FEATURE

Grappling with hypertriglyceridaemia

Rosetta Stone or Pandora's Box?

GERALD F. WATTS DSc, PhD, DM, FRACP, FRCP
DICK C. CHAN BSc, MPhil, PhD, FRCPath
GAURAV PURI MB BS, FRACP

Hypertriglyceridaemia is caused by interactions between many genetic and nongenetic factors, and is a common risk factor for atherosclerotic cardiovascular disease (CVD). 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 and those at moderate-to-high risk of CVD.

Plasma triglyceride concentration can be used to estimate LDL-cholesterol levels by using the Friedewald formula.[1,2] An elevated LDL-cholesterol is a major risk factor for cardiovascular disease (CVD), and is the principal target for therapy in both primary and secondary CVD prevention.[3-5] By contrast, the importance of elevated plasma triglyceride concentrations in similar settings is uncertain.[6] Multiple genes that interact with nongenetic factors, particularly obesity, insulin resistance and diabetes, perturb the production and catabolism of triglyceride-rich lipoproteins, inducing hypertriglyceridaemia.[7] This article provides practical guidance on managing patients with hypertriglyceridaemia and for the prevention and treatment of atherosclerotic CVD.

CARDIOLOGY TODAY 2013; 3(4): 8-15

Professor Watts is Professor of Cardiometabolic Medicine, School of Medicine and Pharmacology, University of Western Australia. Dr Chan is Research Assistant Professor, School of Medicine and Pharmacology, University of Western Australia. Dr Puri is Associate Professor, School of Medicine and Pharmacology, University of Western Australia, WA.

What is hypertriglyceridaemia?

Hypertriglyceridaemia can be defined as a fasting plasma triglyceride concentration above the 95th percentile for age and sex in a population. Plasma triglyceride concentrations are higher in men than in women, are lower in individuals of African or Caribbean descent than in white people, and increase with age and after a high-fat meal.[7] Experts provide arbitrary definitions of hypertriglyceridaemia (see Table 1),[8-10] with a fasting triglyceride concentration of more than 1.7 mmol/L being generally considered abnormal. A simple hierarchical definition is that a fasting plasma triglyceride level of 1.7 to 2.3 mmol/L is mild,

Key points

- **Hypertriglyceridaemia is a common risk factor for atherosclerotic cardiovascular disease.**
- **Hypertriglyceridaemia reflects the accumulation in plasma of proatherogenic lipoproteins, triglyceride-rich lipoprotein remnants and small dense LDL particles.**
- **Extreme hypertriglyceridaemia (triglyceride levels of more than 20 mmol/L) is rare but significantly increases the risk of 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 cardiovascular disease or individuals at moderate-to-high risk of cardiovascular disease, particularly those with the metabolic syndrome or diabetes.**

Secondary causes of hypertriglyceridaemia

Mild and moderate hypertriglyceridaemia

Acquired traits/lifestyle habits

Overweight
Obesity
Physical inactivity
Cigarette smoking
Diet: high energy, fat, glycaemic index and fructose
Excess alcohol intake

Disease/states

Type 2 diabetes
Polycystic ovary syndrome
Hypothyroidism
Renal failure
Nephrotic syndrome
Stress/sepsis
Cushing syndrome
Lipodystrophy
Acromegaly
Systemic lupus erythematosus
Pregnancy
HIV infection
Paraproteinaemia
Glycogen storage disease

Drugs

Oral oestrogens
Tamoxifen
Beta blockers
Thiazides
Retinoic acid derivative
Antipsychotics
Antiretroviral therapy
Bile acid sequestrants
Cyclosporin, sirolimus
L-asparaginase
Interferon

Very high hypertriglyceridaemia

Same as above plus major loss-of-function gene variant

2.3 to 5.5 mmol/L is moderate, 5.5 to 10.0 mmol/L is high, and more than 10.0 mmol/L (a level above which chylomicrons appear) is very high or severe. Extreme hypertriglyceridaemia is rare and defined as a fasting triglyceride concentration of more than 20.0 mmol/L.

About 30% of adults have mild-to-moderate hypertriglyceridaemia, whereas the prevalence of the severe forms is only 1 to 2%.[7,9] In patients with coronary artery disease, including those treated with statins, more than 30% have mild-to-moderate hypertriglyceridaemia with or without a low plasma HDL-cholesterol level.[7,8] The prevalence of hypertriglyceridaemia can be as high as 50% in patients with diabetes.[8,11]

Aetiology of hypertriglyceridaemia

Hypertriglyceridaemia has a complex genetic aetiology.[12,13] Genetic and nongenetic factors interact to affect the production and catabolism of triglyceride-rich lipoproteins. A very small proportion of people (<1 in 10,000) have a purely monogenic disorder. Individuals with severe hypertriglyceridaemia (>10.0 mmol/L) are likely to be homozygous or compound heterozygous for mutations that impair the lipolytic catabolism of triglyceride-rich lipoproteins. Individuals with hypertriglyceridaemia in the range of 1.7 to 10.0 mmol/L are

Table 1. Categories and definitions of hypertriglyceridaemia according to international guidelines[8-10]

Plasma triglyceride levels (mmol/L)		
National Cholesterol Education Program (adult treatment panel III)	Endocrine Society	European Atherosclerosis Society
Normal <1.7	Normal <1.7	Desirable <1.7
Borderline high 1.7–2.3	Mild 1.7–2.3	Elevated 1.7–5.6
High 2.3–5.6	Moderate 2.3–11.2	Very high 5.6–25
Very high >5.6	Severe 11.2–22.4	Extremely high >25
	Very severe >22.4	

likely to be heterozygous for common or rare loss-of-function genetic variants that impair to a varying degree the metabolism of triglyceride-rich lipoproteins.[12] In individuals with mild-to-moderate hypertriglyceridaemia, the risk of CVD is increased in the setting of familial endogenous hypertriglyceridaemia, type III dysbetalipoproteinaemia and familial combined hyperlipidaemia.[7,10,14] Numerous nongenetic factors can precipitate hypertriglyceridaemia (see the box on page 9).

Atherogenic dyslipidaemia and ectopic fat deposition

Atherogenic dyslipidaemia is a hypertriglyceridaemic phenotype associated with increased plasma concentrations of small, dense LDL-cholesterol particles, triglyceride-rich lipoproteins, non-HDL cholesterol and apolipoprotein B (apoB), as well as low HDL-cholesterol levels. It is most typically encountered in patients with insulin resistance, central obesity and plasma triglyceride concentrations in the range of 2 to 5 mmol/L.[8,15,16] An increase in white adipose tissue in obesity leads to decreased capacity for storing free fatty acids, resulting in an increase in substrate delivery for triglyceride synthesis in the liver and enterocytes. Insulin resistance also induces hepatic steatosis. Hepatic steatosis and hypertriglyceridaemia are associated with ectopic fat deposition in the pancreas, kidney, arteries, heart and skeletal muscle, which result in impaired insulin signalling, inflammation and organ dysfunction, as well as an increased risk of CVD.[17-19]

CVD and hypertriglyceridaemia

Whether hypertriglyceridaemia is an independent risk factor for CVD has been controversial.[6] In the largest meta-analysis conducted to date, the risk of coronary heart disease (CHD) was increased, after adjusting for nonlipid risk factors, by 37% for each standard deviation increase in plasma triglyceride level.[20] However, the association was weakened after adjustment for HDL-cholesterol. The lack of an independent association between triglyceride levels and CVD risk in epidemiological studies is not surprising, given that hypertriglyceridaemia is associated with many other risk factors.

Employing the epidemiological technique of Mendelian randomisation has demonstrated that every 1 mmol/L rise in increased nonfasting remnant cholesterol concentration in plasma is associated with a 2.8-fold increase in causal risk for ischaemic heart disease,[21] which implies causality.

The apparent atherogenicity of hypertriglyceridaemia relates directly to small triglyceride-rich lipoprotein remnant particles.[22] Triglyceride-rich lipoprotein remnants induce endothelial dysfunction, inhibit fibrinolysis, and enhance coagulation and vascular inflammation.[23,24] Readily traversing the arterial wall, triglyceride-rich lipoprotein remnants rich in cholesterol and apoE are trapped by the connective tissue matrix and, after phagocytosis, transform arterial wall macrophages into atherogenic foam cells (see Figure 1). Lipolysis of triglyceride-rich lipoproteins also releases toxic products, such as oxidised free fatty acids and lysolecithin, which further induce endothelial cell inflammation and coagulation.[6,25,26]

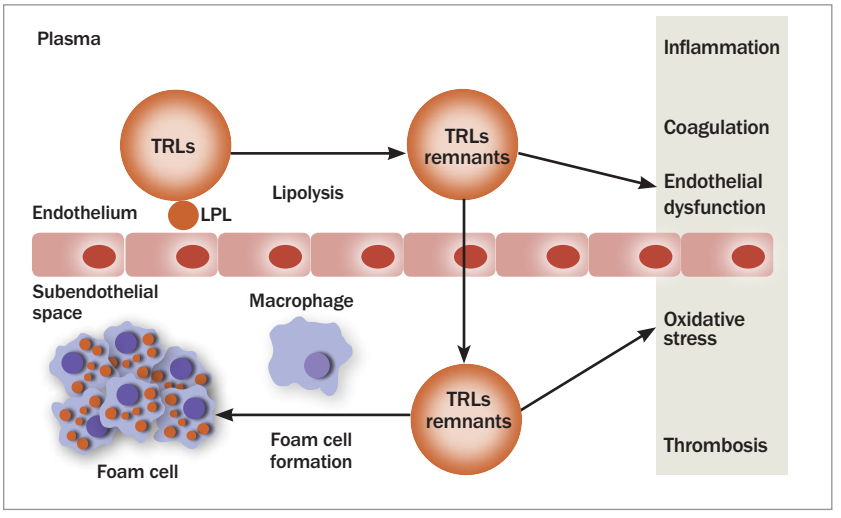


Figure 1. Hypertriglyceridaemia, triglyceride-rich lipoproteins and atherogenesis.
Abbreviations: LPL = lipoprotein lipase; TRL = triglyceride-rich lipoprotein.

Biochemical assessment of dyslipidaemia

The plasma lipid profile is conventionally measured after a nine- to 12-hour fast[2,9] because this increases the precision with which triglyceride concentration can be estimated. Nonfasting

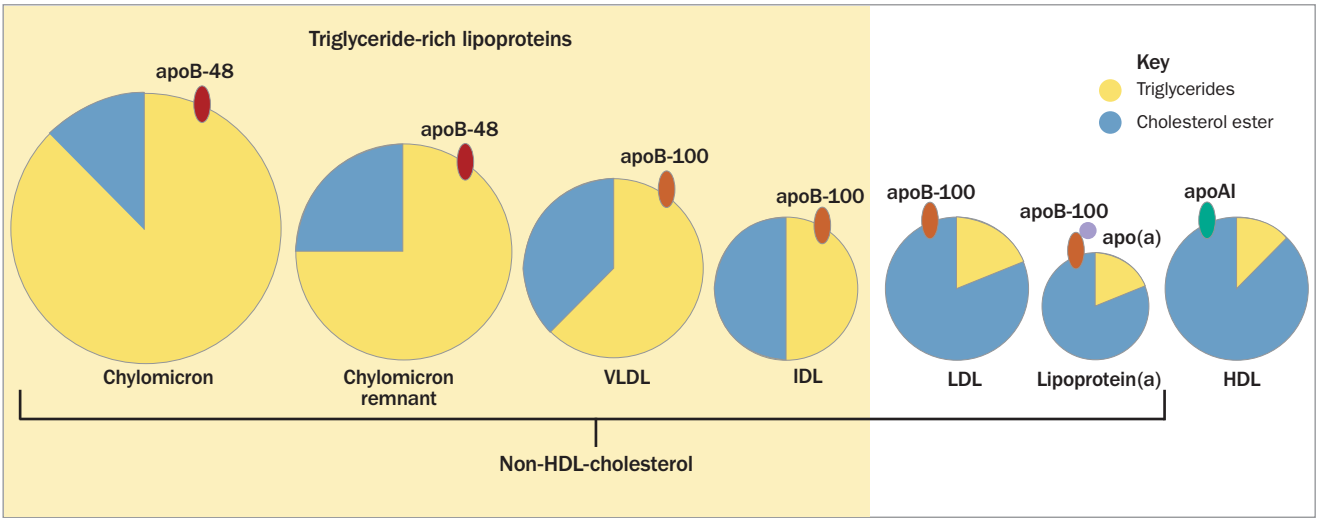


Figure 2. The non-HDL-cholesterol concentration in plasma is the sum of the cholesterol in triglyceride-rich lipoproteins (chylomicrons, chylomicron remnants, VLDL and IDL) and LDL, which can be estimated by subtracting the HDL-cholesterol concentration from the total plasma cholesterol concentration.

Abbreviations: apo(a) = apolipoprotein(a); apoAI = apolipoprotein AI; apoB = apolipoprotein B; HDL = high-density lipoprotein; IDL = intermediate-density lipoproteins; LDL = low-density lipoprotein; VLDL = very-low-density lipoprotein.

triglyceride concentrations are reflective of the postprandial state, however, and can be superior to fasting triglyceride levels in predicting CVD risk.[27,28] A nonfasting blood test is the simplest initial method of screening for hypertriglyceridaemia. However, if the initial triglyceride level is more than 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 the cholesterol content of all the atherogenic apoB-containing lipoproteins (very low-density lipoprotein [VLDL], intermediate-density lipoprotein, LDL and lipoprotein(a); see Figure 2), particularly when the plasma triglyceride level is less than 5.7 mmol/L.[9,29] 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 show that non-HDL-cholesterol is a better predictor of CVD events than LDL-cholesterol.[30-33]

ApoB or non-HDL-cholesterol as a predictor of CVD?

ApoB concentration has been shown to be a better predictor of CVD than non-HDL-cholesterol level in some but not all studies.[30,31,34,35] ApoB and non-HDL-cholesterol are not equivalent in individual patients.[34,35] 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 an 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 familial combined hyperlipidaemia.[34] The authors recommend that measurement of both apoB and non-HDL-cholesterol should be undertaken to target therapy in individuals at high risk of CVD, noting that Medicare does not currently cover the testing of apoB.

Management

Lifestyle modifications

Lifestyle modifications are fundamental to the treatment of hypertriglyceridaemia. These include changes to dietary composition and exercise, as well as regulation of alcohol consumption.[7,8] These interventions can collectively decrease plasma triglyceride concentration by up to 60%.[36,37]

In obese patients, dietary restriction can lower plasma triglyceride concentration by 0.015 mmol/L/kg reduction in body weight.[37] On average, weight loss of 5 to 10% of initial body weight reduces triglyceride concentration by 25% and LDL-cholesterol level by 15% while raising HDL-cholesterol level by 8%.[37]

A low-carbohydrate diet achieves the greatest increase in HDL-cholesterol levels. 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.[38,39] 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. Reductions in glycaemic load and fructose consumption and an increase in soluble fibre intake enhance lowering of triglyceride levels.

Mediterranean-style diets can achieve sustained reductions in plasma triglyceride concentration (10 to 15%),[40] development of insulin resistance, systolic blood pressure level and risk of type 2 diabetes. Such diets can decrease the incidence of major CVD events in a primary prevention setting in people with dyslipidaemia, the metabolic syndrome and type 2 diabetes.[41]

Aerobic exercise of moderate-to-high intensity decreases plasma triglyceride concentrations by up to 20%, particularly in patients with hypertriglyceridaemia who are following a hypocaloric diet.[42,43] Aerobic exercise and moderate weight loss prevents the development of type 2 diabetes in people with impaired glucose tolerance, and corrects dyslipidaemia and other cardiometabolic risk factors in patients with established type 2 diabetes. Resistance training has a minimal effect on plasma levels of triglycerides and triglyceride-rich lipoproteins. Cigarette smoking also has a minimal effect on plasma triglyceride levels, but cessation is fundamental to all cardiovascular prevention strategies.[7-10] Excessive alcohol intake can markedly increase plasma triglyceride levels in susceptible individuals, owing to increased hepatic output of VLDL, but this effect can be quickly reversed by abstention from alcohol.

Pharmacotherapy

Statins

Statins are the most efficacious agents for lowering elevated plasma concentrations of LDL-cholesterol and apoB. Their efficacy in decreasing hypertriglyceridaemia depends on the baseline plasma triglyceride level, and is proportional to the LDL-cholesterol lowering effect.[44] Use of statins may lower plasma triglyceride levels by increasing lipolysis and the hepatic clearance of triglyceride-rich lipoproteins. These effects are most pronounced with higher doses of potent statins, such as atorvastatin and rosuvastatin. 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 benefits of statins relate principally to the lowering of LDL-cholesterol and lipoprotein remnant concentration in plasma.

Fibrates

Fibrates can lower plasma levels of triglycerides, triglyceride-rich lipoprotein remnants and apoB by up to 30%.[45] Fibrates also enhance the formation of large, less-dense LDL particles, and increase HDL concentration by 10%.[45,46] They also reduce triglyceride substrate availability in the liver by stimulating peroxisomal and mitochondrial β-oxidation (via an agonistic effect on peroxisome proliferator-activated receptor-alpha), thereby decreasing hepatic secretion of VLDL. Fibrates also promote intravascular lipolysis of triglyceride-rich lipoproteins.

Fibrates decrease the rate of CVD events (mainly CHD events), particularly in patients with atherogenic dyslipidaemia and type 2 diabetes.[47-55] Data from a meta-analysis of five randomised trials also suggest that fibrates reduce the incidence of CHD events in patients with a high triglyceride and low HDL-cholesterol phenotype.[56] Subgroup analyses from the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study and the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial showed that fenofibrate slowed the progression of diabetic retinopathy, but this outcome was independent of change in plasma lipids and lipoproteins.[57,58] Another meta-analysis suggests that a 0.1 mmol/L reduction in triglyceride level with use of fibrates translates into a 5% reduction in the rate of CVD events, an effect that could partly explain the benefits of these drugs observed in patients with mild-to-moderate chronic kidney disease.[48]

Nicotinic acid

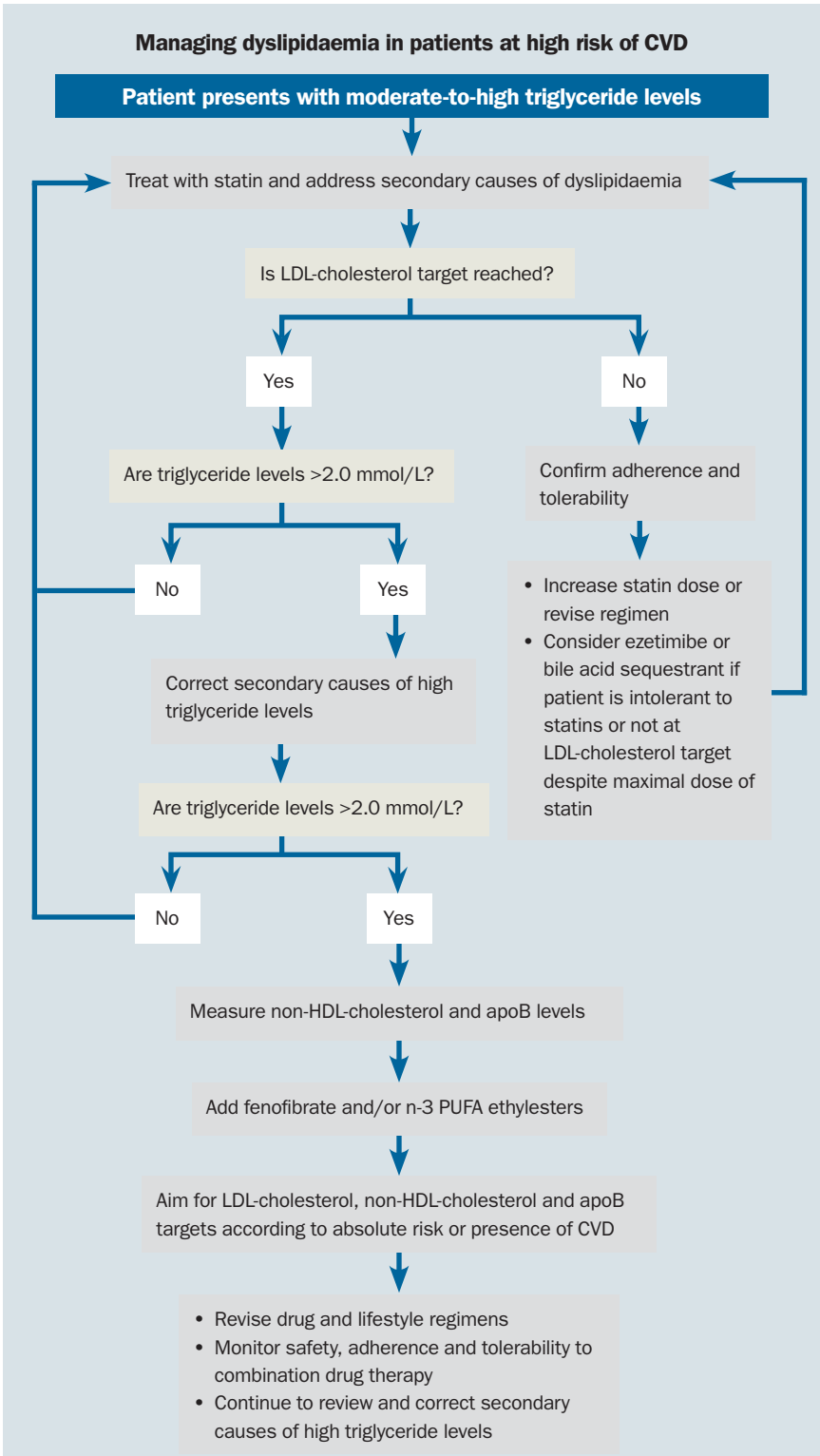
Nicotinic acid can decrease plasma triglyceride levels and elevate HDL-cholesterol levels by up to 30%, with maximal reductions in LDL-cholesterol and lipoprotein(a) levels of 15% and 30%, respectively.[46] Nicotinic acid inhibits lipolysis in adipose tissue and the subsequent flux of free fatty acids to the liver, which in concert with direct inhibition of hepatic triglyceride synthesis decreases the hepatic output of VLDL and the subsequent production of LDL. Two clinical trials published in the past two years have failed to show a significant benefit of nicotinic acid on CVD events in patients with CHD treated with statins,[63,64] questioning the value of nicotinic acid when LDL-cholesterol is optimally treated.[59-64] In one trial, nicotinic acid with use of an antiflushing agent (laropiprant, which is not available in Australia) was also associated with a relatively high incidence of adverse events, including new diabetes.[64]

n-3 polyunsaturated fatty acids

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.

Clinical outcome trials of n-3 PUFA ethylesters have not, however, shown a significant CVD benefit in high-risk individuals, including patients with diabetes.[65,66] In contrast to other trials, n-3 PUFAs were tested against a background of optimal medical therapy for secondary CVD prevention, including statin therapy.[65,66] Patients were not selected on the basis of elevated plasma triglyceride levels, and lower doses of PUFAs (about 850 mg EPA plus DHA per day) were used. At every dose of a statin, 4 g of n-3 PUFAs incrementally lowers non-HDL-cholesterol levels by 6% in patients with hypertriglyceridaemia.[67] Purified EPA (4 g) also incrementally decreases non-HDL-cholesterol levels by 13% and apoB levels by 9% in such individuals.[68]

The value of supplemental, higher doses of EPA on CVD outcomes in higher risk patients taking statins with elevated baseline triglycerides is currently being tested in a large clinical trial. Increased risk of prostate cancer with a high dietary intake of n-3 PUFAs has been reported,[69] but this is based on association, has no causal basis and needs confirmation.



Abbreviations: apoB = apolipoprotein B; CVD = cardiovascular disease; HDL = high-density lipoprotein; LDL = low-density lipoprotein; PUFA = polyunsaturated fatty acids.

Adapted from Watts GF, Karpe F. Triglycerides and atherogenic dyslipidaemia: extending treatment beyond statins in the high-risk cardiovascular patient. Heart 2011; 97: 350-356.[77]

Ezetimibe

Although ezetimibe can lower LDL-cholesterol levels by 10 to 20%, its effect on fasting plasma triglyceride concentration is minimal to modest.[70] Ezetimibe may, however, have a more pronounced effect in improving postprandial lipaemia and lowering triglyceride-rich lipoprotein remnants, even against a background of statin therapy.[71,72] Ezetimibe can regress non-alcoholic fatty liver disease, but the mechanism remains unclear.[73]

Incretin-based therapies

Incretins, such as glucagon-like peptide-1, are insulinotropic, gut-derived hormones secreted in response to dietary nutrients. Incretin receptor analogues are antiglycaemic, and can ameliorate impaired triglyceride-rich lipoprotein metabolism in patients with type 2 diabetes, possibly by inhibition of chylomicron biogenesis.[74,75] Glucagon-like peptide-1 receptor analogues are more effective in correcting hypertriglyceridaemia than dipeptidyl peptidase-IV inhibitors.[76]

Treatment pathway, targets and safety of combination therapy

To manage patients with moderate-to-high plasma triglyceride levels and established CVD or moderate-to-high risk of CVD, the authors recommend the strategy shown in the flowchart on this page.[77] Secondary causes of hypertriglyceridaemia, particularly excessive alcohol consumption, overnutrition, obesity and hyperglycaemia, must be vigorously corrected (also see the box on page 9 for other factors that may need to be identified and corrected). The therapeutic targets for LDL-cholesterol, non-HDL-cholesterol and apoB are shown in Table 2.

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.[78] 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. Levels of alanine and aspartate aminotransferases should be measured three months after adding a fibrate

Table 2. Treatment goals for dyslipidaemia in patients with hypertriglyceridaemia at high risk of CVD

Risk category	Treatment goals		
	LDL-cholesterol (mmol/L)	Non-HDL-cholesterol (mmol/L)	ApoB (g/L)
Highest-risk groups • Known CVD or diabetes plus one more additional major CVD risk factor*	<1.8	<2.6	<0.8
High-risk groups • No diabetes or known CVD, but two or more major CVD risk factors* (or 10-year risk of CVD of 20% or more) • Diabetes but no other major CVD risk factors	<2.6	<3.4	<1.0

* Major CVD risk factors are hypertension, albuminuria, smoking and family history of premature CVD.
Abbreviations: apoB = apolipoprotein B; CVD = cardiovascular disease.

and every 12 months thereafter, or more frequently when increasing the dose of the statin, noting that hepatatoxicity is a potentially serious effect when a statin is combined with a fibrate or nicotinic acid. Plasma creatinine level should be periodically checked in patients taking a statin plus fenofibrate, although the increases in creatinine levels reported with fenofibrate in clinical trials is reversible. If nicotinic acid 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.

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 and exercise can also be beneficial.[7,9,79] The use of dietary medium-chain triglycerides (present in coconut or palm kernel oils) in cooking can also be beneficial,[79] compared with long chain and very long chain triglycerides, as they are directly absorbed into the portal vein and are not incorporated into chylomicrons. In patients with very high triglyceride 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 levels.[80] If chylomicronaemia coexists with atherogenic dyslipidaemia, quadruple pharmacotherapy with fenofibrate, n-3 PUFAs, ezetimibe and a statin might be required.[81] Severe chylomicronaemia complicated by acute pancreatitis is a medical emergency that can require lipoprotein apheresis. Lipoprotein lipase gene therapy has been approved by the FDA for people with lipoprotein lipase deficiency and recurrent pancreatitis, but it is expensive and very rarely indicated.

Conclusion

The causal role of triglyceride-rich lipoproteins in atherosclerotic CVD is supported by recent research. Hypertriglyceridaemia is associated with a broad spectrum of cardiometabolic risk factors, as well as increased lipid deposition in ectopic tissues and atherogenic changes in all plasma lipoproteins. The latter can be estimated by measuring levels of non-HDL-cholesterol and apoB (the key targets for treatment). Atherogenic dyslipidaemia is common in patients with diabetes and mild-to-moderate hypertriglyceridaemia who are obese, are insulin resistant and have poor glycaemic control. Very high plasma triglyceride levels may lead to acute pancreatitis.

Hypertriglyceridaemia is commonly caused by interactions between genetic and nongenetic factors that must be identified and corrected. Lifestyle interventions are fundamental to management. Combination drug therapy may be indicated but more evidence is required from CVD outcome studies, some of which are in progress. Evidence supports the use of fenofibrate for patients with hypertriglyceridaemia, 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. Patient adherence and tolerability to pharmacotherapies require continual review. This involves the simplification of drug regimens, close monitoring of safety variables, enhanced doctor–patient alliance and reduction in the cost of drugs. **CT**

References

A list of references is included in the website version (www.medicinetoday.com.au) of this article.

COMPETING INTERESTS: Professor Watts has received honoraria for Advisory Board participation and lecturing from Abbott, Merck Sharp and Dohme, AstraZeneca, Amgen and Sanofi Aventis. Dr Puri has received speakers honorarium and travel grants from Merck Sharp and Dohme, Bristol-Myers Squibb, Sanofi Aventis, NovoNordisk, Amgen, Eli Lilly and Novartis.
Dr Chan: None.

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GERALD F. WATTS DSc, PhD, DM, FRACP, FRCP; **DICK C. CHAN** BSc, MPhil, PhD, FRCPath; **GAURAV PURI** MB BS, FRACP

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