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Dyslipidemia Management

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Introduction

- What are the causes of dyslipidemia?
- What are current lipid treatment goals?
- What treatments are available for dyslipidemia?
- How should treatment be monitored?
- What special considerations should be given to children, adolescents, and women?

Frederickson Primary Hyperlipidemias

Disease	Primary Type I
Description[1]	• Rare genetic disorder • Also known as ApoCII deficiency, lipoprotein lipase deficiency, or chylomicronemia syndrome
Genetic Defect and Frequency[1]	• Mutations in ApoCII gene (1:1,000,000) or LPL gene • Autosomal recessive
Clinical Findings[1,2]	• Severe HTG (TG >1000 mg/dL, sometimes >10,000 mg/dL) • Partial genetic defects: TG >500 mg/dL • Easily visualizable degrees of chylomicronemia • Eruptive xanthomas • Hepatosplenomegaly • Lipemia retinalis • Focal neurological symptoms (irritability) • Recurrent epigastric pain • Pancreatitis • LPL or ApoCII deficiency
Treatment[3]	• Diet severely restricted in fat (<20 gm/day)

Apo = apolipoprotein; HTG = hypertriglyceridemia; LPL = lipoprotein lipase; TG = triglyceride.

1. Bays HE, et al. *J Clin Lipidol*. 2016 Jan-Feb;10(1 Suppl):S1-43; 2. Yuan G, et al. *CMAJ*. 2007 April;176(8):1113-1120; 3. Burnett JR, et al. Gene Reviews. 2017; Bookshelf ID: NBK1308.

Frederickson Primary Hyperlipidemias

Disease	Primary Type IIa	Primary Type IIb
Description[1]	• Also known as familial hypercholesterolemia	• Also known as familial combined hyperlipidemia
Genetic Defect and Frequency[1,2]	• Polygenic hypercholesterolemia (1:20) – Multiple genetic defects • HeFH (1 in 200 to 1 in 250) • HoFH (1 in 160,000 to 1 in 250,000) • HeFH and HoFH: autosomal dominant; absence or dysfunction of LDL receptor	• Familial combined hyperlipidemia (1:50-1:200) • Multiple genetic defects of various apolipoproteins and/or LPL genes • Autosomal-dominant
Clinical Findings[1,3]	• ↑ LDL-C and/or LPL • Polygenic: ↑LDL-C (>130 mg/dL) • HeFH: ↑ LDL-C (>190 mg/dL) • HoFH: ↑ LDL-C (>350 mg/ dL; often 500-1000 mg/dL) • Polygenic: ↑ ASCVD risk • HeFH and HoFH: Tendon xanthoma and ↑ premature ASCVD risk	• ↑ LDL-C (>160 mg/dL) • ↑ TG (>300 mg/dL) • ↑ VLDL and/or LPL • ↑ premature ASCVD risk
Treatment[4,5]	• Pharmacologic therapy • Dietary control	• Pharmacologic therapy • Dietary control

ASCVD = atherosclerotic cardiovascular disease; FH = familial hypercholesterolemia; HeFH = heterozygous familial hypercholesterolemia; HoFH = homozygous familial hypercholesterolemia; HTG = hypertriglyceridemia; LDL = low-density lipoprotein; LDL-C = low-density lipoprotein cholesterol; LDL-P = low-density lipoprotein particle; LPL = lipoprotein lipase; TG = triglyceride; VLDL = very-low-density lipoprotein.

1. Bays HE, et al. *J Clin Lipidol*. 2016 Jan-Feb;10(1 Suppl):S1-43; 2. Jellinger PS et al. *Endocr Pract.* (2017) Apr;23(Suppl 2):1-87; 3. Yuan G, et al. *CMAJ.* 2007 April;176(8):1113-1120; 4. Youngblom E, et al. Gene Reviews. 2018; Bookshelf ID: NBK1308; Patni N, et al. EndoText. 2016; Bookshelf ID: NBK395584.

Frederickson Hyperlipidemias

Disease	Type III	Type IV	Type V
Description[1]	• Familial dysbetalipoproteinemia	• Familial hypertriglyceridemia	• Hyperprebetalipoproteinemia
Genetic Defect and Frequency[1]	• 1:1000-1:5000 • Genetic defect of apoE gene • Autosomal recessive • More rarely, autosomal dominant	• 1:50-1:100 • Unknown genetic defect • Autosomal dominant	• Unknown frequency; very rare • Unknown genetic defect; possibly related to an LPL inhibitor • Unknown inheritance
Clinical Findings[1,2]	• ↑ TG (>300 mg/dL) • ↑ LDL-C (>220 mg/dL), IDL-C, and/or LDL-P • Palmar xanthomata (orange discoloration of skin creases, tuberoeruptive xantomata of elbows and knees) • ↑ premature ASCVD risk	• ↑ TG (>150 mg/dL), VLDL-C and/or LDL-P • Unclear if ASCVD risk is increased	• ↑ TG (>500 mg/dL) • ↑ CM, VLDL-C, and/or LDL-P • ↑ LDL-C (>130 mg/dL) • Eruptive xanthomas • Pancreatitis • ↑ ASCVD risk • Similar clinical manifestations as Type I but develops in adulthood • Exacerbated by secondary factors
Treatment	• Pharmacologic therapy • Dietary control	• Pharmacologic therapy • Dietary control	• Pharmacologic therapy • Dietary control

Apo = apolipoprotein; ASCVD = atherosclerotic cardiovascular disease; CM = chylomicron; CVD = cardiovascular disease; FH = familial hypercholesterolemia; HTG = hypertriglyceridemia; HTN = hypertension; IDL-C = intermediate-level-density lipoprotein cholesterol; LDL = low-density lipoprotein; LDL-C = low-density lipoprotein cholesterol; LDL-P = low-density lipoprotein particle; LPL = lipoprotein lipase; T2D = type 2 diabetes; TG = triglyceride; VLDL = very-low-density lipoprotein.

1. Bays HE, et al. *J Clin Lipidol*. 2016 Jan-Feb;10(1 Suppl):S1-43;
2. Yuan G, et al. *CMAJ.* 2007 April;176(8):1113-1120.

Common Secondary Causes of Dyslipidemia

Affected Lipids	Conditions
↑ Total Cholesterol and LDL-C	• Hypothyroidism
	• Nephrosis
	• Dysgammaglobulinemia (systemic lupus erythematosus, multiple myeloma)
	• Progestin or anabolic steroid treatment
	• Cholestatic liver disease due to abnormal lipoproteins (eg, primary biliary cirrhosis)
	• Protease inhibitors for treatment of HIV infection
↑ Triglycerides and VLDL-C	• Chronic renal failure
	• Type 2 diabetes
	• Obesity
	• Excessive alcohol intake
	• Hypothyroidism
	• Antihypertensive medications (thiazide diuretics and beta-adrenergic blocking agents)
	• Corticosteroid therapy (or severe stress that increases endogenous corticosteroids)
	• Orally administered estrogens, oral contraceptives, pregnancy
	• Protease inhibitors for treatment of HIV infection

Secondary causes of dyslipidemia must be excluded with a thorough medical and dietary history, as well as laboratory testing for glucose, thyroid, liver, and renal function

Abbreviations: HIV = human immunodeficiency virus; LDL-C = low-density lipoprotein cholesterol; VLDL-C=very low-density lipoprotein cholesterol.

Jellinger P, et al. *Endocr Practice*. (2017) 23(4):479–497; NHLBI. NIH Publication No. 02-5215. 2002; Rodbard et al. *Endocr Pract*. (2007) 13(Suppl 1):1–68; Vodnala et al. *Am J Cardiol.* (2012) 110(6):823–825.

2017 AACE Lipid ASCVD Risk Categories

Dyslipidemia treatment goals should be personalized according to risk levels

Risk Category	Risk Factors/10-Year Risk
Extreme risk	• Progressive ASCVD including unstable angina in individuals after achieving an LDL-C <70 mg/dL • Established clinical CVD in individuals with diabetes, stage 3 or 4 CKD, or HeFH • History of premature ASCVD (<55 male, <65 female)
Very high risk	• Established or recent hospitalization for ACS, coronary, carotid or peripheral vascular disease, 10-year risk >20% • Diabetes or stage 3 or 4 CKD with 1 or more risk factor(s) • HeFH
High risk	• ≥2 risk factors and 10-year risk 10%–20% • Diabetes or stage 3 or 4 CKD with no other risk factors
Moderate risk	• ≤2 risk factors and 10-year risk <10%
Low risk	• 0 risk factors

Abbreviations: ACS = acute coronary syndrome; ASCVD = atherosclerotic cardiovascular disease; CKD = chronic kidney disease; CVD = cardiovascular disease; HeFH = heterozygous familial hypercholesterolemia; LDL-C = low-density lipoprotein cholesterol.

Jellinger P, et al. *Endocr Practice*. (2017) 23(4):479–497.

2017 AACE LDL-C, Non-HDL-C, and Apo B Treatment Goals

ASCVD Risk Category	Treatment Goals (mg/dL)		
	LDL-C	Non-HDL-C	Apo B
Extreme risk	<55	<80	<70
Very high risk	<70	<100	<80
High risk	<100	<130	<90
Moderate risk	<100	<130	<90
Low risk	<130	<160	NR

Abbreviations: Apo B = apolipoprotein B; ASCVD = atherosclerotic cardiovascular disease; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; NR = not recommended.

Barter PJ, et al. *J Intern Med*. (2006) 259:247–258; Boekholdt SM, et al. *J Am Coll Cardiol*. (2014) 64(5):485–494; Brunzell JD, et al. *Diabetes Care*. (2008) 31:811–822; Cannon CP, et al. *N Engl J Med.* (2015) 372(25):2387–2397; Grundy SM, et al. *Circulation.* (2004) 110:227–239; Heart Protection Study Collaborative Group. *Lancet*. (2002) 360:7–22; Jellinger P, et al. *Endocr Practice*. (2017) 23(4):479–497; Lloyd-Jones DM, et al. *Am J Cardiol*. (2004) 94:20–24; McClelland RL, et al. *J Am Coll Cardiol*. (2015) 66(15):1643–1653; NHLBI. NIH Publication No. 02-5215. 2002; Ridker PM, *J Am Coll Cardiol*. (2005) 45:1644–1648; Ridker PM, et al. *JAMA*. (2007) 297(6):611–619; Sever PS, et al. *Lancet*. (2003) 361:1149–1158; Shepherd J, et al. *Lancet*. (2002) 360:1623–1630; Smith SC Jr, et al. *Circulation*. (2006) 113:2363–2372; Stevens RJ, et al. *Clin Sci*. (2001) 101(6):671–679; Stone NJ. *Am J Med*. (1996) 101:4A40S–48S; Weiner DE, et al. *J Am Soc Nephrol.* (2004) 15(5):1307–1315.

2017 AACE TG and HDL-C Treatment Goals

- Moderately elevated TG levels (≥150 mg/dL) may identify individuals at risk for the insulin resistance syndrome
- TG levels ≥200 mg/dL may indicate a substantial increase in ASCVD risk
- Hypertriglyceridemia is also commonly associated with a procoagulant state and hypertension

TG Category	TG Concentration (mg/dL)	TG Goal
Normal	<150	<150 mg/dL
Borderline high	150–199	
High	200–499	
Very high	≥500	

- HDL-C should be >40 mg/dL and also as high as possible

Abbreviations: ASCVD = atherosclerotic cardiovascular disease; HDL-C = high-density lipoprotein cholesterol; TG = triglycerides.

Einhorn D, et al. *Endocr Pract*. (2003) 9:237–252; Frick MH, et al. *NEJM*. (1987) 317:1237–1245; Jellinger P, et al. *Endocr Practice*. (2017) 23(4):479–497; Keech A, et al. *Lancet*. (2005) 366:1849–1861; NHLBI. NIH Publication No. 02-5215. 2002; Tenaknen L, et al. *Arch Intern Med*. (2006) 166:743–748.

Classification of LDL-C Levels in Children and Adolescents

- A body of evidence indicates that atherosclerosis begins early in life and that elevated lipid levels in adolescence predict elevated lipid levels well into adulthood.
- Dyslipidemia in childhood and adolescence should be diagnosed and managed as early as possible.

Category	LDL-C (mg/dL)
Acceptable	<100*
Borderline	100–129
High	≥130

*Some pediatric lipid guidelines have an "acceptable" LDL-C goal of <110 mg/dL

Abbreviation: LDL-C = low-density lipoprotein cholesterol.

AAP NCEP *Pediatrics*. (1992) 89:525–584; Daniels SR, et al. EPIGCVHRRCAFR, 2012; Jellinger P, et al. *Endocr Practice*. (2017) 23(4):479–497.

What Treatments Are Available for Dyslipidemia?

Treatment categories for dyslipidemia:

- Lifestyle changes
  - Physical activity
  - Medical nutrition therapy
  - Smoking cessation
- Pharmacologic therapy
  - Statins
  - Fibrates
  - Omega-3 fish oil
  - Niacin
  - Bile acid sequestrants
  - Cholesterol absorption inhibitors
  - PCSK9 inhibitors
  - MTP inhibitor
  - Antisense apo B oligonucleotide
  - Combination therapies

In individuals at risk for ASCVD, aggressive lipid-modifying therapy is recommended to achieve appropriate LDL-C goals

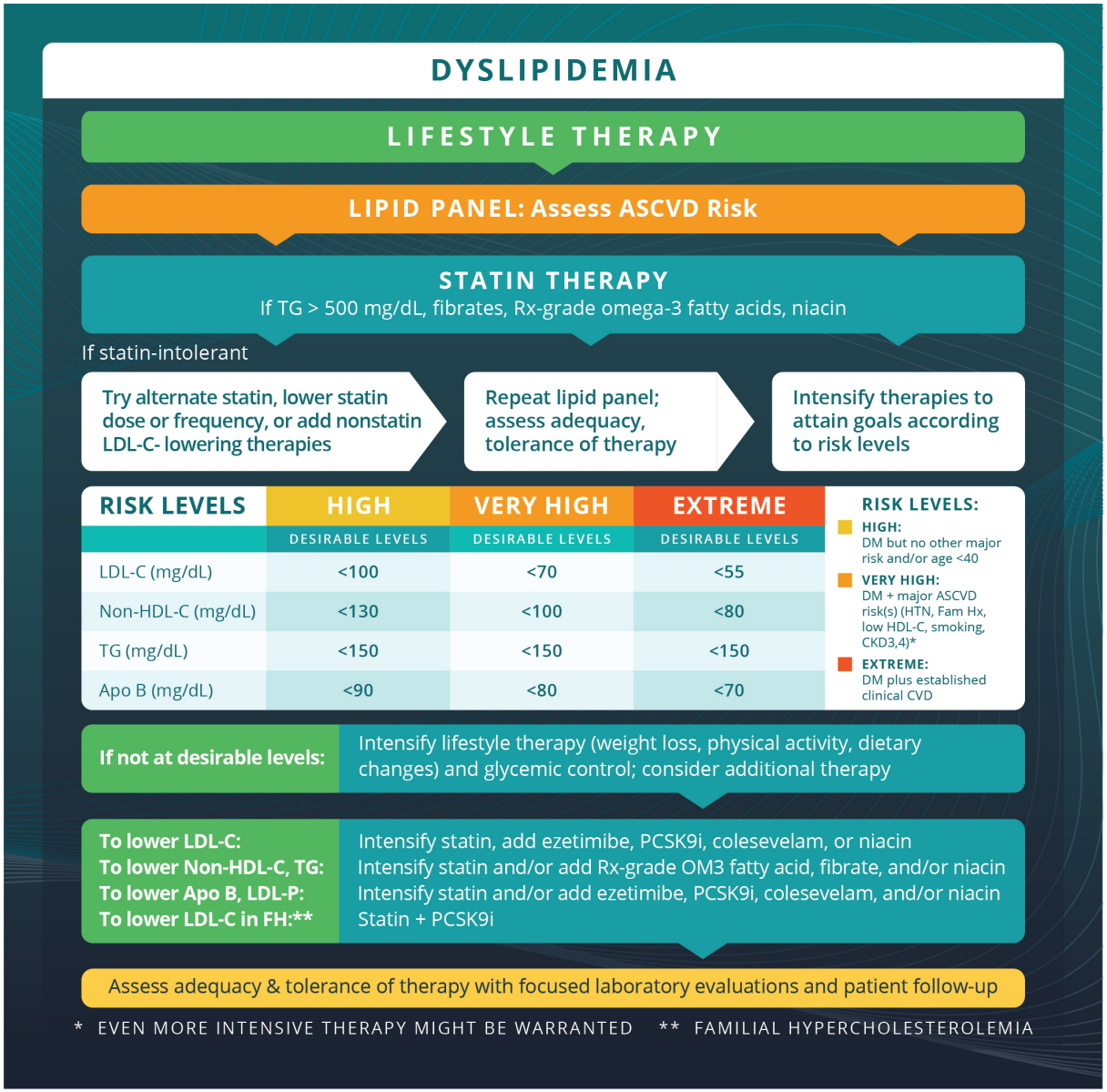
Recommendations associated with this question:

A comprehensive strategy to control lipid levels and address associated metabolic abnormalities and modifiable risk factors is recommended primarily using lifestyle changes and patient education with pharmacotherapy as needed to achieve evidence-based targets

Abbreviations: Apo B = apolipoprotein B;
ASCVD = atherosclerotic cardiovascular disease;
LDL-C = low-density lipoprotein cholesterol;
MTP = microsomal transfer protein;
PCSK9 = proprotein convertase subtilisin/kexin type 9.

Jellinger P, et al. *Endocr Practice*. (2017) 23(4):479–497.

AACE ASCVD Risk Factor Modifications Algorithm



Lifestyle Therapy: Physical Activity

- Regular physical activity is associated with reduced VLDL-C, increased HDL-C, and, for some, reduced LDL-C levels
- A reasonable, feasible approach to fitness therapy is recommended; suggested activities include brisk walking, stationary bike use, water aerobics, cleaning/scrubbing, mowing the lawn, and sporting activities
  - Ideally, exercise programs will include at least 30 minutes of moderate-intensity physical activity 4–6 times weekly (expenditure of at least 200 kcal/day)
- Daily physical activity goals can be met in a single or multiple sessions throughout the course of a day (10 minutes minimum per session)
  - For some individuals, breaking activity up may help improve adherence with physical activity programs
- In addition to aerobic activity, muscle-strengthening activity is recommended at least 2 days a week

Abbreviations: HDL-C = high-density lipoprotein cholesterol; hsCRP = high sensitivity C-reactive protein; LDL-C = low-density lipoprotein cholesterol; VLDL-C = very low-density lipoprotein cholesterol.

Jellinger P, et al. *Endocr Practice*. (2017) 23(4):479–497.

Lifestyle Therapy: Medical Nutrition Therapy and Smoking Cessation

- Intake of saturated fats, trans fats, and cholesterol should be limited
- Consume diet rich in:
  - Fruits and vegetables
    - Combined ≥5 servings/day; ≥1 of these servings/day of dark green or orange vegetables
  - Grains (primarily whole grains)
  - Legumes
  - High-fiber cereals
  - Low-fat dairy products
  - Fish and skinless poultry preferred over processed meats
- LDL-C-lowering macronutrient intake should include plant stanols/sterols (~2 g/day) and soluble fiber (10–25 g/day)
- Tobacco cessation should be strongly encouraged and facilitated

Abbreviation: LDL-C = low-density lipoprotein cholesterol.

Jellinger P, et al. *Endocr Practice*. (2017) 23(4):479–497.

Pharmacologic Therapy: Statins

- Statins are the primary recommended pharmacologic agent to achieve target LDL-C goals
- For high-risk and very high-risk individuals, using statins to further lower LDL-C beyond established targets results in additional ASCVD event reduction and may be considered
- Very high-risk individuals with established coronary, carotid, or peripheral vascular disease, or diabetes, who also have ≥1 additional risk factor, should be treated with statins to an LDL-C treatment goal of <70 mg/dL
- Extreme-risk individuals should be treated with maximally-tolerated statins or combination therapies to target an LDL-C treatment goal of <55 mg/dL
- Mild elevations in blood glucose levels and/or an increased risk of new-onset T2D associated with intensive statin therapy have not been shown to outweigh the benefits of statin therapy for ASCVD risk reduction

Abbreviations: ASCVD = atherosclerotic cardiovascular disease; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; T2D = type 2 diabetes.

Jellinger P, et al. *Endocr Practice*. (2017) 23(4):479–497.

Statins: Starting Doses and Dosage Ranges

Agent	Usual Recommended Starting Daily Dose	Dosage Range	Method of Administration
Statins			
Lovastatin	20 mg	10–80 mg	Oral
Pravastatin	40 mg	10–80 mg	Oral
Simvastatin	20–40 mg	5–80 mg[a]	Oral
Fluvastatin	40 mg	20–80 mg	Oral
Atorvastatin	10–20 mg	10–80 mg	Oral
Rosuvastatin	10 mg	5–40 mg	Oral
Pitavastatin	2 mg	2–4 mg	Oral

[a] Simvastatin, 80 mg, not approved for therapy unless individual has been on treatment for more than 1 year without myopathy.

Crestor (rosuvastatin calcium); [PI]; 2016; Jellinger P, et al. *Endocr Practice*. (2017) 23(4):479–497; Lescol (fluvastatin sodium) [PI]; 2012 Lipitor (atorvastatin calcium) [PI]; 2015; Livalo (pitavastatin) [PI]; 2013; ; Mevacor (lovastatin) [PI]; 2014; Pravachol (pravastatin sodium) [PI]; 2016; Zocor (simvastatin) [PI]; 2015.

Combination Pharmacologic Therapy

- Consider combination therapy of lipid-lowering agents when the LDL-C/non-HDL-C level is markedly increased and monotherapy (usually with a maximally tolerated statin) does not achieve therapeutic goal

HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.

Jellinger et al. *Endocr Practice*. 2017;23(4):479-497.

Triglyceride-Lowering Pharmacologic Therapy: Fibrates, Rx-Grade Omega-3 Fatty Acids, Niacin, and Statins

- Combination therapy usually required
- For TG ≥500 mg/dL, to prevent pancreatitis and atherosclerosis
  - Prescription-grade omega-3 fatty acids (4 grams) and/or
  - Fibrates and/or
  - Nicotinic acid (lowers VLDL-C and VLDL-TG)
- For TG 200-499 mg/dL, to achieve LDL-C and non-HDL-C goal
  - Statins (lower LDL-C and VLDL-C)
  - Omega-3 fatty acids and/or
  - Fibrates and/or
  - Nicotinic acid

HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; TG = triglyceride; VLDL = very low-density lipoprotein; VLDL-C = very low-density lipoprotein cholesterol.

NHLBI. NIH Publication No. 02-5215. 2002. Brahm A, Hegele RA. Hypertriglyceridemia. *Nutrients.* 2013 5(3):981–1001.

Atherogenic Cholesterol-Lowering Pharmacologic Therapy: Bile Acid Sequestrants, Cholesterol Absorption Inhibitors, Niacin and PCSK9 Inhibitors

- **Bile acid sequestrants**
  - Reduce LDL-C (13%-18%) and apo B and modestly increase HDL-C
  - May increase TG levels, but rise in TG is mitigated by use of statins
- **Cholesterol absorption inhibitors**
  - Reduce LDL-C and apo B as monotherapy, especially in statin-intolerant individuals
  - Further reduce both LDL-C and ASCVD risk in combination with statins
- **Niacin**
  - Raises HDL-C (10%-35%) and reduces LDL-C (10%-25%), non-HDL-C, Apo B, LDL-P, TG, small dense LDL-P and Lp(a) in dose-dependent manner
- **PCSK9 inhibitors**
  - Used as monotherapy only in statin-intolerant individuals
  - In combination with statin therapy, lower LDL-C in those with HeFH or HoFH and those with CVD unable to reach LDL-C/non-HDL-C goals with maximally tolerated statin therapy

Apo = apolipoprotein; ASCVD = atherosclerotic cardiovascular disease; CVD = cardiovascular disease; HDL-C = high-density lipoprotein cholesterol; HeFH = heterozygous familial hypercholesterolemia; HoFH = homozygous familial hypercholesterolemia; LDL-C = low-density lipoprotein cholesterol; LDL-P = low-density lipoprotein particles; Lp(a) = lipoprotein a; PCSK9 = Proprotein convertase subtilisin/kexin type 9; TG = triglyceride.

Jellinger et al. *Endocr Practice*. 2017;23(4):479-497.

Statins: Primary Metabolic Effects and Main Considerations

Metabolic Effects

- Primarily ↓ LDL-C 21% to 55% by competitively inhibiting rate-limiting step of cholesterol synthesis in the liver, leading to upregulation of hepatic LDL receptors
- TG and HDL-C effects are less pronounced (↓ TG 6%–30% and ↑ HDL-C 2%–10%)

Main Considerations

- Liver function test prior to therapy and as clinically indicated thereafter
- Myalgias and muscle weakness in some individuals
- Potential for drug-drug interaction between some statins and CYP450 3A4 inhibitors, cyclosporine, warfarin, and protease inhibitors
- Myopathy/rhabdomyolysis in rare cases; increased risk with coadministration of some drugs (see product labeling)
- Simvastatin dosages should not exceed 40 mg in most individuals; dosages of 80 mg are no longer recommended except in those who have tolerated 80 mg for ≥12 months without muscle toxicity
- Do not exceed 20 mg simvastatin daily with amlodipine or ranolazine.
- Plasma elevations of rosuvastatin may be higher among Asian persons than other ethnic groups
- New-onset diabetes is increased in individuals treated with statins; however, it is dose-related, occurs primarily in individuals with metabolic syndrome, appears to be less common with pravastatin and possibly pitavastatin, and occurs overall to a lesser extent than the associated decrease in ASCVD

Bissonnette S, et al. *Can J Cardiol*. (2006) 22:1035–1044; Denke M, et al. *Diab Vasc Dis Res*. (2006) 3:93–102; Jellinger P, et al. *Endocr Practice*. (2017) 23(4):479–497; Preiss D, et al. *JAMA*. (2011) 305: 2556–2564.

Abbreviations: ASCVD = atherosclerotic cardiovascular disease; HDL-C = high-density lipoprotein cholesterol; LDL = low-density lipoprotein; LDL-C = low-density lipoprotein cholesterol; TG = triglycerides.

Fibrates: Starting Doses, Dosage Ranges

Agent	Usual recommended starting daily dose	Dosage range	Method of administration
Fibrates			
Fenofibrate	48-145 mg	48-145 mg	Oral
Gemfibrozil *	1,200 mg	1,200 mg	Oral
Fenofibric acid	45-135 mg	45-135 mg	Oral

* The concomitant administration of gemfibrozil with simvastatin is contraindicated. The risk of myopathy and rhabdomyolysis is increased with combined gemfibrozil and any statin therapy.

Aguilar-Salinas CA, et al. *Metabolism*. (2001) 50:729–733; Athyros VG, et al. *Coron Artery Dis*. (1995) 6:251–256; Avellone G, et al. *Blood Coagul Fibrinolysis*. (1995) 6:543–548; Bröijersen A, et al. *Arterioscler Thromb Vasc Biol.* (1996) 16:511–516; Bröijersén A, et al. *Thromb Haemost*. (1996) 76:171–176; Davidson MH, et al. *Am J Cardiol*. (2007) 99:3C–18C; Farnier M, et al. *Eur Heart J*. (2005) 26:897–905; Guyton JR, et al. *Arch Intern Med*. (2000) 160:1177–1184; Hottelart C, et al. *Nephron*. (2002) 92:536–541; Insua A, et al. *Endocr Pract*. (2002) 8:96–101; Jellinger P, et al. *Endocr Practice*. (2017) 23(4):479–497; Kockx M, et al. *Thromb Haemost*. (1997) 78:1167–1172; Lopid (gemfibrozil) [PI] 2010; McKenney JM, et al. *J Am Coll Cardiol*. (2006) 47:1584–1587; Syvänne M, et al. *Atherosclerosis.* (2004) 172:267–272; Tricor (fenofibrate) [PI]; 2010; Trilipix (fenofibric acid) [PI]; 2016; Westphal S, et al. *Lancet*. (2001) 358:39–40.

Fibrates: Primary Metabolic Effects and Main Considerations

Metabolic Effects:

- Primarily ↓ TG 20%–35%, ↑ HDL-C 6%–18% by stimulating lipoprotein lipase activity
- Fenofibrate may ↓ TC and LDL-C 20%–25%
- Lower VLDL-C and LDL-C; reciprocal rise in LDL-C transforms the profile into a less atherogenic form by shifting fewer LDL particles to larger size
- Fenofibrate ↓ fibrinogen level

Main Considerations

- Gemfibrozil may ↑ LDL-C 10%–15%
- GI symptoms, possible cholelithiasis
- May potentiate effects of orally administered anticoagulants
- Gemfibrozil may ↑ fibrinogen level
- Gemfibrozil and fenofibrate can ↑ homocysteine independent of vitamin concentrations
- May cause muscle disorders; myopathy/rhabdomyolysis when used with statin
- Fibrates are associated with increased serum creatinine levels, which may not reflect renal dysfunction
- Fenofibrate dose should be cut by two-thirds and gemofibrozil by one-half when eGFR is 15–60 ml/min/1.73 m^2, and fibrates should be avoided when eGFR is <15 ml/min/1.73 m^2
- Can improve diabetic retinopathy

Abbreviations: eGFR = estimated glomerular filtration rate; GI = gastrointestinal; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; TC = total cholesterol; TG = triglycerides; VLDL-C = very low-density lipoprotein cholesterol.

Aguilar-Salinas CA, et al. *Metabolism*. (2001) 50:729–733; Athyros VG, et al. *Coron Artery Dis*. (1995) 6:251–256; Avellone G, et al. *Blood Coagul Fibrinolysis*. (1995) 6:543–548; Bröijersen A, et al. *Arterioscler Thromb Vasc Biol.* (1996) 16:511–516; Bröijersén A, et al. *Thromb Haemost*. (1996) 76:171–176; Davidson MH, et al. *Am J Cardiol*. (2007) 99:3C–18C; Farnier M, et al. *Eur Heart J*. (2005) 26:897–905; Guyton JR, et al. *Arch Intern Med*. (2000) 160:1177–1184; Hottelart C, et al. *Nephron*. (2002) 92:536–541; Insua A, et al. *Endocr Pract*. (2002) 8:96–101; Jellinger P, et al. *Endocr Practice*. (2017) 23(4):479–497; Kockx M, et al. *Thromb Haemost*. (1997) 78:1167–1172; Lopid (gemfibrozil) [PI] 2010; McKenney JM, et al. *J Am Coll Cardiol*. (2006) 47:1584–1587; Syvänne M, et al. *Atherosclerosis.* (2004) 172:267–272; Tricor (fenofibrate) [PI]; 2010; Trilipix (fenofibric acid) [PI]; 2016; Westphal S, et al. *Lancet*. (2001) 358:39–40.

Omega-3 Fatty Acids: Starting Doses, Dosage Ranges, and Primary Metabolic Effects

Agent	Usual Recommended Starting Daily Dose	Dosage Range	Method of Administration
Omega-3-acid ethyl esters (Lovaza)	4 g per day	4 g per day	Oral
Icosapent ethyl (Vascepa)	4 g per day	4 g per day	Oral

Metabolic Effects:

- ↓ TG 27%–45%, TC 7%–10%, VLDL-C 20%–42%, apo B 4%, and non-HDL-C 8%–14% in individuals with severe hypertriglyceridemia most likely by reducing hepatic VLDL-TG synthesis and/or secretion and enhancing TG clearance from circulating VLDL particles. Other potential mechanisms of action include: increased ß-oxidation; inhibition of acyl-CoA; 1,2-diacylglyceral acyltransferase; decreased hepatic lipogenesis; and increased plasma lipoprotein activity
- Icosapent ethyl ↓ LDL-C 5%, whereas, omega-3-acid ethyl esters ↑ LDL-C 45%

Abbreviations: Apo B = apolipoprotein B; HDL-C=high-density lipoprotein cholesterol; LDL-C=low-density lipoprotein cholesterol; TC=total cholesterol; TG=triglycerides; VLDL=very low-density lipoprotein.

Jellinger P, et al. *Endocr Practice*. (2017) 23(4):479–497; Lovaza (omega-3-acid ethyl esters) [PI]; 2015; Vascepa (icosapent ethyl) [PI]; 2016.

Omega-3 Fatty Acids: Main Considerations

- Assess TG levels before initiating and periodically during therapy
- Omega-3-acid ethyl esters can increase LDL-C levels; monitor LDL-C levels during treatment
- May prolong bleeding time; monitor coagulation status periodically in patients receiving treatment with omega-3 fatty acids and other drugs affecting coagulation
- Monitor ALT and AST levels periodically during treatment in patients with hepatic impairment; some patients may experience increases in ALT levels only
- Exercise caution when treating patients with a known hypersensitivity to fish and/or shellfish
- The effect of omega-3 fatty acids on cardiovascular morbidity and mortality and the risk of pancreatitis has not been determined in patients with severe hypertriglyceridemia
- In patients with paroxysmal or persistent atrial fibrillation, therapy with omega-3-acid ethyl esters may be associated with increased frequency of symptomatic AF or flutter, especially within the first 2 to 3 months after initiation
- Most common adverse events include arthralgia (2.3%), eructation (4%), dyspepsia (3%), and taste perversion (4%); may also experience constipation, gastrointestinal disorders, vomiting, rash, or pruritus
- Pharmaceutical doses should be used with caution in nursing mothers and only be used in pregnant women if the benefits of treatment outweigh the potential risk of fetal harm

Abbreviations: AF = atrial fibrillation; ALT = alanine transaminase; AST = aspartate aminotransferase; LDL-C = low-density lipoprotein cholesterol; TG = triglycerides.

Jellinger P, et al. *Endocr Practice*. (2017) 23(4):479–497; Lovaza (omega-3-acid ethyl esters) [PI]; 2015; Vascepa (icosapent ethyl) [PI]; 2016.

Niacin: Starting Doses, Dosage Ranges, Primary Metabolic Effects, and Main Considerations

Agent	Usual Recommended Starting Daily Dose	Dosage Range	Method of Administration
Niacin (nicotinic acid)			
Immediate-release	250 mg	250–3000 mg	Oral
Extended-release	500 mg	500–2000 mg	Oral

Metabolic Effects:

- ↓ LDL-C 10%–25%, ↓ TG 20%–30%, ↑ HDL-C 10%–35% by decreasing hepatic synthesis of LDL-C and VLDL-C
- ↓ Lipoprotein (a)
- Transforms LDL-C to less-atherogenic form by increasing average particle size and also decreases LDL particle concentration

Main Considerations:

- Potential for frequent skin flushing, pruritus, abdominal discomfort, hepatoxicity (rare but may be severe), nausea, peptic ulcer, atrial fibrillation
- Deleterious effect on serum glucose at higher dosages
- Increases uric acid levels; may lead to gout

Abbreviations: HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; TG = triglyceride; VLDL-C = very low-density lipoprotein cholesterol.

Guyton JR, et al. *Arch Intern Med.* (2000) 160:1177–1184; Jellinger P, et al. *Endocr Practice*. (2017) 23(4):479–497; Niaspan (niacin extended-release) [PI] 2015.

Bile Acid Sequestrants: Starting Doses, Dosage Ranges, Primary Metabolic Effects, and Main Considerations

Agent	Usual Recommended Starting Daily Dose	Dosage Range	Method of Administration
Bile Acid Sequestrants			
Cholestyramine	8–16 g	4–24 g	Oral
Colestipol	2 g	2–16 g	Oral
Colesevelam	3.8 g	3.8–4.5 g	Oral

Metabolic Effects:

- Primarily ↓ LDL-C 15%–25% by binding bile acids and preventing their reabsorption in the ileum (causing hepatic cholesterol depletion and LDL-receptor upregulation)
- Colesevelam ↓ glucose and hemoglobin A1C (~0.5%); FDA-approved to treat T2D

Main Considerations:

- May ↑ serum TG
- Frequent constipation and/or bloating, which can reduce adherence
- Many potential drug interactions (decreased drug absorption), less so with colesevelam (see product labeling)
- May reduce absorption of folic acid and fat-soluble vitamins such as vitamins A, D, and K

Abbreviations: A1C = glycated hemoglobin; FDA = US Food and Drug Administration; LDL-C = low-density lipoprotein cholesterol; T2D = type 2 diabetes; TG = triglycerides.

Colestid (colestipol hydrochloride) [PI]; 2014; Jellinger P, et al. *Endocr Practice*. (2017) 23(4):479–497; Prevalite (cholestyramine for oral suspension, USP) [PI]; 2015; WelChol (colesevelam hydrochloride) [PI]; 2014; Zieve FJ, et al. *Ther*. (2007) 29:74-839:74–83.

PCSK9 Inhibitors: Starting Doses and Dosage Ranges

Agent	Usual Recommended Starting Daily Dose	Dosage Range	Method of Administration
PCSK9 Inhibitors			
Alirocumab	75 mg every 2 weeks	75–150 mg every 2 weeks	SQ
Evolocumab	140 mg every 2 weeks or 420 mg once monthly	Not applicable	SQ

Abbreviations: PCSK9 = proprotein convertase subtilisin/kexin type 9; SQ = subcutaneous injection.

Jellinger P, et al. *Endocr Practice*. (2017) 23(4):479–497; Praluent (alirocumab) [PI] 2015; Repatha (evolocumab) [PI]; 2016.

PCSK9 Inhibitors: Primary Metabolic Effects and Main Considerations

Metabolic Effects:

- ↓LDL-C 48%–71%, ↓ non-HDL-C 49%–58%, ↓TC 36%–42%, ↓Apo B 42%–55% by inhibiting PCSK9 binding with LDLRs, increasing the number of LDLRs available to clear LDL, and lowering LDL-C levels

Main Considerations:

- Require subcutaneous self-injection; refrigeration generally needed
- Overall levels of adverse reactions and discontinuation very low
- Adverse reactions with significantly different rates between drug and placebo were: local injection site reactions and influenza
- The most common adverse reactions with similar rates for drug vs placebo were:
- **Alirocumab:** Nasopharyngitis, influenza, urinary tract infections, diarrhea, bronchitis, and myalgia
- **Evolocumab:** Nasopharyngitis, back pain, and upper respiratory tract infection

Abbreviations: Apo B = apolipoprotein B; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; LDLR = low-density lipoprotein receptor; PCSK9 = proprotein convertase subtilisin/kexin type 9; SQ = subcutaneous injection; TC = total cholesterol.

Jellinger P, et al. *Endocr Practice*. (2017) 23(4):479–497; Praluent (alirocumab) [PI] 2015; Repatha (evolocumab) [PI]; 2016.

Cholesterol Absorption Inhibitors: Starting Doses, Dosage Ranges, Primary Metabolic Effects, and Main Considerations

Agent	Usual Recommended Starting Daily Dose	Dosage Range	Method of Administration
Cholesterol Absorption Inhibitors			
Ezetimibe	10 mg	10 mg	Oral
Combination Therapies (single pill)			
Ezetimibe/simvastatin	10/20 mg	10/10 to 10/80 mg	Oral

Metabolic Effects

- Primarily ↓ LDL-C 10%–18% by inhibiting intestinal absorption of cholesterol and decreasing delivery to the liver, leading to upregulation of hepatic LDL receptors
- ↓ Apo B 11%–16%
- In combination with statins, additional ↓ LDL-C 25%, total ↓ LDL-C 34%–61%
- In combination with fenofibrate, ↓ LDL-C 20%–22% and ↓ apo B 25%–26% without reducing ↑ HDL-C

Main Considerations

- Myopathy/rhabdomyolysis (rare)
- When coadministered with statins or fenofibrate, risks associated with those drugs remain (eg, myopathy/ rhabdomyolysis, cholelithiasis)

Abbreviations: Apo B = apolipoprotein B; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.

Bays HE, et al. *Clin Ther.* (2001) 23:1209–1230; Bays HE, et al. *Clin Ther*. (2004) 26:1758–1773; Bissonnette S, et al. *Can J Cardiol*. (2006)22:1035–1044; Brohet C, et al. *Curr Med Res Opin*. (2005) 21:571–578; Denke M, et al. *Diab Vasc Dis Res*. (2006)3:93–102; Dujovne CA, et al. *Am J Cardiol*. (2002) 90:1092–1097; Farnier M, et al. *Eur Heart J*. 2005;26:897-905; Gagne C, et al. *Am J Cardiol*. 2002;90:1084-1091; Jellinger P, et al. *Endocr Practice*. (2017) 23(4):479–497; Knopp RH, et al. *Int J Clin Pract*. (2013) 57:363–368; McKenney JM, et al. *J Am Coll Cardiol*. (2006) 47:1584–1587; Zetia (ezetimibe) [PI] 2013.

MTP Inhibitor: Starting Dose, Dosage Range, Primary Metabolic Effects, and Main Considerations

Agent	Usual Recommended Starting Daily Dose	Dosage Range	Method of Administration
MTP Inhibitor			
Lomitapide	5 mg, with subsequent titration	5–60 mg	Oral

Metabolic Effects:

- ↓ Up to LDL-C 40%, TC 36%, apo B 39%, TG 45%, and non-HDL-C 40% (depending on dose) in individuals with HoFH by binding and inhibiting MTP, which inhibits synthesis of chylomicrons and VLDL

Main Considerations:

- Can cause increases in transminases (ALT, AST); monitoring of ALT, AST, alkaline phosphatase, and total bilirubin prior to initiation, and of ALT and AST during treatment, is required per FDA REMS
- Causes increases in hepatic fat (steatosis) with or without concomitant elevated transminases, which may be a risk for progressive liver diseases
- Also causes steatosis of the small intestine with resulting abdominal pain and steatorrhea unless a very low-fat diet is followed; may also cause fat-soluble vitamin deficiency unless vitamin supplements are taken
- Caution should be exercised when used with other drugs with potential hepatoxicity; because of hepatoxicity risk, only available through REMS program

Abbreviations: ALT = aspartate amino transferase; Apo B = apolipoprotein B; AST = amino alanine transferase; FDA = US Food and Drug Administration; HDL-C = high-density lipoprotein cholesterol; HoFH = homozygous familial hypercholesterolemia; LDL-C = low-density lipoprotein cholesterol; MTP = microsomal transfer protein; REMS = risk evaluation and mitigation strategy; TC = total cholesterol; TG = triglycerides; VLDL = very low-density lipoprotein.

Jellinger P, et al. *Endocr Practice*. (2017) 23(4):479–497; Juxtapid (lomitapide) [PI]; 2012.

Mipomerson: Starting Dose, Dosage Range, Primary Metabolic Effects, and Main Considerations

Agent	Usual Recommended Starting Daily Dose	Dosage Range	Method of Administration
Antisense apolipoprotein B oligonucleotide			
Mipomersen	200 mg once weekly	200 mg once weekly	SQ

Metabolic Effects:

- ↓ LDL-C 21%, TC 19%, apo B 24%, and non-HDL-C 22% in individuals with HoFH by degrading mRNA for apo B-100, the principal apolipoprotein needed for hepatic synthesis of VLDL (and subsequent intra-plasma production of IDL and LDL)

Main Considerations:

- Can cause increases in transminases (ALT, AST); monitoring of ALT, AST, alkaline phosphatase, and total bilirubin before initiation, and of ALT and AST during treatment is recommended
- Causes increases in hepatic fat (steatosis) with or without concomitant elevated transminases, which may be a risk for progressive liver diseases
- Caution should be exercised when used with other drugs with potential hepatoxicity; because of hepatoxicity risk, only available through REMS program

Abbreviations: ALT = aspartate amino transferase; Apo B = apolipoprotein B; AST = amino alanine transferase; HDL-C = high-density lipoprotein cholesterol; HoFH = homozygous familial hypercholesterolemia; IDL = intermediate-density lipoprotein; LDL = low-density lipoprotein; LDL-C = low-density lipoprotein cholesterol; mRNA = messenger RNA; REMS = risk evaluation and mitigation strategy; SQ = subcutaneous; TC = total cholesterol; VLDL = very low-density lipoprotein.

Jellinger P, et al. *Endocr Practice*. (2017) 23(4):479–497; Kynamro (mipomersen sodium) Injection [PI]; 2016.

How Should Treatment Be Monitored?

- Reassess individuals' lipid status 6 weeks after therapy initiation and again at 6-week intervals until treatment goal is achieved
- While on stable lipid therapy:
  - Individuals should be tested at 6- to 12-month intervals; the specific testing interval will depend on individual therapeutic adherence and lipid profile consistency
  - If adherence is a concern or the lipid profile is unstable, the individual will probably benefit from more frequent assessment
- Liver transaminase levels should be measured before and 3 months after niacin or fibric acid treatment initiation, because most liver abnormalities occur within this time frame
  - Liver transaminase levels should be measured periodically thereafter (semiannually or annually)
- If a patient reports clinically significant myalgias or muscle weakness on statin therapy, creatine kinase levels should be assessed and the statin discontinued at least temporarily

Jellinger P, et al. *Endocr Practice*. (2017) 23(4):479–497.

What Special Considerations Should Be Given to Children and Adolescents?

Treatment Goals

- An LDL-C goal of <100 mg/dL is considered "acceptable" for children and adolescents, with 100-129 mg/dL considered "borderline" and ≥130 mg/dL considered "high" (based on recommendations from the American Academy of Pediatrics)
- Primary preventive nutrition consisting of healthy lifestyle habits is recommended in all healthy children

Treatment

- Pharmacotherapy is recommended for children and adolescents older than 10 years who do not respond sufficiently to lifestyle modification, particularly those satisfying the following criteria:
  - LDL-C ≥190 mg/dL
  - LDL-C ≥160 mg/dL and the presence of ≥2 CV risk factors, even after vigorous intervention
  - Family history of premature ASCVD (<55 years of age), or
  - Having overweight, obesity, or other elements of the insulin resistance syndrome

Abbreviations: ASCVD = atherosclerotic cardiovascular disease; CV = cardiovascular disease; LDL-C = low-density lipoprotein cholesterol.

Jellinger P, et al. *Endocr Practice*. (2017) 23(4):479–497.

What Special Considerations Should Be Given to Women?

ASCVD is the leading cause of mortality in US women. Women's symptoms are often less overt and/or atypical compared with men's. These differences can lead to delays in evaluation and diagnostic testing, decreased use of appropriate therapy, and increased mortality.

Risk Assessment

- Special attention should be given to assessing women for ASCVD risk by determining the 10-year risk (high, intermediate, or low) of a coronary event using the Reynolds Risk Score or Framingham

Treatment options

- Women should be evaluated for their ASCVD risk and be treated with pharmacotherapy if lifestyle intervention is insufficient
- Hormone replacement therapy for the treatment of dyslipidemia in postmenopausal women is not recommended
- An HDL-C concentration <40 mg/dL is an established independent risk factor for ASCVD in both men and women; however, because HDL-C levels tend to be higher in women than in men, an HDL-C concentration <50 mg/dL in women is also considered a marginal risk factor
- In stark contrast to findings in men, very low HDL-C (<40 mg/dL) is an independent risk factor for ASCVD development and mortality in women, even in the presence of total cholesterol concentrations <200 mg/dL or normal LDL-C and/or TG levels. Compared with women with high HDL-C, women with low HDL-C have a nearly 3-fold elevated risk of ASCVD.

Abbreviations: ASCVD = atherosclerotic cardiovascular disease; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; TG = triglycerides.

Jellinger P, et al. *Endocr Practice*. (2017) 23(4):479–497.

Summary

- The primary causes of dyslipidemia should be identified and secondary causes must be excluded
- Treatment goals for dyslipidemia should be personalized based on individual risk assessment
- Lifestyle changes, patient education, and pharmacotherapy are all recommended
- Lipid status should be monitored at regular intervals
- Children and adolescents, as well as women, require special considerations