrom* 2014;28:1101–6.
48 de Graaf J, Couture P, Sniderman A. A diagnostic algorithm for the atherogenic apolipoprotein B dyslipoproteinemias. *Nat Clin Pract Endocrinol Metab* 2008;4:608–18.
49 Garcia E, Bennett DW, Connelly MA, *et al*. The extended lipid panel assay: a clinically-deployed high-throughput nuclear magnetic resonance method for the simultaneous measurement of lipids and apolipoprotein B. *Lipids Health Dis* 2020;19:247.
50 Williams PT, Zhao X-Q, Marcovina SM, *et al*. Comparison of four methods of analysis of lipoprotein particle subfractions for their association with angiographic progression of coronary artery disease. *Atherosclerosis* 2014;233:713–20.
51 Kuivenhoven JA, Hegele RA. Mining the genome for lipid genes. *Biochim Biophys Acta* 2014;1842:1993–2009.
52 Hegele RA, Ban MR, Cao H, *et al*. Targeted next-generation sequencing in monogenic dyslipidemias. *Curr Opin Lipidol* 2015;26:103–13.
53 Mahley RW. Apolipoprotein E: remarkable protein sheds light on cardiovascular and neurological diseases. *Clin Chem* 2017;63:14–20.
54 Pantelidis P, Lambert-Hammill M, Wierzbicki AS. Simple sequence-specific-primer-PCR method to identify the three main apolipoprotein E haplotypes. *Clin Chem* 2003;49:1945–8.
55 Bennet AM, Di Angelantonio E, Ye Z, *et al*. Association of apolipoprotein E genotypes with lipid levels and coronary risk. *JAMA* 2007;298:1300–11.
56 Koopal C, Retterstøl K, Sjouke B, *et al*. Vascular risk factors, vascular disease, lipids and lipid targets in patients with familial dysbetalipoproteinemia: a European cross-sectional study. *Atherosclerosis* 2015;240:90–7.
57 Koopal C, van der Graaf Y, Asselbergs FW, *et al*. Influence of APOE-2 genotype on the relation between adiposity and plasma lipid levels in patients with vascular disease. *Int J Obes* 2015;39:265–9.
58 Choudhury P, Ramanan VK, Boeve BF. Apoe ε4 allele testing and risk of Alzheimer disease. *JAMA* 2021;325:484–5.
59 Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem* 1972;18:499–502.
60 Langlois MR, Chapman MJ, Cobbaert C, *et al*. Quantifying atherogenic lipoproteins: current and future challenges in the era of personalized medicine and very low concentrations of LDL cholesterol. A consensus statement from EAS and EFLM. *Clin Chem* 2018;64:1006–33.
61 Martin SS, Blaha MJ, Elshazly MB, *et al*. Comparison of a novel method vs the Friedewald equation for estimating low-density lipoprotein cholesterol levels from the standard lipid profile. *JAMA* 2013;310:2061–8.
62 Higgins V, Leiter LA, Delaney SR, *et al*. Validating the NIH LDL-C equation in a specialized lipid cohort: does it add up? *Clin Biochem* 2021.
63 Feingold KR. The outer frontier: the importance of lipid metabolism in the skin. *J Lipid Res* 2009;50 Suppl:S417–22.
64 Frew JW, Murrell DF, Haber RM. Fifty shades of yellow: a review of the xanthodermatoses. *Int J Dermatol* 2015;54:1109–23.
65 Brown RJ, Araujo-Vilar D, Cheung PT, *et al*. The diagnosis and management of lipodystrophy syndromes: a Multi-Society practice guideline. *J Clin Endocrinol Metab* 2016;101:4500–11.
66 Simha V. Management of hypertriglyceridemia. *BMJ* 2020;371:m3109.
67 Hegele RA, Borén J, Ginsberg HN, *et al*. Rare dyslipidaemias, from phenotype to genotype to management: a European atherosclerosis Society Task force consensus statement. *Lancet Diabetes Endocrinol* 2020;8:50–67.
68 Trinder M, Vikulova D, Pimstone S, *et al*. Polygenic architecture and cardiovascular risk of familial combined hyperlipidemia. *Atherosclerosis* 2022;340:35–43.

69 Wiesbauer F, Blessberger H, Azar D, *et al*. Familial-combined hyperlipidaemia in very young myocardial infarction survivors (< or =40 years of age). *Eur Heart J* 2009;30:1073–9.
70 Wierzbicki AS, Graham CA, Young IS, *et al*. Familial combined hyperlipidaemia: under - defined and under - diagnosed? *Curr Vasc Pharmacol* 2008;6:13–22.
71 Veerkamp MJ, de Graaf J, Hendriks JCM, *et al*. Nomogram to diagnose familial combined hyperlipidemia on the basis of results of a 5-year follow-up study. *Circulation* 2004;109:2980–5.
72 Horswell SD, Fryer LGD, Hutchison CE, *et al*. CDKN2B expression in adipose tissue of familial combined hyperlipidemia patients. *J Lipid Res* 2013;54:3491–505.
73 Arner P, Bernard S, Salehpour M, *et al*. Dynamics of human adipose lipid turnover in health and metabolic disease. *Nature* 2011;478:110–3.
74 Brouwers MCGJ, van Greevenbroek MMJ, Stehouwer CDA, *et al*. The genetics of familial combined hyperlipidaemia. *Nat Rev Endocrinol* 2012;8:352–62.
75 Mahley RW, Rall SC. Apolipoprotein E: far more than a lipid transport protein. *Annu Rev Genomics Hum Genet* 2000;1:507–37.
76 Johansen CT, Wang J, Lanktree MB, *et al*. An increased burden of common and rare lipid-associated risk alleles contributes to the phenotypic spectrum of hypertriglyceridemia. *Arterioscler Thromb Vasc Biol* 2011;31:1916–26.
77 Goldberg RB, Chait A. A comprehensive update on the chylomicronemia syndrome. *Front Endocrinol* 2020;11:593931.
78 de Vries MA, Klop B, Alipour A, *et al*. In vivo evidence for chylomicrons as mediators of postprandial inflammation. *Atherosclerosis* 2015;243:540–5.
79 Stroes E, Moulin P, Parhofer KG, *et al*. Diagnostic algorithm for familial chylomicronemia syndrome. *Atheroscler Suppl* 2017;23:1–7.
80 Moulin P, Dufour R, Averna M, *et al*. Identification and diagnosis of patients with familial chylomicronaemia syndrome (FCS): Expert panel recommendations and proposal of an "FCS score". *Atherosclerosis* 2018;275:265–72.
81 Paquette M, Amyot J, Fantino M, *et al*. Rare variants in triglycerides-related genes increase pancreatitis risk in multifactorial chylomicronemia syndrome. *J Clin Endocrinol Metab* 2021;106:e3473–82.
82 Hegele RA, Berberich AJ, Ban MR, *et al*. Clinical and biochemical features of different molecular etiologies of familial chylomicronemia. *J Clin Lipidol* 2018;12:920–7.
83 O'Dea LSL, MacDougall J, Alexander VJ, *et al*. Differentiating familial chylomicronemia syndrome from multifactorial severe hypertriglyceridemia by clinical profiles. *J Endocr Soc* 2019;3:2397–410.
84 Dron JS, Wang J, Cao H, *et al*. Severe hypertriglyceridemia is primarily polygenic. *J Clin Lipidol* 2019;13:80–8.
85 Fallat RW, Glueck CJ. Familial and acquired type V hyperlipoproteinemia. *Atherosclerosis* 1976;23:41–62.
86 Yuan S, Giovannucci EL, Larsson SC. Gallstone disease, diabetes, calcium, triglycerides, smoking and alcohol consumption and pancreatitis risk: Mendelian randomization study. *NPJ Genom Med* 2021;6:27.
87 Miyashita K, Lutz J, Hudgins LC, *et al*. Chylomicronemia from GPIHBP1 autoantibodies. *J Lipid Res* 2020;61:1365–76.
88 Haslam DE, Peloso GM, Guirette M, *et al*. Sugar-Sweetened beverage consumption may modify associations between genetic variants in the ChREBP (carbohydrate responsive element binding protein) locus and HDL-C (high-density lipoprotein cholesterol) and triglyceride concentrations. *Circ Genom Precis Med* 2021;14:e003288.
89 Do R, Stitziel NO, Won H-H, *et al*. Exome sequencing identifies rare LDLR and APOA5 alleles conferring risk for myocardial infarction. *Nature* 2015;518:102–6.
90 Béliard S, Di Filippo M, Kaplanski G, *et al*. Highly efficacious, long-term, triglyceride lowering with rituximab therapy in a patient with autoimmune hypertriglyceridemia. *J Clin Lipidol* 2018;12:883–7.
91 Wojczynski MK, Glasser SP, Oberman A, *et al*. High-Fat meal effect on LDL, HDL, and VLDL particle size and number in the genetics of lipid-lowering drugs and diet network (GOLDN): an interventional study. *Lipids Health Dis* 2011;10:181.
92 Barrows BR, Parks EJ. Contributions of different fatty acid sources to very low-density lipoprotein-triacylglycerol in the fasted and fed states. *J Clin Endocrinol Metab* 2006;91:1446–52.
93 Gormsen LC, Jensen MD, Schmitz O, *et al*. Energy expenditure, insulin, and VLDL-triglyceride production in humans. *J Lipid Res* 2006;47:2325–32.
94 Chiavaroli L, Di Pede G, Dall'Asta M, *et al*. The importance of glycemic index on post-prandial glycaemia in the context of mixed meals: a randomized controlled trial on pasta and rice. *Nutr Metab Cardiovasc Dis* 2021;31:615–25.
95 Gaubatz JW, Gillard BK, Rosales C, *et al*. Dietary alcohol and fat differentially affect plasma cholesteryl ester transfer activity and triglycerides in normo- and hypertriglyceridemic subjects. *Lipids* 2020;55:299–307.
96 Van de Wiel A. The effect of alcohol on postprandial and fasting triglycerides. *Int J Vasc Med* 2012;2012:862504.
97 Escobar M, Scherer JN, Soares CM, *et al*. Active Brazilian crack cocaine users: nutritional, anthropometric, and drug use profiles. *Braz J Psychiatry* 2018;40:354–60.
98 Cornelis MC, van Dam RM. Habitual coffee and tea consumption and cardiometabolic biomarkers in the UK Biobank: the role of beverage types and genetic variation. *J Nutr* 2020;150:2772–88.
99 Jain RB, Ducatman A. Associations between smoking and lipid/lipoprotein concentrations among US adults aged ≥20 years. *J Circ Biomark* 2018;7:1849454418779310.
100 McKenzie KM, Lee CM, Mijatovic J, *et al*. Medium-Chain triglyceride oil and blood lipids: a systematic review and meta-analysis of randomized trials. *J Nutr* 2021;151:2949-2956.
101 Rouis M, Dugi KA, Previato L, *et al*. Therapeutic response to medium-chain triglycerides and omega-3 fatty acids in a patient with the familial chylomicronemia syndrome. *Arterioscler Thromb Vasc Biol* 1997;17:1400–6.
102 Grosskopf I, Ringel Y, Charach G, *et al*. Metformin enhances clearance of chylomicrons and chylomicron remnants in nondiabetic mildly overweight glucose-intolerant subjects. *Diabetes Care* 1997;20:1598–602.
103 Millar JS, Lichtenstein AH, Ordovas JM, *et al*. Human triglyceride-rich lipoprotein apo E kinetics and its relationship to LDL apo B-100 metabolism. *Atherosclerosis* 2001;155:477–85.
104 Stein EA, Lane M, Laskarzewski P. Comparison of statins in hypertriglyceridemia. *Am J Cardiol* 1998;81:66B–9.
105 Baigent C, Keech A, Kearney PM, *et al*. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet* 2005;366:1267–78.
106 Wierzbicki AS, Poston R, Ferro A. The lipid and non-lipid effects of statins. *Pharmacol Ther* 2003;99:95–112.
107 Robinson JG. Models for describing relations among the various statin drugs, low-density lipoprotein cholesterol lowering, pleiotropic effects, and cardiovascular risk. *Am J Cardiol* 2008;101:1009–15.
108 Preiss D, Tikkanen MJ, Welsh P, *et al*. Lipid-modifying therapies and risk of pancreatitis: a meta-analysis. *JAMA* 2012;308:804–11.
109 Lalloyer F, Staels B. Fibrates, glitazones, and peroxisome proliferator-activated receptors. *Arterioscler Thromb Vasc Biol* 2010;30:894–9.
110 Bougarne N, Weyers B, Desmet SJ, *et al*. Molecular actions of PPARα in lipid metabolism and inflammation. *Endocr Rev* 2018;39:760–802.
111 Rubenstrunk A, Hanf R, Hum DW, *et al*. Safety issues and prospects for future generations of PPAR modulators. *Biochim Biophys Acta* 2007;1771:1065–81.
112 Jun M, Foote C, Lv J, *et al*. Effects of fibrates on cardiovascular outcomes: a systematic review and meta-analysis. *Lancet* 2010;375:1875–84.
113 ACCORD Study Group, ACCORD Eye Study Group, Chew EY, *et al*. Effects of medical therapies on retinopathy progression in type 2 diabetes. *N Engl J Med* 2010;363:233–44.
114 Kamanna VS, Kashyap ML. Mechanism of action of niacin. *Am J Cardiol* 2008;101:S20–6.
115 Kamanna VS, Ganji SH, Kashyap ML. The mechanism and mitigation of niacin-induced flushing. *Int J Clin Pract* 2009;63:1369–77.
116 Schandelmaier S, Briel M, Saccilotto R, *et al*. Niacin for primary and secondary prevention of cardiovascular events. *Cochrane Database Syst Rev* 2017;6:CD009744.
117 Bays HE, Ballantyne CM, Kastelein JJ, *et al*. Eicosapentaenoic acid ethyl ester (AMR101) therapy in patients with very high triglyceride levels (from the Multi-center, plAcebo-controlled, Randomized, double-blINd, 12-week study with an open-label Extension [MARINE] trial). *Am J Cardiol* 2011;108:682–90.
118 Oscarsson J, Hurt-Camejo E. Omega-3 fatty acids eicosapentaenoic acid and docosahexaenoic acid and their mechanisms of action on apolipoprotein B-containing lipoproteins in humans: a review. *Lipids Health Dis* 2017;16:149.
119 Oh DY, Talukdar S, Bae EJ, *et al*. GPR120 is an omega-3 fatty acid receptor mediating potent anti-inflammatory and insulin-sensitizing effects. *Cell* 2010;142:687–98.
120 Moniri NH. Free-fatty acid receptor-4 (GPR120): cellular and molecular function and its role in metabolic disorders. *Biochem Pharmacol* 2016;110-111:1–15.
121 Aung T, Halsey J, Kromhout D, *et al*. Associations of Omega-3 Fatty Acid Supplement Use With Cardiovascular Disease Risks: Meta-analysis of 10 Trials Involving 77 917 Individuals. *JAMA Cardiol* 2018;3:225–34.
122 Khan SU, Lone AN, Khan MS, *et al*. Effect of omega-3 fatty acids on cardiovascular outcomes: a systematic review and meta-analysis. *EClinicalMedicine* 2021;38:100997.
123 Chaudhry R, Viljoen A, Wierzbicki AS. Pharmacological treatment options for severe hypertriglyceridemia and familial chylomicronemia syndrome. *Expert Rev Clin Pharmacol* 2018;11:589–98.
124 Sacks FM, Stanesa M, Hegele RA. Severe hypertriglyceridemia with pancreatitis: thirteen years' treatment with lomitapide. *JAMA Intern Med* 2014;174:443–7.
125 Sacks FM. The crucial roles of apolipoproteins E and C-III in apoB lipoprotein metabolism in normolipidemia and hypertriglyceridemia. *Curr Opin Lipidol* 2015;26:56–63.
126 Macchi C, Sirtori CR, Corsini A, *et al*. A new dawn for managing dyslipidemias: the era of RNA-based therapies. *Pharmacol Res* 2019;150:104413.
127 Esan O, Wierzbicki AS. Volanesorsen in the treatment of familial chylomicronemia syndrome or hypertriglyceridaemia: design, development and place in therapy. *Drug Des Devel Ther* 2020;14:2623–36.
128 Witztum JL, Gaudet D, Freedman SD, *et al*. Volanesorsen and Triglyceride Levels in Familial Chylomicronemia Syndrome. *N Engl J Med* 2019;381:531–42.

129 Gelrud A, Digenio A, Alexander V, *et al*. Treatment with Volanesorsen (VLN) reduced triglycerides and pancreatitis in patients with FCS and sHTG vs placebo: results of the approach and COMPASS †. *J Clin Lipidol* 2018;12:537.
130 Alexander VJ, Xia S, Hurh E, *et al*. N-Acetyl galactosamine-conjugated antisense drug to APOC3 mRNA, triglycerides and atherogenic lipoprotein levels. *Eur Heart J* 2019;40:2785–96.
131 Ahmad Z, Pordy R, Rader DJ, *et al*. Inhibition of angiopoietin-like protein 3 with Evinacumab in subjects with high and severe hypertriglyceridemia. *J Am Coll Cardiol* 2021;78:193–5.
132 Wolska A, Lo L, Sviridov DO, *et al*. A dual apolipoprotein C-II mimetic-apolipoprotein C-III antagonist peptide lowers plasma triglycerides. *Sci Transl Med* 2020;12. doi:10.1126/scitranslmed.aaw7905. [Epub ahead of print: 29 01 2020].
133 Gaudet D, Stroes ES, Méthot J, *et al*. Long-Term retrospective analysis of gene therapy with Alipogene Tiparvovec and its effect on lipoprotein lipase deficiency-induced pancreatitis. *Hum Gene Ther* 2016;27:916–25.
134 ACCORD Study Group, Ginsberg HN, Elam MB, *et al*. Effects of combination lipid therapy in type 2 diabetes mellitus. *N Engl J Med* 2010;362:1563–74.
135 Pradhan AD, Paynter NP, Everett BM, *et al*. Rationale and design of the pemafibrate to reduce cardiovascular outcomes by reducing triglycerides in patients with diabetes (prominent) study. *Am Heart J* 2018;206:80–93.
136 Gaudet D, Karwatowska-Prokopczuk E, Baum SJ, *et al*. Vupanorsen, an N-acetyl galactosamine-conjugated antisense drug to ANGPTL3 mRNA, lowers triglycerides and atherogenic lipoproteins in patients with diabetes, hepatic steatosis, and hypertriglyceridaemia. *Eur Heart J* 2020;41:3936–45.
137 Ionis Pharmaceuticals, Pfizer. Pfizer and Ionis announce discontinuation of vupanorsen clinical development program. secondary pfizer and Ionis announce discontinuation of vupanorsen clinical development program 31/01/2022, 2022. Available: https://ir.ionispharma.com/news-releases/news-release-details/pfizer-and-ionis-announce-discontinuation-vupanorsen-clinical
138 Okazaki H, Gotoda T, Ogura M, *et al*. Current diagnosis and management of primary chylomicronemia. *J Atheroscler Thromb* 2021;28:883–904.
139 Newman CB, Blaha MJ, Boord JB, *et al*. Lipid management in patients with endocrine disorders: an endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2020;105. doi:10.1210/clinem/dgaa674. [Epub ahead of print: 01 12 2020].
140 Adiamah A, Kushairi A, Tumilty S, *et al*. Hypertriglyceridaemia as a risk factor for critical care admission in acute pancreatitis: a prospective study. *Clin Nutr ESPEN* 2020;39:227–33.
141 Tsuang W, Navaneethan U, Ruiz L, *et al*. Hypertriglyceridemic pancreatitis: presentation and management. *Am J Gastroenterol* 2009;104:984–91.
142 Stefanutti C, Julius U. Treatment of primary hypertriglyceridemia states-General approach and the role of extracorporeal methods. *Atheroscler Suppl* 2015;18:85–94.
143 Stefanutti C, Labbadia G, Morozzi C. Severe hypertriglyceridemia-related acute pancreatitis. *Ther Apher Dial* 2013;17:130–7.
144 Anderson F, Mbatha SZ, Thomson SR. The early management of pancreatitis associated with hypertriglyceridaemia. *S Afr J Surg* 2011;49:82–4.
145 Badulak JH, Curtis E, Bulger EM. Ecmo membrane lung failure due to hypertriglyceridemia: a case report and review of the literature. *J Extra Corpor Technol* 2020;52:237–41.
146 Ghio A, Bertolotto A, Resi V, *et al*. Triglyceride metabolism in pregnancy. *Adv Clin Chem* 2011;55:133–53.
147 Basaran A. Pregnancy-Induced hyperlipoproteinemia: review of the literature. *Reprod Sci* 2009;16:431–7.
148 Ryckman KK, Spracklen CN, Smith CJ, *et al*. Maternal lipid levels during pregnancy and gestational diabetes: a systematic review and meta-analysis. *BJOG* 2015;122:643–51.
149 Chyzhyk V, Kozmic S, Brown AS, *et al*. Extreme hypertriglyceridemia: genetic diversity, pancreatitis, pregnancy, and prevalence. *J Clin Lipidol* 2019;13:89–99.
150 Goldberg AS, Hegele RA. Severe hypertriglyceridemia in pregnancy. *J Clin Endocrinol Metab* 2012;97:2589–96.
151 Basar R, Uzum AK, Canbaz B, *et al*. Therapeutic apheresis for severe hypertriglyceridemia in pregnancy. *Arch Gynecol Obstet* 2013;287:839–43.
152 Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the National cholesterol education program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III). *JAMA* 2001;285:2486–97.