REVIEW

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Demystifying triglycerides: A practical approach for the clinician

ABSTRACT

Because the landmark trials of lipid-lowering statin drugs excluded patients with very high triglyceride levels, the optimal management of hypertriglyceridemia for atherosclerosis prevention is unknown. The third report of the National Cholesterol Education Program's Adult Treatment Panel (ATP-III) provides a much-needed strategy for managing patients with high triglycerides, based on the best available evidence.

KEY POINTS

A normal fasting triglyceride level is less than 150 mg/dL. Patients with borderline elevated levels (≥ 150 mg/dL) should be evaluated for other elements of the metabolic syndrome. Hypertriglyceridemia is defined as a concentration higher than 200 mg/dL.

For patients with hypertriglyceridemia, the first priority is to meet their goal serum concentration of low-density lipoprotein cholesterol; the second priority is to reach the goal for non-high-density lipoprotein cholesterol.

Patients with a serum triglyceride level of 1,000 mg/dL or more are at risk for acute pancreatitis and should be treated specifically to lower triglyceride levels.

Improving lifestyle—weight loss, decreased consumption of carbohydrates and alcohol, and exercise—can substantially lower serum triglyceride levels.

Fibrates are the most potent triglyceride-lowering drugs, followed by niacin, fish oil, and statins.

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DECIDING WHEN AND HOW to treat hypertriglyceridemia is difficult and complex, for several reasons.

For one thing, elevated triglycerides do not always lead to coronary heart disease, because the risk depends on the type of lipoproteins the triglycerides are packaged in. Different causes of hypertriglyceridemia produce different lipoprotein patterns, with distinct complications.

Furthermore, because the landmark trials of lipid-lowering statin drugs excluded patients with very high triglyceride levels, the optimal management of hypertriglyceridemia for atherosclerosis prevention is unknown.

Despite the uncertainties, the third report of the National Cholesterol Education Program's Adult Treatment Panel (ATP-III), published in 2002, provides a practical framework for approaching hypertriglyceridemia[1] and cites three key reasons clinicians should not ignore the condition:

- It is a marker for atherogenic lipoproteins
- It is a marker for the metabolic syndrome
- A very high level (≥ 1,000 mg/dL) is a risk factor for pancreatitis.

We review the physiology and causes of hypertriglyceridemia, discuss the literature that pertains to its treatment, and provide a practical management strategy adapted from the ATP-III report.

TRIGLYCERIDES AND HEART RISK

The association between triglyceride concentration and heart disease risk is confounded by a tight association with other lipid and metabolic abnormalities. Further, some causes of hypertriglyceridemia have no apparent effect

on atherosclerotic vascular disease, making it difficult to prove that elevated triglycerides are a risk factor for it.

Assman et al[2] found that the risk of nonfatal myocardial infarction and sudden cardiac death rose with triglyceride levels up to 800 mg/dL, but fell off at higher levels. Two meta-analyses found that triglycerides are an independent risk factor for coronary heart disease.[3,4] The relationship with cerebrovascular events is much less certain.[5]

The pattern of high serum triglycerides, low HDL-C, and small, dense LDL is variously known as the lipid triad, diabetic dyslipidemia, and atherogenic dyslipidemia (the ATP-III's preferred term). The pattern is strongly associated with insulin-resistant states such as the metabolic syndrome, polycystic ovary syndrome, and type 2 diabetes, and is an important risk factor for premature atherosclerosis.

TRIGLYCERIDES ARE PACKAGED IN LIPOPROTEINS

The risk depends on the type of lipoproteins the triglycerides are packaged in

In the blood, triglycerides are carried inside five different types of lipoproteins, which vary in their triglyceride content:

- Chylomicrons: 85% to 90% triglycerides
- Very-low-density lipoproteins (VLDL): 50% to 60%
- Intermediate-density lipoproteins (IDL): 20% to 25%
- Low-density lipoproteins (LDL): ≤ 10%
- High-density lipoproteins (HDL): ≤ 10%.

Thus, chylomicrons and VLDL are the primary triglyceride-rich lipoproteins.

Chylomicrons are produced in the gut epithelium from dietary fat: long-chain fatty acids are assembled into triglycerides, and with the help of microsomal transfer protein, combine with dietary cholesterol, proteins (especially apolipoprotein B-48 [apo B-48]), and phospholipids to form chylomicrons (FIGURE 1).

Chylomicrons travel through the lymphatic system to the thoracic duct and enter the circulation, where they interact with lipoprotein lipase, an enzyme attached to the capillary endothelial cells in muscle and adipose tissue. Lipoprotein lipase is activated by apo C-II on the chylomicron surface, cleaving the chylomicron's triglyceride core and releasing free fatty acids, which can be oxidized by muscle for energy or kept in adipose tissue for future use.

Chylomicrons are not known to be atherogenic, perhaps because they are too large to infiltrate the vascular endothelium. However, after most of the triglyceride core is depleted, the remains of the chylomicron break free from the lipoprotein lipase. These compacted chylomicron remnants are drained of much of their triglycerides but retain apo B-48, apo E, and most of the dietary cholesterol. These remnants *are* atherogenic, perhaps because they are small enough to infiltrate artery walls, or perhaps because they can bind to specific sites on macrophages and stimulate their conversion to foam cells.[6]

Ultimately, apo E on the surface of a remnant particle binds to an LDL receptor (or the LDL receptor-related protein) in the liver, and the remnant is removed from circulation.

VLDL particles are smaller and denser than chylomicrons. They are produced in the liver from hepatic triglycerides and cholesterol and bear apo B-100 from hepatic cells in a process requiring microsomal transfer protein. When a VLDL particle is released into the circulation, it incorporates apo C and apo E handed off from other lipoproteins, particularly HDL.

Like chylomicrons, VLDL particles are captured in muscle and adipose tissue by lipoprotein lipase, which cleaves the triglyceride core. Once the core is mostly depleted of triglycerides, the complex is freed from the lipoprotein lipase. The VLDL remnants, also known as intermediate-density lipoproteins (IDLs), can be catabolized by receptors in the liver, mediated by apo E. Alternatively, the IDL may escape catabolism to be further processed into LDL in the circulation by hepatic lipase.

CAUSES OF HYPERTRIGLYCERIDEMIA

Hypertriglyceridemia can arise in many ways. The most important distinction to make is whether it is primary or secondary.

Primary causes

The primary causes are familial syndromes, which tend to be more severe than secondary

Triglycerides and atherosclerosis

Triglycerides are carried inside five different types of lipoproteins, but two of these—chylomicrons and very-low-density lipoproteins (VLDL)—are the primary triglyceride-rich lipoproteins. Chylomicrons are not atherogenic; VLDL probably is atherogenic. Both types of particles become more atherogenic as they are metabolized into smaller particles.

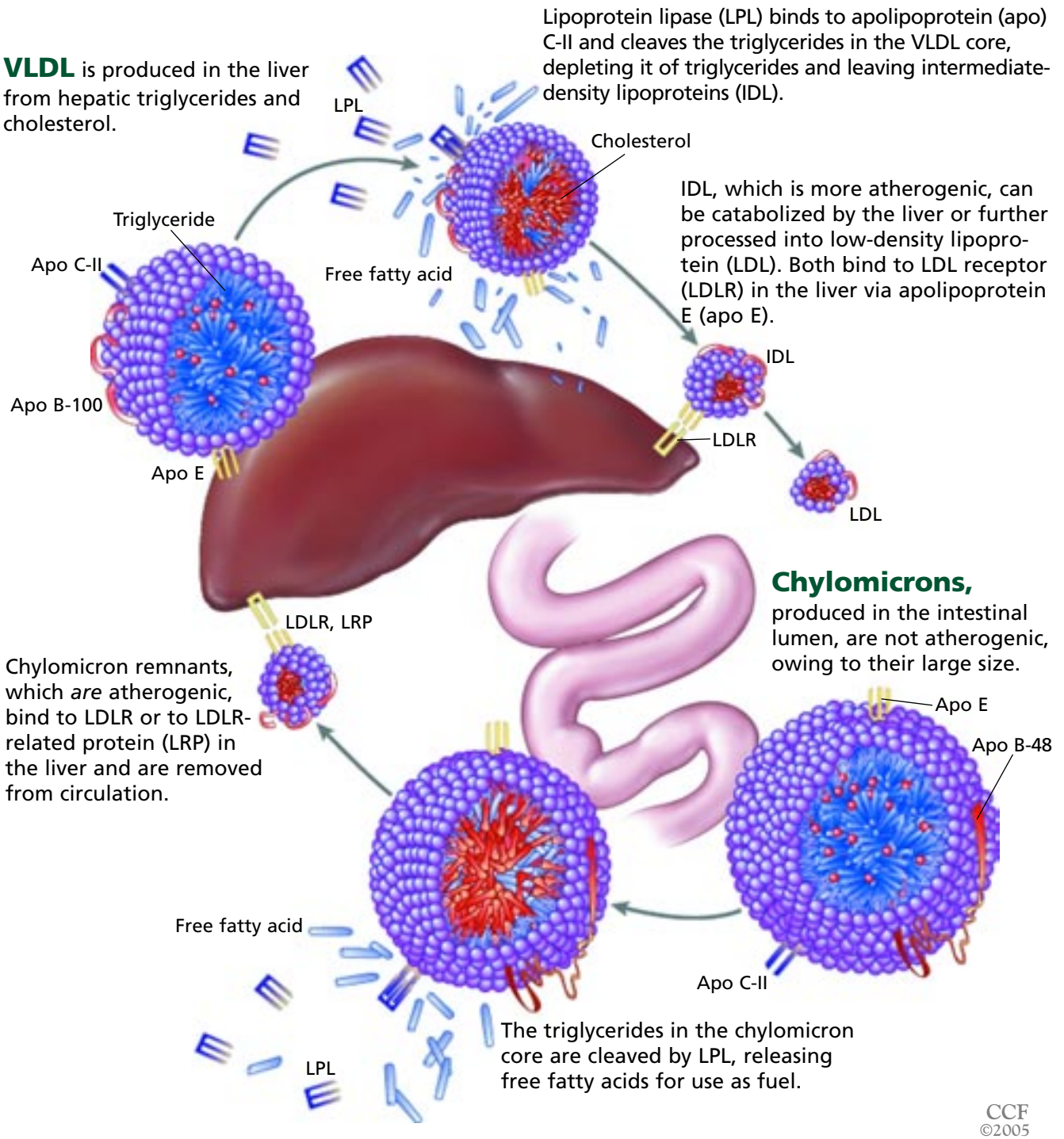

FIGURE 1

triglyceridemia and require drug treatment.

Familial combined hyperlipidemia (type IIb hyperlipoproteinemia), the most common heritable cause of hypertriglyceridemia, occurs in about 1 in 200 people.

Patients usually have a family history of mixed dyslipidemia, with high levels of LDL-C, VLDL-C, and apo B. The high level of apo B distinguishes familial combined hyperlipidemia from familial hypertriglyceridemia. Serum triglyceride levels typically range from 150 mg/dL to 500 mg/dL.

Statins are the best initial choice for treating this condition because the lipid triad is associated with an exceptionally high atherosclerosis risk. However, optimal control often requires combining a statin with niacin or a fibrate.

Familial dysbetalipoproteinemia (a form of type III hyperlipoproteinemia) usually results from a homozygous defect in apo E that weakens the binding of remnant lipoproteins to lipoprotein receptors and impairs their catabolism. This causes an excess of chylomicron and VLDL remnants.

Patients frequently have tuberoeruptive and palmar xanthomas as well as premature cardiovascular disease. The condition is often not fully expressed unless another condition is also present, most commonly alcohol use, hypothyroidism, obesity, diabetes, or renal disease.

If the triglyceride level is > 400 mg/dL, the LDL-C level must be directly measured, not calculated

The levels of triglycerides and total cholesterol are often elevated to the same degree, especially when measured in mmol/L. The serum HDL cholesterol (HDL-C) concentration is typically normal. To help diagnose familial dysbetalipoproteinemia, levels of VLDL-C and triglycerides after ultracentrifugation should be compared. A ratio of VLDL-C to triglycerides greater than 0.3 indicates an enriched cholesterol content of the VLDL and strongly suggests the condition. Although most laboratories use the Friedewald equation for estimating LDL-C (LDL-C = total cholesterol minus [triglycerides/5]), this estimate is invalid in familial dysbetalipoproteinemia and should never be used clinically. LDL-C must be measured directly in these patients.

Most patients with familial dysbetalipoproteinemia require drug therapy.

Familial hypertriglyceridemia is commonly seen in general practice. Patients usually have a family history of isolated hypertriglyceridemia.

The most common blood lipid pattern is that of type IV hyperlipoproteinemia: high VLDL cholesterol (VLDL-C) but normal LDL cholesterol (LDL-C) concentrations. However, some patients have increased chylomicrons in addition to high VLDL-C, similar to the type V hyperlipoproteinemia pattern.

Like type V hyperlipoproteinemia and familial combined hyperlipidemia, (see below) familial hypertriglyceridemia, is commonly associated with insulin resistance. The serum triglyceride level is typically 250 to 1,000 mg/dL, although chylomicronemia may cause the triglyceride level to rise higher. If the level of apo B is also high, the condition is probably familial combined hyperlipidemia instead.

The condition is exacerbated by frequent alcohol use and sometimes leads to early cardiovascular disease.

Familial hypertriglyceridemia with chylomicronemia (type V hyperlipoproteinemia), which presents in adults, is often considered a rare subset of familial hypertriglyceridemia. Triglyceride levels are above 1,000 mg/dL, leading to xanthomas and a high risk of pancreatitis. As with familial hypertriglyceridemia, patients have increased VLDL, but chylomicrons are also markedly elevated.

This disorder is associated with insulin resistance, obesity, and other secondary causes of hypertriglyceridemia. Patients should lose weight, limit dietary fat and simple carbohydrates, and begin drug treatment if serum triglyceride levels persistently exceed 1,000 mg/dL.

Familial chylomicronemia (a form of type I hyperlipoproteinemia) is a very rare condition. Serum triglycerides levels are extremely high from birth (1,000–10,000 mg/dL) because of excess chylomicrons, due to either a defect in lipoprotein lipase, or rarely, its cofactor apo C-II.

Patients present with eruptive xanthomas and recurrent pancreatitis, frequently in childhood, but do not usually develop premature atherosclerosis. Patients should be evaluated by a lipid specialist. The condition usually responds to severely limiting dietary fat, and in some cases, taking fish oil.

Secondary causes

Secondary causes of hypertriglyceridemia (TABLE 1) are more common than the primary ones.

Hypertriglyceridemia increasingly results from the "atherogenic lifestyle," ie, an unhealthy diet, lack of exercise, and drinking too much alcohol. Over time, these indulgences may lead to obesity and insulin resistance, and later, diabetes and coronary heart disease, and they probably explain much of the increase in the metabolic syndrome worldwide.

Excessive calories stimulate hepatic VLDL production resulting in increased triglycerides, and in many cases, low HDL and small, dense LDL. Moreover, excessive consumption of saturated fat and cholesterol may impair hepatic LDL-receptor activity, which can increase LDL independently of the triglyceride changes.

Though regular alcohol use increases lipids in most people, its effects are highly variable. Triglycerides are affected more than HDL or LDL, since alcohol promotes VLDL production by the liver. This is probably because ethanol inhibits the oxidation of free fatty acids, leaving more substrate available for VLDL synthesis. If the atherogenic lifestyle results in insulin resistance, then the potential for hypertriglyceridemia is even higher. This state impairs the activity of lipoprotein lipase, disrupting the catabolism of both chylomicrons and VLDL.

Renal disease may increase triglycerides through impaired clearance of chylomicron and VLDL remnants.

Hypothyroidism can also raise triglycerides indirectly, by downregulating the LDL receptor.

TABLE 1

Secondary causes of hypertriglyceridemia

Lifestyle factors
- Physical inactivity
- High carbohydrate intake (> 60% of energy intake)
- Excessive alcohol intake

Diseases and conditions
- Obesity or overweight
- Metabolic syndrome
- Type 2 diabetes mellitus
- Nephrotic syndrome
- Chronic kidney disease
- Chronic renal failure
- Cushing syndrome
- Hypothyroidism
- Pregnancy

Medications
- Estrogen replacement therapy
- Oral contraceptives
- Tamoxifen
- Corticosteroids
- Beta-blockers
- Thiazide diuretics
- Retinoids
- Protease inhibitors for HIV
- Atypical antipsychotics (chlorpromazine, clozapine, fluperlapine, olanzapine perphenazine, risperidone)
- Immunosuppressants

SCREENING FOR HYPERTRIGLYCERIDEMIA

The ATP-III recommends that all adults be screened with a lipid panel that includes total cholesterol, LDL-C, HDL-C, and triglycerides, starting at age 20. Those at low risk for atherosclerosis should have a repeat panel every 5 years; those with multiple risk factors should be checked more often.

It is strongly preferred that the patient fast for 9 to 12 hours before screening. However, for people at low risk (0–1 risk factors), the ATP-III allows nonfasting screening, followed by a fasting lipid panel if the results warrant it (HDL-C < 40 mg/dL or total cholesterol ≥ 200 mg/dL). Patients with two or more risk factors should always be screened with a fasting lipid panel.

All adults should have a lipid panel every 5 years starting at age 20

Many conditions can bias the results, such as acute illness or infection, cerebrovascular accidents, trauma, surgery, pregnancy, dietary changes, and weight loss.

TREATMENT GOALS

For most patients with hypertriglyceridemia, the ATP-III emphasizes LDL-C as the primary focus of treatment and non-HDL-C as a secondary focus. The non-HDL-C level is the total cholesterol level minus the HDL-C level. It is useful because it is a single value that incorporates all the atherogenic lipoproteins (ie, LDL, VLDL, and remnant lipoproteins). The non-HDL-C goal is determined by adding 30 mg/dL to the patient's LDL-C goal. Most patients with high triglycerides will have other components of the metabolic syndrome (TABLE 2) and insulin

TABLE 2

The metabolic syndrome

Three or more risk factors must be present

RISK FACTOR	DEFINING LEVEL
Abdominal obesity	Waist circumference
Men	> 40 inches
Women	> 35 inches
Serum triglyceride level	≥ 150 mg/dL
Serum high-density lipoprotein cholesterol level	
Men	< 40 mg/dL
Women	< 50 mg/dL
Blood pressure	≥ 130/85 mm Hg
Fasting glucose level	≥ 110 mg/dL*

*The American Diabetes Association recently lowered its recommended cutoff for an impaired fasting glucose level to 100 mg/dL.[7] Although the third National Cholesterol Education Program Adult Treatment Panel (ATP-III) has not formally adopted this change, a smaller consensus conference led by the ATP-III chairman[8] released a joint statement from the National Heart, Lung, and Blood Institute, the American Heart Association, and the American Diabetes Association endorsing the stricter definition as a component of the metabolic syndrome and sanctioning the optional use of an impaired glucose tolerance test instead of an impaired fasting glucose level.

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resistance.[9] Metabolic syndrome should be diagnosed and treated accordingly.

Borderline high triglycerides (150–199 mg/dL)

Patients with borderline high triglycerides should be evaluated for the metabolic syndrome (TABLE 2),[1,7,8] a serious condition that is easily overlooked but can lead to atherosclerosis and diabetes.

High triglycerides (200–499 mg/dL)

In this category, the LDL-C and non-HDL-C levels should be targets of therapy. If the serum triglyceride level exceeds 400 mg/dL, the serum LDL-C level cannot be calculated and must be directly measured.

Very high triglycerides (≥ 500 mg/dL)

The ATP-III advises that the primary goal for this group is to lower serum triglyceride levels. In patients at risk for atherosclerosis, a secondary goal is to lower the LDL-C level. Patients with a serum triglyceride level above 1,000 mg/dL have a high risk of pancreatitis and should always be treated to lower triglyceride levels. The ATP-III suggests that a level over 2,000 mg/dL should prompt urgent treatment.

BENEFIT OF LOWERING TRIGLYCERIDES

Most trials of lipid-lowering therapy were in patients with coronary heart disease who had cholesterol abnormalities, and they often excluded patients with triglyceride levels over 300 mg/dL. Extending the conclusions from such studies to patients with hypertriglyceridemia is fraught with error. However, some trials reported post hoc exploratory analyses of subgroups of patients with hypertriglyceridemia (TABLE 3). We have arranged the discussion from strongest to weakest outcome evidence.

Mortality in patients with high cholesterol

The ultimate goal of atherosclerosis prevention is to reduce mortality: a treatment could possibly decrease the rate of major coronary events yet increase all-cause mortality.[10] Two lipid-altering strategies reduce mortality: statin monotherapy[11] and combination therapy with niacin and clofibrate.[12] Additionally, niacin monotherapy has been shown to lower 15-year mortality rates,[13] but not 6-year rates.[14]

No fibrate reduces all-cause mortality. One trial actually found a highly significant increase in all-cause mortality with clofibrate monotherapy,[10] and another trial found a statistically insignificant increase in all-cause mortality in patients taking gemfibrozil.[15] The Fibrate Consensus Group expressed concern about the excess mortality in the fibrate groups in these trials, though neither trial was designed to evaluate mortality.[16] Subsequently, another large trial found a statistically insignificant reduction in all-cause mortality in patients with coronary heart disease treated with gemfibrozil.[17]

Coronary events in patients with high cholesterol

Large trials support the use of statins,[11] fibrates,[17] niacin,[14] and combined niacin and fibrate[12] to reduce major coronary heart disease events in patients with high cholesterol.

TABLE 3

Selected outcome trials of potential triglyceride-lowering drug strategies

TRIAL (TREATMENT)	EVENTS	EVENTS/1,000 PERSON-YEARS*		RELATIVE RISK REDUCTION	NO. NEEDED TO TREAT
		CONTROL	TREATMENT		
HPS (statin)[11]					
Entire cohort	Total mortality	29	26	12%	57
Entire cohort	Nonfatal MI or fatal CHD	24	18	26%	33
Triglycerides < 177 mg/dL	First MI, CVA, revascularization	48	37	23%	18
Triglycerides 177–353 mg/dL	First MI, CVA, revascularization	55	43	21%	18
Triglycerides ≥ 354 mg/dL	First MI, CVA, revascularization	54	47	14%	26
VA-HIT (fibrate)[17]					
Entire cohort	Total mortality	34	31	NS	NS
Entire cohort	Nonfatal MI or fatal CHD	43	34	20%	23
Triglycerides < 151 mg/dL	Nonfatal MI, fatal CHD, CVA	48	37	23%	18
Triglycerides 151–300 mg/dL	Nonfatal MI, fatal CHD, CVA	52	39	25%	15
CDP (niacin)[14]					
Entire cohort	Total mortality (6 years)	43	41	NS	NS
Entire cohort	Total mortality (15 years)	39	35	11%	16
Entire cohort	Nonfatal MI or fatal CHD (6 years)	50	43	15%	23
Triglycerides < 150 mg/dL	Total mortality (15 years)	38	35	10%	18
Triglycerides ≥ 150	Total mortality (15 years)	39	35	12%	14
SIHD-SPS (niacin + fibrate)[13]					
Entire cohort	Total mortality	59	44	26%	13
Entire cohort	Nonfatal MI or fatal CHD	77	57	25%	10
Triglycerides ≥ 133	Fatal CHD	55	32	42%	9
Triglycerides increased	Fatal CHD	53	49	7%	51
Triglycerides fell 0–29%	Fatal CHD	53	42	20%	19
Triglycerides fell ≥ 30%	Fatal CHD	53	20	63%	6

MI = myocardial infarction, CHD = coronary heart disease, CVA = cerebrovascular accident
HPS = Heart Protection Study: 20,536 men and women with CHD, other occlusive atherosclerosis, or diabetes, randomized to placebo or simvastatin, followed for 5 years; average baseline triglyceride level 186 mg/dL, no exclusion criteria imposed for triglycerides
VA-HIT = Veterans Administration HDL-C Intervention Trial: 2,531 men with CHD, low HDL, and low LDL, randomized to placebo or gemfibrozil, followed for 5.1 years; average baseline triglyceride level 160 mg/dL; excluded patients with triglyceride levels > 300 mg/dL
CDP = Coronary Drug Project: 3,908 male MI survivors, randomized to placebo or niacin, followed for 6 years. Though the difference in mortality was not statistically different at 6 years, 15-year follow-up showed benefit despite cessation of niacin at 6 years. In niacin group, average triglyceride level 192 mg/dL; no exclusion criteria imposed for triglycerides
SIHD-SPS = Stockholm Ischaemic Heart Disease Secondary Prevention Study: 555 MI survivors randomized to open-label niacin combined with clofibrate vs no treatment, followed for 5 years; average triglyceride level was 209 mg/dL
Three types of data are presented for each trial: total mortality, major CHD events, and post hoc exploratory analyses of subgroups with elevated triglycerides. Since many factors bias subgroup analyses, results in hypertriglyceridemic subjects must be interpreted with caution.

Coronary events in subgroups with high triglycerides

The Coronary Drug Project[14] enrolled patients with coronary heart disease, many of whom had hypertriglyceridemia. In the niacin group, the average baseline serum triglyceride level was 192 mg/dL, and almost one fifth of the patients had at least 240 mg/dL.

In the subgroup with triglyceride levels of 150 mg/dL or higher, niacin led to a significant 12% reduction in all-cause mortality (number needed to treat [NNT] 14; z –2.85). Subjects with lower triglyceride levels had an insignificant reduction (10%; NNT 18, z –2.13).[13]

A strong case can be made for extending these results to patients with hypertriglyceridemia.

The Stockholm Ischaemic Heart Disease Secondary Prevention Study (SIHD-SPS)[12] enrolled patients with coronary heart disease regardless of their triglyceride levels. Half of the patients had hypertriglyceridemia (average 209 mg/dL), while only 13% had hypercholesterolemia. Patients were given open-label niacin combined with clofibrate.

Among patients with triglycerides over

133 mg/dL, the combination led to a 42% lower incidence of fatal coronary heart disease (NNT 9), whereas patients with lower triglyceride levels had a 13% lower rate (NNT 33). The authors concluded that the drug combination helped only those with higher triglycerides.[12]

A post-hoc analysis suggested that benefits depended on successfully lowering triglycerides. In treated subjects whose triglyceride level fell more than 30%, the incidence of fatal coronary heart disease was 63% lower (NNT 6).

Assuming that modern fibrates are at least as effective as clofibrate, a strong case can be made for offering this combination to other patients with hypertriglyceridemia.

Whitney et al,[18] in a small angiographic study, found that coronary plaque was arrested in patients taking niacin with gemfibrozil but progressed in patients taking placebo. Treated patients also had 52% fewer events (NNT 7). This study suggests that this newer fibrate can also be used with niacin to reduce atherosclerosis and cardiovascular events.

The Heart Protection Study[11] enrolled a high-risk population without exclusion criteria for triglyceride levels. The average nonfasting triglyceride level was 186 mg/dL. Patients received either simvastatin or placebo.

In the 1,600 patients with triglyceride levels greater than 354 mg/dL, 14% fewer events occurred with simvastatin than with placebo (NNT 26) However, the 95% confidence interval was wide and the upper limit was 1.0. Treated patients with triglyceride levels lower than 177 mg/dL had 23% fewer events vs placebo (NNT 18).

A tentative case can be made for extending these results to patients with hypertriglyceridemia.

The Veterans Affairs HDL-C Intervention Trial[17] enrolled patients with coronary heart disease who had low serum HDL-C and LDL-C levels, and restricted subjects with hypertriglyceridemia to those with levels below 300 mg/dL (average 160 mg/dL). Patients were treated with gemfibrozil or placebo.

In the 1,185 patients with elevated triglyceride levels (151–300 mg/dL), there were 25% fewer events with gemfibrozil than with placebo (NNT 15), and patients with normal triglyceride levels (≤ 150 mg/dL) had 23% fewer events with gemfibrozil (NNT 18).

Since most patients with hypertriglyceridemia have low HDL-C, a case can be made for extending these results to those with serum triglyceride levels less than or equal to 300 mg/dL. It is uncertain if this is relevant for patients with higher triglyceride levels.

TREATMENT

Treatment for hypertriglyceridemia depends on the cause, the severity, and which lipoproteins are elevated (TABLE 4).

Nonpharmacologic approaches

Triglycerides respond particularly well to lifestyle changes, which should always play a prominent role in therapy. Patients with borderline or even high levels can sometimes achieve impressive reductions with such efforts alone. Men may be able to improve their lipid levels better than women with comparable efforts.[19] In general, the more severe the case, the less time one can allow the patient to try vigorous lifestyle changes before adding drug therapy.

Men may be able to lower their triglycerides more than women

Encourage weight loss. Obesity is increasingly seen in patients with hypertriglyceridemia, with or without the metabolic syndrome and insulin resistance. Loss of as little as 10 pounds typically lowers triglyceride levels.

Reducing carbohydrates may help. Recent studies in obese patients found that low-carbohydrate diets lowered triglyceride levels 20%[20] and 28%,[21] and that weight loss and assignment to a low-carbohydrate diet independently predicted lower triglycerides.[20]

Decrease alcohol consumption. Alcohol stimulates VLDL production and perhaps further impairs defective clearance of triglyceride-enriched lipoproteins.

Exercise. Brisk walking most days of the week may lower triglyceride levels.

Control diabetes. Tighter control of diabetes by lifestyle changes, increasing the dosage of antidiabetic medication, or adding new agents may help to lower triglyceride levels.

Alter other medications. Patients taking medications for other conditions may be able

TABLE 4

A focused approach for treating hypertriglyceridemia

Normal serum triglyceride level: < 150 mg/dL
- Primary goal: lower low-density lipoprotein cholesterol (LDL-C)
- No specific intervention for triglycerides

Borderline-high serum triglyceride level: 150 to 199 mg/dL
- Primary goal: lower LDL-C
- Interventions: modify lifestyle (weight loss, exercise, reduce alcohol, reduce carbohydrate intake to < 60% of calories)
- Evaluate for metabolic syndrome

High serum triglyceride level: 200 to 499 mg/dL
- Primary goal: lower LDL-C
- Secondary goal: lower non-high-density lipoprotein cholesterol (non-HDL-C)
- Modify lifestyle
- Evaluate for metabolic syndrome
- Consider drug therapy to achieve LDL-C and non-HDL-C goals
  - (statin, fibrate, niacin, high-dose statin monotherapy, moderate-dose statin plus fibrate, moderate-dose statin plus niacin)

Very high serum triglyceride level: 500 to 999 mg/dL
- Primary goal: lower serum triglyceride level
  - Modify lifestyle
  - Fish oil
  - Triglyceride-lowering medications
    - Most effective: fibrates, niacin
    - Less effective: statins
    - Contraindicated: bile acid resins
- Secondary goal: Prevent coronary heart disease (CHD)
  - Benefit of drug therapy for CHD prevention unknown in patients with very high triglycerides
  - When serum triglyceride level drops below 500 mg/dL, re-evaluate LDL-C-lowering efforts

Extremely high serum triglyceride level: ≥ 1,000 mg/dL
- Primary goal: lower serum triglyceride level to prevent pancreatitis
- Secondary goal: Prevent coronary heart disease
  - Modify lifestyle: abstain from alcohol, institute very low-fat diet (≤ 15% of calories)
  - Triglyceride-lowering medications: fibrates, niacin, fish oil, statins

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to switch or discontinue a drug that exacerbates hypertriglyceridemia. Many drugs worsen hypertriglyceridemia by various mechanisms, frequently via insulin resistance (TABLE 1). However, beta-blockers and thiazides need not be withheld if the patient has a condition in which these drugs offer a well-established benefit, such as a beta-blocker for a patient who has had a myocardial infarction.[1]

Relationship to the metabolic syndrome

Much of the mild hypertriglyceridemia seen in general practice is an expression of the metabolic syndrome, which often progresses to diabetes and atherosclerosis. Lifestyle changes offer considerable potential to ward off further disease.

In two large trials of patients with glucose intolerance,[22,23] intense lifestyle changes decreased progression to diabetes by almost 60%. One trial[23] reported an 18% decline in serum triglyceride levels with lifestyle changes.

In our practice, we incorporate visits to a nutritionist and recommend that, if possible, patients use a personal trainer to help motivate regular exercise. We find it very helpful if physicians and their staff encourage patients and praise them often for even small successes.

Drug treatment of hypertriglyceridemia

Patients whose hypertriglyceridemia is strongly genetically determined are much more likely to need drug therapy. Treatment is complex because different drugs influence triglyceride levels to different degrees, and because the goal of therapy may be to reduce the risk of

TABLE 5

Tips to limit flushing for patients taking niacin

Use an extended-release or slow-release formulation.
Start at a low dose and titrate slowly. For instance, when using Niaspan, start with 500 mg at bedtime for 1 month, then increase to 1,000 mg at bedtime for 1 month and then recheck serum lipid levels and liver function tests. If further lipid-lowering is needed, increase to 1,500 mg at bedtime for 1 month, then 2,000 mg at bedtime. Recheck serum lipid levels and liver function tests.
Advise patient to take aspirin 1/2 hour before the niacin dose, or take aspirin and niacin simultaneously.
Switch to a chewable or other noncoated aspirin as tolerated.
Any nonsteroidal anti-inflammatory drug can prevent or abort flushing.
Advise patient to eat a low-fat snack before taking niacin.
Advise patient to avoid alcohol and spicy foods prior to dosing.

developing either atherosclerosis or pancreatitis. Several medications influence triglyceride levels.

Fibrates can reduce triglyceride levels by 25% to 50%,[1] or even more in severe hypertriglyceridemia. The maximum dose of gemfibrozil is 600 mg twice a day. Fenofibrate lowers triglycerides at least as well as gemfibrozil,[24–26] and may lower LDL-C more.[24,26] Fenofibrate may also interact less with other medications, especially statins.[27–29] The maximum dosage of micronized fenofibrate depends on the brand because of differences in formulation.

Fibrates can lower triglycerides by up to 50%

Niacin reduces triglyceride levels by 20% to 40%.[1] For patients who are close to their serum LDL-C goal, niacin monotherapy sometimes helps achieve both the LDL-C and non-HDL-C goals, although it is not as effective as statins at lowering serum LDL-C levels. Although niacin lowers LDL-C only modestly, it usually raises serum HDL-C levels substantially. Niacin has recently been extensively reviewed by McKenney.[30,31]

Although the makers of niacin tout various pros and cons of the different forms, there are few good head-to-head comparison studies to substantiate claims. In practice, we are most comfortable with the extended-release formulation (Niaspan) approved by the US Food and Drug Administration (FDA) because of its daily dosing, manageable side effects, and excellent safety. This formulation may cause less flushing than immediate-release niacin, as well as less hepatotoxicity than sustained-release formulations.[30]

Even with extended-release niacin, we tell patients to expect flushing when starting niacin and increasing its dose, and offer specific tips to help ensure success (**TABLE 5**). Taking a chewable aspirin one half hour before the niacin is helpful: aspirin 325 mg is more effective at averting flushing than either 80 mg[32] or 165 mg,[33] but works as well as 650 mg.[34]

The usual therapeutic dose of niacin is 1.5 to 2 g/day. Patients should not take niacin if they have active liver disease, active peptic ulcers, gout, or poorly controlled diabetes.

Fish oil reduces triglycerides by 30% to 40%[1] and is a helpful adjunct to medications. It is only modestly effective and compliance is uneven, but adverse drug interactions are of little concern. Omega-3 fatty acids lower intestinal and hepatic secretion of triglycerides and reduce triglyceride levels at high doses. Fish oil is the best studied of the various forms of omega-3 fatty acids available.

Fish oil is generally produced in 1-g capsules and is available over the counter. Although the American Heart Association recommends 1 g daily[35] (**TABLE 6**), higher doses are needed to substantially reduce triglyceride levels (3 g per day typically lowers triglycerides by 30%; 9 g per day may lower levels by 50%).[36] High doses, however, may also increase serum LDL-C levels by 5% to 10%.[37] A typical dosage is 2 g three times a day with meals.

Many patients find it difficult to adhere to a high-dose regimen, although those with extreme hypertriglyceridemia who have had pancreatitis are often more motivated. Patients often better tolerate fish oil by taking capsules with food to mask the fishy aftertaste and belching. Storing the capsules in the

TABLE 6

Recommendations for omega-3 fatty acid intake

POPULATION	RECOMMENDATION
Patients without documented coronary heart disease	Eat a variety of (preferably oily) fish at least twice a week Include foods rich in alpha-linolenic acid (flaxseed, walnuts, and flaxseed, canola, and soybean oils)
Patients with documented coronary heart disease	Consume about 1 g of eicosapentaenoic acid (EPA) plus docosahexaenoic acid (DHA) per day, preferably from oily fish, or in supplements in consultation with a physician
Patients who need to lower triglycerides	EPA and DHA 2 to 4 g/day as capsules, under a physician's care

KRIS-ETHERTON PMM, HARRIS WS, APPEL LJ; AMERICAN HEART ASSOCIATION. NUTRITION COMMITTEE. FISH CONSUMPTION, FISH OIL, OMEGA-3 FATTY ACIDS, AND CARDIOVASCULAR DISEASE. CIRCULATION 2002; 106:2747–2757. ERRATUM IN: CIRCULATION 2003; 107:512.

refrigerator or the freezer may also help. The FDA recently approved Omacor. This highly concentrated form of fish oil also decreases major coronary heart disease events.

Statins lower LDL-C and improve outcomes in patients with atherosclerotic heart disease, but they also lower triglycerides by up to 30%, in proportion to their LDL-C reduction. They act by up-regulating the LDL receptor, resulting in catabolism of serum IDL and VLDL.

Several prospective trials directly compared different doses of multiple statins.[38–40] Even under the ideal circumstances of these clinical trials, statin monotherapy was often inadequate for both LDL-C and non-HDL-C goals.

A focused approach to drug therapy

The decision to use drug therapy to treat hypertriglyceridemia depends on the goals of therapy, the presence of atherosclerosis, and the patient's motivation and prior success in changing his or her lifestyle.

Triglycerides 200 to 499 mg/dL. Statins are generally the first-line drugs in patients with high LDL-C, and many patients need combination therapy to achieve non-HDL-C goals. We are comfortable adding fibrates and niacin to statin therapy, although we avoid the bile acid resins (colestipol, cholestyramine, and colesevelam) because they can raise triglyceride levels. Although the ATP-III sanctions the use of nonstatin monotherapy in patients close to their serum LDL-C goal (ie, within 30 mg/dL), we usually pair it with a statin.

Triglycerides 500 to 1,000 mg/dL. Treatment in this range has not been well studied. The ATP-III recommends lowering triglycerides with fibrates or niacin, with or without fish oil. They de-emphasize the use of statins, citing lower efficacy against triglycerides and uncertain cardiovascular benefits.

Despite the poor evidence, we still use statins to help some patients reach their goal. Hypertriglyceridemia in this range may derive from elevated VLDL, IDL, remnant chylomicrons, or chylomicrons, and may respond differentially to treatment with fibrates, niacin, and statins. Patients at the lower end of this range often do well with statins, and we use fibrates for those at the upper end. Most patients require combination therapy to reach their non-HDL-C goal.

Triglycerides above 1,000 mg/dL. Severe hypertriglyceridemia warrants aggressive management with lifestyle changes and medications to lower the serum triglyceride level to below 1,000 mg/dL to avert acute pancreatitis. The physician should review the patient's diet and alcohol use and recommend a very-low-fat diet (< 15% of total calories from fat) and total abstinence from alcohol. We often start a fibrate at the first visit.

For patients who do not adequately respond to fibrates, either fish oils or niacin should be added. Two studies examined treatment with combined fibrates and niacin,[12,18] although neither enrolled patients with extreme hypertriglyceridemia. The combination was well tolerated, and our experience confirms that most patients do well.

Chewable aspirin 325 mg 1/2 hour before the niacin dose helps prevent flushing

Patients with serum triglyceride levels in the thousands often never achieve normal levels. Treatment to below 1,000 mg/dL is considered adequate to protect against pancreatitis, however, and is viewed as a therapeutic success. Some high-risk patients with cardiovascular disease or diabetes need a statin in addition to a fibrate to further reduce levels of LDL and non-HDL cholesterol to reduce cardiovascular risk.

COMBINED TREATMENTS

Monotherapy is frequently inadequate when treating patients with hypertriglyceridemia. Certain combinations are highly effective and well tolerated.

Fibrate plus statin. A fibrate often reduces serum triglycerides but does not bring serum LDL-C or non-HDL-C to target levels. In such cases, a statin should be added.

Wierzbicki et al[27] extensively reviewed combination fibrate and statin therapy in a meta-analysis that included 1,815 patients treated with various fibrates and statins for an average of 11 months. On average, combination therapy lowered serum triglyceride levels by 42%, raised serum HDL-C levels by 17%, and lowered serum LDL-C levels by 30%. Only 1 subject in 1,000 developed either elevated liver enzymes or an elevated creatine kinase level.

A recent trial[41] compared simvastatin monotherapy and simvastatin combined with fenofibrate in more than 600 patients with triglyceride levels of 150 to 500 mg/dL and LDL levels greater than 130 mg/dL. The lipid-lowering effect was similar to that in the meta-analysis above. There was no difference in muscle symptoms between the groups, though a slight increase in the prevalence of high alanine aminotransferase was seen.

Combining any fibrate and a statin should be done cautiously because of the risk of myopathy and rhabdomyolysis. Gemfibrozil may be more risky than fenofibrate or bezafibrate, perhaps because it inhibits statin glucuronidation, raising the statin level.[28,42] The ATP-III recently advised that "one fibrate, fenofibrate, does not interfere with catabolism of statins and thus likely does not substantially increase the risk for clinical myopathy in patients treated with moderate doses of statins."[43] Even so, many recommend avoiding combining statins and fibrates for patients with renal failure, severe illness, or advanced age (> 70 years old), and for those taking multiple medications or who would be unable to report any muscle symptoms that might develop.[16]

When combining a fibrate with a statin, we advise patients to take the fibrate with breakfast and the statin at bedtime so that the drugs do not peak at the same time. We prefer fenofibrate for combination therapy because it is less likely to cause myopathy.

Niacin plus statin. Though niacin reduces atherosclerosis, we almost always combine it with a statin, because statins reduce events in a broader range of patients. The combination is generally well-tolerated. An approved combination drug pairs extended-release niacin with lovastatin (Advicor), and a combination of extended-release niacin with simvastatin is under development.

In a study of 1,079 patients who received up to 2,000 mg of niacin with lovastatin 40 mg for 2 years, only 1 patient had suspected myopathy.[44]

When one prescribes niacin with a statin, the package inserts should be reviewed for precautions and dose recommendations.

Fibrate plus niacin. Few studies explored the risks and benefits of this combination. In the SIHD-SPS trial,[12] which randomized 555 patients to open-label niacin and clofibrate or no treatment, 18% of the patients in the treatment group withdrew from the study because of side effects ($P < .001$). Anecdotally, modern combinations have been well-tolerated in our clinic; the most common side effect is flushing from the niacin.

Familial syndromes cause very high triglyceride levels, requiring drug therapy

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