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The Polygenic Nature of Hypertriglyceridaemia: Implications for Definition, Diagnosis and Management

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Abstract

Plasma triglyceride concentration is a biomarker of circulating triglyceride-rich lipoproteins and their metabolic remnants. Common mild-to-moderate hypertriglyceridaemia is typically multigenic, and determined by the cumulative burden of common and rare variants in >30 genes, as quantified by genetic risk scores. Rare autosomal recessive monogenic hypertriglyceridaemia can result from mutations of large effect in six different genes. Hypertriglyceridaemia is exacerbated by non-genetic factors. Based on recent genetic data, we re-define two hypertriglyceridaemic states: (i) severe (>10 mmol/L), more likely to have a monogenic cause, and (ii) mild-to-moderate (2 to 10 mmol/L). Due to clustering of susceptibility alleles and secondary factors in families, biochemical screening and counselling of family members is essential, while routine genetic testing is not warranted. Treatment includes management of lifestyle and secondary factors, and pharmacotherapy. In severe hypertriglyceridaemia, intervention is indicated due to pancreatitis risk, and in mild-to-moderate hypertriglyceridaemia, is aimed at preventing cardiovascular disease, depending on triglyceride elevation, concomitant lipoprotein disturbances, and overall cardiovascular risk.

The complex aetiology and classification of hypertriglyceridaemia (HTG) frequently renders diagnosis and management a challenge to many clinicians of diverse specialties. HTG is usually diagnosed when the fasting plasma triglyceride (TG) concentration exceeds a threshold value, such as >1.7 mmol/L (>150 mg/dL). Severe HTG is often defined when plasma TG concentration is >10 mmol/L (>885 mg/dL).¹⁻⁷ Proposed definitions vary (**Table 1**) and none predominates in clinical use.

Traditional classification schemes of HTG have used terms such as “familial HTG” and “familial combined hyperlipidaemia”, which implied a single gene or monogenic aetiology. However, most instances of HTG are the result of multiple genetic factors, i.e. they are multigenic or polygenic, and involve accumulations of both common DNA variants with small effect size, and rare DNA variants with large effect size.⁴ HTG in susceptible individuals is further exacerbated by exposure to non-genetic

secondary factors,⁴ including lifestyle factors such as being overweight and alcohol use.

Although prospective and case-control studies have identified elevated plasma TG concentration as an independent risk factor for cardiovascular disease (CVD), uncertainty remains concerning the specific role of TG-rich lipoproteins in atherogenesis.¹⁻³ Furthermore, intervention studies aimed at reducing TG levels have reported inconsistent effects on CVD outcomes, and no effect on stroke and all-cause mortality.³ Therefore, mild-to-moderate HTG is often viewed as a mere marker of CVD risk, whereas severe HTG remains a well-known risk factor for acute pancreatitis.⁴ While the need to intervene in an individual with severe HTG is straightforward, the appropriate response to mild-to-moderate HTG is less clear. Here we recommend re-defining HTG using a two-group classification to simplify the diagnosis and clinical management of HTG states.

Table 1. Clinical definitions for hypertriglyceridaemia

2011 ESC/EAS Guidelines ^{6,7}		2001 NCEP ATP III Guidelines ⁵		2012 Endocrine Society Guidelines ¹	
Category	Plasma TG (mmol/L)*	Category	Plasma TG (mmol/L)*	Category	Plasma TG (mmol/L)*
Normal	<1.7	Normal	<1.7	Normal	<1.7
Hypertriglyceridaemia	1.7 - 9.9	Borderline	1.7 - 2.3	Mild	1.7 - 2.3
		High		Moderate	2.3 - 11.2
Severe hypertriglyceridaemia	>10	High	2.3 - 5.6	Severe	11.2 - 22.4
		Very high	>5.6	Very severe	>22.4

Abbreviations: EAS European Atherosclerosis Society; ESC European Society of Cardiology; NCEP ATP III National Cholesterol Education Program Adult Treatment Panel III; TG triglyceride.

* To convert from mmol/L to mg/dL multiply by 88.5

Measurement considerations

In most countries, elevated TG is determined by direct laboratory analysis of plasma (usually) or serum after a 10- to 12-hour fasting period. Indeed, clinicians routinely measure plasma TG, since this is usually required for the Friedewald calculation of low-density lipoprotein (LDL) cholesterol concentration. Modern methods for measuring plasma TG determine the free glycerol level after specific lipase action, which is the sum of the glycerol formed from the TG plus the original free glycerol. However, the latter value is usually ignored because of its low plasma concentration. Therefore, HTG can be incorrectly diagnosed in rare patients with glycerol kinase deficiency, who have high baseline plasma glycerol concentrations.⁸ The only procedure that reliably differentiates the specific TG-rich lipoprotein fractions is ultracentrifugation followed by electrophoresis, a method that is performed in some specialised lipid centres.

Most humans - certainly in the Western world - are in the nonfasting or postprandial state for most of the day. While recent guidelines unequivocally recommend measuring fasting TG concentrations,^{1-3,5-7} the importance of measuring nonfasting TG and remnant cholesterol is an emerging aspect of CVD risk stratification, since they reflect in part the capacity of the individual to clear postprandial lipids. Recent population studies demonstrate that despite postprandial elevation in TG, quantitative changes in other lipids, lipoproteins, and apolipoproteins appear minimal in response to the average meal intake in most individuals.^{9,10} In contrast, in dyslipidaemic subjects with or without insulin resistance, the postprandial area under the curve for TG-rich lipoproteins may be increased up to four-fold or more, with pronounced

modification of lipoprotein remodelling, leading to an increase in the potentially atherogenic cholesterol load in these particles.¹⁰

Elevated levels of nonfasting TG are also strongly associated with increased risk of myocardial infarction, ischaemic stroke, and early death.^{11,12} Recent evidence suggests that nonfasting TG-rich lipoproteins or their remnants are causal factors for ischaemic heart disease and myocardial infarction.^{13,14}

Nonfasting levels of total cholesterol, TG, high-density lipoprotein (HDL) cholesterol, non-HDL cholesterol, LDL cholesterol, apolipoprotein B (apoB), apoA-I, total cholesterol/HDL cholesterol, and apoB/A-I ratio are also associated with increased CVD risk.⁹ These findings suggest that, compared to fasting lipids, nonfasting lipid profiles are not only useful, but perhaps equally or more informative for CVD risk prediction, simplifying the sampling process. This approach has already been adopted clinically in some Scandinavian countries.

TG and risk of CVD

The role of elevated plasma TG and TG-rich lipoproteins in CVD was recently reviewed.¹⁻³ The magnitude of the contribution of TG to CVD risk and the exact mechanism(s) by which TG-rich lipoproteins exert their effect(s) on the vascular wall are incompletely established. That non-fasting TG levels are relevant to CVD risk is evident from recent large, long-term prospective studies in the general population,¹¹ thereby corroborating the original Zilversmit hypothesis that atherosclerosis is, at least partially, a postprandial phenomenon.¹⁵ Indeed, TG-rich lipoproteins such as intermediate-density lipoprotein (IDL) and very low-density lipoprotein (VLDL) may be particularly prone to entrapment within the arterial wall, whereas

nascent chylomicrons and very large VLDL are too large to penetrate.¹⁵⁻¹⁹ Consistent with this concept, recent Mendelian randomisation studies indicate that lifelong elevated plasma levels of TG-rich lipoproteins and/or their remnants are causally associated with increased risk of ischaemic heart disease,^{13,14} independent of subnormal levels of HDL cholesterol.¹¹

The relative risk for CVD arising from an increase of 1 mmol/L in plasma TG ranges from 1.14 to 1.80, depending on gender and race, after adjustment for established risk factors, including HDL cholesterol.³ Other studies in various cohorts compared the top versus bottom tertile or quintile for TG levels, and reported adjusted odds ratios between 1.2 and 4.0 for increased CVD risk.² The European and North American assessments of the Emerging Risk Factors Collaboration evaluated 302 430 individuals without CVD at baseline in 68 prospective studies. The hazard ratio (HR) for CVD with TG was 1.37 per standard deviation (95% CI, 1.31 to 1.42) after adjustment for non-lipid risk factors.²⁰ However, this was essentially lost after adjustment for both HDL and non-HDL cholesterol (HR 0.99, 95% CI, 0.94 to 1.05);²⁰ HDL cholesterol alone weakened but did not abolish the association (*Kausik Ray, personal communication*). Importantly, even in nonfasting samples, TG was not independently associated with CVD risk after adjustment for non-HDL cholesterol and HDL cholesterol. While this suggested that HDL cholesterol drove the

relationship with CVD, recent re-examination of the putative atheroprotective role of HDL²¹ indicates that TG-related mechanisms should be re-considered as part of the pathophysiology of CVD. Finally, Mendelian randomisation analyses indicate a relatively direct causal relationship between TG and TG-rich lipoproteins and coronary heart disease (CHD) risk with comparable odds ratios to those found in prospective studies.^{13,14,22} On the basis of total epidemiological and genetic data, one would predict that a randomised clinical trial with a specific TG-lowering agent should demonstrate a causal relationship between plasma TG and CVD morbidity and mortality. Despite this, clinical trials of currently available agents to lower plasma TG, which also affect other components of the lipid profile, have had minimal impact on CVD outcomes.²³⁻²⁶

Historical classification of HTG phenotypes

Phenotypic heterogeneity among HTG individuals was defined in the past by qualitative and quantitative differences in plasma lipoproteins. In the pre-genomic era, the Fredrickson or World Health Organization (WHO) International Classification of Diseases (ICD) hyperlipoproteinaemia (HLP) phenotypes was based on the electrophoretic patterns of lipoprotein fractions (see **Table 2**). Five of the six WHO ICD phenotypes include HTG in their definitions, the only exception being familial hypercholesterolaemia (HLP type 2A).^{27,28}

Table 2. Summary of classical hyperlipoproteinaemia phenotypes

WHO ICD number	Frederickson HLP phenotype	MIM number	Primary lipid change	Primary lipoprotein change	Genetics
E78.3	HLP type 1 Familial chylomicronaemia	238600	↑TG	↑CM	Monogenic; AR due to 2 mutant alleles of <i>LPL</i> , <i>APOC2</i> , <i>APOA5</i> , <i>LMF1</i> , <i>GPIHBP1</i> , or <i>GPD1</i> ; presentation mainly paediatric or early adulthood.
E78.0	HLP type 2A Familial hypercholesterolaemia	143890	↑TC	↑LDL	Monogenic; ACD, Heterozygous form resulting from one mutant allele of <i>LDLR</i> , <i>APOB</i> , or <i>PCSK9</i> ; Homozygous form resulting from two mutants alleles of these, or of <i>LDLRAP1</i> .
E78.4	HLP type 2B Combined hyperlipoproteinaemia	144250	↑TC, ↑TG	↑VLDL, ↑LDL	Polygenic; high GRS for HTG, plus excess of rare variants in HTG associated genes, plus high GRS for LDL-C.
E78.2	HLP type 3 Dysbetalipoproteinaemia	107741	↑TC, ↑TG	↑IDL	Polygenic; high GRS for HTG, plus excess of rare variants in HTG associated genes, plus <i>APOE</i> E2/E2 homozygosity, or heterozygous rare mutation in <i>APOE</i> .
E78.1	HLP type 4 Primary or simple hypertriglyceridaemia	144600 and 145750	↑TG	↑VLDL	Polygenic; high GRS for HTG, plus excess of rare variants in HTG associated genes
E78.3	HLP type 5 Mixed hypertriglyceridaemia	144650	↑TC, ↑TG	↑VLDL, ↑CM	Polygenic; high GRS for HTG, plus excess of rare variants in HTG associated genes, with higher burden of risk alleles than HLP type 4.

ACD autosomal co-dominant; *APOA5* gene encoding apo A5; *APOB* gene encoding apo B; *APOC2* gene encoding apolipoprotein (apo) C-II; *APOE* gene encoding apo E; AR autosomal recessive; CM chylomicrons; *GPD1* gene encoding glycerol-3-phosphate dehydrogenase 1; *GPIHBP1* gene encoding glycosylphosphatidylinositol-anchored HDL-binding protein 1; GRS polygenic genetic risk score created by tallying risk alleles from single nucleotide polymorphisms associated with increased plasma TG levels and HTG; HLP hyperlipoproteinaemia; HTG hypertriglyceridaemia; ICD International Classification of Diseases; IDL intermediate-density lipoprotein; LDL low-density lipoprotein; LDL-C low-density lipoprotein cholesterol; LDLR low-density lipoprotein receptor; *LDLRAP1* gene encoding low density lipoprotein receptor adaptor protein 1; *LMF1* gene encoding lipase maturation factor 1; *LPL* gene encoding lipoprotein lipase; MIM Mendelian Inheritance in Man database; *PCSK9* gene encoding proprotein convertase subtilisin/kexin type 9; TC total cholesterol; TG triglyceride; VLDL very low-density lipoprotein; WHO World Health Organization. Adapted from Hegele (2009).²⁷

The different HTG-associated phenotypes are defined by the specific class or classes of accumulated TG-rich lipoprotein particles, including chylomicrons, and VLDL and their remnants.²⁷ Frequently, TG-rich lipoprotein excess co-exists with other lipoprotein disturbances; for instance, decreased HDL cholesterol is commonly seen in individuals with all forms of HTG. Implicit in this classification system was the idea that differences between

HTG-associated phenotypes were due to genetic differences; however, recent data indicate that this is typically not the case.^{29–33} As a result, this classification system has neither improved scientific insight nor has it been clinically useful in directing therapy or predicting hard outcomes. We suggest that the TG level itself (**Fig 1**), together with the presence of other risk factors, should be the primary driver of clinical management.

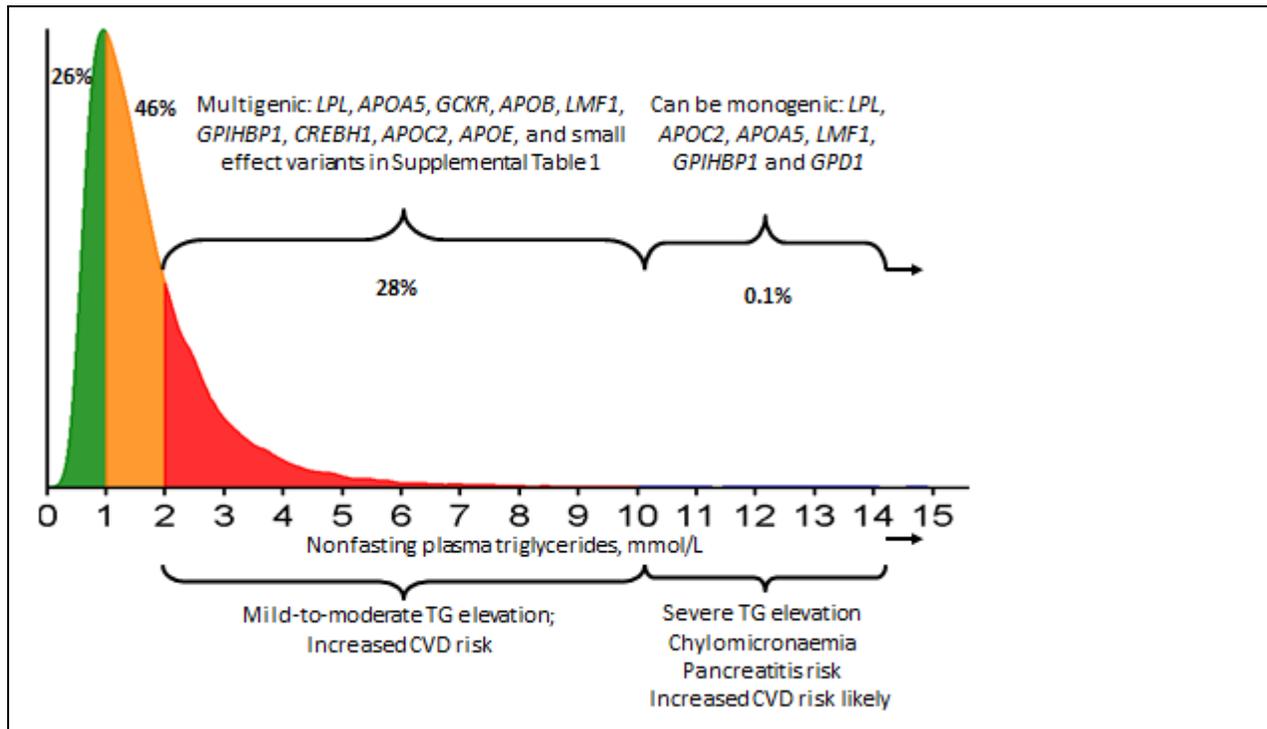


Figure 1. Re-definition of hypertriglyceridaemic states based on new genetic data.

Triglyceride (TG) levels >10 mmol/L, especially in younger patients, are more likely to be due to monogenic causes together with secondary factors, while TG levels between 2 and 10 mmol/L represent a single group based on the interplay of multiple genes (both heterozygous mutations of large effect and cumulative burden of small effect variants causing a high "genetic risk score") (see **Supplemental Table 1** and **Fig 2**), together with secondary factors. Plasma TG levels and approximate population percentages are based on >70 000 adult individuals (>20 years of age) from the Copenhagen General Population Study.

Complex genetic basis for HTG

For several decades, the word “familial” has been used in the definitions and classification of disorders of plasma TG metabolism. However, the constant reinforcement of this terminology has a misleading effect. Colloquially, “familial” often implies a single-gene problem, as in the case of “familial hypercholesterolaemia”, a monogenic disorder characterised by elevated LDL cholesterol levels, xanthelasma palpebrarum, arcus cornealis, tendon xanthomata, and accelerated atherosclerosis.²⁸ Familial hypercholesterolaemia is usually due to loss-of-function mutations in the *LDLR* gene encoding the LDL receptor, and in other genes encoding proteins that interact with the LDL receptor, such as *APOB* or *PCSK9*. In patients with the strongest suspicion of a clinical diagnosis of familial hypercholesterolaemia a clear monogenic cause can be found in >80%, while in the remainder the elevated LDL cholesterol is a polygenic trait due to an increased burden of common risk variants.³⁴ In stark contrast, >95% of individuals with HTG have a multigenic susceptibility component.^{3,29-33}

Multigenic HTG has a complex aetiology consisting of an excess burden of common small-effect variants (Supplemental Table 1), in addition to rare heterozygous large-effect variants in genes either directly or indirectly associated with plasma TG concentration. But “familial” should not be considered synonymous with “monogenic”; most cases of HTG are familial or inherited, but they are not monogenic.^{29,30}

Monogenic HTG

Monogenic HTG in individuals with severe HTG >10 mmol/L displays classic autosomal recessive inheritance, with a population prevalence of approximately one in a million. Typically, the

condition is first evident in childhood and adolescence. Affected individuals are often homozygous or compound heterozygous for large-effect, loss-of-function mutations in genes that regulate catabolism of TG-rich lipoproteins, including *LPL*, *APOC2*, *APOA5*, *LMF1*, *GPIHBP1*, and *GPD1* (Table 2).³¹⁻³³ Individuals with monogenic disorders have dramatically elevated fasting concentrations of chylomicrons, but usually do not develop premature atherosclerosis, likely due to size-exclusion, which limits the ability of chylomicrons to traverse the vascular endothelial barrier.¹⁵⁻¹⁹ In the previous century, a diagnosis of LPL deficiency was established biochemically by the absence of LPL activity in plasma collected after intravenous heparin injection.³⁵ Currently, the diagnosis can be made by DNA sequence analysis, which shows mutations on both *LPL* alleles causing complete LPL deficiency; mutations in the other genes can also be detected by re-sequencing.³⁶

Multigenic HTG: role of rare variants

HTG, with or without concomitant lipid or lipoprotein disturbances, tends to cluster in families. While HTG usually does not result from strong single gene effects that show Mendelian inheritance, it still has a genetic basis, albeit one that is more complex in nature. A sense of the complexity was seen in pre-molecular era family studies of obligate heterozygous parents of individuals with complete LPL deficiency or apoC-II deficiency,^{37,38} or among unrelated heterozygous carriers of disease-causing mutations from the general population.³⁹ These studies showed that heterozygous carriers of disease-causing mutations displayed a very wide spectrum of TG phenotypes, ranging from normotriglyceridaemia to severe HTG,³⁷⁻³⁹ probably due to chance co-inheritance of different numbers of common TG-raising

variants. Similarly, there is a lack of clear penetrance at the biochemical level for heterozygous *APOA5* variants.⁴⁰ On average, the TG levels among carriers of the various heterozygous mutations are higher than in normal family- or population-based controls, but many mutation carriers have normal TG levels.

DNA re-sequencing has shown individuals with TG >3.3 mmol/L (>95th percentile in North America) as a group have a significantly increased frequency – about 2.5-fold - of heterozygous rare loss-of-function mutations in several genes governing TG metabolism compared to normotriglyceridaemic controls.^{41,42} Most of these variants have confirmed loss-of-function *in vitro* or predicted deleterious effects *in silico*.^{41,42} While these rare mutations are strongly associated with HTG in patient groups, they are not necessarily associated with HTG in individual patients. Even within families, carriers of the same mutation show a wide range of TG levels from normal to severe HTG, with inconsistent vertical transmission of TG levels in mutation carriers across generations.⁴³ Such observations emphasise that HTG is not a dominantly inherited trait in the vast majority of families with an HTG proband.

Multigenic HTG: role of common variants

Recent genome-wide association studies (GWAS) of HTG have demonstrated that common variants in several genes, including *APOA5*, *GCKR*, *LPL*, and *APOB*, are strongly associated with susceptibility to HTG.⁴⁴ In fact, common variation in 32 TG-associated genes identified by the Global Lipids Genetics Consortium (GLGC) is robustly associated with HTG;³¹⁻³³ the same GLGC loci are also associated with modest variation in plasma TG levels

within the normal range among healthy subjects (**Supplemental Table 1**). A genetic risk score constructed by tallying carrier status for TG-raising alleles at the 32 GLGC-identified TG-associated loci was higher on average in HTG patients than in healthy controls (**Fig 2**).^{30,44} Thus, as with mutation-negative FH patients and LDL-C-raising variants,³⁴ an increased burden of TG-raising alleles contributes to HTG susceptibility.^{41,42}

Multigenic HTG: common plus rare variants

HTG susceptibility is thus determined by combinations of common small-effect and rare large-effect variants in genes governing production, or catabolism, or both, of TG-rich lipoproteins.^{29-32,41,42} Subjects with average TG levels are suggested to have a balance of protective and deleterious alleles. On the basis of studies of 765 individuals in whom nine HTG-associated genes were re-sequenced, common and rare genetic variants together explained ~25% of total variation (~50% of attributable variation) in HTG susceptibility.^{37,38} Because of the wide range of TG levels and severity of HTG phenotypes within families and among carriers of the same genotype, genetic testing is not recommended. Finally, as mentioned earlier the classical Fredrickson phenotypes characterised by HTG closely resemble each other at the genetic level, with comparable accumulations of common and rare genetic variants, despite different biochemical phenotypes.^{27,29-32,41,42}

Among these, HLP type 3

(dysbetalipoproteinaemia) is unique in that a single gene - *APOE* - can force the expression of HTG and hypercholesterolaemia due to accumulation of remnant particles: here the cumulative effects of polygenic predisposition are compounded by either the binding defective E2 isoform of apoE, or heterozygosity for a rare dysfunctional *APOE* mutation.³⁰

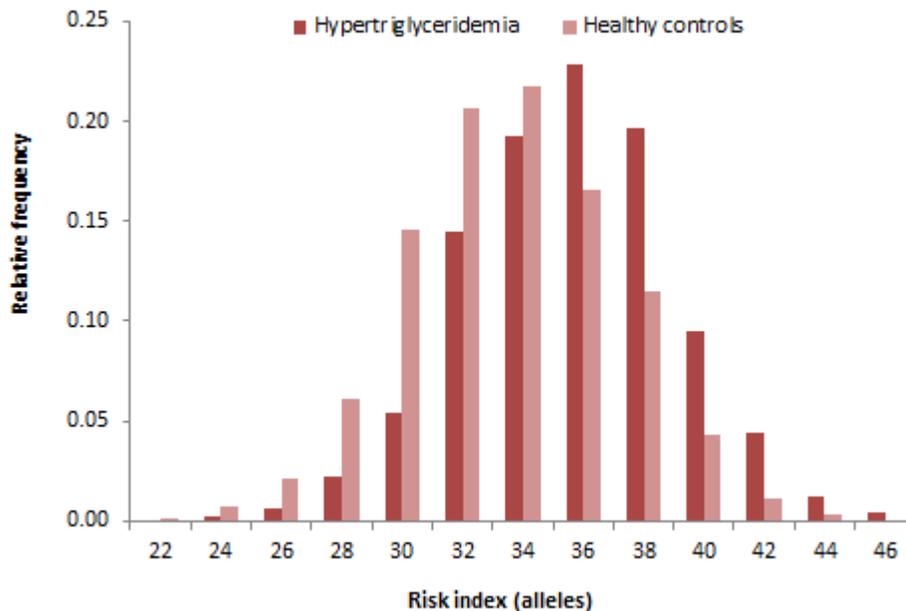


Figure 2. Genetic risk scores composed of triglyceride (TG)-associated risk alleles

Unweighted risk scores composed of risk alleles at 32 TG-associated loci were summed across individuals and compared between HTG patients and controls. The minimum unweighted risk score is 0, whereas the maximum unweighted risk score is 64, but most scores in the population range between 26 and 46. The relative frequency distribution of TG genetic risk scores is shown and is significantly increased in 504 HTG patients versus 1 213 healthy controls ($P=1.6 \times 10^{-53}$).³⁰

Panel 1. Secondary causes of hypertriglyceridaemia

- Obesity
- Metabolic syndrome
- Diet with high positive energy-intake balance and high fat or high glycaemic index
- Increased alcohol consumption*
- Diabetes mellitus (mainly type 2)
- Hypothyroidism
- Renal disease (proteinuria, uraemia or glomerulonephritis)
- Pregnancy (particularly in the third trimester)
- Paraproteinaemia
- Systemic lupus erythematosus
- Medications (including corticosteroids, oral estrogen, tamoxifen, thiazides, non-cardioselective beta-blockers and bile acid sequestrants, cyclophosphamide, L-asparaginase, protease inhibitors, and second generation antipsychotic agents, such as clozapine and olanzapine)

* While the range is variable, clinically the risk of HTG is generally considered to increase with more than two drinks daily in men, and more than one drink daily in women

Secondary causes

HTG is often associated with other conditions that independently increase plasma TG levels, such as type 2 diabetes, obesity, alcohol overuse, hypothyroidism, pregnancy, hepatosteatosis, renal failure, or concomitant drug use, summarised in **Panel 1** and discussed at length elsewhere.^{1,4,6,7}

When one of these factors is present, the HTG is termed "secondary". However, secondary HTG often also has a genetic component, since some secondary factors are frequently but not universally associated with HTG. This suggests that subjects who develop dyslipidaemia might carry inherited defects that confer susceptibility, which becomes clinically expressed in the presence of an external or secondary stress.⁴ For example, abdominal obesity, metabolic syndrome, and non-alcoholic fatty liver disease are associated with increased risk of HTG and are becoming increasingly common in adults, adolescents, and even children. It is important to determine whether there is a strong secondary factor underlying the dyslipidaemia, since this would guide intervention. Furthermore, the severity of secondary HTG in an individual will likely be determined by the genetic susceptibility component. Finally, some of the secondary causes, such as obesity, metabolic syndrome, non-alcoholic fatty liver disease, and diabetes, have their own genetic susceptibility components.

Re-definition of hypertriglyceridaemic states

On the basis of the new genetic data, we recommend a re-definition of HTG states, as follows (see **Panel 2**).

First, TG >10 mmol/L are to be considered more likely as having a monogenic basis, especially in younger patients, together with interacting secondary factors. However, even in this group, there are many instances - particularly in adults - where no monogenic cause can be found; in these cases, there is marked polygenic susceptibility compounded by significant exposure to secondary factors. Thus, except in children and adolescents with severe HTG, we do not recommend routine genetic testing. Second, TG between 2 and 10 mmol/L are to be considered as a single group, irrespective of concomitant lipoprotein disturbances such as increased LDL cholesterol, with elevated TG caused by interaction of multiple genetic effects and secondary factors (see **Figure 1**). For example, individuals with HLP type 2B (often called familial combined hyperlipidaemia) have the same genetic risk score as individuals with similar TG levels who have isolated or HLP type 4 HTG; they differ in that individuals with HLP type 2B have a higher genetic burden of alleles associated with hypercholesterolaemia.³⁰ Again, we do not recommend routine genetic testing in individuals with TG between 2 and 10 mmol/L.

Panel 2. Proposed simplified redefinition of hypertriglyceridemia

Normal	< 2.0 mmol/L (175 mg/dL)
Mild-to-moderate	2.0 - 10.0 mmol/L (175 - 885 mg/dL)
Severe	> 10.0 mmol/L (885 mg/dL)

Desirable levels of TG and related variables

HTG is arbitrarily defined as a plasma TG level >2 mmol/L (>175 mg/dL) on the basis of large prospective observational studies, although plasma TG may start to confer risk or become a marker for CVD at even lower levels.^{4,6,7,11,12} TG levels rising above this threshold, due to increased production and/or decreased clearance of TG-rich lipoproteins from the circulation, are accompanied by changes in the metabolism and composition of other lipoprotein fractions such as LDL and HDL, which may partly explain the increased CVD risk.³

According to the Joint European Society of Cardiology (ESC)/EAS Guidelines for Management of Dyslipidaemia and recent EAS Consensus Panel recommendations, a TG level <1.7 mmol/L (<150 mg/dL) is desirable, especially if HDL cholesterol is <1.0 mmol/L (<40 mg/dL) in men and <1.2 mmol/L (<45 mg/dL) in women.^{3,6,7} In post hoc subgroup analyses of clinical endpoint studies with fibrates, clinical benefit was found in subjects with TG >2.3 mmol/L (>200 mg/dL) and low HDL cholesterol.^{23,24} Thus, when lifestyle measures are insufficient, individuals with high CVD risk and elevated plasma TG may be considered for drug treatment if TG levels exceed this level.^{3,6,7} However, there is inadequate evidence to define treatment targets for plasma TG. Even the TG threshold for diagnosis of HTG is not irrefutable: no high-grade evidence exists to suggest that 2.0 mmol/L is superior to 1.7 or 2.3 mmol/L. Here we have settled on 2.0 mmol/L as the HTG diagnostic threshold, but there is expert opinion for values ± 0.3 mmol/L around this cutpoint.^{1,3,4-7}

An emerging focus for CVD risk reduction in HTG is the level of non-HDL cholesterol (comprising cholesterol in LDL and in remnant TG-rich lipoproteins), which represents the total mass of cholesterol in circulating atherogenic lipoprotein particles.^{3,11,13,14} This variable has been advocated because LDL cholesterol cannot be estimated by the Friedewald equation when TG levels are >4.5 mmol/L; also standardised, directly measured LDL cholesterol is not routinely available in most centres. The desirable level for non-HDL cholesterol is <2.6 mmol/L (<100 mg/dL) in high-risk individuals, and <3.4 mmol/L (<130 mg/dL) in low-risk individuals. Again, there is insufficient high-grade evidence to define specific targets for any of these alternative variables, and treatment should be individually tailored.^{3,6,7}

An alternative estimation of atherogenic lipoprotein levels uses apoB as a substitute for non-HDL cholesterol. ApoB represents the total number of atherogenic apoB-containing lipoprotein particles, and predicts CVD risk at least as well as non-HDL cholesterol.^{6,7} ApoB is reliably measured in the presence of HTG and under nonfasting conditions. Some expert panels have therefore recommended apoB as secondary target in individuals with HTG.^{3,6,7,45} Accordingly, apoB >1.2 g/L identifies individuals at high CVD risk, and the desirable level of <0.8 g/L corresponds to a non-HDL cholesterol <3.4 mmol/L (<130 mg/dL).^{3,6,7} For individuals at very high risk, an apoB target <0.7 g/L may be appropriate, corresponding to a non-HDL cholesterol <2.6 mmol/L (100 mg/dL).^{3,6,7} Desirable levels for TG, non-HDL cholesterol and apoB are summarised in **Panel 3**.

Panel 3. Desirable levels of lipids and apolipoprotein B in patients at high risk of CVD

Triglycerides	<1.7 mmol/L (150 mg/dL)
Non-HDL cholesterol	<2.6 mmol/L (100 mg/dL)
Apolipoprotein B	<0.8 g/L in high-risk <0.7 g/L in very high-risk

Management of HTG

Treatment of HTG has two distinct objectives: (i) immediate prevention of pancreatitis in cases of severe HTG >10 mmol/L; and (ii) reduction of global CVD risk. Since HTG is characterised by elevated levels of remnant TG-rich lipoproteins, non-HDL cholesterol or apoB are considered secondary treatment targets, after LDL cholesterol.⁴⁶

Once secondary causes have been treated, the management of mild-to-moderate HTG should follow guideline recommendations,^{3,6,7} with initial emphasis on diet and exercise. Non-pharmacologic therapy is recommended for individuals with TG levels >2 mmol/L. The decision to initiate pharmacologic therapy depends on the degree of TG elevation. Individuals with TG >10 mmol/L warrant immediate and aggressive TG reduction in order to minimise the risk of acute pancreatitis, using a strict fat-reduced diet and avoiding simple carbohydrates; use of fibrates, niacin, or omega-3 fatty acids may be considered. In the context of abdominal pain, treatment of severe HTG includes hospitalisation, with cessation of oral intake, and supportive measures including fluid replacement, avoiding glucose infusions, and control of obvious precipitating factors such as diabetes. Pharmacologic agents are relatively less effective in this situation; dramatic interventions such as infusions of insulin or heparin, high dose antioxidants, or plasma

exchange are also probably of limited value for many patients.⁴ As noted earlier, due to the uncertain clinical benefit, practice guidelines are not universal or consistent regarding the management of individuals with TG levels between 2 and 10 mmol/L.

Individuals with HTG should be assessed and managed for their global CVD risk, which does not necessarily imply management of their TG levels. A treatment strategy is shown in **Table 3**. A positive family history of CVD, defined as at least one first degree relative or at least two second degree relatives with CVD, must be taken into account, even if this is independent of dyslipidaemia. Since multiple susceptibility alleles, environmental factors, and secondary factors tend to be shared within families, other family members may also have a lipid disorder and evaluation of them for dyslipidaemia and related cardiometabolic risk should be considered. This situation is analogous to that for common type 2 diabetes, which clusters in families, but typically is not associated with a single monogenic cause.

For combined hyperlipidaemia, elevated LDL cholesterol is part of the phenotype, and this will amplify CVD risk. Thus, family members, and particularly first degree relatives of such patients, should be screened. Regardless of clinical designation, individuals with combined hyperlipidaemia in particular, and HTG in general, still need to be managed. Risk assessment and ongoing care requires baseline

and follow-up lipid profiling, especially since HTG can obscure calculation of LDL cholesterol in these instances. Furthermore, non-HDL cholesterol - or if available apoB - may be helpful for both risk assessment and monitoring of treatment when LDL cholesterol levels cannot be determined.

Statins

Statins decrease LDL cholesterol by up to 55%, giving rise to a CVD risk reduction of 23% per mmol/L lowering in LDL cholesterol irrespective of baseline levels of LDL cholesterol, TG, or HDL cholesterol,⁴⁷ so their use in patients with HTG is justifiable based on their proven ability to reduce CVD. They also variably reduce plasma TG levels by up to 30%, with reductions dependent on the baseline TG level and dose of statin used. To achieve recommended targets, the choice of statin should be based on efficacy in LDL cholesterol reduction, taking into account safety considerations.^{6,7} In HTG, because LDL cholesterol often cannot be determined, achieving non-HDL cholesterol or apoB targets should also be a goal of treatment.⁴⁸

Fibrates

With a TG-lowering effect of 40%, depending on baseline TG levels, fibrates are considered first line treatment to decrease the risk of pancreatitis for TG levels >10 mmol/L. Although controversial, a meta-analysis including >45 000 individuals suggests that fibrates could reduce non-fatal acute coronary events and revascularisation by ~9% (together with a lack of overall effect in total and cardiovascular mortality and a non-significant increase in non-cardiovascular deaths),²³ particularly in subjects with TG >2.3 mmol/L and an HDL cholesterol <1.0 mmol/L.²⁴ Therefore a fibrate may be considered as additional therapy for individuals with high TG and low HDL cholesterol.³

However, in monogenic HTG due to LPL deficiency and TG >20 mmol/L, fibrates have minimal to no clinical benefit.

Niacin

Niacin (nicotinic acid) treatment at a dose of 2-3 g/day is associated with up to 30% reduction of TG, 20% increase in HDL cholesterol, up to 20% lowering of LDL cholesterol, and up to 25% reduction in lipoprotein(a). Studies of the CVD benefits of niacin are conflicting. The recent 2011 EAS Consensus Panel recommendations supported the addition of niacin to statin therapy for individuals not at target LDL cholesterol or non-HDL cholesterol, particularly if TG remains high and HDL cholesterol is low.³ Combination therapy that includes niacin is a therapeutic option in statin-intolerant patients. However, niacin is no longer an option in Europe, with the withdrawal of extended-release niacin/laropiprant following the announcement of negative results from the Heart Protection Study 2-Treatment of HDL to Reduce the Incidence of Vascular Events (HPS-2 THRIVE) (<http://www.ctsu.ox.ac.uk/research/mega-trials/hps2-thrive>). Extended-release niacin remains available in North America as Niaspan. The latter was used in the AIM-HIGH study, which was also neutral.²⁵

Bile acid sequestrants

In patients with HTG, bile acid sequestrants can often cause a further increase in TG levels, so these agents should be used with caution in HTG. Colesevelam can reduce LDL cholesterol by 15 - 20% on top of statin therapy,⁴⁹ and may be considered in the context of HTG for individuals whose LDL cholesterol, apoB, or non-HDL cholesterol are not at target levels, or in statin intolerant subjects.

Omega 3 fatty acids

Omega 3 polyunsaturated fatty acids at doses up to 4 g daily reduce TG levels by up to 30%, depending on baseline levels, and may therefore be useful for prevention of

pancreatitis.⁴ A recently published meta-analysis showed that omega-3 supplementation was not significantly associated with reductions in all-cause mortality, myocardial infarction, or stroke.²⁶

Table 3. Treatment strategies in hypertriglyceridaemia

Triglyceride level	Therapeutic goal	Therapeutic strategies
Moderately elevated (2 - 9.9 mmol/L) [175-885 mg/dL]	Priority: prevent cardiovascular disease Primary: achieve LDL-C target Secondary: achieve non-HDL-C goal, which is 0.8 mmol/L higher than LDL-C goal, or apoB <0.8 g/L	Rule out and treat secondary factors Non-pharmacologic strategies: reduce body weight, reduce alcohol intake, reduce simple sugar intake, increase aerobic activity, reduce total carbohydrate, replace trans and saturated fats with monounsaturated fats, increase dietary omega-3 fatty acids Statin if necessary to control LDL-C - If LDL-C is close to goal, titrate statin dose to achieve both LDL-C and non-HDL-C targets - If LDL-C is at goal, but non-HDL-C is still elevated, titrate statin dose or add fibrate, niacin, or omega-3 fatty acid
High (≥10 mmol/L) [≥ 885 mg/dL]	Priority: reduce triglyceride to prevent acute pancreatitis Other goals: achieve LDL-C and non-HDL-C goals once pancreatitis risk is decreased, as described above	Rule out and treat secondary factors Implement non-pharmacologic therapies: eliminate oral intake during acute pancreatitis with intravenous rehydration, then slowly re-introduce foods with small frequent meals, then longer term strict fat-reduced diet (<20% of calories as fat), reduce body weight, reduce alcohol intake, reduce simple sugar intake, reduce total carbohydrate, replace trans and saturated fats with monounsaturated fats, consider oral medium chain triglycerides; increase dietary omega-3 fatty acids; increase aerobic activity Consider: fibrate, niacin, omega-3 fatty acids

apo apolipoprotein; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein

Future research directions for HTG

Recent meta-GWAS, gene-centric analyses, and resequencing studies have begun to further expand and elucidate the genetic underpinnings of different forms of HTG.⁵⁰ Incorporating this knowledge into future exome and genome sequencing studies might facilitate identification of new candidate genes. For example, HTG subjects and families with a high genetic risk score could be sequenced for the known TG GWAS loci to identify the full spectrum of HTG-associated variants in these regions, whereas HTG subjects and families with a low HTG genetic risk score could be

sequenced at the exome or genome level to identify novel variants and genes for HTG.

Such approaches might offer the possibility of personalised medicine in which individuals with HTG are assessed, diagnosed, and treated according to their individual genetic composition and molecular phenotype.⁵⁰ To address the complexity of this task, systems approaches, integrating genomic, transcriptomic, proteomic, and epigenomic data with metabolic and clinical phenotypes are under development.⁵¹ One example is weighted co-expression network analysis (WGCNA) that

correlates gene expression and methylation networks with variants and phenotypes.⁵² WGCNA could provide a functionally oriented way to identify additional novel HTG-associated genes and pathways in tissues relevant to lipid metabolism. However, for many individuals with HTG, the usual treatment options will likely be equally efficacious, irrespective of the underlying combinations of predisposing alleles; this hypothesis will need to be formally studied.

In addition, gene therapy is being studied in individuals with familial chylomicronaemia. Specifically, expression of a recombinant virus containing the human hyper-functional *LPL S447X* variant showed promise in animal models,⁵³ and early clinical trials in human subjects using intramuscular injections of adeno-associated virus mediated local LPL expression were associated with a transient reduction in plasma TG levels.⁵⁴ This treatment (trade name Glybera) was recently approved by the European Medicines Agency for the treatment of classical HLP type 1 (LPL deficiency).

Finally, newer treatments for HTG can trace their rationale for development to genetic studies that have identified causative mutations in rare families in which severely diminished TG levels are part of the phenotype. For example, lomitapide, an inhibitor of microsomal TG transfer protein (MTP) that lowers TG in addition to all apoB-containing lipoproteins, was developed because individuals with homozygous mutations in MTP causing abetalipoproteinaemia have depressed TG levels.⁵⁵ Similarly, low TG levels in other families with monogenic TG deficiency have prompted the development of new biological agents targeting *APOB* (the recently approved agent mipomersen),⁵⁶ *APOC3*⁵⁷ and *ANGPTL3*.⁵⁸

Conclusion

Diagnosing HTG is relevant because: (i) even modest elevation in TG levels is usually associated with increased risk of CVD; (ii) severely elevated TG are associated with increased risk of pancreatitis; and (iii) HTG often co-exists with other metabolic disturbances that are associated with increased cardiometabolic risk. Recent epidemiologic, genetic, and clinical trial evidence has led us to recommend a simplified definition of HTG (Box 1), with severe HTG >10 mmol/L, especially in the paediatric age group, more likely to be related to monogenic causes, while mild-to-moderate HTG of 2 - 10 mmol/L is more likely to have a polygenic basis with secondary factors. The presence of concomitant lipid disturbances depends on additional genetic factors. Knowing the precise molecular defect may be helpful in guiding therapy for monogenic HTG disorders, particularly in children and adolescents with severe HTG due to LPL deficiency and related disorders. However, in polygenic HTG, there is no indication that genotyping will enhance diagnosis or management. Nonfasting lipid determinations might improve the efficiency of screening and diagnosis of HTG, while related variables such as non-HDL cholesterol and apoB can provide guidance for therapy, especially when HTG is moderate to severe. The current mainstay of treatment for all HTG states focuses on risk factor control, diet, and lifestyle choice to ensure maximal health for individuals with HTG. Pharmacotherapy can also be useful in selected subgroups, provided that it is in line with guideline recommendations. Finally, ongoing research, both genetic and non-genetic, may identify new therapeutic targets that could lead to optimisation of clinical management in individuals with HTG.

Search Strategy and Selection Criteria

Data for this review were identified by searches of MEDLINE, Current Contents, PubMed, and relevant references using the search terms: triglyceride, hypertriglyceridaemia, hyperlipidaemia, familial, monogenic, polygenic, polymorphism, mutation, and pharmacogenetics. Main articles published in English between 2000 and 2013 were included. This review was based on discussions at two meetings of the European Atherosclerosis Society (EAS) Consensus Panel organised and chaired by MJC and HNG, where the literature and drafts of the manuscript were critically appraised: most of the document results from a consensus of expert opinions.

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The EAS Consensus Panel met twice in Paris and London at meetings organised and chaired by MJC and HNG. The first meeting critically reviewed the literature while the second meeting scrutinised the first draft of the consensus paper. RAH, MA, JB, EB, ALC, JAK, PP, KKR, AFHS, ES, M-RT, AT-H, MJC and HNG each drafted sections and/or outline for the first version, while the complete draft was revised by RAH, MJC and HNG. All Panel members agreed to the conception and design, contributed to interpretation of available data, and suggested revisions to this document. All Panel members approved the final document before submission.

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