### Title

Treatment options for hypertriglyceridemia: From risk reduction to pancreatitis




### Journal

Best Practice & Research Clinical Endocrinology & Metabolism, 28(3)

### ISSN

1521-690X



### Authors

Berglund, Lars
Brunzell, John D
Goldberg, Anne C
et al.



### Publication Date

2014-06-01

### DOI

10.1016/j.beem.2013.10.002

Peer reviewed

Published in final edited form as:
*Best Pract Res Clin Endocrinol Metab*. 2014 June ; 28(3): 423–437. doi:10.1016/j.beem.2013.10.002.

# Treatment options for hypertriglyceridemia: from risk reduction to pancreatitis

**Lars Berglund, M.D., Ph.D., FAHA**[1,2], **John D. Brunzell, M.D.**[3], **Anne C. Goldberg, M.D.**[4], **Ira J. Goldberg, M.D.**[5], and **Anton Stalenhoef, M.D., Ph.D., FRCP**[6]

Lars Berglund: lars.berglund@ucdmc.ucdavis.edu; John D. Brunzell: JBrunzell@medicine.washington.edu; Anne C. Goldberg: agoldber@dom.wustl.edu; Ira J. Goldberg: ijg3@columbia.edu; Anton Stalenhoef: A.Stalenhoef@aig.umcn.nl

[1]Department of Medicine, University of California, Davis, CA [2]Department of Veterans Affairs, Northern California Health Care System, Sacramento, CA, 2921 Stockton Blvd, Suite 1400, Sacramento, CA, 95817, USA, Tel: 916-703 9207, Fax: 916-703 9124 [3]Department of Medicine, University of Washington, School of Medicine, 1959 NE Pacific Street, UW Mailbox 356426, Seattle, WA 98195-6426; Tel: 206-543-3470, Fax: 206-685-3781 [4]Department of Medicine, Washington University School of Medicine, St. Louis, MO; Campus Box 8127, 660 South Euclid, St Louis, MO 63110, Tel: 314-362-4332, Fax: 314-362-4833 [5]Department of Medicine, Columbia University, Presbyterian Hospital, PH 10-305, 622 West 168th Street, New York, NY 10032; Tel: 212-305-5961, Fax: 212-305-3213 [6]Department of Medicine, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands

## Abstract

While there has been considerable focus on the role and treatment of LDL cholesterol levels, a definitive role of triglycerides in the management of cardiovascular disease has been uncertain. Notably, with increasing triglyceride levels, there is a parallel increase in cholesterol levels carried by triglyceride-rich lipoproteins, which has prompted interest in the use of non-HDL cholesterol levels as a tool guiding interventions. Recent studies have provided evidence for an independent role of triglyceride levels as a cardiovascular risk factor, and recently, an Endocrine Society guideline was published for treatment of hypertriglyceridemia. In contrast to the relative uncertainty regarding triglycerides and cardiovascular disease, a role of very high triglyceride levels as a risk factor for pancreatitis has been well known. The present paper summarizes the underlying evidence for a risk role for triglyceride levels in cardiovascular disease and pancreatitis, current treatment recommendations and areas of future research.

### Keywords

Dyslipidemia; Lipoproteins; coronary heart disease; hypolipidemic therapy; lifestyle intervention

## Introduction

The role of triglycerides as a cardiovascular risk factor has been uncertain. Until recently, recommendations for treatment and prevention of atherosclerotic cardiovascular disease (CVD) have been focused on LDL cholesterol levels in relation to long-term risk. This has largely been driven by the well-documented association between cholesterol levels and CVD or mortality at the population level, with considerable variability between different geographical areas [1, 2]. As LDL is the dominating cholesterol carrier, treatment and prevention efforts have focused on levels of LDL cholesterol, and many clinical trials have demonstrated that lowering LDL cholesterol reduces CVD events or mortality [3]. However, an increased triglyceride and not LDL cholesterol level is a component of the metabolic syndrome, associated with CVD in many studies [4–6]. Although the Framingham score, widely used to assess CVD risk does not specifically include triglyceride levels, its use of total cholesterol implicates a contribution by VLDL cholesterol and therefore triglyceride-rich lipoproteins in the calculation [7]. There is growing support for elevated triglyceride levels as an independent cardiovascular risk factor. A recent summary from the International Atherosclerosis Society suggested that the current Framingham risk scoring system underestimates risk associated with the metabolic syndrome, perhaps because triglyceride is undervalued as a risk factor [8]. However, the extent to which elevated triglycerides constitute a direct risk for cardiovascular disease or represent a marker for other lipoprotein abnormalities associated with CVD risk is unknown and remains a focus for future investigations. Aside from CVD, very high triglyceride levels are a well-established risk factor for pancreatitis.

## Triglycerides – Pathophysiology and metabolism

Triglycerides are an important source of energy and generally constitute a major portion of an individual's caloric intake. After partial hydrolysis, dietary fat is resynthesized into triglycerides in the gut mucosa and secreted into the lymphatic circulation as chylomicrons. Through interaction with lipoprotein lipase (LpL), present on the luminal surface of capillary endothelial cells, triglycerides are lipolyzed to free fatty acids, which are then taken up by tissues. However, the hydrolysis of chylomicron triglycerides is incomplete and some fraction circulates in the form of chylomicron remnants. Chylomicrons and their remnants contain apolipoprotein (apo)B48, representing the N-terminal portion of the full length apoB protein which lack the LDL-receptor binding motif. A number of other apolipoproteins impact on LpL activity and lipoprotein clearance from the plasma. ApoC-II is necessary for the function of LpL. ApoC-III may inhibit LpL and also blocks lipoprotein uptake by the liver, and apoE is important for the uptake of triglyceride-rich remnants by the liver.

In response to the uptake of lipoprotein triglycerides or free fatty acids and/or endogenous production of fatty acids from carbohydrates, the liver produces triglyceride-rich VLDL particles, containing the full length apoB-100. Similar to chylomicron triglycerides, triglycerides in VLDL particles are metabolized to free fatty acids by the action of LpL, with subsequent tissue uptake. The lipolytic process leads to production of VLDL remnants, also referred to as intermediate-density lipoproteins (IDL), and eventually to conversion to LDL

particles. Depending on the relative presence of apo C-III and apoE, VLDL subfractions differ in their metabolic properties and the propensity to hypertriglyceridemia [9]. Notably, hypertriglyceridemic VLDL particles are heterogeneous and often have a high apoC-III/apoE ratio, causing reduced clearance and increased conversion to LDL.

The plasma triglyceride level is a marker for the concentration of triglyceride-carrying lipoproteins (VLDL and chylomicrons). As the relative proportion of lipoprotein components differ, the VLDL cholesterol and apoB concentration is substantially higher than the corresponding chylomicron concentrations [10]. It is noteworthy that these lipoproteins contain at least as much cholesterol per particle as LDL and it has been suggested that cholesterol carried in triglyceride-rich particles might contribute to plaque development [11]. Thus, a narrow focus on LDL cholesterol may not take the full amount of atherogenic risk carried by lipoproteins into consideration.

Recently, there has been much interest in understanding the wider metabolic consequences of hypertriglyceridemia. Increased tissue accumulation of triglycerides can result from increased triglyceride uptake, greater de novo formation of triglyceride, or reduced utilization or secretion of triglyceride. Excess tissue triglyceride has become the signature of a number of metabolic diseases that are termed lipotoxicities; these include non-alcoholic fatty liver disease (NAFLD), type 2 diabetes mellitus and some forms of cardiomyopathy, and patients with acquired generalized lipodystrophy and extensive fat loss often have hepatic steatosis as circulating triglyceride is unable to be stored in adipose tissue [1213]. Secondarily, an increased ectopic fat deposition may lead to insulin resistance associated with type 2 diabetes mellitus and metabolic syndrome [14]. This defect in insulin signaling is thought to be due not to triglyceride itself, but to the associated accumulation of signaling lipids such as diacylglycerol and ceramides.

Although the association of central obesity and insulin resistance with dyslipidemia is well established, underlying mechanisms remain unclear. An increase in the level of portal vein long-chain non-esterified fatty acids (NEFAs) has been suggested as an underlying factor that would potentially inhibit hepatic apoB-100 degradation and increase the likelihood of secretion of triglyceride-containing lipoproteins. Secondarily, this could contribute to increased triglyceride levels with a higher number of VLDL and LDL particles in patients with insulin resistance [15]. Because hypertriglyceridemia, increased intra-abdominal fat, and NAFLD occur with insulin resistance and excess caloric intake, a cause-and-effect relationship is difficult to conclude. The increased use of imaging tools coupled with metabolic and genetic studies may provide novel insights.

## Hypertriglyceridemia – what is a relevant definition?

The definition of normal vs. elevated triglyceride levels under fasting conditions has been subject to revision over time. Earlier versions of the NCEP Adult Treatment Panel (Panel I and II) defined elevated triglycerides as a level >200 mg/dL [16]. The current NCEP Adult Treatment Panel III (ATP III) has classified fasting serum triglycerides into 4 different classes with an elevated serum triglyceride level in adults classified as >150 mg/dL (>1.7 mmol/L) [5]. Although to some extent an arbitrary cutoff, the level is based on findings from

large prospective observational studies. However, the exact level at which serum triglycerides start to confer risk or become a marker for cardiovascular disease is unknown, but could be lower than a level of 150 mg/dL [17]. Age, gender and race/ethnicity impact the averages (normal) within the population. Serum triglycerides are higher in men and increase with age in both men and women; these changes parallel the frequency of the metabolic syndrome with age [18]. In support of the current definition of hypertriglyceridemia, serum triglyceride levels <150 mg/dL (<1.7 mmol/L) usually are <75th percentile at a population level, although there are well-established inter-ethnic differences, with generally lower levels among African Americans [19]. The more stringent definition of increased triglycerides, together with a higher frequency of overweight and obesity, has resulted in a high hypertriglyceridemia prevalence [20]. Thus, a third of the NHANES 1999–2004 participants were hypertriglyceridemic. Hypertriglyceridemia was greatest with higher ages, however, a quarter of younger subjects had increased triglyceride levels [21].

The recently published Endocrine Society guidelines specifically addressed the risk for pancreatitis in subjects with very high triglyceride levels [22]. The guidelines classified triglyceride levels in four hypertriglyceridemic categories, where the two lowest categories, together spanning triglyceride levels of 150–999 mg/dL, were considered as mild and moderate hypertriglyceridemia, respectively. The focus for this group is primarily on reducing CVD risk, while the highest category level, defined as very severe hypertriglyceridemia (>2,000 mg/dL), is associated with risk for pancreatitis. Triglyceride levels of 1000 – 1999 mg/dL, classified as severe hypertriglyceridemia, indicate risk for development of very severe hypertriglyceridemia, causative of pancreatitis [23, 24]. A recent meta-analysis, classifying increased triglyceride levels as >500 mg/dL, confirmed an association between hypertriglyceridemia and pancreatitis [25]. Although this new categorization attempts to provide a more clear association between triglyceride levels and pancreatitis, it adheres to the same treatment guidelines used in NCEP-ATP III. Triglyceride levels over 500 mg/dL approach and exceed the saturation level for triglyceride removal, are associated with rapid increases in post-prandial triglyceride levels, and are an indication for dietary and pharmacologic treatment.

## Measurement of hypertriglyceridemia - Fasting vs. non-fasting triglyceride levels in clinical practice

Historically, lipid and lipoprotein levels, including triglycerides, have been routinely measured under fasting conditions. While this has allowed comparisons across studies and populations, it brings an element of inconvenience with regard to the practical clinical situation. The possibility that the postprandial status would represent an atherogenic condition was initially suggested by Zilversmit [26] and has been substantiated in many subsequent studies, primarily using a heavy lipid load with standardized blood sampling [27]. Results from several recent prospective studies indicate that compared to fasting levels, non-fasting serum triglyceride levels may be a better or similar predictor of CVD events in the general population [28–30]. The potential ability to make treatment decisions based on non-fasting lipid levels has therefore attracted interest. In one recent study, results showed a similar ability to predict nonfatal or fatal coronary heart disease by average fasting and non-

fasting triglyceride levels [31]. However, an important factor in using fasting conditions is the ability for the treatment provider to calculate LDL-cholesterol levels, the keystone in many cardiovascular risk reduction guidelines for intervention decisions regarding lipid risk factors [5]. Further, given the close and frequently inverse association between triglyceride and HDL cholesterol levels, hypertriglyceridemia and postprandial lipemia may affect measurement of HDL cholesterol and therefore the calculation of non-HDL cholesterol, an alternative treatment goal beyond LDL cholesterol [5].

Several large population-based studies have addressed the association of non-fasting triglyceride levels with CVD risk. One of these studies, including more than 26,000 US women healthy at baseline and followed for about 11 years, tested fasting levels in 20,118 subjects and non-fasting in 6,391 women [29]. Fasting triglyceride levels predicted CVD events but no independent association with cardiovascular events was seen after adjustment for potential confounders. Non-fasting triglyceride levels were independently associated with an increased risk of future events with a significant trend with increasing tertiles of triglyceride levels. Notably, the associations weakened with increasing time after the participants' last meal and there was some concern regarding compliance.

Another study, undertaken in Copenhagen and representing the general population, enrolled both women (n=7,587) and men (n=6,394) over a broad age range, with a mean follow-up of 26 years [28]. After adjustment for other CVD risk factors, associations with myocardial infarction, ischemic heart disease, and total death were significant for trend with increasing triglyceride level for both men and women. Some limitations to note were the limited number of subjects with high triglycerides, lack of adjustment made for HDL-cholesterol, and no comparison with fasting triglyceride levels. Triglyceride levels and event rates in this study were higher compared to the healthy US women [29]. While non-fasting conditions represent an advantage with regard to patient convenience and compliance, a number of issues remain to be resolved allowing a more general use. Lack of standardization and reference levels impede a general implementation of non-fasting triglyceride or remnant particle levels, requiring further studies to recommend an optimal procedure for postprandial sampling [32]. Finally, any postprandial effects on triglyceride measurement needs to be addressed [33].

## Hypertriglyceridemia – causes

Hypertriglyceridemia can result from increased production, reduced catabolism, or a combination thereof. A common cause of hypertriglyceridemia is seen in conditions with insulin resistance, such as metabolic syndrome and type 2 diabetes mellitus. An increase in triglyceride production under these conditions may be due to excess free fatty acids returning to the liver, as well as an increased de novo triglyceride production [15, 34]. Although insulin resistance is associated with high triglycerides, VLDL and triglyceride concentrations can be similar in patients with widely divergent insulin sensitivity, and in African Americans, low triglyceride levels may occur in the context of severe insulin resistance [35, 36]. Thus, the contribution of insulin resistance to overproduction of triglycerides and VLDL may be variable. Foods that contain potent substrates for

triglyceride production such as free carbohydrates, fructose, and alcohol can substantially increase triglyceride levels in susceptible individuals [37].

Mechanisms underlying a reduced catabolism contributing to hypertriglyceridemia include defective triglyceride hydrolysis and reduced hepatic clearance of VLDL and chylomicron remnants. Defective lipolysis can result from a variety of genetic defects, such as defects in LpL, apoC-II, glycosylphosphatidylinositol anchored high density lipoprotein binding protein 1 (GPIHBP1, an LpL-binding protein), or mutated lipase maturation factor 1 (LMF1), leading to defective intracellular LpL processing [38, 39]. Other causes may be defective association of LpL with the vascular wall due to heparin antibodies [40]. In addition, a number of additional genetic factors influence human triglyceride levels, including mutations in apoC-III, apoE, apoA-V, and angiopoietin-like protein 3, 4 and 8. Reduced VLDL clearance may in part be due to saturation of clearance pathways [41]. For this reason, there is concern that triglyceride levels >1,000 mg/dL can rapidly increase following a fat-rich meal.

As hypertriglyceridemia frequently constitute a component of metabolic abnormalities, many of which are associated with an increased risk for CVD, triglyceride levels may be seen as a canary in a mine. Beyond the presence of the metabolic syndrome, as mentioned above, elevated serum triglyceride levels are seen in overweight or obese people, a sedentary lifestyle, excess alcohol intake, and presence of endocrine or metabolic diseases. In addition, there are several genetic conditions with hypertriglyceridemia, including familial hypertriglyceridemia (FHTG), familial combined hyperlipidemia (FCHL), and familial dysbetalipoproteinemia (Type III hyperlipidemia). A combination of environmental and genetic factors underlying a hypertriglyceridemic condition is therefore not uncommon.

## Genetic causes of hypertriglyceridemia

Elevated triglycerides can occur in the absence or presence of other lipid or lipoprotein disturbances. Patients with elevations in the levels of both total plasma cholesterol and triglyceride can be divided into three categories. In the first category, VLDL and/or LDL cholesterol levels are elevated, as in familial combined hyperlipidemia. In the second category VLDL and chylomicron remnant cholesterol are elevated, as in familial dysbetalipoproteinemia. The third category consists of patients with severe and very severe hypertriglyceridemia, such as chylomiconemia.

### Familial Combined Hyperlipidemia (FCHL)

FCHL is a relatively common condition with a prevalence of about 1% to 2%. Notably, it is more common in patients with coronary artery disease, where the frequency has been reported to be at least 10% [42], highlighting the importance of diagnosis and treatment. The FCHL phenotype is variable, within families and in single individuals, and ranges from isolated hypertriglyceridemia to isolated hypercholesterolemia suggesting an environmental modulating impact [42]. However, elevated apoB levels and small, dense LDL particles are always seen [43]. In addition, patients with FCHL frequently have other cardiovascular risk factors (i.e. central obesity, hypertension, insulin resistance, and impaired glucose tolerance), highlighting the need for comprehensive risk factor treatment.

### Familial Hypertriglyceridemia (FHTG)

FHTG is another variant of genetic hypertriglyceridemia with triglyceride levels ranges from about 250 to 1,000 mg/dL where the CVD risk is low [44]. Determination of whether an individual patient with hypertriglyceridemia is at increased risk for CVD is challenging. Family history and associated other risk factors that contribute to the metabolic syndrome are useful guides, and a concomitant increased apoB or LDL cholesterol concentration is suggestive of greater CVD risk and might assist in differentiating FCHL from more benign FHTG [4245].

Many, if not most, patients with hypertriglyceridemia have a concomitant reduction in HDL cholesterol levels, and most forms of severe genetic HDL deficiency, such as Tangiers Disease, apoA-I deficiency, and lecithin cholesterol acyl transferase (LCAT) deficiency, are associated with mild-to-moderate hypertriglyceridemia. It has been suggested that familial hypoalpha-lipoproteinemia (FHA) might be a separate disorder with elevated triglyceride and low HDL cholesterol associated with premature coronary artery disease [46].

### Chylomicronemia Syndrome

Severe hyperchylomicronemia is associated with very severe hypertriglyceridemia and abdominal pain, eruptive xanthomas on the buttocks and the extensor surfaces of the upper limb, and transient memory loss. If uncorrected, the chylomicronemia syndrome may result in acute, recurrent pancreatitis. The risk of pancreatitis markedly increases with triglyceride levels >2,000 mg/dL, and can be prevented by maintaining triglyceride levels <1,000 mg/dL. To reduce risk for acute, recurrent pancreatitis, patients must be treated with moderate to severe dietary fat restriction to reduce plasma triglyceride levels [42]. Although underlying mechanisms need to be resolved, a release of excess fatty acids and lysolecithin from chylomicrons, exceeding the binding capacity of albumin in pancreatic capillaries may contribute. Importantly, severe hyperchylomicronemia may be due to a secondary cause of hypertriglyceridemia, such as diabetes or pregnancy, in combination with an underlying genetic defect [42]. Attention should also be directed to any use of drugs that could raise triglyceride levels. Occasionally, chylomicronemia may occur together with a genetic defect in the LpL-related triglyceride clearance system, such as LpL deficiency or rarely, as apoC-II, apoA-V, or GPIHBP 1 deficiency (see above).

### Type III hyperlipidemia or Dysbetalipoproteinemia

Dysbetalipoproteinemia, also called type III hyperlipoproteinemia or remnant removal disease, is seen when an apoE genetic variant resulting in a reduced lipoprotein clearance (almost always the E2/E2 genotype) is present together with another condition (genetic or acquired, such as intake of steroids or estrogen or following surgery) resulting in VLDL overproduction (e.g. FCHL) or reduced LDL receptor activity (e.g. heterozygous FH or hypothyroidism). The net result is an impaired hepatic uptake of apoE-containing lipoproteins and a reduction in the conversion of VLDL and IDL to LDL particles, with concomitant elevations in both cholesterol and triglyceride levels [47]. VLDL particles in patients with dysbetalipoproteinemia are cholesterol-enriched, as determined after isolation of VLDL by ultracentrifugation. In the absence of a second contributing factor beyond apoE, the accumulation of remnant lipoproteins is generally not sufficient to cause hyperlipidemia

under fasting conditions. It can be useful to confirm the diagnosis by demonstrating the presence of the E2/E2 genotype.

Due to the accumulation of triglyceride-rich lipoprotein remnants, patients with dysbetalipoproteinemia are at increased risk for premature coronary artery disease and peripheral vascular disease. Clinical characteristics include palmar xanthomas, orange lipid deposits in the palmar creases, which are pathognomonic but not always present, and tuberoeruptive xanthomas occasionally seen at pressure sites on the elbows, buttocks, and knees. The presence of dysbetalipoproteinemia should be suspected in a person with elevated total cholesterol and triglyceride levels that range from 300 to 1,000 mg/dL and are roughly equal.

## Secondary causes of hypertriglyceridemia

An isolated elevation in triglyceride levels may arise secondary to the use of various drugs, a high carbohydrate diet, or as a component of endocrine and other diseases, inflammation, or some rare genetic diseases. In the setting of common, underlying genetic dyslipidemias, such secondary causes can lead to severe and very severe elevations of triglyceride levels and risk of pancreatitis.

### Metabolic Syndrome and Endocrine Disorders

Hypertriglyceridemia is one of the components of the metabolic syndrome, a constellation of metabolic risk factors including triglycerides >150 mg/dL, HDL cholesterol <40 mg/dL in men or <50 mg/dL in women, blood glucose >100 mg/dL, blood pressure >130 mm Hg systolic or >85 mm Hg diastolic, and waist circumference >102 cm in men or >88 cm in women, recognized as conferring cardiovascular risk [6]. Although criteria for defining the metabolic syndrome have differed among health organizations and some cutoff levels differ across ethnicities, leading cardiovascular and diabetes organizations have agreed on a harmonized definition [48]. Notably, presence of endocrine conditions such as type 2 diabetes mellitus, polycystic ovary syndrome, and FCHL may account for up to 50% of premature coronary artery disease in some populations with metabolic syndrome [49]. Importantly, in normal, randomly selected healthy populations, isolated visceral obesity and insulin resistance were associated with only modest increases in triglyceride and decreases in HDL cholesterol levels [50]. Increased waist circumference and plasma triglyceride levels together confer greater cardiovascular risk in these patients [51].

Other conditions with hypertriglyceridemia include acromegaly, oral estrogen treatment, tamoxifen therapy (less pronounced with raloxifene), and pregnancy [52]. These changes relate to increased insulin resistance, to decreased activity of both hepatic lipase and LpL, or estrogen-induced stimulation of the secretion of triglyceride-rich lipoproteins [53]. This latter effect does not occur with transdermal estrogen [54]. In patients with familial hypertriglyceridemia or LpL deficiency, the use of oral estrogens can provoke severe pancreatitis [55]. Glucocorticoids lead to increased fatty acid synthesis due to increased expression of fatty acid synthase, and decreased clearance of triglyceride-rich lipoproteins[56]. Patients with untreated diabetes mellitus commonly have hypertriglyceridemia, more frequently seen in type 2 than in type 1, and appropriate diabetes management reduces

triglyceride levels. One of the most commonly used triglyceride-increasing agents is alcohol, which increases hepatic VLDL secretion due to increased hepatic fatty acid synthesis and decreased fatty acid oxidation. The effects of alcohol are dose-dependent and tend to be amplified in subjects with underlying lipid disorders [57].

### Rare Diseases

Loss of adipose tissue as seen in inherited and congenital lipodystrophies is associated with moderate-to-severe hypertriglyceridemia [58]. Some forms are present already at birth while others become clinically apparent in childhood and puberty [59]. In some rare varieties of familial partial lipodystrophy, such as the Kobberling variety, fat loss is more prominent from the extremities [60]. Hypertriglyceridemia is also seen in several types of glycogen storage disease in children [61].

### HIV, Autoimmune disease, Renal and Hepatic disease

The finding of hypertriglyceridemia and acquired lipodystrophy in patients with HIV infection treated with highly active antiretroviral therapy has attracted much attention and a large number of studies have addressed potential mechanisms. At present, the HIV condition in itself as well as some antiretroviral regimens, such as combinations including ritonavir or lopinavir, have been associated with hypertriglyceridemia and decreased HDL cholesterol levels [62, 63]. Some autoimmune or malignant diseases show presence of lipodystrophy or hypertriglyceridemia, including systemic lupus erythematosis involving autoantibodies to LpL, apoC-II, or heparin, juvenile dermatomyositis, and multiple myeloma. Further, immunosuppressants such as sirolimus increase triglyceride levels [64]. Hypertriglyceridemia with increased VLDL production has been reported in infections including inflammation and sepsis [65], and hypertriglyceridemia in severe stress may be related to possible catecholamine induction of adipose tissue lipolysis and reduced LpL activity [66]. Interestingly, acute hepatitis may be associated with increased VLDL production and hypertriglyceridemia [67]. Hypertriglyceridemia due to varying mechanisms is seen in some conditions of kidney disease. Nephrotic syndrome causes increased hepatic production of apoB-containing lipoproteins, including VLDL [68], and hypertriglyceridemia is common in patients with renal failure, possibly related to decreased clearance of triglyceride-rich lipoproteins [69].

### Drugs

The association between bile acid sequestrants (cholestyramine, colestipol, colesevelam) and triglyceride levels is well established. While patients with normal baseline triglyceride levels experience minimal triglyceride increases, those with moderate hypertriglyceridemia may experience substantial further elevation [70]. Bile acid sequestrants are contraindicated in patients with severe hypertriglyceridemia (>1,000 mg/dl) and in patients with dysbetalipoproteinemia.

Antihypertensive drugs with a potential to increase triglyceride levels are thiazide and furosemide diuretics and β-adrenergic blocking agents and the effects are most relevant in patients with underlying genetic hypertriglyceridemia [56]. Retinoids (e.g. isotretinoin and bexarotene) are associated with increased triglyceride levels, and mechanisms may involve both increased hepatic VLDL and apoC-III production and decreased LpL [71].

Hypertriglyceridemia can be seen with certain second-generation antipsychotic medications associated with weight gain, insulin resistance and worsening of the metabolic syndrome [72].

## Hypertriglyceridemia and lipoprotein composition – clinical practice applications

Triglyceride is a component of all lipoproteins, and triglyceride metabolism has a major impact on lipoprotein distribution and properties. In particular, triglyceride and HDL cholesterol levels are often inversely related, and HDL particles are closely involved in the catabolism of triglyceride-rich lipoproteins. Further, triglyceride-rich lipoproteins contain cholesterol, and under hypertriglyceridemic conditions, the amount of cholesterol carried in triglyceride-rich lipoproteins and their remnants can be substantial. These particles have an atherogenic potential. In addition, hypertriglyceridemia affects LDL and HDL particle properties, with a shift to smaller particle sizes [15]. Thus, in patients with hypertriglyceridemic conditions due to the metabolic syndrome, treated type 2 diabetes mellitus, or familial combined hyperlipidemia, the number of small, dense LDL and HDL particles are increased [43, 49]. Whether measurement of these changes in particle size is of clinical value is debated.

Several plasma proteins or enzymes, such as hepatic lipase and cholesterol ester transfer protein (CETP) contribute to the lipoprotein particle remodeling processes, and their relative impact depends on the VLDL triglyceride content [73, 74]. There has been much interest in the potential impact of variability of LDL size and density [75]. However, while there is wide agreement that the LDL concentration predicts coronary heart disease, epidemiological studies assessing any independent association between large or small LDL and atherosclerotic CVD have yielded variable results [5, 76]. Statins reduce the concentration of all sizes of LDL, and their benefits to reducing cardiovascular disease are universal across population groups that have large or small LDL [5, 77]. Further, as for LDL, epidemiological studies have not provided conclusive evidence that measurement of HDL size contributes to risk prediction [78].

As pointed out above, the amount of cholesterol carried in triglyceride-rich lipoproteins may significantly contribute to atherogenic risk in some patients, and measurement of non-HDL cholesterol and/or apoB levels can indicate the presence of increased numbers of atherogenic particles, including LDL and triglyceride-rich lipoproteins [5]. An advantage of non-HDL-cholesterol (total serum cholesterol minus HDL-cholesterol) is that this level reflects the amount of cholesterol in all atherogenic lipoprotein particles, including lipoprotein remnants and lipoprotein(a), [Lp(a)]. Lp(a) contains apoB and has many properties in common with LDL. As recent studies have underscored the importance of Lp(a) as a CVD risk factor, measurement of Lp(a) may inform CVD risk assessment [79, 80]. In addition to measurement of LDL and non-HDL cholesterol, the apoB level has been suggested as a useful tool. Not unexpectedly, there is a good correlation between apoB and non-HDL-cholesterol levels, as one apoB molecule is present on the surface of each chylomicron, VLDL, IDL, LDL and Lp(a) particle and resides with the particle during its metabolism. Elevated levels of apoB often occur in FCHL and might assist in differentiating it from more benign familial hypertriglyceridemia. Non-HDL cholesterol can then be

followed as the therapeutic target. Regarding overall measurement of lipoprotein heterogeneity, the Endocrine Society guidelines recommended against a routine measurement of lipoprotein particle heterogeneity in patients with hypertriglyceridemia, but stated that measurement of apoB or Lp(a) levels could be of value.

## Management of Hypertriglyceridemia

There is general agreement that lifestyle therapy, including appropriate diet composition, physical activity and a program to achieve weight reduction is the foundation of treatment for mild-to-moderate hypertriglyceridemia. In some cases, such as more severe forms, addition of hypolipidemic drugs may be needed.

### Lifestyle therapy

The increase in serum triglycerides with aging is likely driven by changes in lifestyle, such as weight gain, lack of exercise, and a high calorie diet rich in simple carbohydrates and sugar-sweetened beverages. There has been much debate regarding diet approaches in hyperlipidemia. Under weight-stable conditions, the combination of reduced carbohydrate intake and increased fat intake lowers triglyceride levels, with a linear relation between replacement of dietary carbohydrate with fat and a reduction in serum triglycerides [81]. There is no clear difference between fatty acid classes with regard to triglyceride-lowering effect. However, dietary saturated fat and trans-fatty acids increase LDL cholesterol levels, while monounsaturated or polyunsaturated fat lower LDL cholesterol levels [81]. Notably, the ability of n-3 polyunsaturated fat to uniquely lower serum triglycerides has been used in drug development.

Recently, studies have focused on the type of carbohydrate that may affect serum triglyceride levels, and in particular on the role of fructose [37]. However, while a reduced intake of sugar-sweetened beverages is recommended as an important part of lowering serum triglycerides, more information is needed to ascertain whether fructose as a component of sugar-sweetened beverages is more detrimental than sucrose or glucose [82]. Following intake of carbohydrate-rich foods, a correlation between an increase in triglyceride levels and the glycemic index, i.e. the rise in blood glucose provided by 50 g of carbohydrate in a specific food compared with either 50 g glucose or white bread, has been observed [83].

Diet modification may vary across ethnicity as diet modification had less effect on triglyceride levels in African Americans compared to Caucasians, matched for baseline triglyceride levels [84]. For conditions where triglyceride clearing mechanisms are compromised (triglycerde levels >500 mg/dL) as well as in severe and very severe hypertriglyceridemia (triglyceride levels >1,000 mg/dL), combining reduction of dietary fat and simple carbohydrate intake with drug treatment is recommended to reduce the risk of pancreatitis [22].

### Exercise

Although benefits may be transient, there is some support for a hypotriglyceridemic effect of exercise. Thus, exercise the day before ingestion of a high-fat meal is associated with a

marked dampening of the postprandial triglyceride increase. Further, a period of 30–60 minutes of intermittent aerobic or mild resistance exercise is reported to be effective in lowering plasma and VLDL triglycerides [85]. However, a recent meta-analysis comparing aerobic exercise programs showed favorable effects only for high-intensity programs with an increase in the HDL cholesterol, while triglyceride reductions appeared less often [86].

## Weight loss

Treatment of excess weight is critical to reduce triglyceride levels. The macronutrient composition of a weight-loss diet is considerably less important for lowering triglycerides than the amount of weight lost. Two recent large-scale clinical trials of 2 years duration did not find differences in effects on triglyceride levels between low-fat, high-carbohydrate diets and low-carbohydrate diets [87, 88]. Many studies have shown that ongoing counseling by dietitians and behavioral therapists, and support from peers, is important to most people who are successful in losing weight and maintaining weight loss.

## Drug therapy

Three drug classes are clinically available for treatment of hypertriglyceridemia, fibrates, niacin and n-3 fatty acids. Each of these classes has limitations. There is inconsistency in the evidence base for cardiovascular risk reduction using fibrates, the use of niacin is associated with significant side effects, and there are limited data on the use of n-3 fatty acids to reduce cardiovascular risk. Considering that elevated triglycerides may be a marker for metabolic disease and/or other lipoprotein abnormalities, it is uncertain whether we should treat moderate hypertriglyceridemia in itself or other lipoprotein abnormalities associated with this degree of hypertriglyceridemia. A reasonable approach may be that if the primary goal is to lower triglyceride levels, fibrates and perhaps n-3 fatty acids are best. On the other hand, if the primary goal is to modify the size and density of LDL and HDL particles, niacin might be best. As statin treatment is becoming common in patients with elevated cholesterol levels, it is likely that in most cases with hypertriglyceridemia, many patients will already be on statins. A hypotriglyceridemic drug might then be added to a statin-based regimen. In view of differences in underlying mechanisms for the three hypotriglyceridemic drug classes described above, there is a considerable potential for use of drug combinations based on complementary mechanisms [89].

**Statins—**While HMG-CoA reductase inhibitors, or statins, are potent cholesterol-lowering drugs, their triglyceride-lowering effect is modest, typically about 10 –15 %, and dose-dependent. At higher doses (e.g. atorvastatin 80 mg or rosuvastatin 40 mg), plasma triglyceride levels can be lowered by 25–30%. Therefore, statin monotherapy is unlikely to be effective in severe or very severe hypertriglyceridemia. However, statins can be considered to reduce cardiovascular risk in patients with mild-to-moderate hypertriglyceridemia and elevated non-HDL cholesterol. Side effects of statins include muscle symptoms ranging from leg cramps to aching to weakness, present in about 10% of patients, while rhabdomyolysis is rare [90]. Conditions predisposing to severe myopathy include advanced age, renal failure, drug interactions and acute illness.

**Fibrates—**Fibrates reduce triglyceride levels through several mechanisms, including increased fatty acid oxidation, increased LpL synthesis, and reduced apo C-III expression. The net effect is a decrease in VLDL triglyceride production and an increase in catabolism of triglyceride-rich lipoproteins [91]. Fibrates should be considered in patients with moderate and severe hypertriglyceridemia as they generally decrease triglyceride levels by 30–50% and sometimes increase HDL cholesterol [92]. In patients with high triglyceride levels, LDL cholesterol levels may increase during therapy, likely due to an increased conversion of VLDL to LDL particles, while LDL cholesterol levels may decrease in mild hypertriglyceridemia. In patients with triglyceride-induced pancreatitis, treatment of underlying causes and concomitant fibrate therapy to maintain triglyceride levels <2,000 mg/dL is beneficial to prevent recurrent disease. Due to a large excursion of triglyceride levels in the setting of severe and very severe hypertriglyceridemia, a treatment goal of <500–1,000 mg/dL is recommended. Below this level, the main effort should be directed towards prevention of premature atherosclerosis.

Studies to date have not shown a reduction in total mortality in response to fibrate treatment. However, studies have demonstrated that fibrate treatment resulted in a decrease in composite cardiovascular events, including nonfatal coronary events in patients with moderate hypertriglyceridemia. A recent meta-analysis showed a significant benefit of fibrate treatment in subjects with hypertriglyceridemia and low HDL cholesterol [88, 91, 93]. Therefore, it is reasonable to expect that fibrate treatment of patients with at least moderate hypertriglyceridemia will produce some cardiovascular benefit. However, these studies also indicate a lack of benefit in patients with mild hypertriglyceridemia, i.e. triglycerides <200 mg/dL. Due to a possible increase in the incidence of cholesterol gallstones, fibrates are contraindicated in patients with liver and gall bladder disease. Further, due to their renal excretory pathway, fibrates should be used with great caution in the setting of renal insufficiency. In view of the likely combination therapy of fibrates with a statin, it should be noted that fenofibrate does not interfere with statin metabolism and has a lower risk of causing myopathy. Other potential interactions include warfarin due to effects on protein binding, requiring careful monitoring.

**Niacin—**Niacin lowers triglyceride levels and increases HDL cholesterol levels. At doses of 500 to 2,000 mg/d, niacin lowers triglycerides by 10–30%, increases HDL cholesterol by 10–40%, and lowers LDL cholesterol by 5–20%. Further, it is one of the few agents to date with a Lp(a)-lowering effect. Although higher doses of immediate-release (crystalline) niacin have been used, the maximum dose of the prescription extended-release formulation is 2,000 mg/day, achieved by a slow dose increase over time. Clinical trials using niacin go back more than 40 years, and administration of niacin, alone or in combination with other lipid medications, have been shown to provide benefits in decreasing cardiovascular event rates and atherosclerosis [94, 95]. However, two recent placebo-controlled studies have not shown any incremental benefit of adding niacin to statin therapy. Both of these studies included patients with normal triglyceride levels or mild hypertriglyceridemia. Probably most important was that the subjects were taking statins and had low LDL cholesterol levels. In the AIM-HIGH study, mean triglyceride levels at baseline were about 165 mg/dL and in the HPS2-THRIVE study, so far reported as a press release, mean baseline triglycerides

were in the normal range (125 mg/dL) [96]. The latter study, addressing a combination of statin and extended-release niacin with laropiprant, a prostaglandin receptor blocker included to reduce vasodilatation and cutaneous flushing, was stopped early due to lack of benefit and increased side-effects in the niacin/laropiprant arm. Other approaches to reduce niacin-induced flushing include postprandial intake of niacin or pre-meal administration of uncoated aspirin, e.g. 325 mg. Complications of niacin therapy include hepatotoxicity, impaired glucose tolerance or hyperuricemia requiring laboratory monitoring [97]. Niacin is contraindicated in patients with active peptic ulcer disease, but can be used safely in patients with glucose intolerance and can be considered in diabetic patients with moderate to good glycemic control.

**N-3 Fatty Acids—**Many studies have demonstrated a dose-dependent triglyceride-lowering effect of long chain marine omega-3 fatty acids (eicosapentaenoic acid, C20:5n-3; or EPA and docosahexaenoic acid, C22:6n-3; or DHA). However, no studies using high-dose n-3 fatty acids in hypertriglyceridemic patients have demonstrated any beneficial cardiovascular outcomes to date. Omega-3 fatty acids may be considered for treatment of severe and very severe hypertriglyceridemia (>1,000 mg/dL), and to achieve a reduction of hypertriglyceridemia by 20–50%, administration of 3 to 4 g/d of EPA plus DHA is required [98]. With reductions of triglyceride levels, there can be increased levels of LDL cholesterol due to increased conversion of VLDL to LDL, while HDL cholesterol levels commonly are mildly increased. Omega-3 acid ethyl esters are available by prescription while over-the-counter preparations of omega-3 fatty acids have variable quantities of EPA and DHA [99]. Side effects of large doses of omega-3 fatty acids include fishy taste and burping.

## Summary

Hypertriglyceridemia is common and present in about a third of the population. In recent meta-analyses, triglyceride levels have been associated with cardiovascular events but not with mortality. The majority of hypertriglyceridemic patients have mild or moderate triglyceride levels (<1,000 mg/dL) and treatment should be focused on reduction of cardiovascular risk. Patients with severe or very severe hypertriglyceridemia (>1,000 mg/dL) are at risk for pancreatitis. Cholesterol is a constituent of triglyceride-rich lipoproteins and contributes to overall plasma cholesterol levels. Through the lipolytic cascade, triglyceride-rich lipoproteins are converted to remnant particles with an atherogenic potential. As remnant cholesterol levels are not captured through measurement of LDL cholesterol, non-HDL cholesterol levels as defined by the NCEP-ATP III guidelines should be considered as treatment goal in patients with moderate hypertriglyceridemia. Although results are suggestive of an association between non-fasting triglyceride levels and cardiovascular risk, diagnosis of hypertriglyceridemia is best based on fasting levels until standardized sampling conditions are established. Given the frequent combination of genetic and environmental factors underlying hypertriglyceridemia, patients with hypertriglyceridemia should be evaluated for secondary causes of hyperlipidemia. Subjects with primary hypertriglyceridemia should be evaluated for family history of dyslipidemia and cardiovascular disease. Treatment for hypertriglyceridemia should be initiated as lifestyle therapy, while addition of hypotriglyceridemic drugs may be considered if patients

do not reach treatment goals. In patients with severe or very severe hypertriglyceridemia, a fibrate should be used as a first-line agent, while in patients with moderate hypertriglyceridemia, a statin-based combination therapy is more common.

## Reference List


1. Stamler J. Diet and coronary heart disease. Biometrics. 1982; 38 (Suppl):95–118. [PubMed: 7046825]
2. Keys A, Menotti A, Aravanis C, Blackburn H, Djordevic BS, Buzina R, Dontas AS, Fidanza F, Karvonen MJ, Kimura N, et al. The seven countries study: 2,289 deaths in 15 years. Preventive medicine. 1984; 13:141–154. [PubMed: 6739443]
3. Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, Bhala N, Peto R, Barnes EH, Keech A, Simes J, Collins R. Efficacy and safety of more intensive lowering of ldl cholesterol: A meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet. 2010; 376:1670–1681. [PubMed: 21067804]
4. Lorenzo C, Williams K, Hunt KJ, Haffner SM. The national cholesterol education program - adult treatment panel iii, international diabetes federation, and world health organization definitions of the metabolic syndrome as predictors of incident cardiovascular disease and diabetes. Diabetes care. 2007; 30:8–13. [PubMed: 17192325]
5. Third report of the national cholesterol education program (ncep) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel iii) final report. Circulation. 2002; 106:3143–3421. [PubMed: 12485966]
6. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, Gordon DJ, Krauss RM, Savage PJ, Smith SC Jr, Spertus JA, Costa F. American Heart A, National Heart L, Blood I. Diagnosis and management of the metabolic syndrome: An american heart association/national heart, lung, and blood institute scientific statement. Circulation. 2005; 112:2735–2752. [PubMed: 16157765]
7. Franco OH, Massaro JM, Civil J, Cobain MR, O'Malley B, D'Agostino RB Sr. Trajectories of entering the metabolic syndrome: The framingham heart study. Circulation. 2009; 120:1943–1950. [PubMed: 19884471]
8. Global recommendations for the management of dyslipidemia. Full report. An International Atherosclerosis Society Position Paper. 2013
9. Zheng C, Khoo C, Furtado J, Sacks FM. Apolipoprotein c-iii and the metabolic basis for hypertriglyceridemia and the dense low-density lipoprotein phenotype. Circulation. 2010; 121:1722–1734. [PubMed: 20368524]
10. Karpe F, Bell M, Bjorkegren J, Hamsten A. Quantification of postprandial triglyceride-rich lipoproteins in healthy men by retinyl ester labeling and simultaneous measurement of apolipoproteins b-48 and b-100. Arteriosclerosis, thrombosis, and vascular biology. 1995; 15:199–207.
11. Tabas I, Williams KJ, Boren J. Subendothelial lipoprotein retention as the initiating process in atherosclerosis: Update and therapeutic implications. Circulation. 2007; 116:1832–1844. [PubMed: 17938300]
12. Tessari P, Coracina A, Cosma A, Tiengo A. Hepatic lipid metabolism and non-alcoholic fatty liver disease. Nutrition, metabolism, and cardiovascular diseases : NMCD. 2009; 19:291–302.
13. Huang-Doran I, Sleigh A, Rochford JJ, O'Rahilly S, Savage DB. Lipodystrophy: Metabolic insights from a rare disorder. The Journal of endocrinology. 2010; 207:245–255. [PubMed: 20870709]
14. Szendroedi J, Roden M. Ectopic lipids and organ function. Current opinion in lipidology. 2009; 20:50–56. [PubMed: 19133412]
15. Ginsberg HN. New perspectives on atherogenesis: Role of abnormal triglyceride-rich lipoprotein metabolism. Circulation. 2002; 106:2137–2142. [PubMed: 12379586]
16. Summary of the second report of the national cholesterol education program (ncep) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel ii).

JAMA : the journal of the American Medical Association. 1993; 269:3015–3023. [PubMed: 8501844]

17. Heiss G, Tamir I, Davis CE, Tyroler HA, Rifkand BM, Schonfeld G, Jacobs D, Frantz ID Jr. Lipoprotein-cholesterol distributions in selected north american populations: The lipid research clinics program prevalence study. Circulation. 1980; 61:302–315. [PubMed: 7351055]
18. Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among us adults: Findings from the third national health and nutrition examination survey. JAMA : the journal of the American Medical Association. 2002; 287:356–359. [PubMed: 11790215]
19. Assmann, G.; Schulte, H. Results and conclusions of the prospective cardiovascular munster (procam) study. In: Assmann, G., editor. Lipid metabolism disorders and coronary heart disease. Munich: MMV Medizin Verlag GmbH; 1993. p. 19-68.
20. Wildman RP, Muntner P, Reynolds K, McGinn AP, Rajpathak S, Wylie-Rosett J, Sowers MR. The obese without cardiometabolic risk factor clustering and the normal weight with cardiometabolic risk factor clustering: Prevalence and correlates of 2 phenotypes among the us population (nhanes 1999–2004). Archives of internal medicine. 2008; 168:1617–1624. [PubMed: 18695075]
21. Centers for Disease C, Prevention. Prevalence of abnormal lipid levels among youths --- united states, 1999–2006. MMWR Morbidity and mortality weekly report. 2010; 59:29–33. [PubMed: 20094024]
22. Berglund L, Brunzell JD, Goldberg AC, Goldberg IJ, Sacks F, Murad MH, Stalenhoef AF. Evaluation and treatment of hypertriglyceridemia: An endocrine society clinical practice guideline. The Journal of clinical endocrinology and metabolism. 2012; 97:2969–2989. [PubMed: 22962670]
23. Brunzell JD, Schrott HG. The interaction of familial and secondary causes of hypertriglyceridemia: Role in pancreatitis. J Clin Lipidol. 2012; 6:409–412. [PubMed: 23009776]
24. Chait A, Brunzell JD. Severe hypertriglyceridemia: Role of familial and acquired disorders. Metabolism: clinical and experimental. 1983; 32:209–214. [PubMed: 6827992]
25. Murphy MJ, Sheng X, MacDonald TM, Wei L. Hypertriglyceridemia and acute pancreatitis. JAMA internal medicine. 2013; 173:162–164. [PubMed: 23183821]
26. Zilversmit DB. Atherogenesis: A postprandial phenomenon. Circulation. 1979; 60:473–485. [PubMed: 222498]
27. Karpe F. Postprandial lipoprotein metabolism and atherosclerosis. Journal of internal medicine. 1999; 246:341–355. [PubMed: 10583705]
28. Nordestgaard BG, Benn M, Schnohr P, Tybjaerg-Hansen A. Nonfasting triglycerides and risk of myocardial infarction, ischemic heart disease, and death in men and women. JAMA : the journal of the American Medical Association. 2007; 298:299–308. [PubMed: 17635890]
29. Bansal S, Buring JE, Rifai N, Mora S, Sacks FM, Ridker PM. Fasting compared with nonfasting triglycerides and risk of cardiovascular events in women. JAMA : the journal of the American Medical Association. 2007; 298:309–316. [PubMed: 17635891]
30. Mora S, Rifai N, Buring JE, Ridker PM. Fasting compared with nonfasting lipids and apolipoproteins for predicting incident cardiovascular events. Circulation. 2008; 118:993–1001. [PubMed: 18711012]
31. Eberly LE, Stamler J, Neaton JD. Multiple Risk Factor Intervention Trial Research G. Relation of triglyceride levels, fasting and nonfasting, to fatal and nonfatal coronary heart disease. Archives of internal medicine. 2003; 163:1077–1083. [PubMed: 12742806]
32. Ridker PM. Fasting versus nonfasting triglycerides and the prediction of cardiovascular risk: Do we need to revisit the oral triglyceride tolerance test? Clinical chemistry. 2008; 54:11–13. [PubMed: 17998265]
33. Warnick GR, Nakajima K. Fasting versus nonfasting triglycerides: Implications for laboratory measurements. Clinical chemistry. 2008; 54:14–16. [PubMed: 18039717]
34. Cohn JS, Patterson BW, Uffelman KD, Davignon J, Steiner G. Rate of production of plasma and very-low-density lipoprotein (vldl) apolipoprotein c-iii is strongly related to the concentration and level of production of vldl triglyceride in male subjects with different body weights and levels of insulin sensitivity. The Journal of clinical endocrinology and metabolism. 2004; 89:3949–3955. [PubMed: 15292332]

35. Lee SJ, Moye LA, Campos H, Williams GH, Sacks FM. Hypertriglyceridemia but not diabetes status is associated with vldl containing apolipoprotein ciii in patients with coronary heart disease. Atherosclerosis. 2003; 167:293–302. [PubMed: 12818412]
36. Sumner AE, Finley KB, Genovese DJ, Criqui MH, Boston RC. Fasting triglyceride and the triglyceride-hdl cholesterol ratio are not markers of insulin resistance in african americans. Archives of internal medicine. 2005; 165:1395–1400. [PubMed: 15983289]
37. Havel PJ. Dietary fructose: Implications for dysregulation of energy homeostasis and lipid/carbohydrate metabolism. Nutrition reviews. 2005; 63:133–157. [PubMed: 15971409]
38. Olivecrona G, Ehrenborg E, Semb H, Makoveichuk E, Lindberg A, Hayden MR, Gin P, Davies BS, Weinstein MM, Fong LG, Beigneux AP, Young SG, Olivecrona T, Hernell O. Mutation of conserved cysteines in the ly6 domain of gpihbp1 in familial chylomicronemia. Journal of lipid research. 2010; 51:1535–1545. [PubMed: 20026666]
39. Peterfy M, Ben-Zeev O, Mao HZ, Weissglas-Volkov D, Aouizerat BE, Pullinger CR, Frost PH, Kane JP, Malloy MJ, Reue K, Pajukanta P, Doolittle MH. Mutations in lmf1 cause combined lipase deficiency and severe hypertriglyceridemia. Nature genetics. 2007; 39:1483–1487. [PubMed: 17994020]
40. Gin P, Yin L, Davies BS, Weinstein MM, Ryan RO, Bensadoun A, Fong LG, Young SG, Beigneux AP. The acidic domain of gpihbp1 is important for the binding of lipoprotein lipase and chylomicrons. The Journal of biological chemistry. 2008; 283:29554–29562. [PubMed: 18713736]
41. Brunzell JD, Hazzard WR, Porte D Jr, Bierman EL. Evidence for a common, saturable, triglyceride removal mechanism for chylomicrons and very low density lipoproteins in man. The Journal of clinical investigation. 1973; 52:1578–1585. [PubMed: 4352459]
42. Brunzell JD. Clinical practice. Hypertriglyceridemia. The New England journal of medicine. 2007; 357:1009–1017. [PubMed: 17804845]
43. Ayyobi AF, McGladdery SH, McNeely MJ, Austin MA, Motulsky AG, Brunzell JD. Small, dense ldl and elevated apolipoprotein b are the common characteristics for the three major lipid phenotypes of familial combined hyperlipidemia. Arteriosclerosis, thrombosis, and vascular biology. 2003; 23:1289–1294.
44. Austin MA, McKnight B, Edwards KL, Bradley CM, McNeely MJ, Psaty BM, Brunzell JD, Motulsky AG. Cardiovascular disease mortality in familial forms of hypertriglyceridemia: A 20-year prospective study. Circulation. 2000; 101:2777–2782. [PubMed: 10859281]
45. Veerkamp MJ, de Graaf J, Hendriks JC, Demacker PN, Stalenhoef AF. Nomogram to diagnose familial combined hyperlipidemia on the basis of results of a 5-year follow-up study. Circulation. 2004; 109:2980–2985. [PubMed: 15184285]
46. Genest JJ Jr, Martin-Munley SS, McNamara JR, Ordovas JM, Jenner J, Myers RH, Silberman SR, Wilson PW, Salem DN, Schaefer EJ. Familial lipoprotein disorders in patients with premature coronary artery disease. Circulation. 1992; 85:2025–2033. [PubMed: 1534286]
47. Mahley RW, Huang Y, Rall SC Jr. Pathogenesis of type iii hyperlipoproteinemia (dysbetalipoproteinemia). Questions, quandaries, and paradoxes. Journal of lipid research. 1999; 40:1933–1949. [PubMed: 10552997]
48. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, Fruchart JC, James WP, Loria CM, Smith SC Jr. International Diabetes Federation Task Force on E, Prevention, Hational Heart L, Blood I, American Heart A, World Heart F, International Atherosclerosis S, International Association for the Study of O. Harmonizing the metabolic syndrome: A joint interim statement of the international diabetes federation task force on epidemiology and prevention; national heart, lung, and blood institute; american heart association; world heart federation; international atherosclerosis society; and international association for the study of obesity. Circulation. 2009; 120:1640–1645. [PubMed: 19805654]
49. Carr MC, Brunzell JD. Abdominal obesity and dyslipidemia in the metabolic syndrome: Importance of type 2 diabetes and familial combined hyperlipidemia in coronary artery disease risk. The Journal of clinical endocrinology and metabolism. 2004; 89:2601–2607. [PubMed: 15181030]
50. Nieves DJ, Cnop M, Retzlaff B, Walden CE, Brunzell JD, Knopp RH, Kahn SE. The atherogenic lipoprotein profile associated with obesity and insulin resistance is largely attributable to intra-abdominal fat. Diabetes. 2003; 52:172–179. [PubMed: 12502509]

51. Blackburn P, Lemieux I, Almeras N, Bergeron J, Cote M, Tremblay A, Lamarche B, Despres JP. The hypertriglyceridemic waist phenotype versus the national cholesterol education program-adult treatment panel iii and international diabetes federation clinical criteria to identify high-risk men with an altered cardiometabolic risk profile. Metabolism: clinical and experimental. 2009; 58:1123–1130. [PubMed: 19481769]
52. Tamburrano G, Durante C, Baldelli R. Therapy of diabetes and dyslipidemia in acromegaly. Pituitary. 2002; 5:27–31. [PubMed: 12638723]
53. Carr MC, Knopp RH, Brunzell JD, Wheeler BS, Zhu X, Lakshmanan M, Rosen AS, Anderson PW. Effect of raloxifene on serum triglycerides in women with a history of hypertriglyceridemia while on oral estrogen therapy. Diabetes care. 2005; 28:1555–1561. [PubMed: 15983300]
54. Walsh BW, Schiff I, Rosner B, Greenberg L, Ravnikar V, Sacks FM. Effects of postmenopausal estrogen replacement on the concentrations and metabolism of plasma lipoproteins. The New England journal of medicine. 1991; 325:1196–1204. [PubMed: 1922206]
55. Stuyt PM, Demacker PN, Stalenhoef AF. Pancreatitis induced by oestrogen in a patient with type i hyperlipoproteinaemia. British medical journal. 1986; 293:734. [PubMed: 3094633]
56. Stone NJ. Secondary causes of hyperlipidemia. The Medical clinics of North America. 1994; 78:117–141. [PubMed: 8283927]
57. Brinton EA. Effects of ethanol intake on lipoproteins and atherosclerosis. Current opinion in lipidology. 2010; 21:346–351. [PubMed: 20616714]
58. Garg A, Agarwal AK. Lipodystrophies: Disorders of adipose tissue biology. Biochimica et biophysica acta. 2009; 1791:507–513. [PubMed: 19162222]
59. Simha V, Garg A. Inherited lipodystrophies and hypertriglyceridemia. Current opinion in lipidology. 2009; 20:300–308. [PubMed: 19494770]
60. Herbst KL, Tannock LR, Deeb SS, Purnell JQ, Brunzell JD, Chait A. Kobberling type of familial partial lipodystrophy: An underrecognized syndrome. Diabetes care. 2003; 26:1819–1824. [PubMed: 12766116]
61. Bandsma RH, Smit GP, Kuipers F. Disturbed lipid metabolism in glycogen storage disease type 1. European journal of pediatrics. 2002; 161 (Suppl 1):S65–69. [PubMed: 12373575]
62. Carr A, Samaras K, Chisholm DJ, Cooper DA. Pathogenesis of hiv-1-protease inhibitor-associated peripheral lipodystrophy, hyperlipidaemia, and insulin resistance. Lancet. 1998; 351:1881–1883. [PubMed: 9652687]
63. Anuurad E, Bremer A, Berglund L. Hiv protease inhibitors and obesity. Current opinion in endocrinology, diabetes, and obesity. 2010; 17:478–485.
64. Hakeam HA, Al-Jedai AH, Raza SM, Hamawi K. Sirolimus induced dyslipidemia in tacrolimus based vs. Tacrolimus free immunosuppressive regimens in renal transplant recipients. Annals of transplantation : quarterly of the Polish Transplantation Society. 2008; 13:46–53. [PubMed: 18566560]
65. Grunfeld C, Kotler DP, Shigenaga JK, Doerrler W, Tierney A, Wang J, Pierson RN Jr, Feingold KR. Circulating interferon-alpha levels and hypertriglyceridemia in the acquired immunodeficiency syndrome. The American journal of medicine. 1991; 90:154–162. [PubMed: 1996584]
66. Nonogaki K, Moser AH, Feingold KR, Grunfeld C. Alpha-adrenergic receptors mediate the hypertriglyceridemia induced by endotoxin, but not tumor necrosis factor, in rats. Endocrinology. 1994; 135:2644–2650. [PubMed: 7988454]
67. Luo L, Pu X, Wang Y, Xu N. Impaired plasma lipid profiles in acute hepatitis. Lipids in health and disease. 2010; 9:5. [PubMed: 20096126]
68. Kronenberg F. Dyslipidemia and nephrotic syndrome: Recent advances. Journal of renal nutrition : the official journal of the Council on Renal Nutrition of the National Kidney Foundation. 2005; 15:195–203.
69. Kaysen GA. Lipid and lipoprotein metabolism in chronic kidney disease. Journal of renal nutrition : the official journal of the Council on Renal Nutrition of the National Kidney Foundation. 2009; 19:73–77.
70. Crouse JR 3rd. Hypertriglyceridemia: A contraindication to the use of bile acid binding resins. The American journal of medicine. 1987; 83:243–248. [PubMed: 3618626]

71. Vu-Dac N, Gervois P, Torra IP, Fruchart JC, Kosykh V, Kooistra T, Princen HM, Dallongeville J, Staels B. Retinoids increase human apo c-iii expression at the transcriptional level via the retinoid x receptor. Contribution to the hypertriglyceridemic action of retinoids. The Journal of clinical investigation. 1998; 102:625–632. [PubMed: 9691099]
72. Casey DE. Dyslipidemia and atypical antipsychotic drugs. The Journal of clinical psychiatry. 2004; 65 (Suppl 18):27–35. [PubMed: 15600382]
73. Mann CJ, Yen FT, Grant AM, Bihain BE. Mechanism of plasma cholesteryl ester transfer in hypertriglyceridemia. The Journal of clinical investigation. 1991; 88:2059–2066. [PubMed: 1752964]
74. Zambon A, Hokanson JE, Brown BG, Brunzell JD. Evidence for a new pathophysiological mechanism for coronary artery disease regression: Hepatic lipase-mediated changes in ldl density. Circulation. 1999; 99:1959–1964. [PubMed: 10208998]
75. Austin MA. Triglyceride, small, dense low-density lipoprotein, and the atherogenic lipoprotein phenotype. Current atherosclerosis reports. 2000; 2:200–207. [PubMed: 11122745]
76. Austin MA, King MC, Vranizan KM, Krauss RM. Atherogenic lipoprotein phenotype. A proposed genetic marker for coronary heart disease risk. Circulation. 1990; 82:495–506. [PubMed: 2372896]
77. Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, Kirby A, Sourjina T, Peto R, Collins R, Simes R. Cholesterol Treatment Trialists C. Efficacy and safety of cholesterol-lowering treatment: Prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet. 2005; 366:1267–1278. [PubMed: 16214597]
78. Mora S. Advanced lipoprotein testing and subfractionation are not (yet) ready for routine clinical use. Circulation. 2009; 119:2396–2404. [PubMed: 19414657]
79. Erqou S, Kaptoge S, Perry PL, Di Angelantonio E, Thompson A, White IR, Marcovina SM, Collins R, Thompson SG, Danesh J. Emerging Risk Factors C. Lipoprotein(a) concentration and the risk of coronary heart disease, stroke, and nonvascular mortality. JAMA : the journal of the American Medical Association. 2009; 302:412–423. [PubMed: 19622820]
80. Anuurad E, Enkhmaa B, Berglund L. Enigmatic role of lipoprotein(a) in cardiovascular disease. Clinical and translational science. 2010; 3:327–332. [PubMed: 21167011]
81. Mensink RP, Zock PL, Kester AD, Katan MB. Effects of dietary fatty acids and carbohydrates on the ratio of serum total to hdl cholesterol and on serum lipids and apolipoproteins: A meta-analysis of 60 controlled trials. The American journal of clinical nutrition. 2003; 77:1146–1155. [PubMed: 12716665]
82. Johnson RK, Appel LJ, Brands M, Howard BV, Lefevre M, Lustig RH, Sacks F, Steffen LM, Wylie-Rosett J. American Heart Association Nutrition Committee of the Council on Nutrition PA, Metabolism, the Council on E, Prevention. Dietary sugars intake and cardiovascular health: A scientific statement from the american heart association. Circulation. 2009; 120:1011–1020. [PubMed: 19704096]
83. Ludwig DS. The glycemic index: Physiological mechanisms relating to obesity, diabetes, and cardiovascular disease. JAMA : the journal of the American Medical Association. 2002; 287:2414–2423. [PubMed: 11988062]
84. Furtado JD, Campos H, Sumner AE, Appel LJ, Carey VJ, Sacks FM. Dietary interventions that lower lipoproteins containing apolipoprotein c-iii are more effective in whites than in blacks: Results of the omniheart trial. The American journal of clinical nutrition. 2010; 92:714–722. [PubMed: 20826623]
85. Graham TE. Exercise, postprandial triacylglyceridemia, and cardiovascular disease risk. Canadian journal of applied physiology = Revue canadienne de physiologie appliquee. 2004; 29:781–799. [PubMed: 15630150]
86. Tambalis K, Panagiotakos DB, Kavouras SA, Sidossis LS. Responses of blood lipids to aerobic, resistance, and combined aerobic with resistance exercise training: A systematic review of current evidence. Angiology. 2009; 60:614–632. [PubMed: 18974201]
87. Foster GD, Wyatt HR, Hill JO, Makris AP, Rosenbaum DL, Brill C, Stein RI, Mohammed BS, Miller B, Rader DJ, Zemel B, Wadden TA, Tenhave T, Newcomb CW, Klein S. Weight and

metabolic outcomes after 2 years on a low-carbohydrate versus low-fat diet: A randomized trial. Annals of internal medicine. 2010; 153:147–157. [PubMed: 20679559]

88. Sacks FM, Bray GA, Carey VJ, Smith SR, Ryan DH, Anton SD, McManus K, Champagne CM, Bishop LM, Laranjo N, Leboff MS, Rood JC, de Jonge L, Greenway FL, Loria CM, Obarzanek E, Williamson DA. Comparison of weight-loss diets with different compositions of fat, protein, and carbohydrates. The New England journal of medicine. 2009; 360:859–873. [PubMed: 19246357]
89. Sharma M, Ansari MT, Abou-Setta AM, Soares-Weiser K, Ooi TC, Sears M, Yazdi F, Tsertsvadze A, Moher D. Systematic review: Comparative effectiveness and harms of combination therapy and monotherapy for dyslipidemia. Annals of internal medicine. 2009; 151:622–630. [PubMed: 19884623]
90. Graham DJ, Staffa JA, Shatin D, Andrade SE, Schech SD, La Grenade L, Gurwitz JH, Chan KA, Goodman MJ, Platt R. Incidence of hospitalized rhabdomyolysis in patients treated with lipid-lowering drugs. JAMA : the journal of the American Medical Association. 2004; 292:2585–2590. [PubMed: 15572716]
91. Abourbih S, Filion KB, Joseph L, Schiffrin EL, Rinfret S, Poirier P, Pilote L, Genest J, Eisenberg MJ. Effect of fibrates on lipid profiles and cardiovascular outcomes: A systematic review. The American journal of medicine. 2009; 122:962, e961–968. [PubMed: 19698935]
92. Rubins HB, Robins SJ, Collins D, Fye CL, Anderson JW, Elam MB, Faas FH, Linares E, Schaefer EJ, Schectman G, Wilt TJ, Wittes J. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. Veterans affairs high-density lipoprotein cholesterol intervention trial study group. The New England journal of medicine. 1999; 341:410–418. [PubMed: 10438259]
93. Jun M, Foote C, Lv J, Neal B, Patel A, Nicholls SJ, Grobbee DE, Cass A, Chalmers J, Perkovic V. Effects of fibrates on cardiovascular outcomes: A systematic review and meta-analysis. Lancet. 2010; 375:1875–1884. [PubMed: 20462635]
94. Carlson LA, Bottiger LE. Ischaemic heart-disease in relation to fasting values of plasma triglycerides and cholesterol. Stockholm prospective study. Lancet. 1972; 1:865–868. [PubMed: 4111826]
95. Brown BG, Zhao XQ, Chait A, Fisher LD, Cheung MC, Morse JS, Dowdy AA, Marino EK, Bolson EL, Alaupovic P, Frohlich J, Albers JJ. Simvastatin and niacin, antioxidant vitamins, or the combination for the prevention of coronary disease. The New England journal of medicine. 2001; 345:1583–1592. [PubMed: 11757504]
96. Boden WE, Probstfield JL, Anderson T, Chaitman BR, Desvignes-Nickens P, Koprowicz K, McBride R, Teo K, Weintraub W. Niacin in patients with low hdl cholesterol levels receiving intensive statin therapy. N Engl J Med. 2011; 365:2255–2267. [PubMed: 22085343]
97. Bhardwaj SS, Chalasani N. Lipid-lowering agents that cause drug-induced hepatotoxicity. Clinics in liver disease. 2007; 11:597–613. vii. [PubMed: 17723922]
98. Musa-Veloso K, Binns MA, Kocenas AC, Poon T, Elliot JA, Rice H, Oppedal-Olsen H, Lloyd H, Lemke S. Long-chain omega-3 fatty acids eicosapentaenoic acid and docosahexaenoic acid dose-dependently reduce fasting serum triglycerides. Nutrition reviews. 2010; 68:155–167. [PubMed: 20384846]
99. Harris WS, Ginsberg HN, Arunakul N, Shachter NS, Windsor SL, Adams M, Berglund L, Osmundsen K. Safety and efficacy of omacor in severe hypertriglyceridemia. Journal of cardiovascular risk. 1997; 4:385–391. [PubMed: 9865671]

**Practice points**

- Patients with mild-moderate hypertriglyceridemia should be assessed for cardiovascular risk
- The use of fibrates is recommended in patients with severe or very severe hypertriglyceridemia
- Patients with hypertriglyceridemia should be evaluated for secondary causes
- FCHL is differentiated from FHTG by increased apo B levels and presence of small, dense LDL
- With the exception of apoB or Lp(a) levels, there is limited value of measuring lipoprotein subfractions or heterogeneity

**Research agenda**

- Trials are needed directly comparing the cardiovascular risk associated with fasting vs. non-fasting triglycerides
- The pro-inflammatory action of triglycerides needs to be investigated
- Factors regulating fatty acid oxidation and mitochondrial capacity need to be explored in relation to hypertriglyceridemia
- The importance of ectopic tissue triglyceride accumulation for cardiovascular risk needs to be investigated