MSD MANUAL
Professional Version

Dyslipidemia

(Hyperlipidemia)

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Dyslipidemia is *elevation* of plasma cholesterol, triglycerides (TGs), or both, or a low high-density lipoprotein cholesterol level that contributes to the development of atherosclerosis. Causes may be primary (genetic) or secondary. Diagnosis is by measuring plasma levels of total cholesterol, TGs, and individual lipoproteins. Treatment involves dietary changes, exercise, and lipid-lowering drugs.

(See also Overview of Lipid Metabolism.)

There is no natural cutoff between normal and abnormal lipid levels because lipid measurements are continuous. A linear relation probably exists between lipid levels and cardiovascular risk, so many people with “normal” cholesterol levels benefit from achieving still lower levels. Consequently, there are no numeric definitions of dyslipidemia; the term is applied to lipid levels for which treatment has proven beneficial. Proof of benefit is strongest for lowering elevated low-density lipoprotein cholesterol (LDL) levels. In the overall population, evidence is less strong for a benefit from lowering elevated TG and increasing low high-density lipoprotein cholesterol (HDL) levels.

HDL levels do not always predict cardiovascular risk. For example, high HDL levels caused by some genetic disorders may not protect against cardiovascular disorders, and low HDL levels caused by some genetic disorders may not increase the risk of cardiovascular disorders. Although HDL levels predict cardiovascular risk in the overall population, the increased risk may be caused by other factors, such as accompanying lipid and metabolic abnormalities, such as hypertriglyceridemia, rather than the HDL level itself.

Classification of Dyslipidemia

Dyslipidemias were traditionally classified by patterns of elevation in lipids and lipoproteins (Fredrickson phenotype—see table Lipoprotein Patterns). A more practical system categorizes dyslipidemias as primary or secondary and characterizes them by

- Increases in cholesterol only (pure or isolated hypercholesterolemia)
- Increases in TGs only (pure or isolated hypertriglyceridemia),

- Increases in both cholesterol and TGs (mixed or combined hyperlipidemias)

This system does not take into account specific lipoprotein abnormalities (eg, low HDL or high LDL) that may contribute to disease despite normal cholesterol and TG levels.

Etiology of Dyslipidemia

Dyslipidemias may be

- Primary: Genetic
- Secondary: Caused by lifestyle and other factors

Both primary and secondary causes contribute to dyslipidemias in varying degrees. For example, in familial combined hyperlipidemia, expression may occur only in the presence of significant secondary causes.

Primary causes

Primary causes are single or multiple gene mutations that result in either overproduction or defective clearance of triglycerides and LDL, or in underproduction or excessive clearance of HDL (see table Genetic (Primary) Dyslipidemias). The names of many primary disorders reflect an old nomenclature in which lipoproteins were detected and distinguished by how they separated into alpha (HDL) and beta (LDL) bands on electrophoretic gels.

Secondary causes

Secondary causes contribute to many cases of dyslipidemia in adults.

The **most important** secondary cause of dyslipidemia in high-resource countries is

- A sedentary lifestyle with excessive dietary intake of total calories, saturated fat, cholesterol, and trans fats

Trans fats are polyunsaturated or monounsaturated fatty acids to which hydrogen atoms have been added; they are used in some processed foods and are as atherogenic as saturated fat.

Other common secondary causes of dyslipidemia include

- Diabetes mellitus
- Chronic kidney disease
- Alcohol overuse
- Hypothyroidism
- Primary biliary cirrhosis and other cholestatic liver diseases
- Drugs, such as thiazides, beta-blockers, retinoids, highly active antiretroviral agents, cyclosporine, tacrolimus, estrogen and progestins, and glucocorticoids

Secondary causes of low levels of HDL cholesterol include cigarette smoking, anabolic steroids, HIV infection, and nephrotic syndrome.

Diabetes is an especially significant secondary cause because patients tend to have an atherogenic combination of high TGs; high small, dense LDL fractions; and low HDL (diabetic dyslipidemia, hypertriglyceridemic hyperapo B). Patients with type 2 diabetes are especially at risk. The combination may be a consequence of obesity, poor control of diabetes, or both, which may increase circulating free fatty acids (FFAs), leading to increased hepatic very-low-density lipoprotein (VLDL) production. TG-rich VLDL then transfers TG and cholesterol to LDL and HDL, promoting formation of TG-rich, small, dense LDL and clearance of TG-rich HDL. Diabetic dyslipidemia is often exacerbated by the increased caloric intake and physical inactivity that characterize the lifestyles of some patients with type 2 diabetes. Women with diabetes may be at special risk of cardiac disease as a result of this form of dyslipidemia.

Symptoms and Signs of Dyslipidemia

Dyslipidemia itself usually causes no symptoms but can lead to symptomatic vascular disease, including coronary artery disease (CAD), stroke, and peripheral arterial disease.

High levels of triglycerides (> 500 mg/dL [> 5.65 mmol/L]) can cause acute pancreatitis. Very high triglyceride levels can also cause hepatosplenomegaly, paresthesias, dyspnea, and confusion.

High levels of LDL can cause arcus corneae and tendinous xanthomas at the Achilles, elbow, and knee tendons and over metacarpophalangeal joints. Other clinical findings that occur in patients with high LDL (eg, in familial hypercholesterolemia) include xanthelasma (lipid rich yellow plaques on the medial eyelids). Xanthelasma can also occur in patients with primary biliary cirrhosis and normal lipid levels.

Patients with the homozygous form of familial hypercholesterolemia may have arcus corneae, tendinous xanthomas and xanthelasma plus planar or tuberous xanthomas. Planar xanthomas are flat or slightly raised yellowish patches. Tuberous xanthomas are painless, firm nodules typically located over extensor surfaces of joints.

Patients with severe elevations of TGs can have eruptive xanthomas over the trunk, back, elbows, buttocks, knees, hands, and feet.

buttocks, knees, hands, and feet.

Patients with the rare dysbetalipoproteinemia can have palmar and tuberous xanthomas.

Severe hypertriglyceridemia (> 2000 mg/dL [> 22.6 mmol/L]) can give retinal arteries and veins a creamy white appearance (lipemia retinalis). Extremely high lipid levels also give a lactescent (milky) appearance to blood plasma. Symptoms can include paresthesias, dypsnea, and confusion.

Creamy Plasma due to Severe Hypertriglyceridemia

IMAGE COURTESY OF MICHAEL H. DAVIDSON, MD.

Xanthoma Manifestations

Diagnosis of Dyslipidemia

- Serum lipid profile (measured total cholesterol, TG, and HDL cholesterol and calculated LDL cholesterol and VLDL cholesterol)

Dyslipidemia is suspected in patients with characteristic physical findings or complications of dyslipidemia (eg, atherosclerotic disease).

Primary lipid disorders are suspected when patients have

- Physical signs of dyslipidemia such as tendon xanthomas, which are pathognomonic for familial hypercholesterolemia
- Onset of premature atherosclerotic disease (men < 55 years, women < 60 years)
- A family history of premature atherosclerotic disease or severe hyperlipidemia
- Serum cholesterol > 190 mg/dL (> 4.9 mmol/L)

Dyslipidemia is diagnosed by measuring serum lipids. Routine measurements (lipid profile) include total cholesterol (TC), TGs, HDL cholesterol, and LDL cholesterol.

Lipid profile measurement

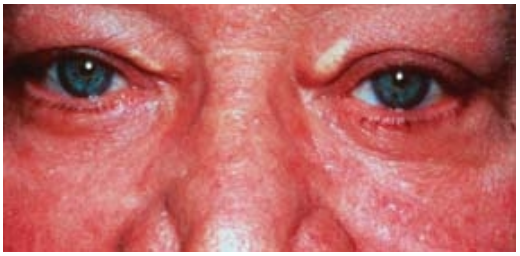
Total cholesterol, triglycerides, and HDL cholesterol are

Xanthelasma of the Eyelid

IMAGE COURTESY OF MICHAEL H. DAVIDSON, MD.

Xanthelasma of the Eyelid

measured directly. TC and TG values reflect cholesterol and TGs in all circulating lipoproteins, including chylomicrons, VLDL, intermediate-density lipoprotein (IDL), LDL, and HDL. TC values can vary by 10% and TGs by up to 25% day-to-day even in the absence of a disorder. TC and HDL cholesterol can be measured in the nonfasting state, but most patients should have all lipids measured while fasting (usually for 12 hours) for maximum accuracy and consistency.



Testing should be postponed until after resolution of acute illness because TG and lipoprotein(a) levels increase and cholesterol levels decrease in inflammatory states. Lipid profiles can vary for about 30 days after an acute myocardial infarction (MI); however, results obtained within 24 hours after MI are usually reliable enough to guide initial lipid-lowering therapy.

LDL cholesterol values are most often calculated as the amount of cholesterol not contained in HDL and VLDL. VLDL is estimated by TG ÷ 5 because the cholesterol concentration in VLDL particles is usually one fifth of the total lipid in the particle. Thus,

Pearls & Pitfalls

- Total and HDL cholesterol can be measured in the nonfasting state, but most patients should have all lipids measured while fasting (usually for 12 hours) for maximum accuracy and consistency.

$$LDL\ cholesterol = Total\ cholesterol - \left[HDL\ \ cholesterol + \left(\frac{Triglycerides}{5}\right)\right]$$

This calculation is valid only when TGs are < 400 mg/dL (< 4.5 mmol/L) and patients are fasting because eating increases TGs. The calculated LDL cholesterol value incorporates measures of all non-HDL, nonchylomicron cholesterol, including that in IDL and lipoprotein (a) [Lp(a)].

LDL can also be measured directly using plasma ultracentrifugation, which separates chylomicrons and VLDL fractions from HDL and LDL, and by an immunoassay method. Direct measurement may be useful in some patients with elevated TGs, but these direct measurements are not routinely necessary.

The role of apo B testing is under study because values reflect all non-HDL cholesterol (in VLDL, IDL, and LDL) and may be more predictive of CAD risk than LDL cholesterol. Non-HDL cholesterol (TC − HDL cholesterol) may also be more predictive of CAD risk than LDL cholesterol, especially in patients with hypertriglyceridemia.

Other tests

CLINICAL CALCULATOR:

Very Low Density Lipoprotein (VLDL)

Patients with premature atherosclerotic cardiovascular disease, cardiovascular disease with normal or near-normal lipid levels, or high LDL levels refractory to drug therapy should have Lp(a) levels measured. Lp(a) levels may also be directly measured in patients with borderline high LDL cholesterol levels to determine whether drug

therapy is warranted.

C-reactive protein may be measured in the same populations.

Measurements of LDL particle number or apoprotein B-100 (apo B) may be useful in patients with elevated TGs and the metabolic syndrome. Apo B provides similar information to LDL particle number because there is one apo B molecule for each LDL particle. Apo B measurement includes all atherogenic particles, including remnants and Lp(a).

Secondary causes

Tests for secondary causes of dyslipidemia should be done in most patients with newly diagnosed dyslipidemia and when a component of the lipid profile has inexplicably changed for the worse. Such tests include measurements of

- Creatinine
- Fasting glucose
- Liver enzymes
- Thyroid-stimulating hormone (TSH)
- Urinary protein

CLINICAL CALCULATOR:

Friedewald Equation for Low Density Lipoprotein (LDL-C SI units)

CLINICAL CALCULATOR:

Friedewald Equation for Low Density Lipoprotein (LDL-C)

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Screening

Screening is done using a fasting lipid profile (TC, TGs, HDL cholesterol, and calculated LDL cholesterol). Different medical societies have different recommendations on when to begin screening.

Lipid measurement should be accompanied by assessment for other cardiovascular risk factors, including

- Cigarette use
- Diabetes mellitus
- Family history of CAD in a male 1st-degree relative before age 55 or a female 1st-degree relative before age 65
- Hypertension

Screening in children

Most physicians recommend screening per the 2012 National Heart Lung and Blood Institute Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents as follows

- Children with risk factors (eg, diabetes, hypertension, family history of severe hyperlipidemia or premature CAD): Fasting lipid profile once at age 2 to 8

- Children with no risk factors: Non-fasting or fasting lipid profile once before puberty (usually age 9 to 11) and once more at age 17 to 21

Screening in adults

Adults are screened at age 20 years (1, 2) and every 5 years thereafter.

A definite age after which patients no longer require screening has not been established, but evidence supports screening of patients into their 80s, especially in the presence of atherosclerotic cardiovascular disease.

Patients with an extensive family history of heart disease should also be screened by measuring Lp(a) levels.

Diagnosis references

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2. Grundy SM, Stone NJ, Bailey AL, et al: 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation 139: e1082–e1143, 2019. doi: 10.1161/CIR.0000000000000625

Treatment of Dyslipidemia

- Risk assessment by explicit criteria
- Lifestyle changes (eg, exercise, dietary modification)
- For high LDL cholesterol, statins, bile acid sequestrants, ezetimibe, bempedoic acid, and PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitors
- For high TG, fibrates, omega-3 fatty acids, and sometimes other measures

General principles

The main indication for dyslipidemia treatment is prevention of atherosclerotic cardiovascular disease (ASCVD), including acute coronary syndromes, stroke, transient ischemic attack, or peripheral arterial disease presumed caused by atherosclerosis. Treatment is indicated for all patients with ASCVD (secondary prevention) and for some without (primary prevention).

Treatment of children is controversial; dietary changes may be difficult to implement, and no data suggest that lowering lipid levels in childhood effectively prevents heart disease in adulthood. Moreover, the safety and effectiveness of long-term lipid-lowering treatment are questionable. Nevertheless, the American Academy of Pediatrics (AAP) recommends treatment for some children

Nevertheless, the American Academy of Pediatrics (AAP) recommends treatment for some children who have elevated LDL cholesterol levels. Children with heterozygous familial hypercholesterolemia should be treated beginning at age 8 to 10. Children with homozygous familial hypercholesterolemia require diet, drugs, and often LDL apheresis to prevent premature death; treatment is begun when the diagnosis is made.

Treatment options depend on the specific lipid abnormality, although different lipid abnormalities often coexist. In some patients, a single abnormality may require several therapies; in others, a single treatment may be adequate for several abnormalities. Treatment should always include treatment of hypertension and diabetes, smoking cessation, and in patients (age 40 to 79 years) with a low risk of bleeding and with a 10-year risk of myocardial infarction or death due to coronary artery disease of ≥ 20% , low-dose daily aspirin. In general, treatment options for men and women are the same.

Elevated LDL cholesterol treatment

CLINICAL CALCULATOR:

Cardiovascular Risk Assessment (10-year, Revised Pooled Cohort Equations 2018)

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For all individuals, the prevention of ASCVD requires an emphasis on a heart-healthy lifestyle, particularly diet and exercise. Other options to lower LDL cholesterol in all age groups include drugs, dietary supplements, procedural interventions, and experimental therapies. Many of these options are also effective for treating other lipid abnormalities.

Dietary changes include

- Decreasing intake of saturated fats and cholesterol
- Increasing the proportion of dietary fiber and complex carbohydrates
- Maintaining ideal body weight

Referral to a dietitian is often useful, especially for older people.

Exercise lowers LDL cholesterol in some people and also helps maintain ideal body weight.

Dietary changes and exercise should be used whenever feasible, but AHA/ACC guidelines recommend also using drug treatment for certain groups of patients after discussion of the risks and benefits of statin therapy.

For **drug treatment in adults,** the 2018 AHA/ACC/ Guideline on the Management of Blood Cholesterol recommends treatment with a statin for 4 groups of patients, comprised of those with any of the following:

- Clinical ASCVD
- LDL cholesterol ≥ 190 mg/dL (≥ 4.9 mmol/L)
- Age 40 to 75, with diabetes and LDL cholesterol 70 to 189 mg/dL (1.8 to 4.9 mmol/L)
- Age 40 to 75, LDL cholesterol 70 to 189 mg/dL (1.8 to 4.9 mmol/L), and estimated 10-year risk of ASCVD > 7.5%

Risk of ASCVD is estimated using the pooled cohort risk assessment equations, which replace previous risk calculation tools. This new risk calculator is based on sex, age, race, total and HDL cholesterol, systolic and diastolic blood pressure , diabetes and smoking status, and use of antihypertensives or statins. When considering whether to give a statin, clinicians may also take into account other factors, including LDL cholesterol ≥ 160 mg/dL (4.1 mmol/L), family history of premature ASCVD (ie, age of onset < 55 in male 1st degree relative, or < 65 in female 1st degree relative), high-sensitivity C-reactive protein ≥ 2 mg/L (≥ 19 nmol/L), coronary artery calcium score ≥ 300 Agatston units (or ≥ 75th percentile for the patient's demographic), ankle-brachial index < 0.9, and increased lifetime risk. Increased lifetime risk (identified using the ACC/AHA risk calculator) is relevant because 10-year risk may be low in younger patients, in whom longer-term risk should be taken into account.

Statins are the treatment of choice for LDL cholesterol reduction because they demonstrably reduce cardiovascular morbidity and mortality. Statins inhibit hydroxymethylglutaryl CoA reductase, a key enzyme in cholesterol synthesis, leading to up-regulation of LDL receptors and increased LDL clearance. They reduce LDL cholesterol by up to 60% and produce small increases in HDL and modest decreases in TGs. Statins also appear to decrease intra-arterial inflammation, systemic inflammation, or both by stimulating production of endothelial nitric oxide and may have other beneficial effects. Other classes of lipid-lowering drugs are not the first choice because they have not demonstrated equivalent efficacy for decreasing ASCVD.

Statin treatment is classified as high, moderate, or low intensity and is given based on treatment group and age (see table Statins for ASCVD Prevention). The choice of statin may depend on the patient's co-morbidities, other drugs, risk factors for adverse events, statin intolerance, cost, and patient preference.

Adverse effects with statins are uncommon but include liver enzyme elevations and myositis or rhabdomyolysis. Liver enzyme elevations are uncommon, and serious liver toxicity is extremely rare. Muscle problems occur in up to 10% of patients taking statins and may be dose-dependent. Muscle symptoms can occur without enzyme elevation. Adverse effects are more common among older patients, patients with several disorders, and patients taking several drugs. In some patients, changing from one statin to another or lowering the dose (after temporarily discontinuing the drug) relieves the problem. Muscle toxicity seems to be most common when some of the statins are used with drugs that inhibit cytochrome P3A4 (eg, macrolide antibiotics, azole antifungals, cyclosporine) and with fibrates, especially gemfibrozil. Statins are contraindicated during pregnancy and lactation.

In patients with ASCVD, the more that LDL-C is reduced by statin therapy the greater the risk reduction. Thus, initial treatment is a statin at maximally tolerated dose to lower LDL cholesterol by > 50% (high-intensity therapy). For very high risk ASCVD patients (eg, those with a recent myocardial infarction or unstable angina, or with high-risk comorbidities such as diabetes), LDL-C level > 70 mg/dL (> 1.2 mmol/L) despite maximal statin therapy should prompt the addition of ezetimibe or a PCSK9 inhibitor (eg, evolocumab, alirocumab). These therapies have been proven to reduce major adverse cardiovascular events in conjunction with statin therapy in large clinical outcome trials (2, 3).

The **adenosine triphosphate citrate lyase inhibitor,** bempedoic acid, is a first-in-class oral drug that impairs cholesterol synthesis in the liver and increases LDL receptors. It lowers LDL cholesterol by 15 to 17%. Bempedoic acid is especially useful in patients with statin-associated muscle adverse effects because it does not cause muscle pain or weakness. It can be used as monotherapy or as an add-on to other lipid-lowering therapy. It is also commercially available in combination with ezetimibe. Risks include hyperuricemia and tendon rupture.

Bile acid sequestrants block intestinal bile acid reabsorption, forcing up-regulation of hepatic LDL receptors to recruit circulating cholesterol for bile synthesis. They are proved to reduce cardiovascular mortality. Bile acid sequestrants are usually used with statins or with nicotinic acid to augment LDL cholesterol reduction and are the drugs of choice for women who are or are planning to become pregnant. Bile acid sequestrants are safe, but their use is limited by adverse effects of bloating, nausea, cramping, and constipation. They may also increase TGs, so their use is contraindicated in patients with hypertriglyceridemia. Cholestyramine, colestipol, and colesevelam (but to a lesser degree), interfere with absorption of other drugs—notably thiazides, beta-blockers, warfarin, digoxin, and thyroxine—an effect that can be decreased by administration at least 4 hours before or 1 hour after other drugs. Bile acid sequestrants should be given with meals to increase their efficacy.

Cholesterol absorption inhibitors, such as ezetimibe, inhibit intestinal absorption of cholesterol and phytosterol. Ezetimibe usually lowers LDL cholesterol by 15 to 20% and causes small increases in HDL and a mild decrease in triglycerides. Ezetimibe can be used as monotherapy in patients intolerant to statins or added to statins for patients taking maximum statin doses with persistent LDL cholesterol elevation. Adverse effects are infrequent.

PCSK9 monoclonal antibodies are available as subcutaneous injections given once or twice per month. These drugs keep PCSK9 from attaching to LDL receptors, leading to improved function of these receptors. LDL cholesterol is lowered by 40 to 70%. Cardiovascular outcomes trials with evolocumab and alirocumab showed a decrease in cardiovascular events in patients with prior atherosclerotic cardiovascular disease (2).

Dietary supplements that lower LDL cholesterol levels include fiber supplements and commercially available margarines and other products containing plant sterols (sitosterol, campesterol) or stanols. Fiber supplements decrease cholesterol levels in multiple ways, including decreased absorption and increased excretion. Oat-based fiber supplements can decrease total cholesterol by up to 18%. Plant sterols and stanols decrease cholesterol absorption by displacing cholesterol from intestinal micelles and can reduce LDL cholesterol by up to 10% without affecting HDL or TGs.

Drugs for homozygous familial hypercholesterolemia include PCSK9 inhibitors, lomitapide, and

evinacumab. Lomitapide is an inhibitor of microsomal triglyceride transfer protein that interferes with the secretion of TG-rich lipoproteins in the liver and intestine. Dose is begun low and gradually titrated up about every 2 weeks. Patients must follow a diet with less than 20% of calories from fat. Lomitapide can cause gastrointestinal adverse effects (eg, diarrhea, increased hepatic fat, elevated liver enzymes). Evinacumab is a recombinant human monoclonal antibody that binds to and inhibits angiopoietin-like protein 3, an inhibitor of LPL and endothelial lipase. It can decrease LDL cholesterol (by 47%), TG, and HDL cholesterol. Evinacumab is given by intravenous infusion once monthly. It can cause gout, influenza-like illness, and infusion reactions.

Procedural approaches are reserved for patients with severe hyperlipidemia (LDL cholesterol > 300 mg/dL [> 7.74 mmol/L]) and no vascular disease. LDL apheresis may be done in patients with LDL cholesterol > 200 mg/dL (> 5.16 mmol/L) and vascular disease that is refractory to conventional therapy, such as occurs with familial hypercholesterolemia. Options include LDL apheresis (in which LDL is removed by extracorporeal plasma exchange) and, rarely, ileal bypass (to block reabsorption of bile acids) and liver transplantation (which transplants LDL receptors). LDL apheresis is the procedure of choice in most instances when maximally tolerated therapy fails to lower LDL adequately. Apheresis is also the usual therapy in patients with the homozygous form of familial hypercholesterolemia who have limited or no response to drug therapy.

Elevated LDL cholesterol in children

Childhood risk factors besides family history and diabetes include cigarette smoking, hypertension, low HDL cholesterol (< 35 mg/dL [< 0.9 mmol/L]), obesity, and physical inactivity.

For children, the American Academy of Pediatrics recommends dietary treatment for children with LDL cholesterol > 110 mg/dL (> 2.8 mmol/L).

Drug therapy is recommended for children > 8 years and with either of the following:

- Poor response to dietary therapy, LDL cholesterol ≥ 190 mg/dL (≥ 4.9 mmol/L), and no family history of premature cardiovascular disease
- LDL cholesterol ≥ 160 mg/dL (≥ 4.13 mmol/L) and a family history of premature cardiovascular disease or ≥ 2 risk factors for premature cardiovascular disease

Drugs used in children include many of the statins. Children with familial hypercholesterolemia may require a second drug to achieve LDL cholesterol reduction of at least 50%.

Elevated triglycerides

Although it is unclear whether elevated TGs independently contribute to cardiovascular disease, they are associated with multiple metabolic abnormalities that contribute to coronary artery disease (eg, diabetes, metabolic syndrome). Consensus is emerging that lowering elevated TGs is beneficial. No target goals exist, but levels < 150 mg/dL (< 1.7 mmol/L) are generally considered desirable. No guidelines specifically address treatment of elevated TGs in children.

The **overall treatment strategy** is to first implement lifestyle changes, including exercise, weight loss, and avoidance of concentrated dietary sugar and alcohol. Intake of 2 to 4 servings/week of marine fish

high in omega-3 fatty acids may be effective, but the amount of omega-3 fatty acids is often lower than needed; supplemental doses may be helpful. In patients with diabetes, glucose levels should be tightly controlled. If these measures are ineffective, lipid-lowering drugs should be considered. Patients with very high TG levels (> 1,000 mg/dL [> 11 mmol/L]) may need to begin drug therapy at diagnosis to more quickly reduce the risk of acute pancreatitis.

Fibrates reduce TGs by about 50%. They appear to stimulate endothelial lipoprotein lipase (LPL), leading to increased fatty acid oxidation in the liver and muscle and decreased hepatic VLDL synthesis. They also increase HDL by up to 20%. Fibrates can cause gastrointestinal adverse effects, including dyspepsia, abdominal pain, and elevated liver enzymes. They uncommonly cause cholelithiasis. Fibrates may potentiate muscle toxicity when used with statins and potentiate the effects of warfarin.

Statins can be used in patients with TGs < 500 mg/dL (< 5.65 mmol/L) if LDL cholesterol elevations are also present; statins may reduce both LDL cholesterol and TGs through reduction of VLDL. If only TGs are elevated, fibrates are the drug of choice.

Omega-3 fatty acids in high doses (1 to 6 g a day of eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA]) can be effective in reducing TGs. The omega-3 fatty acids EPA and DHA are the active ingredients in marine fish oil or omega-3 capsules. Adverse effects include eructation and diarrhea. These effects may be decreased by giving the fish oil capsules with meals in divided doses (eg, twice a day or 3 times a day). Omega-3 fatty acids can be a useful adjunct to other therapies. Prescription omega-3 fatty acid preparations are indicated for triglyceride levels > 500 mg/dL (> 5.65 mmol/L).

The **Apo CIII inhibitor** (an antisense inhibitor of apo CIII), volanesorsen, is now available in some countries. It lowers triglyceride levels in patients with severely elevated triglyceride levels, including people with lipoprotein lipase deficiency. It is given as a weekly injection.

Low HDL

Although higher HDL levels predict lower cardiovascular risk, it is not clear whether treatments to increase HDL cholesterol levels decrease risk of death. Guidelines in the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATPIII) define low HDL cholesterol as < 40 mg/dL [< 1.04 mmol/L]; the guidelines do not specify an HDL cholesterol target level and recommend interventions to raise HDL cholesterol only after LDL cholesterol targets have been reached. Treatments for LDL cholesterol and triglyceride reduction often increase HDL cholesterol, and the 3 objectives can sometimes be achieved simultaneously.

No guidelines specifically address treatment of low HDL cholesterol in children.

Treatment includes **lifestyle changes** such as an increase in exercise and weight loss. Alcohol raises HDL cholesterol but is not routinely recommended as a therapy because of its many other adverse effects. Drugs may be successful in raising levels when lifestyle changes alone are insufficient, but it is uncertain whether raising HDL levels reduces

Pearls & Pitfalls

- Although higher HDL levels predict lower cardiovascular risk, it is not clear whether

but it is uncertain whether raising HDL levels reduces mortality.

treatments to increase HDL cholesterol levels decrease risk of cardiovascular events or death.

Nicotinic acid (niacin) is the most effective drug for increasing HDL. Its mechanism of action is unknown, but it appears to both increase HDL production and inhibit HDL clearance; it may also mobilize cholesterol from macrophages. Niacin also decreases TGs and, in doses of 1500 to 2000 mg/day, reduces LDL cholesterol. Niacin causes flushing, pruritus, and nausea; premedication with low-dose aspirin may prevent these adverse effects. Extended-release preparations cause flushing less often. However, most over-the-counter slow-release preparations are not recommended; an exception is polygel controlled-release niacin. Niacin can cause liver enzyme elevations and occasionally liver failure, insulin resistance, and hyperuricemia and gout. It may also increase homocysteine levels. The combination of high doses of niacin with statins may increase the risk of myopathy. In patients with average LDL cholesterol and below-average HDL cholesterol levels, niacin combined with statin treatment may be effective in preventing cardiovascular disorders. In patients treated with statins to lower LDL cholesterol to < 70 mg/dL (< 1.8 mmol/L), niacin does not appear to have added benefit and may cause increased adverse effects, including ischemic stroke.

Fibrates increase HDL. Fibrates may decrease cardiovascular risk in patients with TGs > 200 mg/dL (> 2.26 mmol/L) and HDL cholesterol < 40 mg/dL (< 1.04 mmol/L).

Cholesterol ester transport protein (CETP) inhibitors raise HDL levels by inhibiting CETP. Several studies have not shown a benefit.

Studies with infusion of recombinant apo A1 Milano have not shown benefit.

Elevated Lp(a)

The upper limit of normal for Lp(a) is about 30 mg/dL (75 nmol/L), but values in African Americans run higher. Few data exist to guide the treatment of elevated Lp(a) or to establish treatment efficacy. Niacin is the only drug that directly decreases Lp(a); it can lower Lp(a) by > 20% at higher doses. The usual approach in patients with elevated Lp(a) is to lower LDL cholesterol aggressively. LDL apheresis has been used to lower Lp(a) in patients with high Lp(a) levels and progressive vascular disease. An antisense inhibitor of apo (a) is in development.

Secondary causes of dyslipidemia

Treatment of diabetic dyslipidemia should always involve lifestyle changes and statins to reduce LDL cholesterol. To decrease the risk of pancreatitis, fibrates can be used to decrease TGs when levels are > 500 mg/dL (> 5.65 mmol/L). Metformin lowers TGs, which may be a reason to choose it over other oral antihyperglycemic drugs when treating diabetes. Some thiazolidinediones (TZDs) increase both HDL cholesterol and LDL cholesterol. Some TZDs also decrease TGs. These antihyperglycemic drugs should not be chosen over lipid-lowering drugs to treat lipid abnormalities in patients with diabetes but may be useful adjuncts. Patients with very high TG levels and less than optimally controlled diabetes may have a better response to insulin than to oral antihyperglycemic drugs.

Treatment of dyslipidemia in patients with hypothyroidism, chronic kidney disease, liver disease, or a

Treatment of dyslipidemia in patients with hypothyroidism, chronic kidney disease, liver disease, or a combination of these disorders involves treating the underlying disorders primarily and lipid abnormalities secondarily. Abnormal lipid levels in patients with low-normal thyroid function (high-normal TSH levels) improve with hormone replacement. Reducing the dosage of or stopping drugs that cause lipid abnormalities should be considered.

Monitoring treatment

Lipid levels should be monitored periodically after starting treatment. No data support specific monitoring intervals, but measuring lipid levels 2 to 3 months after starting or changing therapies and once or twice yearly after lipid levels are stabilized is common practice.

Liver and severe muscle toxicity with statin use occurs in 0.5 to 2% of all users. Routine monitoring of liver enzyme levels is not necessary, and routine measurement of creatine kinase (CK) is not useful to predict the onset of rhabdomyolysis. Muscle enzyme levels need not be checked regularly unless patients develop myalgias or other muscle symptoms. If statin-induced muscle damage is suspected, statin use is stopped and CK may be measured. When muscle symptoms subside, a lower dose or a different statin can be tried. If symptoms do not subside within 1 to 2 weeks of stopping the statin, another cause should be sought for the muscle symptoms (eg, polymyalgia rheumatica).

Treatment references

1. Grundy SM, Stone NJ, Bailey AL, et al: 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation 139: e1082–e1143, 2019. doi: 10.1161/CIR.0000000000000625

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Key Points

- **Elevated lipid levels are a risk factor for atherosclerosis and thus can lead to symptomatic coronary artery disease and peripheral arterial disease.**
- **Causes of dyslipidemia include a sedentary lifestyle with excessive dietary intake of calories, saturated fat, cholesterol, and trans fats and/or genetic (familial) abnormalities of lipid metabolism.**
- **Diagnose using serum lipid profile (measured total cholesterol, triglycerides, and high-density lipoprotein [HDL] cholesterol and calculated low-density lipoprotein [LDL]**

density lipoprotein [HDL] cholesterol and calculated low-density lipoprotein [LDL] cholesterol and very low-density lipoprotein [VLDL]).

- Screening tests should be done at age 9 to 11 years and again at age 17 to 21 years (age 2 to 8 if there is a strong family history of severe hyperlipidemia or premature coronary artery disease or other risk factors); adults are screened every 5 years beginning at age 20.
- Treatment with a statin is indicated to reduce risk of atherosclerotic cardiovascular disease for all patients in 4 major risk groups as defined by the American College of Cardiology/American Heart Association and for those without who have certain other combinations of risk factors and elevated lipid levels.
- Optimize adherence, lifestyle changes, and statin usage before adding a non-statin drug; if a patient has an LDL cholesterol level > 70 mg/dL (> 1.8 mmol/L) with high risk atherosclerotic cardiovascular disease, adding ezetimibe or PSCK9 inhibitor is reasonable.
- Other treatment depends on the specific lipid abnormality but should always include lifestyle changes, treatment of hypertension and diabetes, smoking cessation, and in some patients with increased risk of myocardial infarction or death due to coronary artery disease, daily low-dose aspirin.