Management of Hypertriglyceridemia for Prevention of Atherosclerotic Cardiovascular Disease

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KEYWORDS

• Hypertriglyceridemia • Atherosclerosis • Cardiovascular disease • Triglycerides

KEY POINTS

- Mendelian randomization data strongly suggest that hypertriglyceridemia (HTG) causes atherosclerotic cardiovascular disease (ASCVD), and so triglyceride (TG) level–lowering treatment in HTG is now more strongly recommended to address the residual ASCVD risk than has been the case in (generally earlier) published guidelines.
- Fibrates are the best-established agents for TG level lowering and are generally used as first-line treatment of TG levels greater than 500 mg/dL.
- In addition to better ASCVD evidence, potential advantages of omega-3 compared with fenofibrate include that it is a natural product, it lacks any associated myopathy, and it might provide antiinflammatory, mood, cognitive, or other benefits.
- Statins are the best-established agents for ASCVD prevention, and so are usually used as first-line treatment of TG levels less than 500 mg/dL.

EPIDEMIOLOGY AND PATHOPHYSIOLOGY OF HYPERTRIGLYCERIDEMIA

About 40 million US adults have hypertriglyceridemia (HTG), defined as a fasting triglyceride (TG) level more than 200 mg/dL. Of these, about 36 million have a TG level of 200 to 500 mg/dL and about 4 million have a TG level greater than 500 mg/dL.[1] Thus, moderate HTG is common, and very high TG level (>500 mg/dL) is more common than numerically similar cholesterol level increases. Further, the prevalence of HTG has increased several-fold over the past few decades.[2,3] This increase is coincident with, and most likely largely driven by, increasing obesity.[4] Although there is some controversy regarding categorization of HTG, most categories have a reasonable consensus, as noted in **Table 1**.

Increase of plasma TG level is related to an excess of one or more of the 3 main types of TG-rich lipoproteins: (1) chylomicrons, (2) very-low-density lipoprotein (VLDL), or (3) intermediate-density lipoprotein (IDL). In the case of chylomicronemia, TG levels usually exceed about 800 mg/dL and may be 10,000 mg/dL or higher.[5] The underlying cause is decreased lipolysis of TG in plasma caused by decreased (or absent) activity of lipoprotein lipase (LPL) in the vascular endothelium. Decreased TG lipolysis also tends to increase the TG content of VLDL and all other TG-rich lipoproteins, but decreased lipolysis has the greatest effect on chylomicrons because they have the greatest TG content. Because the TG/cholesterol ratio in chylomicrons is generally about 10:1, the plasma TG level is usually close to 10-fold higher than the plasma cholesterol level. Nevertheless, the total cholesterol level can

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Table 1
Categorization of HTG

TG Range (mg/dL)	NCEP ATP-III 2004[1]	AHA Statement 2011[2]	Disease Risk	FDA Approval
<100	Desirable	Optimal	None	No apparent interest
<150		Normal	Dyslipidemia	
150–199	Borderline high	Borderline	More dyslipidemia	
200–499	High	High	↑CVD	Approve if ↓CVD likely
≥500	Very high	Very high	↑CVD and ↑pancreatitis (especially ↑if >2000 mg/dL)	Approve if reasonable safety

Abbreviations: AHA, American Heart Association; CVD, cardiovascular disease; FDA, US Food and Drug Administration; NCEP ATP-III, Third Adult Treatment Panel of the National Cholesterol Education Program.

far exceed 200 mg/dL in severe chylomicronemia, and so clinicians must always remember to look for severe HTG as a possible hidden cause of hypercholesterolemia.[6] Familial chylomicronemia classically is caused by homozygous deficiency of LPL but is more commonly caused by a combination of other genetic factors, such as absence or severe functional defects in the function of LPL-related factors, such as apolipoproteins C-II, C-III, and V; lipase maturation factor-1; and angiopoietinlike proteins 3, 4, and 8.[5,7] Environmental factors such as central obesity, insulin resistance, and diabetes mellitus can also play important contributory roles in decreasing LPL activity sufficient to cause chylomicronemia, with or without identifiable genetic abnormalities.[5]

In increased VLDL levels, by far the most common type of moderate HTG, the primary cause seems to be hepatic overproduction of VLDL. Two terms for increased VLDL levels are found in the scientific literature but do not seem to be clinically useful. Familial combined hyperlipoproteinemia (FCHL) is a term that has been used for moderate HTG presenting with or without increased cholesterol levels (or even as high cholesterol with normal TG), depending on environmental factors.[8] Familial HTG (FHTG) has been said always to present without hypercholesterolemia and to carry no increased risk of atherosclerotic cardiovascular disease (ASCVD),[9] whereas FCHL was said to increase ASCVD considerably.[8] However, subsequent research has not clearly sustained the original proposed distinctions between FCHL and FHTG, so there is little clinical impetus at present for distinguishing between them. A family history of ASCVD and the presence of hypercholesterolemia added to hypertriglyceridemia increase ASCVD risk, but pure HTG also carries excess risk, even in the absence of a clearly positive family history. Thus, efforts to make the distinction between FCHL and FHTG are probably not clinically beneficial, and treatment should instead be directed according to lipid levels and other standard risk factors.

Increased IDL levels seem to be caused primarily by reduced hepatic clearance of IDL particles caused by impaired binding to the apolipoprotein (apo) B/E receptor. Although IDL levels should be increased with any loss of apo B/E receptor activity, such as familial hypercholesterolemia (which primarily involves decreased low-density lipoprotein [LDL] clearance), in some cases IDL clearance is selectively impaired. This condition is familial dysbetalipoproteinemia (sometimes referred to as type III disease), which is well documented to carry a high risk of ASCVD, beyond that expected from the moderately increased plasma TG levels.[10] It has been thought that dysbetalipoproteinemia is rare, occurring in only 1 in 10,000 in the general population and it has also been thought to require apo E2 homozygosity plus another, as yet unspecified metabolic defect.[10] However, recent studies have shown that apo E2 homozygosity is present only in a small minority of cases and that familial dysbetalipoproteinemia may affect as many as 1 in 200 of the general population.[11,12] However, it is difficult to diagnose dysbetalipoproteinemia. Suspicion of the existence of this disorder should be increased in the presence of roughly equally increased TG and TG levels, both within the range of 150 to 500 mg/dL, in an adult man or postmenopausal woman (uncommon in other demographics), especially if an ASCVD event has already occurred. Presence of palmar xanthomas (orange-yellow color in the palmar creases) is pathognomonic but often absent. The diagnoses can be made by one of several special tests: (1) confirming VLDL cholesterol (VLDL-C) enrichment (documented as a VLDL-C/plasma TG ratio >0.3 by beta-quantification), (2) a broad beta band on lipoprotein electrophoresis, (3) increased IDL levels by density gradient ultracentrifugation or nuclear magnetic resonance, or (4)