Demystifying the management of hypertriglyceridaemia

Gerald F. Watts, Esther M. M. Ooi and Dick C. Chan

Abstract | Hypertriglyceridaemia (typical triglyceride level 1.7–5.0 mmol/l) is caused by interactions between many genetic and nongenetic factors, and is a common risk factor for atherosclerotic cardiovascular disease (CVD). Patients with hypertriglyceridaemia usually present with obesity, insulin resistance, hepatic steatosis, ectopic fat deposition, and diabetes mellitus. Hypertriglyceridaemia reflects the accumulation in plasma of proatherogenic lipoproteins, triglyceride-rich lipoprotein (TRL) remnants, and small, dense LDL particles. Mendelian randomization studies and research on inherited dyslipidaemias, such as type III dysbetalipoproteinaemia, testify that TRLs are causally related to atherosclerotic CVD. Extreme hypertriglyceridaemia (a triglyceride level >20 mmol/l) is rare, often monogenic in aetiology, and frequently causes pancreatitis. Treatment of hypertriglyceridaemia relies on correcting secondary factors and unhealthy lifestyle habits, particularly poor diet and lack of exercise. Pharmacotherapy is indicated for patients with established CVD or individuals at moderate-to-high risk of CVD, primarily those with metabolic syndrome or diabetes. Statins are the cornerstone of treatment, followed by fibrates and *n*-3 fatty acids, to achieve recommended therapeutic levels of plasma LDL cholesterol, non-HDL cholesterol, and apolipoprotein (apo) B-100. The case for using niacin has been weakened by the results of clinical trials, but needs further investigation. Extreme hypertriglyceridaemia requires strict dietary measures, and patients with a diagnosis of genetic lipoprotein lipase deficiency might benefit from LPL gene replacement therapy. Several therapies for regulating TRL metabolism, including inhibitors of diacylglycerol O-acyltransferase and microsomal triglyceride transfer protein, and apoC-III antisense oligonucleotides, merit further investigation in patients with hypertriglyceridaemia.

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Introduction

Triglyceride concentration is integral to the plasma lipid profile, and is conventionally employed in estimating the LDL-cholesterol level using the Friedewald formula.[1,2] An elevated level of LDL cholesterol is a major causal factor for atherosclerotic cardiovascular disease (CVD), and is the principal target for therapies in both primary and secondary CVD prevention.[3–5] By contrast, the importance of elevated plasma triglyceride concentrations in similar settings is uncertain,[6] partly owing to overemphasis on HDL cholesterol.[7,8]

Hypertriglyceridaemia can be defined as a fasting plasma triglyceride concentration >95th percentile for age and sex in a population. Plasma triglyceride concentrations are higher in men than in women, lower among individuals of African or Caribbean descent than in white people, and increase with age and after a high-fat meal in all individuals.[9] The population distribution of plasma triglyceride concentration is skewed to the right (positively skewed); the concentration of triglyceride-rich lipoprotein (TRL) remnants follows a similar distribution and increases with triglyceride levels.[10] Groups of experts have provided arbitrary definitions of hypertriglyceridaemia (Table 1),[10–16] a fasting triglyceride concentration >1.7 mmol/l being generally considered abnormal. A simple hierarchical definition is that a fasting plasma triglyceride level of 1.7–2.3 mmol/l is considered mild; 2.3–5.5 mmol/l is moderate; 5.5–10.0 mmol/l is high, and >10.0 mmol/l (a level above which chylomicrons appear) as very high or severe. Extreme hypertriglyceridaemia, which is rare, is defined as a fasting triglyceride concentration >20 mmol/l. Approximately 30% of adults have mild-to-moderate hypertriglyceridaemia, although the prevalence of the severe forms is only 1–2%.[9,11] Among patients with coronary artery disease, including those treated with statins, >30% exhibit mild-to-moderate hypertriglyceridaemia with or without a low plasma HDL-cholesterol level.[9,10] The prevalence of hypertriglyceridaemia can be as high as 50% in patients with diabetes mellitus.[10,17] In this Review, we present contemporary knowledge in the field of hypertriglyceridaemia, which is currently undergoing a renaissance,[9–12,18] and provide practical guidance on managing this condition for the prevention and treatment of atherosclerotic CVD.

Competing interests
G. F. Watts declares associations with the following companies: Abbott, Amgen, Genfit, Merck & Co., and Sanofi. See the article online for full details of the relationships. The other authors declare no competing interests.

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Key points

- Hypertriglyceridaemia is a common indicator of cardiometabolic risk factors and atherosclerotic cardiovascular disease (CVD)
- Hypertriglyceridaemia can be caused by genetic and nongenetic factors, such as obesity, insulin resistance, and type 2 diabetes mellitus
- Moderately elevated plasma triglyceride concentrations (1.7–5.0 mmol/l) reflect the accumulation of triglyceride-rich lipoprotein (TRL) remnants and small dense LDL particles that are highly atherogenic
- Treatment of hypertriglyceridaemia involves correction of secondary factors and unhealthy lifestyle habits; pharmacotherapy is indicated for patients with established CVD or those at moderate-to-high risk of CVD
- Statin therapy is the cornerstone of pharmacological treatment for hypertriglyceridaemia, followed by fibrates and *n*-3 fatty acids to achieve recommended target levels of LDL cholesterol, non-HDL cholesterol, and apolipoprotein B-100 in plasma
- Several agents that regulate TRL metabolism are in development, but their clinical efficacy, safety, cost-effectiveness, and indications are yet to be established

Table 1 | Categories of hypertriglyceridaemia

International Guideline	Categories	Triglyceride concentration (mmol/l)
NCEP ATPIII[11]	Normal	<1.7
	Borderline	1.7–2.3
	High	2.3–5.6
	Very high	>5.6
Endocrine Society[12]	Normal	<1.7
	Mild	1.7–2.3
	Moderately high	2.3–11.2
	Severely high*	11.2–22.4
European Atherosclerosis Society[10]	Desirable	<1.7
	Elevated	1.7–5.5
	Very high	5.5–25.0
	Extremely high	>25.0
Canadian Cardiovascular Society[13]	Desirable	<2.0
	Elevated	2.0–5.0
	Moderately high	5.0–10.0
	Extremely high	>10.0
Japanese Expert Guidelines[14–16]	Desirable	<1.7
	Elevated	1.7–4.5
	Very high	4.5–22.5
	Extremely high	>22.5

*Very severely high is >22.4 mmol/l. Abbreviation: NCEP ATP, National Cholesterol Education Program Adult Treatment Panel.

Molecular and metabolic aetiology

Genetic (primary) factors

Hypertriglyceridaemia has a complex genetic aetiology.[19,20] Multiple genes, which interact with nongenetic factors and perturb the production and catabolism of TRLs, account for hypertriglyceridaemia in >95% of susceptible individuals.[9,20] A very small proportion of people (<1 in 100,000) have a purely monogenic disorder.[20] Individuals with severe hypertriglyceridaemia (>10.0 mmol/l) are likely to be homozygotes or compound heterozygotes for mutations in at least six genes (*LPL, APOC2, LMF1, GPIHBP1, APOA5, GPD1*), which impair the lipolytic catabolism of TRLs.[21] Individuals with hypertriglyceridaemia in the range 1.7–10.0 mmol/l are likely to be heterozygotes for common genetic variants or rare loss-of-function mutations in, for example, *APOA5, APOC3*, and *LPL*, which impact TRL metabolism to varying degrees.[20] The effects are greater with rare mutations than for common variants. At least one-quarter of individuals who are susceptible to this level of hypertriglyceridaemia (1.7–10.0 mmol/l) have both common and rare gene variants.[19,20,22]

In individual with mild-to-moderate hypertriglyceridaemia, the risk of CVD is increased in the settings of familial endogenous hypertriglyceridaemia, dysbetalipoproteinaemia, and familial combined hyperlipidaemia (FCHL).[9,12,18] All of these conditions are multigenic and co-express with nongenetic secondary factors, particularly obesity, insulin resistance, and diabetes. Familial endogenous hypertriglyceridaemia has a prevalence of between 0.3% and 10%, and can be associated with later-onset atherosclerotic CVD owing to excessive postprandial lipaemia, a low HDL-cholesterol level, and accumulation of small, dense LDL particles.[23] Homozygosity for the *APOE**2 allele (prevalence 1%) is a necessary, but not sufficient, cause of type III dysbetalipoproteinaemia (that is, the presence of other risk factors, such as obesity, insulin resistance, or type 2 diabetes, is also required). This genotype is rare (1 in 10,000 of the population) and causes premature atherosclerosis owing to accumulation of TRL remnants that are not cleared by the liver.[23] By contrast, FCHL has a prevalence of 1–2% in the general population, but can be detected in 10% of patients with premature coronary disease.[23] Although the genetic basis of this phenotype has yet to be fully unveiled, FCHL is a real clinical entity.[24–28] This disorder is highly complex, however, involving multiple genes that affect the metabolism of adipose tissue (such as *USF1* and *PNPLA2*), TRLs (such as *APOA1, APOC3, APOA4, APOA5*, and *USF1*), and LDL (such as *LDLR* and *PCSK9*).[24] FCHL is associated with a fivefold increased risk of CVD[25,26] related to atherogenic dyslipidaemia, which involves increased free fatty acid (FFA) flux from adipose tissue to liver, hepatic oversecretion of very-low-density lipoprotein (VLDL) apolipoprotein (apo)B-100, overproduction of small, dense LDL, and increased catabolism of HDL.[23,24,27] The phenotype is vertically transmitted within families as a mixed and variable hyperlipidaemia,[23,24] and is diagnosed using a simple algorithm requiring plasma apoB-100 concentration in the index case, and a personal and family history of dyslipidaemia and premature CVD.[28]

Primary chylomicronaemia due to lipoprotein lipase (LPL) deficiency related to a loss-of-function mutation in the *LPL* gene is very rare (1.5 per 1,000,000 of the population),[9,16,18] with a higher prevalence in certain populations subject to a gene founder effect.[29] Secondary chylomicronaemia can be caused by autoantibodies to LPL.[30] LPL deficiency manifests in youth as the chylomicronaemia syndrome, with eruptive xanthoma, lipaemia retinalis, and acute pancreatitis, but no appreciably increased risk of CVD.[9,12,16,18,31]

Nongenetic (secondary) factors

Several factors can precipitate hypertriglyceridaemia, including diet; obesity with insulin resistance; uncontrolled diabetes; endocrinopathies; nephropathies;

autoimmune conditions; systemic infections; pregnancy; excessive alcohol consumption; and the use of certain drugs, such those for the treatment of hypertension, severe mental illness, HIV infection, autoimmune conditions and solid organ transplant rejection, as well as glucocorticoids and oral contraceptives containing oestrogen (Box 1).[9,10,12,18] These factors do not universally induce hypertriglyceridaemia; therefore, secondary hypertriglyceridaemia must also have a genetic component.[9,19] The degree of hypertriglyceridaemia is determined by the severity of the loss-of-function gene variants and secondary factors.[9,20]

Atherogenic dyslipidaemia

Atherogenic dyslipidaemia is a hypertriglyceridaemic phenotype, associated with increased plasma concentrations of small, dense LDL particles, TRLs, non-HDL-cholesterol, and apoB, and a low HDL-cholesterol level that is characteristic of individuals with the metabolic syndrome or type 2 diabetes.[32–34] Atherogenic dyslipidaemia is most-typically encountered in patients with insulin resistance, central obesity, and plasma triglyceride concentrations in the range 2–5 mmol/l.[10,34] An increase in white adipose tissue in obesity leads to decreased capacity for storage of FFAs, resulting in an excess of substrate for triglyceride synthesis in the liver and enterocytes.[35,36] Insulin resistance also induces *de novo* lipogenesis by increasing expression of sterol regulatory element binding protein 1c and delaying the intrahepatic degradation of apoB-100.[6] Collectively, these processes result in hepatic steatosis and hepatic oversecretion of larger triglyceride-rich VLDLs,[37] as well as increased enterocyte secretion of chylomicrons containing apoB-48.[36] Hepatic steatosis occurs in the setting of an imbalance between fatty acid uptake, *de novo* lipogenesis, and VLDL-triglyceride synthesis, on the one hand, and fatty acid oxidation and VLDL-triglyceride secretion, on the other.[38] Hepatic steatosis is frequently found in patients with obesity, hypertriglyceridaemia, and insulin resistance, and is a prelude to steatohepatitis and cirrhosis. Hepatic steatosis and hypertriglyceridaemia are also associated with ectopic fat deposition in the pancreas, kidney, arteries, heart, and skeletal muscle, which results in impaired insulin signalling, inflammation, and organ dysfunction, as well as increased risk of CVD.[39–41]

Competition between VLDLs, chylomicrons, and their remnants for lipolytic and receptor-mediated clearance further induces postprandial dyslipidaemia. Brown adipose tissue activity might contribute to the regulation of triglyceride clearance.[42] In insulin resistance, the concentration of apolipoprotein C-III (apoC-III) is increased in TRLs, which further delays their catabolism by inhibiting LPL and receptor-mediated uptake by the liver.[43,44] Accumulation of TRLs in plasma also enhances exchange of triglycerides for cholesterol esters from LDL and HDL via the action of cholesteryl ester transfer protein (CETP) (Figure 1). Under the action of hepatic triglyceride lipase and, to a lesser extent LPL, triglyceride-enriched LDL particles become smaller, denser, and more pro-atherogenic.[32,33,37] Similar changes in HDL particles could make them less antiatherogenic.[10,45,46]

Box 1 | Secondary causes of hypertriglyceridaemia*

Acquired traits and lifestyle habits
- Overweight
- Obesity
- Physical inactivity
- Cigarette smoking
- High-energy, high-fat diet
- High glycaemic index and high fructose intake
- Excessive alcohol intake

Conditions
- Type 2 diabetes mellitus
- Polycystic ovary syndrome
- Hypothyroidism
- Renal failure
- Nephrotic syndrome
- Stress
- Sepsis
- Cushing syndrome
- Lipodystropy
- Acromegaly
- Systemic lupus erythematosus
- HIV infection
- Paraproteinaemia
- Glycogen storage disease
- Pregnancy

Drugs
- Oral oestrogens
- Tamoxifen
- β-Blockers
- Thiazides
- Retinoic acid derivatives
- Antipsychotics (atypical)
- Antiretroviral therapy
- Bile-acid sequestrants
- Cyclosporine
- Sirolimus
- *L*-asparaginase
- Interferon

*High and very-high triglyceride levels (>5.5 mmol/l) are also caused by loss-of-function gene variants.

CVD and hypertriglyceridaemia

The epidemiological evidence that hypertriglyceridaemia is an independent risk factor for CVD has been controversial.[6–8] In the largest meta-analysis conducted to date, the risk of coronary heart disease (CHD) was increased by 37% for each SD increase in plasma triglyceride level adjusted for non-lipid risk factors.[47] However, the association was weakened after adjustment for levels of HDL-cholesterol and non-HDL-cholesterol.[47] Uncertainty exists concerning sex-related differences in hypertriglyceridaemia as a risk factor.[6] The lack of an independent association between triglyceride levels and CVD risk in epidemiological studies is not surprising, given that hypertriglyceridaemia is associated with a wide spectrum of other risk factors.[7,8]

The epidemiological technique of Mendelian randomization has been used to address the causal association between TRLs and CVD.[48] Two studies published in the past year demonstrated that a genetically increased level of remnant cholesterol in hypertriglyceridaemia, particularly due to genetic variation in the *APOA5* and *LPL* genes, was associated with an increased risk of myocardial

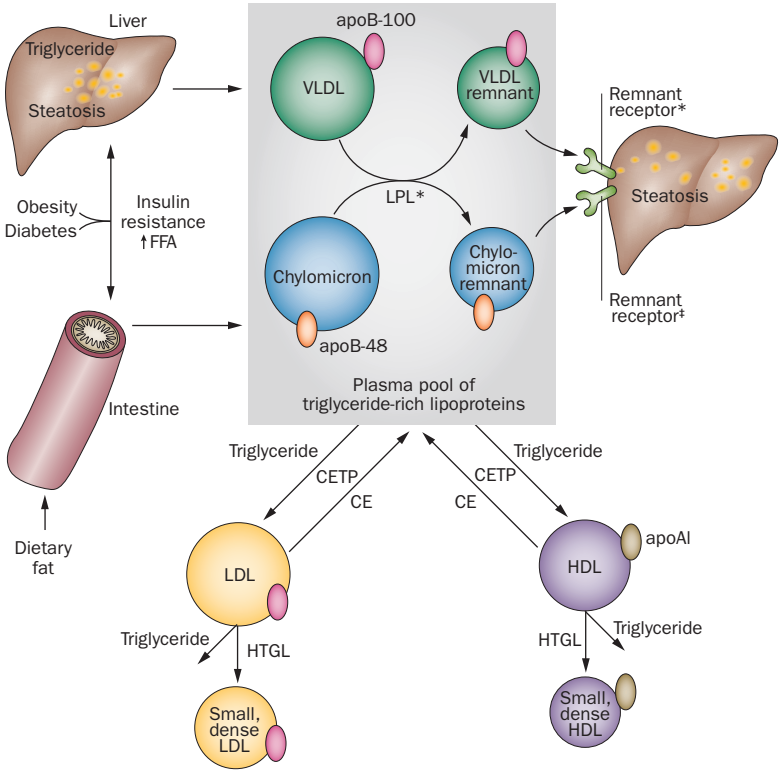

Figure 1 | Pathogenesis of atherogenic dyslipidaemia in the setting of hypertriglyceridaemia, insulin resistance, and hepatic steatosis; central obesity and type 2 diabetes mellitus are common clinical phenotypes. Oversecretion of VLDL and chylomicrons by the liver and intestine, coupled with decreased catabolism, increases the plasma pool of TRLs, including remnant lipoproteins; increased heteroexchange of neutral lipids between TRLs and LDLs and HDLs via CETP results in remodelling of LDLs and HDLs to form correspondingly smaller, denser particles. *LPL activity is decreased in skeletal muscle and adipose tissue owing to the inhibitory effects of insulin resistance and apoC-III; ‡insulin resistance and increased apoC-III also decrease hepatic remnant receptor activity. Abbreviations: ApoAI, apolipoprotein AI; ApoB, apolipoprotein B; CE, cholesteryl ester; CETP, cholesteryl ester transfer protein; FFA, free fatty acids; HDL, high-density lipoprotein; HTGL, hepatic triglyceride lipase; LDL, low-density lipoprotein; LPL, lipoprotein lipase; TRL, triglyceride-rich lipoprotein; VLDL, very-low-density lipoprotein.

infarction.[48,49] A 1 mmol/l increase in nonfasting remnant cholesterol concentration in plasma was associated with a 2.8-fold increase in causal risk for ischaemic heart disease.[49] The observation with *APOA5* gene variants is supported by a large meta-analysis.[50] Consistent with these genetic studies, type III dysbetalipoproteinaemia caused by homozygosity for *APOE**2 provides a causal link between the presence of TRL remnants and CVD.[23] Other multigenic disorders, such as FCHL, also increase the risk of CVD.[23,24,26] Importantly, elevated plasma levels of triglycerides and non-HDL-cholesterol remain significant predictors of CVD events in statin trials.[51–53]

The apparent atherogenicity of hypertriglyceridaemia relates to small TRL remnant particles as opposed to larger TRLs, such as chylomicrons.[54,55] TRL remnants induce endothelial dysfunction, inhibit fibrinolysis, and enhance coagulation and vascular inflammation.[55–61] Readily traversing the arterial wall,[55] TRL remnants rich in cholesterol and apoE are trapped by connective tissue matrix[56] and, after phagocytosis, transform arterial wall macrophages into atherogenic foam cells.[57] TRL lipolysis also releases toxic products, such as oxidized FFAs and lysolecithin, that further induce endothelial cell inflammation and coagulation (Figure 2).[6,62]

Biochemical assessment of dyslipidaemia

The plasma lipid profile is conventionally measured after a 9–12 h fast,[2,11] which increases the precision with which triglyceride concentration can be estimated. Nonfasting triglyceride concentrations are reflective of the postprandial state, however, and can be superior to fasting triglyceride levels for prediction of CVD risk.[63,64] A nonfasting blood test is the simplest initial method of screening for hypertriglyceridaemia. However, if the initial triglyceride level is >2.0 mmol/l, a second nonfasting measurement is recommended, and levels of non-HDL-cholesterol and apoB should also be estimated. Non-HDL-cholesterol measurement has several advantages. First, this method provides a simple index of all the atherogenic, apoB-containing lipoproteins—VLDL, intermediate-density lipoprotein (IDL), LDL, and lipoprotein(a) (Figure 3)—particularly when plasma the triglyceride level is <5.7 mmol/l.[11,65] Second, non-HDL-cholesterol concentration can be derived from the standard lipid profile, with no additional tests required.[2] Third, non-HDL-cholesterol level can be assessed in nonfasting samples and, in contrast to a calculated LDL-cholesterol level, does not rely on fasting triglyceride concentration. Fourth, several epidemiological studies have shown that the non-HDL-cholesterol level is a better predictor of CVD events than the LDL-cholesterol level.[53,66–70]

Measurement of apoB is also a better predictor of CVD events than LDL-cholesterol level.[66,67,70,71] ApoB concentration has also been shown to be a better predictor of CVD than non-HDL-cholesterol level in some, but not all, studies and might not to be equivalent to non-HDL-cholesterol concentration in individual patients.[72,73] ApoB measurement does not require fasting, and reflects the total number of atherogenic LDL and VLDL particles. However, apoB measurement involves a separate assay at additional expense and does not adequately reflect chylomicron remnants. An elevated plasma concentration of apoB in a patient with hypertriglyceridaemia and a family history of premature CVD is indicative of FCHL.[72] Equimolar plasma concentrations of triglycerides and cholesterol, as well as homozygosity for the *APOE**2 allele, establishes the diagnosis of type III dysbetalipoproteinaemia.[23]

Assessment of LDL size or HDL subspecies has no substantial practical value.[34] TRLs can also be quantified by measuring concentrations of remnant-like particle cholesterol, apoC-III, and apoB-48, but these assays are expensive and not established clinically.

Established therapies

Lifestyle modifications

Lifestyle interventions—including changes to dietary composition, exercise, and regulation of alcohol consumption—are fundamental to the treatment of patients with hypertriglyceridaemia.[9,10] Depending on clinical

context, these interventions can collectively decrease plasma triglyceride concentration by up to 60%.[74,75] In obese patients, dietary restriction can lower plasma triglyceride concentration by 0.015 mmol/l/kg reduction in body weight.[75] On average, weight loss of 5–10% of initial body weight reduces triglyceride concentration by 25% and LDL-cholesterol level by 15%, while raising HDL-cholesterol level by 8%.[75] Various weight-loss diets with different fat, protein, and carbohydrate compositions reduce plasma triglyceride levels and blood pressure to a comparable degree,[76] although a low-fat diet achieves the greatest reduction in LDL-cholesterol levels and a low-carbohydrate diet achieves the greatest increase in HDL-cholesterol levels.[77] Under isocaloric conditions, diets high in carbohydrates elevate plasma triglyceride concentration, whereas substitution of carbohydrates with protein or unsaturated fat reduces plasma levels of triglycerides and small, dense LDL particles, and elevates HDL-cholesterol levels.[78,79] Diets enriched in plant-based proteins and unsaturated fat significantly lower plasma triglyceride concentration by up to 0.2 mmol/l compared with a carbohydrate-rich diet.[80] Reductions in glycaemic load and fructose consumption, and an increase in soluble fibre intake, enhance triglyceride-lowering via independent effects.[81,82] Mediterranean-style diets can achieve sustained reductions in plasma triglyceride concentration (10–15%), insulin resistance, systolic blood pressure, and risk of type 2 diabetes.[83] Such diets have been shown to decrease the incidence of major CVD events in a primary prevention setting in people with dyslipidaemia, metabolic syndrome, and type 2 diabetes.[84]

Aerobic exercise of moderate-to-high intensity can reduce plasma triglyceride concentrations by up to 20%, particularly in patients with hypertriglyceridaemia who are following a hypocaloric diet.[85,86] Aerobic exercise and moderate weight loss prevents diabetes in people with impaired glucose tolerance, and corrects dyslipidaemia and other cardiometabolic risk factors in patients with established diabetes.[85,86] Resistance training has a minimal effect on plasma levels of triglycerides and TRLs.[87] Cigarette smoking also has a minimal effect on plasma triglyceride levels, but cessation is fundamental to all cardiovascular prevention strategies.[9–12,65] Excessive alcohol intake can markedly increase plasma triglyceride levels in susceptible individuals, owing to increased hepatic output of VLDL,[88] but this effect can be quickly reversed by abstention from alcohol. Notably, an intensive lifestyle intervention study conducted by Wing and colleagues, employing weight loss through caloric restriction and increased physical activity, did not reduce the rate of cardiovascular events in patients with type 2 diabetes.[89] Whether additional changes in dietary composition, as with the Mediterranean diet,[84] improves clinical outcome in patients with diabetes merits further investigation.

Pharmacotherapies

Statins

Statins are the most efficacious agents for lowering elevated plasma concentrations of LDL cholesterol and apoB.[11,32] The efficacy of these drugs in decreasing hypertriglyceridaemia depends on the baseline plasma triglyceride level, and is proportional to the LDL-cholesterol lowering effect.[90] Statins might lower plasma triglyceride by increasing lipolysis and the clearance of TRLs.[91] These effects are most pronounced with higher doses of potent statins, such as atorvastatin and rosuvastatin.[92] Statins significantly lower the rate of CVD events in high-risk patients, including those with type 2 diabetes (with or without CVD).[3,4] The cardiovascular

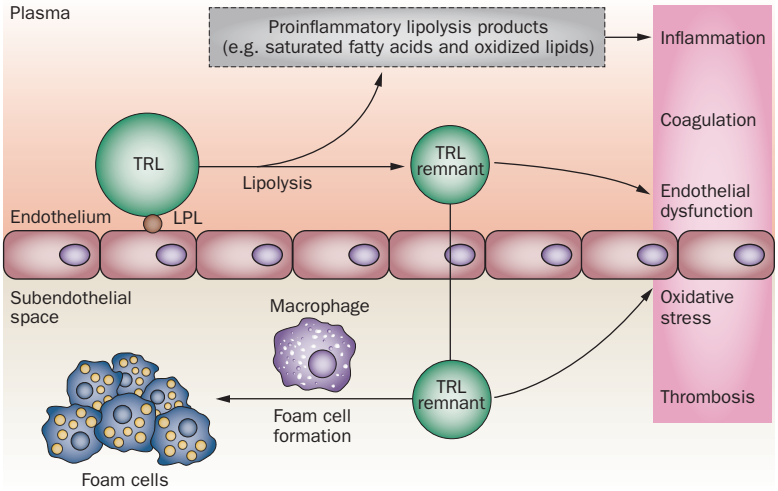

Figure 2 | Hypertriglyceridaemia, triglyceride-rich lipoproteins, and atherogenesis. Lipolysis of TRLs induces atherogenesis by generating TRL remnants that transverse the endothelium and lead to foam cell formation in the subendothelial space. Lipolysis of TRLs also contributes to atherosclerosis and endothelial dysfunction by generating pro-inflammatory, pro-coagulant and pro-oxidant lipid products. Abbreviations: LPL, lipoprotein lipase; TRL, triglyceride-rich lipoprotein.

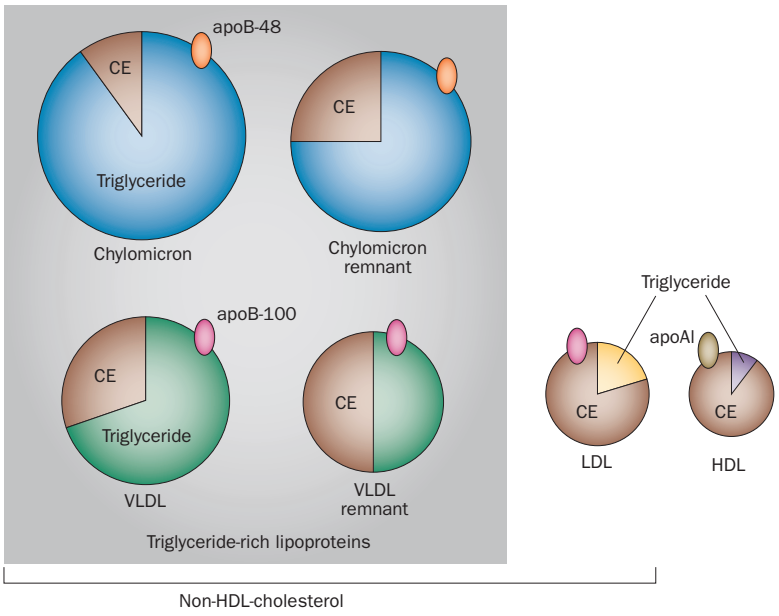

Figure 3 | Non-HDL-cholesterol concentration in plasma is the sum of cholesterol in triglyceride-rich lipoproteins (chylomicrons, chylomicron remnants, VLDL and IDL) and LDL, which can be estimated by subtracting the HDL-cholesterol concentration from the total plasma cholesterol concentration. Abbreviations: ApoAI, apolipoprotein AI; ApoB, apolipoprotein B; CE, cholesteryl ester; HDL, high-density lipoprotein; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; VLDL, very-low-density lipoprotein.

Table 2 | Effects of fibrates on cardiovascular events in large randomized controlled trials

Trial	Patient characteristics	Fibrate	Primary end point	Trial duration (years)	RR reduction for entire cohort	Lipid/metabolic subgroup	RR reduction in subgroup
HHS[91,92]	Non-HDL-C >5.2 mmol/l No CHD Men	Gemfibrozil	MI and cardiac death	5.0	–34% (*P*<0.02)	Triglycerides >2.3 mmol/l LDL-C and HDL-C >5.0 mmol/l	–71% (*P*=0.005)
VA-HIT[93,94]	HDL-C <1.0 mmol/l CHD Men	Gemfibrozil	Nonfatal MI and CHD death	1.8	–22% (*P*=0.006)	Type 2 diabetes	–32% (*P*=0.004)
BIP[95]	Previous MI or angina Men and women	Bezafibrate	Nonfatal MI and CHD death	6.2	–7.3% (*P*=0.24)	Triglycerides >2.3 mmol/l	–39.5% (*P*=0.02)
FIELD[96,97]	Type 2 diabetes Some patients receiving statins Men and women	Fenofibrate	Nonfatal MI and CHD death	5.0	–11% (*P*=0.16)	Triglycerides >2.3 mmol/l HDL-C <1.1 mmol/l	–27% (*P*=0.005)
ACCORD[98]	Type 2 diabetes CVD or >2 CVD risk factors Patients receiving simvastatin Men and women	Fenofibrate	Nonfatal MI, nonfatal stroke, and CVD death	4.7	–8% (*P*=0.32)	Triglycerides >2.3 mmol/l HDL-C <0.9 mmol/l	–32% (*P*=0.06)

Reproduced from *Heart*, Triglycerides and atherogenic dyslipidaemia: extending treatment beyond statins in the high-risk cardiovascular patient. Watts, G. F. & Karpe, F. **97**, 350–356 © 2011, with permission from BMJ Publishing Group Ltd. Abbreviations: CHD, coronary heart disease; CVD, cardiovascular disease; HDL-C: high-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; MI, myocardial infarction.

benefits of statins relate principally to the lowering of LDL-cholesterol level and concentration of lipoprotein remnants in plasma. The decrease in CVD events is, on average, 20% for each 1 mmol/l reduction in plasma LDL-cholesterol level.[93] In addition, a direct 1:1 relationship exists between the percentage fall in non-HDL-cholesterol levels and reduction in CVD events, at least during the 5-year duration of clinical trials.[94] Triglyceride reductions with statin therapy could explain the reduction in CHD events in some trials,[95] and on-treatment non-HDL-cholesterol level is an independent predictor of regression of coronary atherosclerosis.[96] However, residual CVD risk in patients receiving statins remains high, possibly as a result of atherogenic dyslipidaemia.[97] Data from the ACCORD trial[98] showed that patients with atherogenic dyslipidemia had 70% more CVD events than those without dyslipidaemia.

Fibrates

Fibrates can lower plasma levels of triglycerides, TRL remnants, and apoB by up to 30%.[99] Fibrates also enhance the formation of large, less-dense LDL particles (in terms of the relative spectrum of particle density), and increase HDL concentration by 10%.[99,100] Fibrates reduce triglyceride substrate availability in the liver by stimulating peroxisomal and mitochondrial β-oxidation (via an agonistic effect on peroxisome proliferator-activated receptor alpha [PPAR-α]), thereby decreasing hepatic secretion of VLDL.[99] Fibrates also promote intravascular lipolysis of TRLs by inducing and repressing the gene expression of LPL and apoC-III, respectively,[32,100] and increase the turnover of HDL-apoA-I.[101]

Fibrates decrease the rate of CVD (mainly CHD) events, particularly in patients with atherogenic dyslipidaemia and type 2 diabetes (Table 2).[98,102–109] Data from a meta-analysis of five randomized trials of fibrates also suggest that these agents reduce the incidence of CHD events in patients with a high triglyceride and low HDL cholesterol phenotype.[110] Subgroup analyses from the FIELD study[111] and the ACCORD trial[112] showed that fenofibrate slowed the progression of diabetic retinopathy, but this outcome was independent of change in plasma lipids and lipoproteins. A meta-analysis by Jun *et al.* suggests that a 0.1 mmol/l reduction in triglyceride level with fibrates translates into a 5% reduction in the rate of CVD events,[102] an effect that could partly explain the benefits of these drugs observed in patients with mild-to-moderate CKD.[113]

Niacin

Niacin can decrease plasma triglyceride levels and elevate HDL-cholesterol levels by up to 30%, with maximal reductions in LDL-cholesterol and lipoprotein(a) levels of 15% and 30%, respectively.[100] Niacin inhibits lipolysis in adipose tissue and the subsequent flux of FFA to the liver, which in concert with direct inhibition of hepatic triglyceride synthesis, results in reduction in the hepatic output of VLDL and the subsequent production of LDL.[32] As expected from the triglyceride-lowering effect, niacin causes a change in distribution from small, dense LDL to larger, buoyant LDL particles.[33,100] Increased secretion and delayed catabolism of HDL-apoA-I might explain the HDL-cholesterol elevating effect of niacin.[32]

The early promise of studies in patients with CHD treated with niacin[114–117] was not realised in two clinical trials, published in the past 2 years, that failed to show significant benefits of this agent on CVD events.[118,119] In the AIM-HIGH study,[118] the impact of extended-release niacin taken before retiring at night was compared with that of placebo in 3,414 simvastatin-treated patients with established atherosclerotic disease, low HDL-cholesterol levels, and hypertriglyceridaemia. The study was underpowered and confounded, partly owing to use of higher doses of statin, ezetimibe, and 200 mg immediate-release niacin in the simvastatin

group compared with the simvastatin plus niacin group. However, in a subgroup of 439 individuals with baseline triglyceride levels >2.2 mmol/l and HDL-cholesterol levels <0.9 mmol/l, a trend to a significant benefit ($P = 0.07$) with niacin was observed.[120] This finding, together with the cardiometabolic consequences of the dosing regimen of niacin, requires further investigation. It is possible that night-time administration of niacin leads to a greater rebound in plasma FFA levels with impaired myocardial energetics than mealtime dosing,[121] which was used in earlier trials that showed positive effects of niacin. In HPS2-THRIVE,[119] the largest trial of niacin, the effect of Tredaptive® (Merck Sharp & Dohme Corp., Whitehouse Station, NJ, USA; extended-release niacin combined with the prostaglandin D2 inhibitor laropiprant) were examined in patients with CVD who had simvastatin-controlled LDL-cholesterol levels, and who were receiving or not receiving ezetimibe. Serious adverse events in HPS2-THRIVE included diabetic complications (3.7%), new-onset type 2 diabetes (1.8%), haemorrhagic stroke (0.2%), infections (1.4%), gastrointestinal intracranial bleeding (0.7%), and gastrointestinal complications (1%). Despite a mean 20% reduction in LDL-cholesterol level and a mean 17% increase in HDL-cholesterol level, Tredaptive® had no significant benefit on the primary CVD end point.[119] However, a subanalysis showed an 11% reduction in the relative risk of coronary revascularization with Tredaptive®.[119] Notably, the lack of benefit (or potential harm) of Tredaptive® might not necessarily be related to niacin, but to laropiprant. An unfavourable risk-to-benefit ratio has resulted in withdrawal of niacin–laropiprant from the market, but it should be conceded that HPS2-THRIVE might not fully reflect the context in which niacin should be used in clinical practice. Analyses of the effects of niacin on CVD events in subgroups of patient with high triglyceride and low HDL-cholesterol levels in HPS2-THRIVE are awaited.

n-3 polyunsaturated fatty acids

The cardioprotective effects of supplemental *n*-3 polyunsaturated fatty acids (PUFAs), mainly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), might be mediated by improvement in hypertriglyceridaemia, but also by their antiarrhythmic, antioxidant, and antithrombotic properties.[122] Clinical outcome trials of *n*-3 PUFA ethyl esters have not, however, shown a significant CVD benefit in high-risk individuals, including patients with diabetes.[123,124] In contrast to other trials,[125] *n*-3 PUFAs were tested against a background of optimal medical therapy for secondary CVD prevention, including statins.[123,124] Patients were not selected on the basis of elevated plasma triglyceride levels, and low doses of PUFAs (~850 mg EPA plus DHA per day) were used. At every dose of a statin, 4 g of *n*-3 PUFAs could incrementally lower non-HDL-cholesterol levels by 6% in patients with hypertriglyceridaemia.[126] Purified EPA (4 g) could incrementally reduce non-HDL-cholesterol levels by 13% and apoB levels by 9% in such individuals.[127] However, in contrast to DHA, EPA does not lower plasma apoC-III concentration.[128] Whether the absence of this effect impacts on the antiatherogenic effect of purified EPA remains to be investigated in ongoing clinical end point trials.[129] Use of a mineral oil as the 'placebo' comparator oil in these studies might confound the findings, and 'placebo corrected' results need to be interpreted with caution.[127]

Whether high-dose *n*-3 PUFA, as purified EPA (4 g per day), improves CVD outcomes is being addressed in the ongoing clinical REDUCE-IT trial[129] of high-risk patients with hypertriglyceridaemia who have achieved target LDL-cholesterol levels with statin therapy. Notably, an earlier clinical trial suggested that the benefit of EPA might be greatest in patients with hypertriglyceridaemia and other CVD risk factors, including prediabetes.[130] Data published in 2013 suggest an increased risk of prostate cancer with a high dietary intake of *n*-3 PUFAs.[131] Therefore, in men, caution is required when recommending that the intake of *n*-3 PUFAs be increased in the long-term.

Ezetimibe

Although ezetimibe can lower LDL-cholesterol levels by 10–20%, its effect on fasting plasma triglyceride concentration is modest.[132] Ezetimibe might, however, have a more-pronounced effect in improving postprandial lipaemia and lowering TRL remnants, even against a background of statin therapy.[133,134] This agent regresses nonalcoholic fatty liver,[135] but the mechanism remains unclear. Ezetimibe inhibits the enterocytic absorption of cholesterol and the hepatic pool of cholesterol and, as a consequence, increases LDL-receptor activity and the clearance of LDL particles from plasma.[136] This effect is complementary to statin-induced inhibition of cholesterol synthesis. Therefore, the combined effect of ezetimibe with a low-dose of statin can match or surpass the effect of high-dose statin therapy alone in lowering the plasma levels of LDL and non-HDL cholesterol.[137] However, intensive lipid lowering with a statin plus ezetimibe might not consistently prevent CVD events.[117,138] Regression of carotid atherosclerosis in patients with type 2 diabetes receiving ezetimibe plus a statin could be proportional to the fall in LDL-cholesterol level.[139] An ultrasonographic trial, in which a similar hypothesis concerning the adding of ezetimibe to a statin was tested in patients with familial hypercholesterolaemia, was negative.[140] However, the study was underpowered and confounded by use of high-intensity statin and the near-normal carotid intima-media thickness prior to randomization.[140]

The findings of the SEAS trial[138] indicated that, in patients with aortic stenosis, adding ezetimibe to simvastatin may decrease total CVD events, but not events related to aortic stenosis. According to an analysis of data from three trials of ezetimibe, this drug does not increase the risk of cancer.[141] In SHARP,[142] the largest trial of lipid intervention in patients with CKD, the combination of ezetimibe and simvastatin safely lowered LDL-cholesterol levels by 0.8 mmol/l, which translated into a 17% reduction in major cardiovascular events. Whether some of this benefit was mediated by the 30% reduction

Table 3 | Therapies in development for hypertriglyceridaemia

Therapeutic agent	Target site of action	Secretion*	Catabolism*	Expected mean reduction in plasma triglyceride concentration (%)	Clinical trials with lipid outcomes	Clinical trials with CVD outcomes
Dual PPAR-α/δ agonist	Liver, muscle, adipocytes	↓↓	↑	30	Yes	No
CETP inhibitor	Plasma	=	↑	20	Yes	Yes
MTP inhibitor	Liver, enterocyte	↓↓	=	30	Yes	No
DGAT-1 inhibitor	Liver, enterocyte, adipocytes	↓↓	=	40	Yes	No
DGAT-2 inhibitor	Liver	↓↓	=	40	No	No
ANGPTL inhibitor	Muscle, adipocytes	=	↑	40	No	No
ApoB antisense	Liver	↓↓	=	30	Yes	No
ApoC-III antisense	Liver	=	↑↑	40	Yes	No
PCSK9 inhibitor	Liver	?	↑	15	Yes	No
LPL gene replacement	Muscle, adipocytes	=	↑↑	40	Yes	No

*Postulated effect on TRL metabolism. The number of arrows indicates the magnitude of decrease/increase. Abbreviations: ↓, decrease; ↑, increase; =, no change; ?, uncertain; ANGPTL, angiopoietin-like protein; ApoB, apolipoprotein B; CETP, cholesteryl ester transfer protein; CVD, cardiovascular disease; DGAT-1, diacylglycerol O-acyltransferase 1; LPL, lipoprotein lipase; MTP, microsomal triglyceride transfer protein; PCSK9, proprotein convertase subtilisin kexin type 9; PPAR, peroxisome proliferator-activated receptor.

in non-HDL-cholesterol is unclear. Notably, neither the SEAS trial[138] nor SHARP[142] were designed to address the question of whether any specific benefit is conferred by adding ezetimibe to statin therapy. Definitive evidence for the role of ezetimibe in high-risk individuals receiving optimal statin therapy awaits the outcome of the IMPROVE-IT study.[143]

Incretin-based therapies

Incretins, such as glucagon-like peptide 1 (GLP-1) are insulinotropic, gut-derived hormones secreted in response to dietary nutrients.[144] Incretin receptor analogues are antiglycaemic, and can ameliorate impaired TRL metabolism in type 2 diabetes.[144] The mechanism could involve inhibition of chylomicron biogenesis,[145] an action that might extend to dipeptidyl peptidase 4 inhibitors that increase GLP-1 activity.[144] GLP-1 directly improves endothelial function, blood pressure, and inflammation in patients with diabetes.[144] Dipeptidyl peptidase 4 inhibitors could, therefore, prevent CVD events independent of changes in glucose and lipid metabolism.[146]

LPL gene replacement therapy

Glybera® (alipogene tiparvovec; Amsterdam Molecular Therapeutics, Amsterdam, the Netherlands) is the first approved gene-replacement therapy for an orphan disease (LPL deficiency).[147,148] Glybera® contains an *LPL*^{S447X} gain-of-function gene construct, within an adenovirus type 1 delivery vehicle, that increases the expression of LPL in muscle. Owing to its expense and mode of administration, Glybera® is indicated under exceptional circumstances for adult patients genetically diagnosed with familial LPL deficiency who have detectable plasma LPL levels and a history of severe or multiple episodes of pancreatitis despite dietary fat restriction.[148] The clinical experience with Glybera® is limited; this agent has only been studied in 27 patients with LPL deficiency who were following a low-fat diet, in whom it significantly lowered plasma triglyceride concentration and the frequency of acute pancreatitis.[147] Glybera® is generally well-tolerated, but lower limb myalgia related to the intramuscular administration of the agent might be experienced by up to 30% of patients.[147] Co-administration of an immunosuppressant is also required. Cost-effectiveness analyses are required, and a registry of patients taking Glybera® needs to be established.[149]

Therapies in development

Several novel therapies for hypertriglyceridaemia are in development (Table 3). These agents operate by increasing the clearance or reducing the production of TRLs. A new dual PPAR-α/δ agonist (GFT505) improves hypertriglyceridaemia (–17%) and both peripheral and hepatic insulin sensitivity[150] in patients with diabetes who are obese.[151] On the basis of hepatoprotective effect in rodent models,[152] this agent is currently being trialled for the treatment of nonalcoholic steatohepatitis. The dual PPAR-α/γ agonist aleglitazar dose-dependently improves dyslipidaemia and glycated haemoglobin (HbA_{1c}) in patients with type 2 diabetes.[153] However, a phase III clinical trial of this class of drug in patients with type 2 diabetes was terminated owing to safety concerns.[154] CETP inhibitors principally elevate HDL-cholesterol concentration and have variable effects on plasma triglyceride and LDL-cholesterol levels;[155] no significant cardiovascular benefits have been reported to date.[156,157] Diacylglycerol O-acyltransferase 1 inhibitors have been shown to reduce plasma triglyceride levels by 40% in patients with primary chylomicronaemia[158] and improve postprandial lipaemia by up to 80%.[159] Microsomal triglyceride transfer protein (MTP) inhibition and apoB antisense therapies are currently indicated only for patients with homozygous familial hypercholesterolaemia,[160,161] as both therapies can cause hepatic steatosis. ApoC-III antisense oligonucleotides lower plasma triglyceride and apoC-III concentrations in healthy individuals.[162] Moreover, a phase II study of apoC-III antisense oligonucleotides

in patients with type 2 diabetes and high plasma triglyceride levels showed promising results, with significant improvements in plasma apoC-III (−88%), triglyceride (−72%), and HDL-cholesterol (+40%) concentrations.[163] Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors might increase catabolism of TRLs via hepatic receptors,[164] but their role in the treatment of hypertriglyceridaemia remains unclear. Inhibition of angiopoietin-like proteins (ANGPTL3 and ANGPTL4) enhances LPL activity and triglyceride lipolysis,[165] but the effects on TRL mechanism in humans have not yet been tested.

Guidelines

Guidelines for the management of hypertriglyceridaemia[5,9,10,12,166] are especially relevant to individuals at high-risk of CVD, particularly those with diabetes or metabolic syndrome. The consensus of opinion is that elevation in plasma triglyceride concentrations, in the range 1.7–10.0 mmol/l, is a marker of the atherogenic effects of TRL remnants, low HDL concentration, and insulin resistance. Non-HDL-cholesterol concentration is considered the most convenient indicator of TRLs (in a triglyceride range 2–5 mmol/l), but the value of measuring apoB is also emphasized, noting additional assay costs. The predictive merits of risk assessment on the basis of a nonfasting lipid profile, including triglyceride levels, are well recognized. One expert group recommends estimating postprandial lipaemia,[63] but this would be impractical in routine clinical settings. With moderate hypertriglyceridaemia, therapeutic targets for non-HDL-cholesterol of <3.3 mmol/l (apoB <1.0 g/l) and <2.6 mmol/l (apoB <0.8 g/l) are recommended for individuals at high and very-high absolute risk of CVD, respectively.[166] Achieving these targets requires appropriate dietary and exercise regimens and drug therapy, where indicated.[9,10,12] All guidelines specify the safe use of statins to achieve primary therapeutic LDL cholesterol targets, with a choice of niacin, a fibrate, or high-dose of *n*-3 PUFAs to lower triglycerides and attain secondary targets of non-HDL cholesterol or apoB.[9–12] Recommendations on the use of niacin in patients with well-controlled plasma LDL-cholesterol concentrations, even in high-risk individuals, will need revision in the light of clinical trial data published in the past 2 years.[118,119] The results of the ongoing REDUCE-IT trial[129] should clarify the cardiovascular value of adding purified EPA to a statin in high risk patients with initial mild-to-moderate hypertriglyceridaemia. Systematic approaches for evaluating severe hypertriglyceridaemia, including primary chylomicronaemia, and dietary, lifestyle, and drug management to prevent pancreatitis and steatohepatitis, have also been published.[9,12,16]

Proposed treatment strategies

Moderate-to-high triglyceride levels

From existing data and guidelines, we recommend the strategy shown in Figure 4 for managing moderate-to-high plasma triglyceride levels in patients with established CVD or moderate-to-high risk of CVD. We acknowledge that the proposed scheme needs to be formally tested for efficacy and cost-effectiveness in routine clinical care.

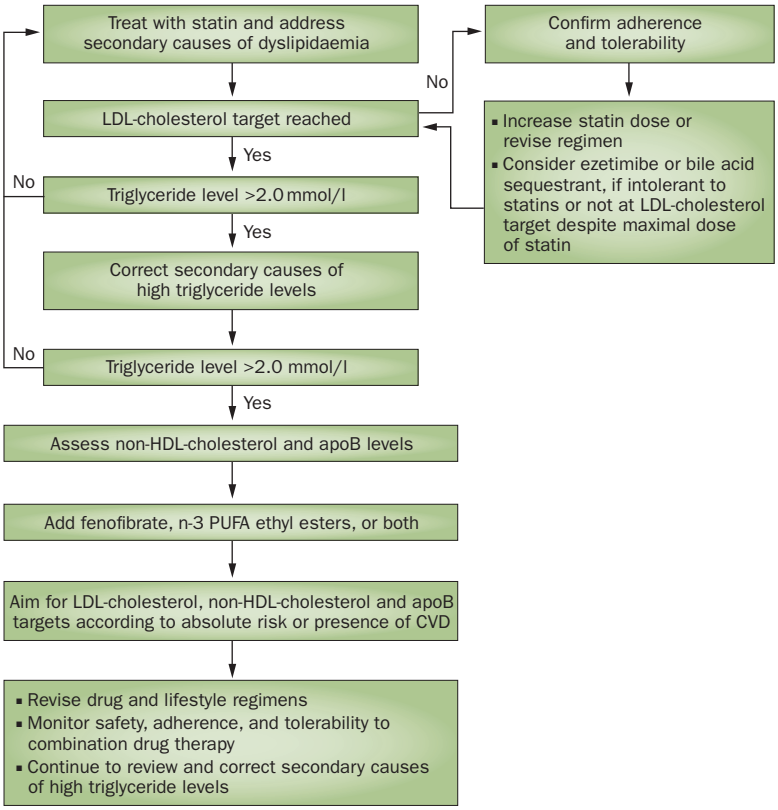

Figure 4 | Algorithm for managing dyslipidaemia in patients at high risk of cardiovascular disease. Abbreviations: ApoB, apolipoprotein B; CVD, cardiovascular disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PUFA, polyunsaturated fatty acid. Reproduced from *Heart,* Triglycerides and atherogenic dyslipidaemia: extending treatment beyond statins in the high-risk cardiovascular patient, Watts, G. F. & Karpe, F. **97**, 350–356 © 2011, with permission from BMJ Publishing Group Ltd.

These patients, who frequently have type 2 diabetes, should be treated initially with a statin and lifestyle measures, and all secondary causes of hypertriglyceridaemia corrected. When initiating and altering drug therapy, a fasting lipid profile should be used, noting that when plasma triglyceride >4.5 mmol/l[2,167,168] the Friedewald formula is invalid and a direct assay for LDL-cholesterol is required. Evidence exists that the deviation of calculated from actual LDL-cholesterol level can be >10% at a plasma triglyceride concentration >3.5 mmol/l in patients with type 2 diabetes.[168] The therapeutic targets for LDL cholesterol, non-HDL cholesterol, and apoB are shown in Box 2. Notably, no specific targets for treating triglycerides or HDL-cholesterol to prevent or reverse CVD risk have been recommended by expert bodies. When LDL cholesterol targets are not attained, adherence to treatments must be checked and rectified prior to considering adding other agents, which will be required in 15–20% of patients to correct atherogenic dyslipidaemia.[97] In patients with a fasting triglyceride level >2.0 mmol/l, non-HDL cholesterol and, ideally, apoB should be used as secondary therapeutic targets.[11,97,166] As non-HDL cholesterol and apoB are not equivalent

Box 2 | Treatment goals in hypertriglyceridaemia[166]

Very high-risk groups*
- LDL cholesterol <1.8 mmol/l
- Non-HDL cholesterol <2.6 mmol/l
- Apolipoprotein B <0.8 g/l

High-risk groups‡
- LDL cholesterol <2.6 mmol/l
- Non-HDL cholestero: <3.4 mmol/l
- Apolipoprotein B <1.0 g/l

*Known CVD or diabetes plus >1 additional major CVD risk factor (hypertension, albuminuria, smoking, and family history of premature CVD). ‡No known CVD or diabetes but >2 major CVD risk factors (or 10-year risk of CVD >20%), or diabetes but no other major CVD risk factors. Abbreviation: CVD, cardiovascular disease.

in individual patients,[72,73] both therapeutic end points should strictly be targeted, but this recommendation requires verification in prospective trials. Nevertheless, statins result in cholesterol depletion of LDL such that, in certain individuals, the change in level of apoB will lag behind that of non-HDL cholesterol,[169] with clear implications for clinical practice.

If therapeutic LDL-cholesterol targets are not attained with high doses of the weaker types of statin, such as fluvastatin or pravastatin, introduction of ezetimibe or a more-potent statin, such as atorvastatin or rosuvastatin, should be considered. Increasing doses of statins can incrementally lower non-HDL-cholesterol and apoB levels in patients with hypertriglyceridaemia.[170,171] An advantage of ezetimibe is the statin dose-sparing effect in patients intolerant to high doses of statins. If an incremental reduction in HbA_{1c} is required in a patient with diabetes, colesevelam can be considered.[172] However adverse gastrointestinal effects can be a problem with bile acid sequestrants, and hypertriglyceridaemia can be exacerbated in patients with a pretreatment plasma triglyceride level >2.2 mmol/l. Persuasive, but not definite, evidence from subgroup analyses supports adding fenofibrate to a statin in patients with diabetes if the plasma triglyceride level is >2.0 mmol/l, particularly in those with an HDL-cholesterol level <1.0 mmol/l.[97,98,109] Adding fenofibrate to a moderate dose of a statin has an incremental lowering effect on plasma levels of triglyceride, non-HDL cholesterol, and apoB.[173] On the bases of clinical outcome, as well as adverse pharmacokinetic interactions with statins that can lead to myotoxicity, we recommend the use of fenofibrate rather than gemfibrozil or bezafibrate.[97,174] Fenofibrate can also decrease the progression of mild-to-moderate retinopathy in patients with type 2 diabetes who are receiving statins.[111,112] Cholelithiasis is an important contraindication to the use of fibrates. The efficacy of statins and fibrates in lowering LDL-cholesterol and non-HDL-cholesterol levels might be diminished by elevation in the plasma PCSK9 level,[175] creating an opportunity for future use of PSCK9 inhibitors.[164]

No reliable clinical outcome data exist to support the addition of *n*-3 PUFAs or niacin to a statin in patients with or without hypertriglyceridaemia.[118,119,123,124] However, if fenofibrate cannot be tolerated, or is contraindicated, high-doses of *n*-3 PUFAs (up to 4 g) might be the safest option for combination therapy with a statin. In patients who are intolerant of statins,[176] the combination of *n*-3 PUFAs, fenofibrate, and ezetimibe might be required to control dyslipidaemia, although no clinical outcome nor long-term safety data exist to support this approach. Adding niacin to a statin does not seem to be a beneficial strategy in high-risk patients whose LDL-cholesterol level is well controlled.[118,119] There could be a role for niacin, however, in managing high-risk patients with hypertriglyceridaemia who are intolerant to statins and have elevated levels of LDL-cholesterol, lipoprotein(a), or both, but this theory needs to be verified in clinical trials.

Very high triglyceride levels

The risk of acute pancreatitis with very high plasma triglyceride levels (>10 mmol/l) is the result of chylomicronaemia. As the first therapeutic approach, a very low fat diet (<10% of total energy intake) can diminish the risk,[9,11,16] and exercise can also be beneficial.[9,10] Secondary causes of hypertriglyceridaemia, particularly excessive alcohol consumption, overnutrition, obesity, and hyperglycaemia, must be vigorously corrected. The use of dietary medium-chain triglycerides (present in coconut or palm kernel oils) in cooking can be beneficial[16] as, by contrast to long-chain and very-long-chain triglycerides, they are directly absorbed into the portal vein and are not incorporated into chylomicrons. In patients with very high triglycerides levels, purified EPA supplementation could have the advantage over other PUFAs in effectively lowering plasma triglyceride and LDL particle concentrations with no elevation in LDL-cholesterol.[177] If chylomicronaemia co-exists with atherogenic dyslipidaemia, quadruple pharmacotherapy with fenofibrate, *n*-3 PUFAs, ezetimibe, and a statin might be required.[178] Severe chylomicronaemia complicated by acute pancreatitis is a medical emergency that can require lipoprotein apheresis. Glybera® has been approved, in combination with a low-fat diet, for treating patients with extreme hypertriglyceridaemia with increased risk of pancreatitis owing to LPL deficiency.[147,148] Whether the use of other agents currently in development, including inhibitors of MTP and diglyceride acyltransferase and apoC-III antisense, will improve the treatment of extreme hypertriglyceridaemia merits further investigation.

Safety aspects of combination drug therapy

Plasma levels of aminotransferases, creatine kinase, creatinine, and glucose should be measured before initiating a second agent in patients receiving lipid-lowering therapy. Musculoskeletal symptoms are reported in up to 20% of patients treated with a statin and a fibrate.[174] If the level of plasma creatine kinase exceeds five-times the upper limit of normal, or if musculoskeletal symptoms are severe, the second agent should be discontinued. Alanine and aspartate aminotransferases should be measured 3 months after adding a fibrate and every 12 months thereafter, or more frequently when increasing the dose of the statin, noting that hepatoxicity is a potentially serious effect when a statin is combined with

a fibrate or niacin. The plasma creatinine level should be periodically checked in patients receiving statins plus fenofibrate, although the increases in creatinine reported with fenofibrate in clinical trials is reversible and not associated with adverse events.[179] If niacin is used in patients with a history of diabetes, impaired glucose tolerance, or gout, levels of plasma glucose, HbA_{1c}, and urate should be monitored closely.[180]

Conclusions

The multigenic origin of hypertriglyceridaemia and the causal role of TRLs in atherosclerotic CVD are supported by the latest research. Hypertriglyceridaemia is associated with a broad spectrum of cardiometabolic risk factors, including increased lipid deposition in ectopic tissues and atherogenic changes in all plasma lipoproteins, which can be estimated by measuring levels of non-HDL cholesterol and apoB (the targets for treatment). Atherogenic dyslipidaemia is common in patients with diabetes and mild-to-moderate hypertriglyceridaemia who are obese and insulin resistant. Very-high plasma triglyceride levels causes acute pancreatitis and hepatic steatosis. Hypertriglyceridaemia is commonly caused by interactions between genetic and nongenetic factors that must be identified and corrected. Some patients have multigenic disorders that cause premature CVD within families, and need to be clearly identified and treated aggressively with lifestyle changes and lipid-regulating drugs. Patients with rare monogenic disorders, which cause severe hypertriglyceridaemia, are at risk of acute pancreatitis and require special dietary advice and close monitoring, with the possible addition of a fibrate and, exceptionally, Glybera® if licensed for use. Lifestyle interventions are fundamentally important to the management of all patients with hypertriglyceridaemia. For patients with established CVD, or those with multiple CVD risk factors including type 2 diabetes or metabolic syndrome, statins are the cornerstone treatment to lower plasma levels of LDL cholesterol and triglycerides. Combination drug therapy may be indicated, but before a categorical recommendation can be made, more evidence is required from CVD outcome studies, some of which are in progress. Evidence supports the use of fenofibrate, especially in patients with type 2 diabetes, and *n*-3 PUFAs might be particularly useful in patients intolerant to combination therapy with statins and fibrates. Evidence precludes use of niacin in patients with hypertriglyceridaemia although, in exceptional circumstances, this agent might have a role in the management of patients who are intolerant of other drugs but remain at high risk owing to elevated levels of LDL cholesterol and possibly lipoprotein(a). Patient adherence and tolerability to pharmacotherapies require continual review, and could involve the simplification of drug regimens, close monitoring of safety variables, enhanced doctor–patient alliance, and reductions in the cost of drugs. Several therapies for correcting TRL metabolism, including inhibitors of diglyceride acyltransferase and MTP, and apoC-III antisense oligonucleotides are under development, but their clinical efficacy, safety, and cost-effectiveness remains to be demonstrated.

Review criteria

A search for original articles was performed in the PubMed database using the following key terms: "triglyceride", "hypertriglyceridaemia", "triglyceride-rich lipoproteins", "atherosclerosis", "treatment", and "cardiovascular disease" either alone or in combination. All articles selected were English language, full-text papers, with no restriction applied to the date of publication.

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