Hypertriglyceridaemia: an update

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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)B100 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 (apoB100), while hepatocytes secrete very low-density lipoprotein (VLDL) with full length apoB (apoB100). 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 women10 and elevated TGs are common in lipid clinics.9 11

EPILEDIOLOGY 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 cohorts13 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-C18–20 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.3 22 23

High TGs, reduced HDL-C and atherogenic sdLDL (the atherogenic triad) form part of the metabolic insulin resistance syndrome (M-IRS).3 24 This is defined as (population-specific25) 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/L27 increasing to 360-fold in patients with TG >20 mmol/L and...
CHYLOMICRON SYNDROMES

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. Most hospital admissions seem to occur with TG >35 mmol/L, but interactions occur between TGs, inflammation and other factors.

TRIGLYCERIDE-RELATED LABORATORY TECHNIQUES

Triglycerides can be measured in fasting and postprandial states. 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. The standard assays measure glycerol released after hydrolysis of triglycerides. Patients with some inherited errors of glycolysis or those receiving intravenous fat emulsions, which contain glycerol can have pseudo-hypertriglyceridaemia. While TGs are usually measured in plasma or serum, they can be used in the diagnosis of chylolothorax either by a significant discrepancy of lipids and apoB from plasma levels or by TG >1 mmol/L with cholesterol <5 mmol/L. 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. Automated analysers also detect CM particles through the lipaemia index and ideally all specimens with a high lipaemia index should have TG measured. Elevated indices indicate TG interference with some assays e.g. plasma sodium or liver transaminases.

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 These may be superseded by fast protein liquid chromatography as problems with recovery of ‘sticky’ CMs occur with centrifuge assays exist.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

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 (online supplemental figure 3). Assays for apoB100 distinguish VLDL from CMs while apoB48 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. They are mostly used in research as they add little to standard profiles and show poor intermethod agreement.

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. 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. Different isoforms can be separated on amphotolyte isoelectric focusing gels (phenotyping) or identified by genetic techniques. ApoE acts a marker of macrophage function and apoE deficient mice are a long-established model of atherosclerosis. 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). Many individuals with apoE2/E2 do not develop lipid abnormalities or CVD so secondary genetic or environmental factor are likely to be necessary. Homozygosity for apoE2 allied with remnant hyperlipidaemia is associated with an 8–9-fold increased risk of CVD. 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). However, apoE


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.

<table>
<thead>
<tr>
<th>Category</th>
<th>Definition (mmol/L; mg/dL)</th>
<th>Fredrickson class</th>
<th>Prevalence in general population (%)</th>
<th>Prevalence in lipid clinics (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;1.7 (150)</td>
<td>2A LDL</td>
<td>67</td>
<td>59.9</td>
</tr>
<tr>
<td>Borderline</td>
<td>1.7–2.2 (150–200)</td>
<td>2A LDL</td>
<td>15</td>
<td>3.9</td>
</tr>
<tr>
<td>Raised</td>
<td>2.3–5.5 (200–500)</td>
<td>2B LDL &gt;VLDL</td>
<td>16.5</td>
<td>10.3</td>
</tr>
<tr>
<td>High</td>
<td>5.6–10.9 (500–1000)</td>
<td>3 or 4 IDL and VLDL</td>
<td>1.5</td>
<td>1.7</td>
</tr>
<tr>
<td>Severe</td>
<td>11.0–19.9 (1000–1800)</td>
<td>4 Excess VLDL</td>
<td></td>
<td>24.1</td>
</tr>
<tr>
<td>Extreme</td>
<td>&gt;20–22 (&gt;1800–2000)</td>
<td>5 VLDL and CM</td>
<td>NA</td>
<td>0.13</td>
</tr>
<tr>
<td>&gt;20–22</td>
<td>(&gt;1800–2000)</td>
<td>1 CM and CM remnants</td>
<td>1 in 10⁶</td>
<td>NA</td>
</tr>
</tbody>
</table>
also associates with the function of brain-associated macrophage lineage cells (microglia) and a dose proportional risk (heterozygote OR 4–6; homozgyote OR 8–12) for Alzheimer’s disease. 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.

**Influence of TGs on calculating LDL-C**

Most laboratories do not measure LDL-C but calculate its level using the Friedewald equation. 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, which is increased with aggressive lipid-lowering therapies as these change the relative loading of TGs and cholestrol in TGRLs. Improved methods of calculating LDL-C can be improved using direct LDL assays, but these are not reliably free of interference by TGRLs. 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 either as tables or in a new equation valid up to TG of 8 mmol/L but remain to be fully validated in populations with rare dyslipidaemias or on lipid-lowering therapies. LDL-C=TC/0.948–HDL-C/2140–(TGxTG/21400))–9.44 in mg/dL.

**CLINICAL ASPECTS OF HYPERTRIGLYCERIDAEMIA**

**Physical and pathological signs**

The skin is a major organ for lipid metabolism. Severe hypertriglyceridaemia is associated with deposition of lipids in the skin. 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 cholestrol 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.

**GENETIC LIPID SYNDROMES**

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

**Familial combined hyperlipidaemia**

FCHL has a frequency of 0.48%–11.4% depending on the criteria used. 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. 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. 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. 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). 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. 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. It is associated with 7–9-fold excess of CVD distributed across all vascular beds. Dermal skin crease lipid deposits may be

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**Table 2** Principal causes of secondary hypertriglyceridaemia

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

Many of these causes interact with polygenic risk factors for hypertriglyceridaemia in susceptible individuals.
binding protein—
ners with their pro-
circulation is associated with free fatty acid toxicity and allied
naemia syndrome (MCS), heterozygosity for rare pathogenic
of patients with high TG levels with multifactorial chylomicro-
seems to have a polygenic cause.
A monogenic cause has been found in 75% of patients with clin-
rangeline 5–30
molar potential, so many patients with FCS have TG in the
In contrast, VLDL particles seem to have a lower inflam-
more typical of patients with excess VLDL. The risk of pancre-
mmol/L.30 A

TREATMENT OF HYPERTRIGLYCERIDAEMIA

Dietary interventions
High-fat diets increase postprandial triglycerides, including both
CMs and VLDL, but most VLDL-TG is derived from adipose
tissue fatty acid recycling, action
of the liver.93 As the production of TGs is
affected by insulin action in the liver.95 As the production of TGs is
interact with environmental factors, for example, a carbohydrate
responsive element binding protein polymorphism interacts with
sugar drink consumption affecting TG levels.88
Severe TG syndromes are commonly associated with pancre-
should be correlated with dietary factors, the amount of calories, carbohydrate
and their glycaemic index will affect TG levels, modify HbA1c
and apoC2), and these may merit treatment with immune modu-
antibodies to LPL pathway proteins (including GPIHBP1, apoA5
and apoC2), and these may merit treatment with immune modu-
comprise of the lipolytic pathway—
specifically LPL and its controlling cofactors (apoC2; apoA5;
phospho-
density lipoprotein—

visible and in extreme cases planar palmar xanthomata develop.
ApoE genotype or phenotype assays are specialist tests so algo-
ries to improve clinical diagnosis or to guide requesting exist
(figure 2).39 40 This hyperlipidaemia is commonly treated with
fibrate-
though no specific trials exist for this indication.

Table 3  Points scoring system for familial chylomicronaemia
syndrome.79 80

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting TG &gt;10 mmol/L (at least 3 times; measured 1 month apart)</td>
<td>+5</td>
</tr>
<tr>
<td>Fasting TG &gt;20 mmol/L (at least once)</td>
<td>+1</td>
</tr>
<tr>
<td>Previous TG &lt;2 mmol/L</td>
<td>−5</td>
</tr>
<tr>
<td>No secondary factors (except pregnancy or oestrogen therapy)</td>
<td>+2</td>
</tr>
<tr>
<td>Exclude alcohol, diabetes, metabolic syndrome, hypothyroidism, corticosteroids and additional drugs</td>
<td></td>
</tr>
<tr>
<td>History of pancreatitis</td>
<td>+1</td>
</tr>
<tr>
<td>Unexplained recurrent abdominal pain</td>
<td>+1</td>
</tr>
<tr>
<td>No history of FCHL</td>
<td>+1</td>
</tr>
<tr>
<td>TG response to drug therapy &lt;20%</td>
<td>+1</td>
</tr>
<tr>
<td>Age of onset</td>
<td></td>
</tr>
<tr>
<td>&lt;10 years</td>
<td>+3</td>
</tr>
<tr>
<td>&lt;20 years</td>
<td>+2</td>
</tr>
<tr>
<td>&lt;40 years</td>
<td>+1</td>
</tr>
<tr>
<td>FCS likely &gt;10 pts; FCS unlikely &lt;9 pts; FCS very unlikely &lt;8 pts.</td>
<td></td>
</tr>
<tr>
<td>AUROC 0.91; Sensitivity 88%; Specificity 85%</td>
<td></td>
</tr>
<tr>
<td>FCHL, familial combined hyperlipidaemia; FCS, familial chylomicronaemia syndrome; TG, triglycerides.</td>
<td></td>
</tr>
</tbody>
</table>

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
genes associated with the lipolytic pathway—
specifically LPL and its controlling cofactors (apoC2; apoA5;
lipid maturation factor—
and a cell surface receptor for LPL
added 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 inflam-
atory 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 pancre-
atitis is associated exponentially with TGs28 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 chylomicro-
naemia syndrome (MCS), heterozygosity for rare pathogenic
variants is associated with a more severe phenotype than poly-
genic disease.85 Polycyclic risk scores for high TGs for have been
proposed but have not been widely validated.76 82 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)67 or genes
directly associated with pancreatitis.66 Polymorphisms also
interact with environmental factors, for example, a carbohydrate
responsive element binding protein polymorphism interacts with
sugar drink consumption affecting TG levels.88
Severe TG syndromes are commonly associated with pancre-
atitis rather than CVD events but apoA5 variants are inde-
pendently 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 modu-
lating drugs such as rituximab if such autoantibodies are found.90

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 (non-HDL-C) and apolipoprotein B (apoB)40 and those also
providing ultracentrifuged-derived beta quantification of very low-density
lipoprotein-cholesterol (VLDL-C).39

Best practice

Best practice

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-hydroxymethylglutarateLDL receptors. The LDL receptor can clear TGRLs through binding apoE and LDL by binding apoB48.103 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 synthesis106 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 (PPAR-γ) (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 (glucocorticoids). 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 clearance by increasing the apoE/apoC3 ratio 125 by upregulating apoC2 function—an activator of LPL.132

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/L117 by reducing production rates of CM and VLDL118 mediated by the free fatty acid receptor-4 and have anti-inflammatory actions.119 120 At low doses, their effects on CVD outcomes are minimal121 but higher doses, particularly of eicosapentaenoic acid (EPA), seem to be associated with lipid-independent effects in reducing CVD events.21 122 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 ratio125 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 thrombocytopenia. Regular platelet monitoring is required and most cases of thrombocytopenia 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 5447X, 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—vupanosen. 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 of
of combination therapy.\textsuperscript{134} However, recently the Pemafibrate to Reduce Cardiovascular OutcoMes by Reducing Triglycerides IN patiENts With diabeTes (PROMINENT) trial\textsuperscript{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 vapanorsen was discontinued despite efficacy in reducing triglycerides.\textsuperscript{136, 137}

### Triglyceride emergences

Extreme hypertriglyceridaemia is a medical emergency.\textsuperscript{138, 139} The risk of pancreatitis increases up to 200-fold at TG $>20$ mmol/L.\textsuperscript{28} In clinical practice, most admissions for TG-associated pancreatitis seem to occur with TG $>35$ mmol/L.\textsuperscript{30} Admissions are precipitated by infections (often viral), gallstones or alcohol intake and only 5\%–10\% are due to hypertriglyceridaemia alone.\textsuperscript{140, 141} On admission patients need to be assessed through standard pancreatitis protocols and managed nil-by-mouth with fluids and pain relief (\textbf{figure 3}).\textsuperscript{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.\textsuperscript{144} Insulin therapy (allied with heparin) is used to manage TGs with hyperglycaemia in patients with diabetes.\textsuperscript{139} Supportive management allied to fasting is superior to combined insulin-dextrose therapy.\textsuperscript{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\%.\textsuperscript{139, 143}

In a series of five observational studies totaling 59 patients with FCS where 10\% died, plasmapheresis was associated with a fat restriction (often less than 10 g/m²/day).\textsuperscript{149, 150} Drug intervention with MCT oil and/or omega-3 fatty acids is suggested at TG $>10$ mmol/L.\textsuperscript{150} Any hyperglycaemia needs to be managed aggressively with metformin and, if necessary, insulin. Intermit- tent plasma exchange or plasmapheresis may be required to keep TG $<20$ mmol/L.\textsuperscript{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.\textsuperscript{181} Extreme hypertriglyceridaemia associated with pancreatitis and/or pregnancy is a lipid emergency and requires urgent secondary care management.

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