Chapter 8: Dyslipidemia

INTRODUCTION

- *Dyslipidemia* is defined as elevated total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), or triglycerides (TG); low high-density lipoprotein cholesterol (HDL-C); or a combination of these abnormalities.

PATHOPHYSIOLOGY

- Cholesterol, triglycerides, and phospholipids are transported in blood as complexes of lipids and proteins (lipoproteins). Lipid abnormalities increase the risk of coronary, cerebrovascular, and peripheral arterial disease, collectively known as atherosclerotic cardiovascular disease (ASCVD).
- Atherogenesis is a progressive process initiated by migration of LDL-C and remnant lipoprotein particles into vessel walls. These particles undergo oxidation and are taken up by macrophages, which induces endothelial cell dysfunction that reduces the ability of the endothelium to dilate the artery and causes a prothrombotic state. Unregulated uptake of cholesterol by macrophages leads to foam cell formation and the development of atherosclerotic plaques. Macrophages eventually produce and secrete matrix metalloproteinases, which degrade the collagen matrix of the plaques and cause them to be unstable.
- Repeated injury and repair within an atherosclerotic plaque eventually lead to a fibrous cap protecting the underlying core of lipids, collagen, calcium, and inflammatory cells. Maintenance of the fibrous plaque is critical to prevent plaque rupture and coronary thrombosis. Potential clinical outcomes include angina, myocardial infarction (MI), arrhythmias, stroke, peripheral arterial disease, abdominal aortic aneurysm, and sudden death.
- Primary dyslipidemias include genetic defects resulting in hypercholesterolemia, hypertriglyceridemia, combined hyperlipidemia, and disorders of HDL-C metabolism and an excess of lipoproteins. These disorders have an increased risk of premature ASCVD due to significant elevations in cholesterol levels. In homozygous and heterozygous familial hypercholesterolemia (FH), the primary defect is the inability to bind LDL-C to LDL-C receptors. This leads to lack of LDL-C degradation by cells and unregulated biosynthesis of cholesterol.
- Secondary or acquired dyslipidemias can accompany genetic disorders and may be associated with diet (excessive alcohol use, anorexia, weight gain, excessive intake of carbohydrates or saturated fat), medications (eg, progestins, thiazide diuretics, glucocorticoids, β-blockers, isotretinoin, protease inhibitors, cyclosporine, mirtazapine, sirolimus), and comorbid conditions (eg, nephrotic syndrome, renal failure, hypothyroidism, obesity, diabetes).

CLINICAL PRESENTATION AND DIAGNOSIS

- Most patients are asymptomatic for years before they develop ASCVD, which may produce symptoms including chest pain, palpitations, sweating, anxiety, shortness of breath, loss of consciousness, difficulty with speech or movement, or abdominal pain.
- Perform a thorough medical history in patients presenting with dyslipidemia, including individual characteristics (age, race, gender, pregnancy), history of high-risk comorbid conditions (eg, hypertension, diabetes, peripheral arterial disease, coronary heart disease [CHD], chronic kidney disease [CKD], carotid artery stenosis), family history (eg, early-onset CHD), current medication and prior lipid-lowering medication use, lifestyle assessment (smoking status, exercise, diet, alcohol use), and ischemic symptoms.
- Measure height, weight, BMI, and blood pressure. Physical signs may include eruptive xanthomas, peripheral polyneuropathy, increased blood pressure, and abdominal obesity.

- Laboratory tests may show elevated TC, LDL-C, TG, apolipoprotein B, and high-sensitivity C-reactive protein (hsCRP); HDL-C may be low. Perform other baseline testing (eg, AST/ALT, TSH, glucose, serum creatinine, BUN, and urinalysis). Calculate 10-year ASCVD risk in primary prevention situations.
- Screening may be conducted for manifestations of vascular disease, including carotid ultrasound, coronary calcium score, ankle-brachial index, and heart catheterization.

TREATMENT

- Goals of Treatment: Prevent ASCVD-related morbidity and mortality, including revascularization procedures, MI, and ischemic stroke. Surrogate markers include achieving desired levels of TC, LDL-C, HDL-C, and TG (**Table 8-1**).

TABLE 8-1

Classification of Total-, LDL-, HDL-Cholesterol, and Triglycerides in Adults

Total Cholesterol	
<200 mg/dL (5.17 mmol/L) 200–239 mg/dL (5.17–6.20 mmol/L) ≥240 mg/dL (6.21 mmol/L)	Desirable Borderline high High
Low-Density Lipoprotein Cholesterol	
<100 mg/dL (2.59 mmol/L) 100–129 mg/dL (2.59–3.35 mmol/L) 130–159 mg/dL (3.36–4.13 mmol/L) 160–189 mg/dL (4.14–4.90 mmol/L) ≥190 mg/dL (4.91 mmol/L)	Optimal Near or above optimal Borderline high High Very high
High-Density Lipoprotein Cholesterol	
<40 mg/dL (1.03 mmol/L) <50 mg/dL (1.3 mmol/L)	Low (Men) Low (Women)
Triglycerides	
<150 mg/dL (1.70 mmol/L) 150–199 mg/dL (1.70–2.25 mmol/L) 200–499 mg/dL (2.26–5.64 mmol/L) ≥500 mg/dL (5.65 mmol/L)	Normal Borderline high High Very high

General Approach

- A comprehensive approach to treating dyslipidemia and modifiable major ASCVD risk factors is required to reduce the risk of first and recurrent ASCVD events. Therapeutic lifestyle changes (TLC) are first-line therapy for any lipoprotein disorder, including reducing the percent of calories from saturated and trans fats, increased intake of soluble fiber, weight reduction if overweight or obese, increased physical activity, and avoiding or quitting tobacco use. Hypertensive patients should achieve optimal blood pressure control, and persons with diabetes mellitus should receive glucose-lowering therapies known to reduce ASCVD risk.

- If TLC is insufficient, lipid-lowering agents should be chosen based on which lipid is at an undesirable level and the degree to which it is expected to increase the risk of ASCVD. The decision to initiate lipid-lowering therapy should be based on an individual's ASCVD risk and not merely plasma levels of atherogenic lipoproteins (eg, LDL-C) alone. Patients with established ASCVD are at highest risk and most likely to benefit from lipid-lowering therapy. Risk assessment in patients without established ASCVD requires careful consideration of risk factors, the risks of lipid-lowering therapy, and patient preference. For patients between 40 and 79 years of age and no history of ASCVD, the ASCVD Risk Estimator Plus (www.tools.acc.org/ascvd-risk-estimator-plus) should be used to facilitate a clinician–patient discussion regarding the benefits and risks of lipid-lowering therapy, especially in patients whose 10-year risk is ≥7.5%. An estimated lifetime risk for ASCVD can also be performed for patients between ages 20 and 39, but the results should only be used to justify the need for lifestyle changes and not initiation of lipid-lowering therapy.
- HMG-CoA reductase inhibitors (statins) are the drugs of choice for most patients with dyslipidemia based on demonstrated effectiveness in reducing first and recurrent cardiovascular (CV) events, CV mortality, and all-cause mortality. The 2018 American College of Cardiology/American Heart Association (ACC/AHA) Blood Cholesterol Guideline identified patient groups for whom clinical trial data demonstrate clear evidence that the benefits of statin therapy outweigh the potential risks (**Table 8-2**).
- Nonstatin therapies (eg, ezetimibe, PCSK9 inhibitors) may be added when adequate LDL-C lowering cannot be achieved with statins alone or in patients unable to tolerate the recommended dose of a statin.

TABLE 8-2

Key Recommendations to Reduce the Risk of ASCVD in Adults[a]

Heart-healthy lifestyle for everyone	
Patient Groups Likely to Benefit from Statin Therapy	
Clinical ASCVD[b]	
Very high risk[c]	High-intensity or maximally tolerated statin therapy (Class I)
Not at very high risk	
Age <75 years	High-intensity statin therapy (Class I) If high-intensity not tolerated, use moderate-intensity statin therapy (Class I)
Age >75 years	Initiation of moderate- or high-intensity statin is reasonable (Class IIa)
1. Primary prevention: Severe hypercholesterolemia (LDL-C ≥190 mg/dL [4.91 mmol/L])	Rule out secondary causes of dyslipidemia Age 20–75 years: Maximally tolerated statin therapy (Class I)
2. Primary prevention: Diabetes 40–75 years and LDL-C 70–189 mg/dL (1.81–4.89 mmol/L)	Moderate-intensity statin therapy regardless of 10-year ASCVD risk (Class I) High-intensity statin therapy is reasonable in patients with diabetes and multiple ASCVD risk factors (Class IIa) It is reasonable to continue statin therapy in adults ≥75 years of age with diabetes previously taking statin therapy (Class IIa) It is reasonable to initiate statin therapy in adults ≥75 years of age with diabetes after a discussion of risks and benefits (Class IIb) It is reasonable to initiate statin therapy in adults 20–30 years of age with diabetes if any of the following apply (Class IIb): • Long duration of diabetes (≥10 years for type 2 diabetes; ≥20 years for type 1 diabetes)

	• Albuminuria (≥30 mg/g albumin/mg creatinine [3.4 mg/mmol creatinine]) • Estimated glomerular filtration rate <60 mL/min/1.73 m^2 • Retinopathy • Neuropathy • Ankle-brachial index <0.9
3. Primary prevention: No diabetes, 40–75 years, and LDL-C 70–189 mg/dL (1.81–4.89 mmol/L)	Emphasize heart-healthy lifestyle and address other risk factors Estimate 10-year ASCVD-risk score based on Pooled Cohort Equation: • High Risk (≥20%): Initiate high-intensity statin therapy (Class I) • Intermediate Risk (≥7.5% to <20%): If risk enhancers[d] present, consider moderate-intensity statin therapy (Class I) • If risk decision is uncertain, consider measuring CAC in select adults: ✔ Consider no statin if CAC = 0 unless patient has diabetes or significant family history of ASCVD ✔ Consider initiating statin therapy if CAC 1–99, especially if age >55 years ✔ Initiate statin therapy if CAC ≥100 • Borderline risk (5%–<7.5%): If risk enhancers[d] present, risk discussion regarding moderate-intensity statin therapy (Class IIb) • Low risk (<5%): Emphasize heart-healthy lifestyle (Class I)
4. Primary prevention: No diabetes, 20–39 years, and LDL-C 70–189 mg/dL (1.81–4.89 mmol/L)	Estimate lifetime ASCVD-risk based on Pooled Cohort Equation to encourage lifestyle to reduce ASCVD risk Consider statin therapy if family history of premature ASCVD and LDL-C ≥160 mg/dL (4.14 mmol/L)

[a]American College of Cardiology/American Heart Association (ACC/AHA) Level of Evidence and Class of Recommendation.

[b]Clinical ASCVD includes nonfatal MI, CHD death, and nonfatal and fatal stroke, TIA or peripheral arterial disease presumed to be of atherosclerotic origin.

[c]Very high risk includes history of >1 major ASCVD events including recent acute coronary syndrome (past 12 months), history of MI, ischemic stroke, or peripheral arterial disease; OR one major ASCVD event PLUS multiple high-risk conditions: >65 years, familial hypercholesterolemia, history of coronary bypass graft surgery, diabetes mellitus, hypertension, CKD, current smoking, LDL-C >100 mg/dL (2.59 mmol/L) despite maximally tolerated statin and ezetimibe, or history of heart failure.

[d]Risk enhancers include LDL-C 160–189 mg/dL (4.14–4.89 mmol/L), family history of premature ASCVD, metabolic syndrome, CKD, chronic inflammatory conditions (eg, rheumatoid arthritis), premature menopause (before age 40), preeclampsia, high-risk race/ethnicities (eg, South Asian), TG ≥175 mg/dL (1.98 mmol/L), hsCRP ≥2 mg/L, lipoprotein(a) ≥50 mg/dL (0.5 g/L), apoB ≥130 mg/dL (1.3 g/L), or ankle-brachial index <0.9.

ASCVD, atherosclerotic cardiovascular disease; CAC, coronary artery calcium; CKD, chronic kidney disease; hsCRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; NYHA, New York Heart Association.

Nonpharmacologic Therapy

- Employ TLC in all patients, including those receiving lipid-lowering therapy. Lifestyle modification alone is inappropriate for patients with established ASCVD given the benefit of statins in these high-risk patients.
- Determine weight and BMI at each visit and discuss lifestyle changes to induce a 5%–10% weight loss in overweight or obese persons.

- Recommend moderate-to-vigorous intensity physical activity three to four times per week with each session lasting 40 minutes on average.
- Counsel all patients to stop smoking and avoid tobacco products altogether.
- Advise patients to reduce the percent of daily calories from saturated and trans fats by following a diet that emphasizes vegetables, fruits, whole grains, low-fat dairy, poultry, fish, legumes, and nuts while limiting intake of sweets, sugary beverages, and red meat. Adapt the dietary pattern to a patient's caloric requirements, cultural food preferences, and other medical conditions (eg, diabetes mellitus). It is important to involve all family members, especially if the patient is not the primary person preparing food.
- Increased intake of soluble fiber (oat bran, pectins, certain gums, and psyllium) can reduce total and LDL cholesterol but has little effect on HDL-C or TG. Total daily fiber intake should be about 25 g/day. Fiber products may also help manage constipation associated with bile acid sequestrants (BAS).
- Ingestion of modest to large amounts of oily, cold-water fish (eg, salmon, tuna) may provide CV benefits; however, there are concerns about environmental contaminants and long-term sustainability. Alternatively, fish oil supplementation provides a consistent daily intake of omega-3 polyunsaturated fatty acids (PUFA) such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) (see Pharmacologic Therapy section below).
- Ingestion of 2–3 g daily of plant sterols and stanols isolated from vegetable oils reduces LDL-C by 5%–15%. They are usually available in butter-like spreads (eg, Benecol). Phytosterols should be administered 2–4 hours before or after BAS to avoid binding of phytosterols in the gut.
- Red yeast rice contains monacolin K, which is chemically identical to lovastatin. However, the amount of monacolin K in OTC products varies by over 120-fold, with some products containing negligible amounts and others likely having higher levels than described on the label, resulting in cases of rhabdomyolysis, liver toxicity, and renal failure. Red yeast rice is not a suitable alternative to statins, but if patients choose to take it, recommend that they purchase a reputable product and avoid concurrent use with prescription statins.

Pharmacologic Therapy

- Evidence from controlled clinical trials demonstrates that reducing LDL-C lowers ASCVD event rates in the setting of primary and secondary prevention. Epidemiological studies suggest that every 38 mg/dL (0.98 mmol/L) reduction in LDL-C produces a 21% reduction in ASCVD event rates over 5 years. There is a dose-dependent, log-linear association between LDL-C and ASCVD risk, and evidence suggests that lower levels of LDL-C achieve greater risk reductions.
- Lipid-lowering drugs can be broadly divided into agents that primarily decrease atherogenic cholesterol-containing lipoprotein particles (eg, statins) and those that primarily decrease TG levels (eg, fibrates).

Statins

- Statins inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, interrupting conversion of HMG-CoA to mevalonate, the rate-limiting step in cholesterol biosynthesis. Reduced LDL synthesis and enhanced LDL catabolism mediated through LDL receptors appear to be the principal mechanisms for lipid-lowering effects.
- Statins significantly reduce LDL-C (20%–60%), modestly increase HDL-C (6%–12%), and decrease TG (10%–29%).
- Statins are first-line lipid-lowering therapy for dyslipidemia due to strong evidence from many controlled trials demonstrating significant reduction in the risk of first (primary prevention) and recurrent (secondary prevention) CV events.
- Statin selection is primarily based on the indicated intensity (**Table 8-3**). Products in order of decreasing LDL-C lowering potency include **rosuvastatin**, **atorvastatin**, **pitavastatin**, **simvastatin**, **lovastatin**, **pravastatin**, and **fluvastatin**.
- Statins are generally well tolerated. Statin-associated muscle symptoms (SAMS) are reported by 10%–25% of users and are often a reason for discontinuation. Myalgia is the most common SAMS and involves bilateral muscle achiness, weakness, or cramps affecting larger muscle groups (such as thighs and back). The most concerning SAMS is rhabdomyolysis, which is rapid breakdown of skeletal muscle resulting in creatine kinase

(CK) elevations >10 times the upper limit of normal and potentially acute kidney injury. Rhabdomyolysis may be associated with dark ("tea-colored") urine, nausea, vomiting, confusion, coma, cardiac arrhythmias, electrolyte disturbances, and even death. Fortunately, rhabdomyolysis is quite rare (0.1% of statin-treated patients vs 0.04% of patients receiving placebo in controlled clinical trials). Risk factors for developing SAMS include advanced age, female gender, low body mass index, frequent heavy exercisers, comorbidities (eg, kidney disease, hypothyroidism), and increased serum statin concentrations due to drug–drug interactions. Lower starting doses may be advisable for patients with multiple risk factors, with dose titration to the desired potency after the initial dose is tolerated.

- Statins (except pravastatin) are metabolized to some degree by CYP isoenzymes. Lovastatin, simvastatin, and atorvastatin have more significant drug–drug interactions because they are predominantly metabolized by CYP3A4, whereas fluvastatin, pitavastatin, and rosuvastatin are metabolized by other CYP isoenzymes (eg, CYP2C9, CYP2C8, CYP2C19). Concurrent medications that compete with or inhibit the same CYP isoenzyme can increase serum statin concentrations and the risk for SAMS. Concurrent use of medications such as gemfibrozil that interfere with statin glucuronidation, which is responsible for statin clearance, also increase the risk of SAMS.

- A Statin Intolerance App (http://www.acc.org/statinintoleranceapp) can be used to determine the possibility of SAMS and provide guidance on managing patients with possible SAMS. Statin therapy should generally be discontinued in patients with intolerable symptoms. If symptoms resolve, start a different statin at a lower dose. Additionally, hydrophilic statins (eg, atorvastatin, rosuvastatin) may be better tolerated than lipophilic statins (eg, simvastatin). If symptoms do not improve, investigate other potential causes of muscle pain (eg, hypothyroidism, severe vitamin D deficiency) before a statin rechallenge. Every-other-day dosing using statins with long half-lives (eg, atorvastatin, rosuvastatin) may also be considered. Nonstatin therapies may be considered in patients who fail multiple statins. Routine CK monitoring is not recommended, but testing in a patient with symptoms can be used to exclude rhabdomyolysis and help confirm myalgia.

- Mild elevations in serum transaminase levels (primarily alanine aminotransferase [ALT]) may occur, but routine monitoring of liver enzymes is not recommended. Obtain hepatic enzymes before starting statin therapy as a baseline value for comparison if enzymes are later found to be elevated. Statins may be initiated in patients with chronic liver disease, compensated cirrhosis, and nonalcoholic fatty liver disease but are contraindicated in decompensated cirrhosis or acute liver failure.

- Statin use is also associated with a small (<1%) increased risk of new-onset diabetes. Common attributes of statin users who develop new-onset diabetes include higher statin doses and presence of other risk factors for diabetes, including obesity, impaired fasting glucose, A1C >6% (0.06; 42 mmol/mol Hb), or metabolic syndrome.

- Statin products and usual adult starting doses are provided in **Table 8-4**.

TABLE 8-3

Intensity of Statin Therapy by Drug and Dose

High-Intensity Therapy	Moderate-Intensity Therapy	Low-Intensity Therapy
Daily dose lowers LDL on average by ≥50%	Daily dose lowers LDL on average by 30% to <50%	Daily dose lowers LDL on average by <30%
Atorvastatin 40–80 mg **Rosuvastatin 20–40 mg**	**Atorvastatin 10–20 mg** **Rosuvastatin 5–20 mg** **Simvastatin 20–40 mg**[a] **Pravastatin 40–80 mg** **Lovastatin 40 mg** Fluvastatin XL 80 mg **Fluvastatin 40 mg BID** Pitavastatin 2–4 mg	Simvastatin 10 mg **Pravastatin 10–20 mg** **Lovastatin 20 mg** Fluvastatin 20–40 mg Pitavastatin 1 mg

[a]Simvastatin is not recommended by the U.S. Food and Drug Administration (FDA) to be started at 80 mg/day due to increased risk of myopathy and rarely rhabdomyolysis.

Boldface type indicates medications that have cardiovascular outcome data from randomized controlled trials when given in the specified dose.

TABLE 8-4

Select Drugs Used for Treatment of Dyslipidemia

Generic (Brand) Name	Dosage Forms	Recommended Adult Starting Dose	Maximum Total Daily Dose
Statins			
Rosuvastatin (Crestor)	5, 10, 20, 40 mg tablets	5 mg once daily	40 mg
Atorvastatin (Lipitor)	10, 20, 40, 80 mg tablets	10–20 mg once daily	80 mg
Pitavastatin (Livalo)	1, 2, 4 mg tablets	2 mg once daily	4 mg
Simvastatin (Zocor)	5, 10, 20, 40, 80 mg tablets	10–20 mg once daily	80 mg
Lovastatin (Mevacor)	20, 40 mg tablets	20 mg once daily with the evening meal	80 mg
Pravastatin (Pravachol)	20, 40, 80 mg tablets	40 mg once daily	80 mg
Fluvastatin (Lescol)	20, 40 mg capsules; 80 mg XL tablets	40–80 mg once daily	80 mg
Cholesterol Absorption Inhibitors			
Ezetimibe (Zetia)	10 mg tablets	10 mg once daily	10 mg
Colesevelam (Welchol)	625 mg tablets; 3.75 and 1.875 g oral	6 tablets once daily or 3 tablets twice daily; suspension: 3.75	3750 mg

	suspension packets	g packet once daily or one 1.875 g packet twice daily	
Colestipol hydrochloride (Colestid)	1 g tablets; 5 g granule packets, bulk powder	Tablets: 2 g once or twice daily; granules: 5 g once or twice daily	16 g tablets; 30 g packets
Cholestyramine (Questran)	4 g packets, bulk powder	4 g once or twice daily	24 g
Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Inhibitors			
Alirocumab (Praluent)	75 mg, 150 mg SC injection	75 mg SC every 2 weeks	150 mg
Evolocumab (Repatha)	140 mg, 420 mg SC injection	140 mg SC every 2 weeks or 420 mg SC once monthly	420 mg
Fibric Acid Derivatives (Fibrates)			
Gemfibrozil (Lopid)	600 mg capsules	600 mg twice daily	1200 mg
Fenofibrate (Tricor, others)	(product dependent)	(product dependent)	(product dependent)
Omega-3 Polyunsaturated Fatty Acids (PUFA)			
Omega-3-acid ethyl esters (Lovaza)	1 g capsules	4 capsules once daily or 2 capsules twice daily	4 g
Omega-3-carboxylic acids (Epanova)	1 g capsules	2 or 4 capsules once daily	4 g
Icosapent ethyl (Vascepa)	0.5, 1 g capsules	Four 0.5 g capsules or two 1 g capsules twice daily	2 g
Niacin			
Niacin (generic)	50, 100, 250, 500 mg tablets; others	250 mg once daily	6 g
Extended-release niacin (Niaspan)	500, 750, 1000 mg tablets	500 mg once daily	2 g
Mipomersen (Kynamro)	200 mg SC injection	200 mg SC once weekly	200 mg
Lomitapide (Juxtapid)	5, 10, 20 mg capsules	5 mg once daily	60 mg
Select Combination Products			
Extended-release niacin + lovastatin tablets (Advicor)	Niacin/lovastatin 500 mg/20 mg, 750 mg/20 mg, 1000 mg/20 mg, 1000 mg/40 mg	500 mg/20 mg once daily at bedtime	1000 mg/40 mg
Ezetimibe + simvastatin tablets (Vytorin)	Ezetimibe/simvastatin 10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg, 10 mg/80 mg	10 mg/10 mg or 10 mg/20 mg once daily	10 mg/80 mg

SC, subcutaneously.

Cholesterol Absorption Inhibitors

- **Ezetimibe** (**Table 8-4**) is a preferred adjunct therapy because it modestly reduces the risk of recurrent CV events when used in combination with statin therapy. Its primary effect is modest reduction in LDL-C (15%–24%) with higher reductions achievable in combination with statin therapy. Ezetimibe reduces LDL-C by inhibiting the NPC1L1 protein, an important transporter of cholesterol absorption in the small intestine and hepatocytes. Ezetimibe is generally well tolerated and is associated with mild gastrointestinal (GI) complaints (eg, diarrhea), myalgia, and ALT elevations when used with statins. Ezetimibe has no effects on the CYP450 enzyme system; however, concomitant use with cyclosporine can lead to increased exposure to both ezetimibe and cyclosporine.

- **Colesevelam**, **colestipol**, and **cholestyramine** are BAS that modestly reduce LDL-C (13%–20%) and reduce CV events when used as monotherapy (**Table 8-4**). They are generally combined with statins when desired LDL-C levels are not achieved with statins alone. BAS are considered first line during pregnancy because they are not systemically absorbed and pose no risk to the fetus.

  ✔ BAS bind bile acids in the intestinal lumen, interrupting enterohepatic circulation of bile acids, which decreases the bile acid pool size and stimulates hepatic synthesis of bile acids from cholesterol. Depletion of the hepatic cholesterol pool increases cholesterol biosynthesis and the number of LDL receptors on hepatocyte membranes, which enhances the rate of catabolism from plasma and lowers LDL levels. Increased hepatic cholesterol biosynthesis may be paralleled by increased hepatic VLDL production; consequently, BAS may aggravate hypertriglyceridemia and should be avoided in patients with TG levels >300 mg/dL (3.39 mmol/L).

  ✔ Cholestyramine powders that require mixing with water or juice to create a slurry for oral administration are associated with GI complaints of constipation, bloating, epigastric fullness, nausea, and flatulence. These effects can be minimized by increasing fluid intake, increasing dietary bulk, and using stool softeners. Tablet forms of colesevelam are generally better tolerated than resin powders. Other potential adverse effects include impaired absorption of fat-soluble vitamins A, D, E, and K; GI obstruction; and reduced bioavailability of other drugs such as warfarin, levothyroxine, and phenytoin. Drug–drug interactions may be avoided by taking other medications 1 hour before or 4 hours after the BAS.

  ✔ Given the better safety and tolerability profile of ezetimibe, BAS should be reserved for patients unable to tolerate ezetimibe who need additional LDL-C lowering despite maximally tolerated statin therapy.

Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Inhibitors

- **Alirocumab** and **evolocumab** are fully human monoclonal antibodies to PCSK9; inhibiting PCSK9 promotes intracellular degradation of hepatic LDL-C, prevents LDL receptor recycling to the cell surface, and reduces LDL-C clearance from the circulation. They reduce LDL-C by as much as 60% when added to statin therapy. Clinical trials have shown that these agents reduce recurrent CV events when added to statin therapy. The drugs are administered by subcutaneous injection either biweekly or once monthly.

- The most common adverse effect is injection site reactions, which can be minimized by allowing the injection to come to room temperature before use and icing the site before injecting. Some patients report flu-like symptoms after the injection. Patients who reach very low LDL-C levels (<20 mg/dL [0.53 mmol/L]) do not appear to be at increased risk of adverse events. Nevertheless, the long-term effects of achieving very low LDL-C levels remain unknown.

- Despite their favorable clinical benefits, PCSK9 inhibitor use has been limited because of high cost. Although these agents should primarily be used in combination with maximally tolerated statins in high-risk patients unable to achieve desired LDL-C levels with a statin alone, evolocumab is FDA-approved for use as monotherapy in patients with primary hyperlipidemia (such as heterozygous FH).

Fibric Acid Derivatives (Fibrates)

- **Gemfibrozil** and **fenofibrate** are potent TG-lowering therapies (20%–50%) but may cause a modest reciprocal rise in LDL-C in patients with severely elevated TG levels. Plasma HDL concentrations may rise 10%–15% or more with fibrates. Gemfibrozil increases the activity of lipoprotein lipase (LPL) and reduces secretion of VLDL from the liver into the plasma. Fenofibrate increases LPL activity and reduces apoprotein C-III (an inhibitor of LPL) by activating peroxisome-proliferator-activated receptor α (PPARα), which regulates the expression of genes involved in the

regulation of lipids and other metabolic processes.

- Fibrates have been shown to reduce CV events when used as monotherapy, but there is less evidence to support combination therapy with statins. Fibrates are primarily used in patients with TG levels >500 mg/dL (5.65 mmol/L) to reduce the risk of acute pancreatitis.
- Fibrates are generally well tolerated, but GI complaints and transient hepatic transaminase elevations have been reported. Both agents require dose adjustments for significant renal impairment, and fenofibrate has been reported to transiently worsen renal function.
- SAMS can occur when fibrates are used alone but are more common when used in combination with statins. Gemfibrozil and its glucuronide metabolite have potent effects on CYP450 enzymes (such as CYP3A4) and intestinal, hepatic, and renal transporters making it highly prone to significantly increase serum statin concentrations and the risk of SAMS. Consequently, current guidelines do not recommend gemfibrozil in patients receiving statin therapy; fenofibrate should be used instead.
- Fenofibrate and gemfibrozil may rarely enhance gallstone formation. Fibrates may potentiate the effects of warfarin; the international normalized ratio (INR) should be monitored closely with this combination.

Omega-3 Polyunsaturated Fatty Acids (PUFA)

- High doses of omega-3 PUFA (2–4 g/day of EPA/DHA) significantly reduce TG and VLDL cholesterol levels (20%–50%), but PUFA supplementation has either no effect on TC and LDL-C or may cause slight elevations. Omega-3 PUFA reduce TG levels by increasing hepatic oxidation of free fatty acids, increasing LDL hydrolysis by activating PPARα, and inhibiting apoprotein C-III.
- The omega-3 PUFA formulations approved by the FDA for treating TG levels ≥500 mg/dL (5.65 mmol/L) include **omega-3-acid ethyl esters of EPA/DHA** (Lovaza), **omega-3-carboxylic acids of EPA/DHA** (Epanova), and **ethyl ester of EPA only** (icosapent ethyl; Vascepa). Prescription omega-3 PUFA products contain approximately 1 g of EPA/DHA per capsule, whereas the EPA/DHA content of non–FDA-regulated OTC fish oil supplements is often <300 mg per capsule. Unless patient affordability is an issue, prescription omega-3 PUFA are preferred to minimize pill burden and ensure product quality.
- Randomized clinical trials of omega-3 PUFA have shown mixed results due to variability in study designs and products used. Current recommendations suggest that low-dose omega-3 PUFA supplementation is reasonable in secondary prevention patients with heart failure or at high risk of sudden cardiac death. Low-dose omega-3 PUFA supplementation is not recommended for primary prevention, especially in patients with diabetes. In late 2019, icosapent ethyl received U.S. FDA approval for reducing the risk of CV events in adults with triglyceride levels ≥150 mg/dL and with established CV disease or diabetes plus at least two other CV risk factors and who are already taking maximally tolerated doses of statins.
- GI complaints (eg, abdominal pain, “fishy burps”) are common with OTC omega-3 PUFA products but may be minimized by refrigerating the capsules. These products should be used with caution in patients with known sensitivities or allergies to fish or shellfish. Drug–drug interactions are minimal with omega-3 PUFA, although caution is advised when used concomitantly with antiplatelet agents or anticoagulants because omega-3 PUFA may prolong bleeding time.

Niacin

- **Niacin (nicotinic acid)** lowers TG levels (20%–50%) by inhibiting lipolysis with a decrease in free fatty acids in plasma and decreased hepatic esterification of TG. It also significantly raises HDL-C (5%–30%) by reducing its catabolism and decreasing hepatic removal. Niacin reduces hepatic synthesis of VLDL, leading to a modest dose-dependent decrease in LDL-C (5%–20%). Despite these favorable changes, niacin has not been shown to improve CV outcomes in patients already receiving statin therapy with relatively well-controlled lipids at baseline.
- Adverse events frequently limit niacin use. Cutaneous flushing and itching appear to be prostaglandin mediated and can be reduced by taking aspirin 325 mg shortly before niacin ingestion. Flushing seems to be related to rising plasma niacin concentrations and use of immediate-release formulations; taking the dose with meals and slowly titrating the dose upward may also minimize these effects. Concomitant alcohol and hot drinks may magnify flushing and pruritus with niacin and should be avoided at the time of ingestion.
- Niaspan, the only prescription form, is an extended-release product with pharmacokinetics intermediate between immediate- and sustained-

release products that are sold as OTC dietary supplements. In controlled trials, Niaspan had fewer dermatologic reactions and a lower risk for hepatotoxicity.

- Niacin therapy may be associated with elevated hepatic enzymes, hyperuricemia, and hyperglycemia. It is contraindicated in patients with active liver disease and active peptic ulcer disease. Nicotinamide should not be used as an alternative to niacin because it does not effectively lower cholesterol or triglyceride levels.

Mipomersen

- **Mipomersen** is indicated as an adjunct to diet and lipid-lowering treatments to reduce LDL-C, TC, apolipoprotein B, and non-HDL-C in patients with homozygous FH. It is an oligonucleotide inhibitor of apolipoprotein B-100 synthesis. When given in combination with maximum tolerated doses of lipid-lowering therapy, mipomersen can produce an additional 25% reduction in LDL-C. Adverse reactions include injection site reactions, flu-like symptoms, nausea, headache, and elevations in serum transaminases. The labeling contains a black box warning for severe hepatotoxicity, and mipomersen is only available through a restricted Risk Evaluation and Mitigation Strategy (REMS) program.

Lomitapide

- **Lomitapide** has the same indication for FH as mipomersen. Lomitapide is a microsomal triglyceride transfer protein (MTP) inhibitor that reduces the amount of cholesterol that the liver and intestines assemble and secrete into the circulation. It may reduce LDL cholesterol by about 40% in patients on maximum tolerated lipid-lowering therapy and LDL apheresis. Like mipomersen, lomitapide contains a black box warning for severe hepatotoxicity and is only available through a restricted REMS program.

Treatment Recommendations

Familial Hypercholesterolemia

- Persons with FH have a very high lifetime risk of developing ASCVD. FH should be suspected in adults with untreated LDL-C levels ≥190 mg/dL (4.91 mmol/L) or non-HDL-C levels ≥220 mg/dL (5.69 mmol/L) who have a family history of high cholesterol or ASCVD in first-degree relatives.
- Mipomersen and lomitapide are indicated for patients with FH and reduce LDL-C levels by ~25% and ~40%, respectively, when added to maximum tolerated doses of lipid-lowering therapy.
- Other treatment options for FH patients include LDL apheresis (a process that removes LDL from the blood) and liver transplantation.

Hypertriglyceridemia

- Elevated TG levels are strongly associated with increased ASCVD risk, but the direct role of TG in ASCVD development is debatable.
- Advise all patients with elevated TG to implement lifestyle interventions shown to reduce TG levels, including 5%–10% reduction in body weight, reduced consumption of sugar and refined carbohydrates, increased physical activity, smoking cessation, and restricted alcohol intake.
- Identify and address secondary causes of hypertriglyceridemia (eg, uncontrolled diabetes and CKD, medications such as protease inhibitors and atypical antipsychotics).
- Statins are generally considered first-line therapy after optimizing lifestyle interventions and addressing secondary causes; they can reduce TG levels by up to 30% at higher doses and help achieve desired levels of LDL-C.
- The role of TG-lowering therapies such as fibrates and omega-3 PUFA in patients with TG of 200–499 mg/dL (2.26–5.64 mmol/L) is unclear.
- Fasting TG levels >500 mg/dL (5.65 mmol/L) are associated with pancreatitis and other complications. Dietary fat restriction is essential because it reduces synthesis and entry of additional chylomicrons into the circulation. Lipid-lowering therapies that primarily lower TG (eg, fibrates, omega-3 PUFA, niacin) are recommended as first-line agents. Statins may be reasonable first-line options in patients with an ASCVD risk of ≥7.5%. Treatment success is defined as reducing TG below 500 mg/dL (5.65 mmol/L) and preventing pancreatitis.

Low HDL Cholesterol

- Low HDL-C is a strong independent risk predictor of CHD and is defined as <40 mg/dL (1.03 mmol/L) for men and <50 mg/dL (1.29 mmol/L) for women. There is no specified goal for HDL-C raising, and the primary target in these patients remains lowering LDL-C.
- Lifestyle modifications (eg, smoking cessation, increasing physical activity) are the preferred treatment approach.
- Niacin can produce the greatest increase in HDL-C compared to other lipid-lowering therapies, but no randomized clinical trial data have shown reduction in ASCVD risk by raising HDL-C.

Patients with Diabetes

- Diabetic dyslipidemia is often characterized by hypertriglyceridemia, low HDL-C, and modestly elevated but dense LDL-C forms that are highly atherogenic. Statins are the first-line therapy based on evidence from randomized clinical trials that statins reduce ASCVD events and mortality in persons with diabetes. However, individual risk among patients with no history of ASCVD varies, so the 10-year ASCVD risk score is used to determine the appropriate statin intensity (**Table 8-2**). High-intensity statin therapy is preferred in patients with a history of ASCVD (secondary prevention) because these patients are at very high risk of recurrent ASCVD events.
- The role of nonstatin therapies in patients with diabetes is complex. Both ezetimibe and evolocumab have shown improved outcomes when added to statin therapy. Although diabetes is associated with a mixed dyslipidemia, the combination of fenofibrate and a statin did not reduce the rate of CV events compared to simvastatin alone in patients with type 2 diabetes. Fenofibrate may offer potential benefit with TG levels >204 mg/dL (2.31 mmol/L) and HDL-C <34 mg/dL (0.88 mmol/L), but this has not been evaluated in a prospective clinical trial. Additionally, fenofibrate appears to reduce the progression of diabetic retinopathy and the need for laser treatment. Colesevelam is FDA-approved to improve both glycemic and lipid control, but it can exacerbate hypertriglyceridemia, which is common in diabetes. Niacin modestly increases fasting plasma glucose (4%–5%) and A1C levels (~0.25%); consequently, niacin should not be routinely used in persons with diabetes.

EVALUATION OF THERAPEUTIC OUTCOMES

- For short-term evaluation, obtain a complete lipid panel 4–12 weeks after initiation or following a dose adjustment of lipid-lowering therapy to assess therapeutic response.
- For long-term evaluation, obtain a repeat lipid panel every 3–12 months to ensure adherence to lipid-lowering therapy and maintenance of desired levels of LDL-C.

  ✔ Although TC, HDL-C, and TG levels are directly measured, LDL-C is typically estimated using the Friedewald equation: LDL-C = TC - HDL-C - (TG/5) [or LDL-C = TC - HDL-C - (TG/2.2) when lipid levels are all expressed in mmol/L]. However, the equation does not provide an accurate estimate of VLDL-C and can underestimate LDL-C in patients with high TG or very low LDL-C. Useful alternatives in these patients include non-HDL-C (TC - HDL-C) and direct LDL-C measurements, which are more accurate than estimated LDL-C using the Friedewald equation.

  ✔ A nonfasting lipid panel is generally acceptable except in patients with hypertriglyceridemia, where a fasting lipid panel is preferred to minimize interference from chylomicrons.
- Routine safety monitoring of hepatic function and CK levels is not recommended in statin-treated patients, but these may be obtained if the patient has signs or symptoms suggestive of liver or muscle injury. Perform hepatic function tests in patients taking niacin at baseline, after each dosage increase, and every 6 months thereafter while taking a stable dose.
- Monitor A1C periodically in persons with diabetes receiving niacin and patients treated with statins who are at high risk for developing diabetes.
- In patients treated with lipid-lowering therapy for secondary prevention, symptoms such as angina or intermittent claudication may improve over months to years. Xanthomas or other external manifestations of dyslipidemia should regress with therapy.
- Evaluate modifiable risk factors such as hypertension, smoking, exercise, weight control, and glycemic control in persons with diabetes. Use of food diaries and recall surveys enable collection of information about diet in a systematic manner and may improve patient adherence to dietary

recommendations.

See Chapter 31, Dyslipidemia, authored by Dave L. Dixon and Daniel M. Riche, for a more detailed discussion of this topic.