Chapter 11
Dyslipidemia

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Abbreviations

ApoB	Apolipoprotein B
ASCVD	Atherosclerotic cardiovascular disease
CKD	Chronic kidney disease
DLD	Dyslipidemia
FH	Familial hypercholesterolemia
HDL-C	High-density lipoprotein-cholesterol
LDL-C	Low-density lipoprotein-cholesterol
Lp(a)	Lipoprotein(a)
SAMS	Statin-associated muscle symptoms
TC	Total cholesterol
TG	Triglycerides

Introduction and Definitions

- Dyslipidemia (DLD) is a metabolic derangement causing a persistent elevation in plasma cholesterol and/or triglycerides. The three manifestations of dyslipidemia are:

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  - Hypercholesterolemia
  - Hypertriglyceridemia
  - Mixed hyperlipidemia [1, 2]

- Common manifestations of DLD include:
  - High total cholesterol (TC)
  - High triglycerides (TG)
  - High low-density lipoprotein-cholesterol (LDL-C)
  - Low high-density lipoprotein-cholesterol (HDL-C)
  - Elevated non-high-density lipoprotein-cholesterol (non-HDL-C)
  - Altered lipoprotein compositions such as increased apolipoprotein B (apoB) and lipoprotein(a) [Lp(a)] [2, 3]
- Primary disorders of lipid metabolism include familial hypercholesterolemia (FH), familial combined hyperlipidemia, and familial dysbetalipoproteinemia [4].
- The most common primary disorder is FH, which affects ~1 in 200 individuals; most cases are due to a heterozygous mutation. Combined hyperlipidemia affects ~1 in 100 individuals [5, 6].
- Patients with phenotype for FH (LDL-C > 190 mg/dL) have a 20-fold increased risk for cardiovascular disease and accelerated atherosclerosis [7].
- Secondary dyslipidemia can be a consequence of obesity, diabetes mellitus type I or II, hypothyroidism, obstructive liver diseases, chronic kidney disease, and certain drugs (i.e., progestins, androgens, beta-blockers, anabolic steroids, retinoids, cyclosporine, and phenothiazines) [8].
- Table 11.1 shows reference values for TG, LDL-C, and HDL-C levels [8, 9] for patients without known atherosclerotic cardiovascular disease (ASCVD).

Dyslipidemia and Cardiovascular Disease

- ASCVD remains the leading cause of morbidity and mortality globally. In the United States, this results in an annual estimated cost of >$200 billion [9, 10].

Table 11.1 Low-density lipoprotein-cholesterol (LDL-C), low high-density lipoprotein-cholesterol (HDL-C)

Fasting triglyceride level	Normal: <150 mg/dL Mild hypertriglyceridemia: 150–175 mg/dL Moderate hypertriglyceridemia: 175–499 mg/dL Severe hypertriglyceridemia: >500 mg/dL
LDL-C level	Optimal: <100 mg/dL Near optimal: 100–129 mg/dL Borderline high: 130 to 159 mg/dL High: 160–189 mg/dL Very high: >190 mg/dL
HDL-C level	Low: <40 mg/dL High: >60 mg/dL

- It is crucial to screen, diagnose,and treat dyslipidemia in the general population due to the high attributable risk for atherosclerotic and non-atherosclerotic cardiovascular disease.
- Dyslipidemia increases atherosclerosis and ASCVD risk by accelerating the atherogenic process.

Therapeutic Agents

- Statin therapies have a proven substantial benefit in the primary and secondary prevention of ASCVD, and recent evidence reveals that this benefit far outweighs potential risks [9].
- Other lipid-lowering therapies include:
  - LDL-C-lowering agents:

    Ezetimibe
    Bile acid sequestrants
    Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors

  - Triglyceride-lowering agents:

Fibrates
Niacin
Icosapent ethyl (a pure omega-3 fatty acid derivative of EPA) [9]

- Statins remain the cornerstone of treatment. Table 11.2 outlines the currently available statins with intensity levels [9].
- High-intensity statins have a ≥50% reduction of LDL-C, moderate-intensity statins result in 30–49% reduction of LDL-C, and low intensity confers a <30% reduction of LDL-C [9].
- Statins interact with several medications. Risk mitigation strategies should be used when co-prescribing with one of these medications (either limiting the dose, avoiding co-administration, or using an alternative statin which does not have a direct effect). Table 11.3 lists common medications [9].

Table 11.2 Intensity of statin therapy with current available statins

	High intensity	**Moderate intensity**	**Low intensity**
Statins	Atorvastatin 40 mg, 80 mg Rosuvastatin 20 mg, 40 mg	Atorvastatin 10–20 mg Rosuvastatin 5–10 mg Simvastatin 20–40 mg	Simvastatin 10 mg
	–	Pravastatin 40–80 mg Lovastatin 40 mg Fluvastatin 80 mg Pitavastatin 1–4 mg	Pravastatin 10–20 mg Lovastatin 20 mg Fluvastatin 20–40 mg

Table 11.3 Adapted from 2019 cholesterol guidelines[6] Statins requiring a risk mitigation approach

Amiodarone	Darunavir plus ritonavir	Nefazodone
Amlodipine	Diltiazem	Nelfinavir
Atazanavir plus ritonavir	Dronedarone	Niacin
Boceprevir	Erythromycin	Posaconazole
Clarithromycin	Fenofibrate/ fenofibric acid	Ranolazine
Cobicistat-containing products	Fluconazole	Rifampin
Colchicine	Fosamprenavir	Saquinavir plus ritonavir
Cyclosporine	Gemfibrozil[a]	Telaprevir
Danazol	Itraconazole	Telithromycin
	Ketoconazole	Tipranavir plus ritonavir
	Lomitapide	Verapamil
	Lopinavir plus ritonavir	Voriconazole
		Warfarin

[a]Absolutely do not use with any statin

Guidelines

- The American College of Cardiology/American Heart Association (ACC/AHA) 2019 combined cholesterol guidelines emphasize the importance of a heart-healthy lifestyle throughout the lifetime.
- In patients with clinical ASCVD, high-risk ASCVD, severe primary hypercholesterolemia, and populations with diabetes mellitus, statin therapy is recommended as first line. Table 11.4 highlights primary and Table 11.5 highlights secondary prevention strategies.

Clinical Pearl
In patients (age 40–75 years) without known ASCVD, the first step is to use the pooled cohort equation (PCE) calculator to calculate an individual's ASCVD risk

score which is divided into low risk (<5%), borderline risk (5 to <7.5%), intermediate risk (≥7.5 to <20%), and high risk (≥20%). In patients with low and intermediate categories, the risk-enhancing factors (outlined in Table 11.6) should be considered.

Table 11.4 Primary prevention guidelines from ACC/AHA 2019 for initiating statin therapy in patients without prior ASCVD

Risk	Recommendation
Low risk (<5%)	Lifestyle to reduce risk factors (Class I)
Borderline risk (5 to <7.5%)	If risk enhancers present, consider moderate-intensity statin (Class IIb)
Intermediate risk (≥7.5 to <20%)	If risk estimate + risk enhancers present, initiate moderate-intensity statin to reduce LDL-C by 30–49% (Class I) If risk uncertain, obtain calcium score (CAC). If CAC = 0, no statin. CAC 1–99, favor statin. CAC 100+, initiate statin therapy
High risk (≥20%)	Initiate statin to reduce LDL-C ≥ 50% (Class I)
LDL-C ≥190 mg/dL	No risk assessment; high-intensity statin (Class I)
Diabetes mellitus (age 40–75 y)	At least moderate-intensity statin (Class I) Additional risk-enhancing factors present = consider high intensity
Age >75 y	Clinical assessment, risk discussion (shared decision-making)

LDL-C low-density lipoprotein-cholesterol

Table 11.5 Secondary prevention guidelines for known clinical ASCVD as per ACC/AHA guidelines, statin as first line after healthy lifestyle emphasis

Very high risk[a] ASCVD	ASCVD not at very high risk
Initiate high-intensity or maximally tolerated statin (Class I)	Initiate high-intensity statin with goal LDL-C reduction of ≥50% (Class I) If high-intensity statin not tolerated, use moderate intensity (Class I)
If on maximal statin and LDL-C ≥70 mg/dL, add ezetimibe (Class IIa)	If on maximal statin and LDL-C ≥70 mg/dL, add ezetimibe (Class IIb)
If on maximal statin + ezetimibe and LDL-C ≥70 mg/dL, add PCSK9-I (Class IIb)	

Clinical ASCVD is acute coronary syndrome, history of myocardial infarction, stable or unstable angina, coronary or other arterial revascularizations, stroke, transient ischemic attack, or peripheral artery disease, all of atherosclerotic origin. In age >75 y, okay to initiate and/or continue moderate- or high-intensity statin for secondary prevention (Class IIa)

[a]Very high risk = multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions. Low-density lipoprotein-cholesterol (LDL-C), proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9-I)

Monitoring

- Monitoring response to LDL-C lowering agents is recommended and should be undertaken after initiation of agents or addition of agents.

Clinical Pearl

- Effects should be assessed by measuring fasting or non-fasting lipid levels 4–12 weeks after starting statin therapy or after a dose adjustment. After that, consider measuring every 3–12 months based on need to assess adherence or safety [9].

Table 11.6 Risk enhancers as outlined by ACC/AHA Guidelines which confer additional ASCVD risk

Risk enhancers
Family history of premature ASCVD
Persistently elevated LDL-C ≥160 mg/dL
Chronic kidney disease
Metabolic syndrome
Conditions specific to women
Preeclampsia
Premature menopause
Inflammatory diseases
Rheumatoid arthritis
Psoriasis
HIV
Ethnicity
South Asian Ancestry
Lipid/biomarkers:
Persistently elevated triglycerides (≥175 mg/dL)
In select individuals if measured:
Hs-CRP ≥2.0 mg/L
Lp(a) >50 mg/dL
ApoB ≥130 mg/dL
Ankle-brachial index (ABI) <0.9

ApoB Apolipoprotein B, *LDL-C* low-density lipoprotein-cholesterol, *hs-CRP* high-sensitivity C-reactive protein, *(Lp(a))* lipoprotein (a)

Special Populations

- Special consideration should be given to the following:
  - Elderly (age >75 years) patients
  - Racial/ethnic backgrounds
  - Women
  - Adults with HIV
  - Adults with CKD
- See Table 11.7 for a summary of these populations.

Table 11.7 Special populations to consider for lipid-lowering agents, based on ACC/AHA 2019 guidelines

Population	Recommendation
Elderly (age >75 y)	1. If LDL-C 70–189 mg/dL, reasonable to start moderate-intensity statin 2. Stop statin if functional decline, frailty, or reduced life expectancy 3. Adults 76–80, reasonable to measure CAC to reclassify risk
Specific ethnic/racial backgrounds	1. Reasonable to review race/ethnic features that influence ASCVD risk 2. Heightened risk of ASCVD in South Asians 3. Increased sensitivity to statins in East Asians 4. Increased prevalence of hypertension in Blacks 5. High rates of risk factors for ASCVD in Native Americans/Alaskan natives
Women	1. Consider conditions specific to women such as premature menopause (age < 40 y), history of pregnancy-associated disorders (hypertension, preeclampsia, gestation diabetes mellitus, small for gestational age infants, preterm deliveries 2. Women of childbearing age on statin therapy must be counseled to use contraception 3. Women who plan to become pregnant and are on statin should stop the agent 1–2 months before pregnancy is attempted or stop statin as soon as pregnancy is identified
Patients with HIV	1. Inflammatory conditions, especially HIV is risk enhancing. Start statin if ASCVD score >7.5% 2. Obtain baseline lipid panel for all patients with HIV
Patients with CKD	1. Adults 40–75 y with LDL-C 70–189 mg/dL with ASCVD score >7.5%, start moderate-intensity statin (if not on dialysis or kidney transplantation) 2. Moderate-intensity statin can be combined with ezetimibe

LDL-C low-density lipoprotein-cholesterol, *CAC* coronary artery calcium, *HIV* human immunodeficiency virus, *CKD* chronic kidney disease

Triglyceride-Lowering Therapy

- Hypertriglyceridemia (HTG) is a distinct lipid abnormality, and certain triglyceride-lowering agents have been found to reduce either ASCVD risk or the risk of pancreatitis. These include prescription strength omega-3 fatty acids and fibrates such as fenofibrate and gemfibrozil, which are peroxisome proliferator-activated receptor-α (PPAR-α) agonists.
- Recent trials have shown benefit with icosapent ethyl (a pure omega-3 fatty acid derivative of EPA). REDUCE-IT showed a 25% reduction in the risk of ischemic events and CVD death with 4 grams of icosapent ethyl superimposed on use of moderate- to high-intensity statins in high-risk patients with either ASCVD or diabetes mellitus with elevated fasting triglyceride levels of 135–499 mg/dL [11]. However, guidelines have yet to endorse its use, and it should be considered on a case-by-case basis.
- Statins remain the first-line therapy for TG lowering. See Table 11.8 for the most recent recommendations from the American Heart Association.
- Fibric acid derivatives (fenofibrate and gemfibrozil) are renally excreted, and the safety of these needs to be considered with possible dose adjustments, particularly in those on statin therapy.

Clinical Pearl

- The National Kidney Foundation and National Lipid Association recommend dose adjustment of fibrates based on estimated glomerular filtration rate (eGFR).
- Fenofibrate is the preferred fibrate to use with statin therapy; gemfibrozil inhibits the glucuronidation of statins which increases the blood level of the statin and therefore increases the risk of myopathy and rhabdomyolysis. Gemfibrozil should not be combined with statin therapy [12, 13].

Table 11.8 Highlights the treatment for moderate and severe hypertriglyceridemia as outlined by the most recent ACC/AHA guidelines [6]

Recommendations for hypertriglyceridemia	
Moderate hypertriglyceridemia (fasting or non-fasting TG 175–499 mg/dL)	Age >20 y: treat lifestyle factors (obesity, metabolic syndrome) and secondary factors Age 40–75 y: If ASCVD risk >7.5%, favor initiation of statin with lifestyle modification
Severe hypertriglyceridemia (fasting or non-fasting TG ≥500 mg/dL)	Age 40–75 y: Address reversible causes, initiate or intensify statin therapy If TG >1000 mg/dL: implement very low-fat diet, avoid refined carbohydrates and consumption of omega-3 fatty acids, and fibrate therapy can be considered

Addressing Side Effects

- Statin therapy is safe and generally well tolerated. Statin-associated side effects may be present in a few patients [9].
- Statin-associated muscle symptoms (SAMS) are the most common side effect and include myalgias (observationally reported in 5–20% of patients).
- The rarer SAMS:
  - Myositis/myopathy with elevated creatine kinase (CK)
  - Rhabdomyolysis (CK >10x upper limit of normal [ULN])
  - Statin-associated autoimmune myopathy (only in case reports)
- Statins have also been associated with new-onset diabetes mellitus in predisposed individuals with BMI > 30, fasting glucose >100, metabolic syndrome, and prediabetes [9].
- Observational studies report transaminase elevation >3× ULN and rarely hepatic failure, but these are rare to infrequent occurrences [9].

- To address SAMS, a statin rechallenge should be considered with an alternative statin, or a dose reduction with or without decrease in frequency of administration.
- It is crucial to have a clinician-patient risk discussion (CPRD) regarding potential adverse effects, drug-drug interactions, ASCVD risk reduction benefit, and patient preferences to promote a shared decision-making (SDM) process before prescribing therapy.

Emerging Lipid-Lowering Agents

- Several newer lipid-lowering agents are on the horizon. Several new therapies target atherogenic lipids (LDL-C, Lp(a), non-HDL-C, remnants) using a variety of different mechanisms [14].
- These newer agents are promising and may prove beneficial for patients, highlighted in Table 11.9.

Key Learning Points

1. Dyslipidemia (DLD) is a metabolic derangement causing a persistent elevation in plasma cholesterol and/or triglycerides. The three manifestations of dyslipidemia are hypercholesterolemia, hypertriglyceridemia, and mixed hyperlipidemia.
2. It is crucial to screen, diagnose, and treat dyslipidemia in the general population due to the high attributable risk for cardiovascular disease. Dyslipidemia increases atherosclerosis and ASCVD risk by accelerating the atherogenic process.
3. Statin therapies have a substantial benefit in the primary and secondary prevention of ASCVD, and recent evidence reveals that this benefit far outweighs potential risks.

Table 11.9 Current and new lipid-lowering therapeutics

Therapeutic drug	Major effect on plasma lipids/proteins
Statins	↓ LDL ↓ TC
Fibrates	↓ TG
Omega-3 fatty acids	↓ TG
PCSK9 inhibitors	↓ LDL ↓ Lp(a)
Bempedoic acid	↓ LDL ↓ non-HDL
Inclisiran	↓ PCSK9
AKACEA-APO(a)-LRx	↓ Lp(a)
Evinacumab	↓ TG
Volanesorsen	↓ TG

LDL low-density lipoprotein, *TC* total cholesterol, *TG* triglyceride, *PCSK9* proprotein convertase subtilisin/kexin type 9, *(Lp(a))* lipoprotein(a)

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