CHAPTER 6

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Lipoprotein Disorders

CHAPTER OUTLINE

ABBREVIATIONS

ABCA	ATP-binding cassette transporter A
ABCG	ATP-binding cassette transporter G
ACS	Acute Coronary Syndrome
ATPIII	Adult Treatment Panel III
CAD	Coronary artery disease
CE	Cholesterol esters
CETP	Cholesterol ester transfer protein
CHD	Coronary Heart Disease
CK	Creatine kinase
CKD	Chronic kidney disease
CM	Chylomicron
CV	Cardiovascular
DM	Diabetes Mellitus
FA	Fatty acid
FC	Free cholesterol
FCH	Familial combined hyperlipidemia
FDB	Familial defective apolipoprotein B
FFA	Free fatty acids
FH	Familial hypercholesterolemia
FRS	Framingham Risk Score
GFR	Glomerular Filtration Rate
GI	Gastrointestinal
HDL	High density lipoprotein
HDL-C	High density lipoprotein cholesterol
IDL	Intermediate density lipoprotein
LCAT	Lecithin cholesterolacyl transferase
LDL	Low density lipoprotein
LDL-C	Low density lipoprotein cholesterol
LDL-R	LDL receptor
LFTs	Liver function tests
LPL	Lipoprotein lipase
MetS	Metabolic syndrome
MI	Myocardial Infarction
Non-HDL-C	Non high density lipoprotein cholesterol
NCEP	National Cholesterol Education Program
PCI	Percutaneous intervention
PL	Phospholipids
PPARa	Peroxisome proliferator-activated receptor alpha
RCT	Randomized control trial
RF	Risk factors

TC	Total cholesterol
TLC	Therapeutic lifestyle changes
TG	Triglycerides
T2D	Type 2 diabetes mellitus
VLDL	Very low density lipoprotein

INTRODUCTION

Disorders of serum lipid and lipoproteins account for approximately 50 % of population-attributable risk for myocardial infarction (MI) [1, 2]. Randomized control trial (RCT) data demonstrate that treating elevated levels of low density lipoprotein (LDL) cholesterol results in substantial reductions in cardiovascular events and death [3]. Evidence-based guidelines identify serum lipids and lipoprotein disorders as important targets in primary and secondary prevention of coronary heart disease (CHD) [4, 5].

OVERVIEW OF LIPOPROTEIN METABOLISM

- Three major types of lipids circulate in the serum:
  - Cholesterol-essential component of cell membranes and substrate for synthesis of steroid hormones and bile acids
  - Triglycerides (TG)-macromolecules consisting of glycerol backbone connected to three fatty acids (FA)
  - Phospholipids (PL)-important constituents of cell membranes
- Serum lipids are packaged and transported in lipoproteins (Fig. 6-1), which consist of a hydrophobic lipid core of TG, and a polar shell consisting of hydrophilic PL, free cholesterol (FC), and specialized apolipoproteins.
- Lipoproteins are classified according to their density in plasma (Table 6-1)
- Lipoprotein(a) or Lp(a) is an LDL-like lipoprotein that confers a modest increased risk of CHD independent of LDL-C
- Lp(a) contains the Apo(a) apolipoprotein, which has structural homology to plasminogen but lacks any fibrinolytic activity
- Apo(a) may interfere with plasminogen activity and contribute to the pro-thrombotic state associated with Lp(a)
- Routine measurement of Lp(a) is not recommended as a part of risk factor assessment
- Apolipoproteins (Apo; Table 6-2) participate in:
  - lipoprotein assembly and secretion (Apo A-I, Apo B100, Apo B48)
  - catalysis (Apo A-I, Apo A-V, Apo C-II) or inhibition (Apo C-III) of enzymes
  - lipoprotein binding to receptors (Apo B48, B100)
- Lipoprotein transport serves two important functions:
  - Transport of TG from the intestine to the liver and sites of TG uptake (muscle & fat)
  - Transport of cholesterol to peripheral tissues
- Two important pathways coordinate lipoprotein transport:
- Intestinal pathway (Fig. 6-2):
  - Coordinates transfer of dietary TG to the liver and peripheral tissues
  - Dietary TG in intestinal epithelial cells are packaged with Apo B48 and a small amount of cholesterol to form chylomicron (CM) lipoproteins
  - CM are secreted into the circulation and acquire Apo C and E from HDL
  - CM undergo hydrolysis by lipoprotein lipase (LPL) on endothelial cells
  - Free fatty acids (FFA) released by TG hydrolysis are taken up for energy storage

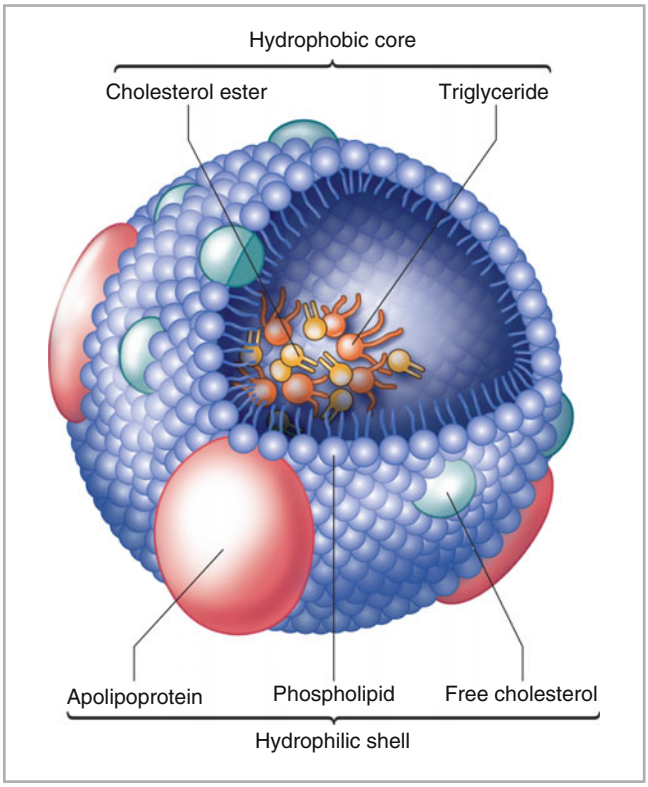

FIGURE 6-1

Schematic of a lipoprotein

TABLE 6-1

PLASMA LIPOPROTEINS

LIPOPROTEIN	DENSITY (G/ML)	PRIMARY LIPID COMPONENT	MAJOR APOLIPOPROTEIN
Chylomicron (CM)	<0.95	TG	B48
CM remnant	0.95–1.006	TG	B48, E
Very low density lipoprotein (VLDL)	<1.006	TG	B100
Intermediate density lipoprotein (IDL)	1.006–1.019	TG, CE	B100, E
LDL	1.019–1.063	CE	B100
High density lipoprotein (HDL)	1.063–1.210	CE, TG	A-I, A-II

TABLE 6-2

MAJOR APOLIPOPROTEINS

APOLIPOPROTEIN	PREDOMINANT LIPOPROTEIN	ROLE
A (A-I, A-II, A-IV, A-V)	HDL VLDL (A-V)	ACAT activation (A-I) Structural integrity (A-II, A-IV) TG metabolism (A-V)
B48	CM, CM remnants	Structural integrity
B100	VLDL, IDL, LDL	Structural integrity LDL-R binding
C (C-I, C-II, C-III)	CM (C-I, C-II, C-III) VLDL (C-II, C-III)	TG Metabolism (C-I) LPL activation (C-II) LPL Inhibition (C-III)
E	CM remnants, IDL	LDL-R, Apo E-Receptor binding

ACAT acetyl-coenzyme A acetyltransferase, *LDL-R* LDL receptor, *LPL* lipoprotein lipase

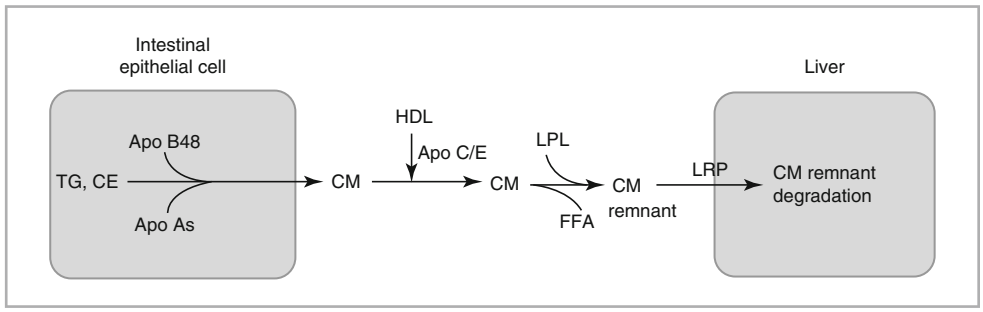

FIGURE 6-2

Schematic of intestinal pathway. Chylomicrons (*CM*) are assembled in intestinal epithelial cells and secreted into the circulation, where they undergo lipolysis by lipoprotein lipase (*LPL*). CM-remnants are taken up by the liver. *LRP* lipoprotein receptor-related protein

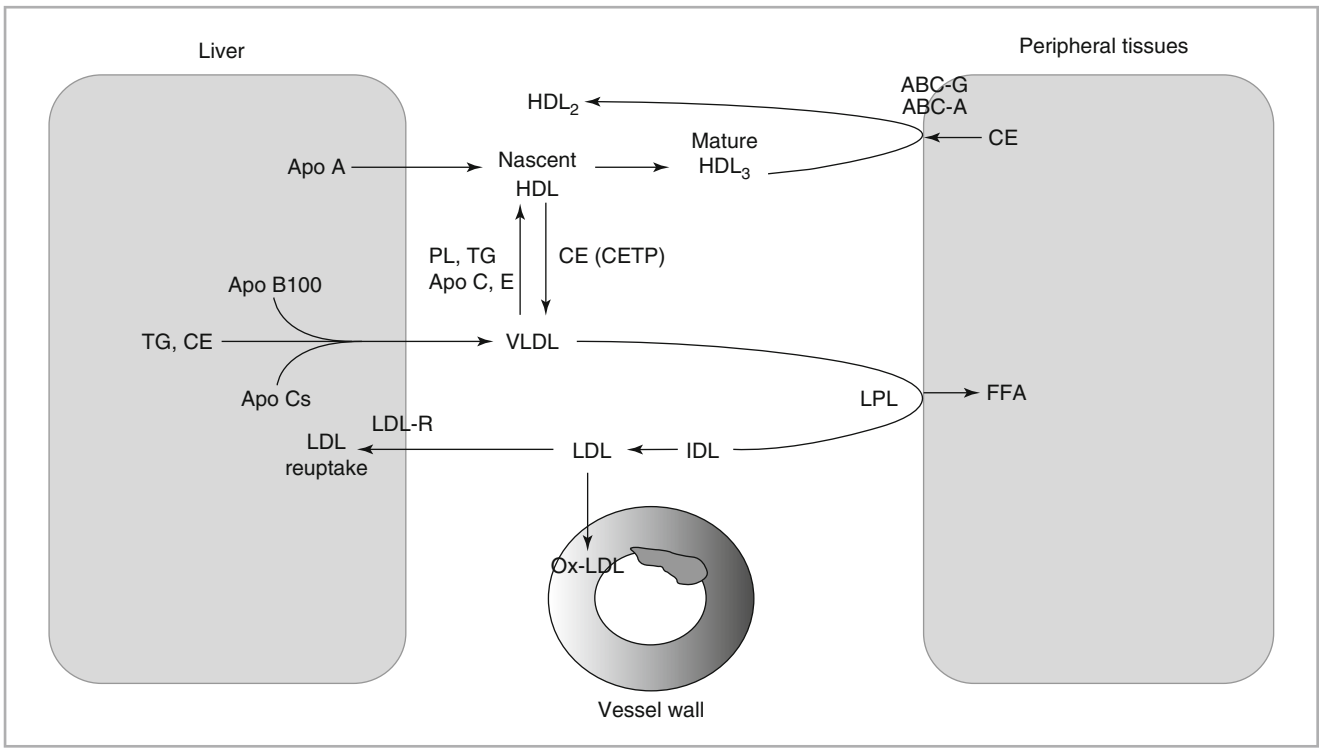

FIGURE 6-3

Schematic of hepatic pathway. TG-rich VLDL are assembled in the liver and secreted into the circulation. Cholesteryl ester transfer protein (*CETP*) facilitates transfer of TG from VLDL to HDL in exchange for cholesterol. VLDL is hydrolyzed by LPL to release FFA that are taken up by peripheral tissues (fat, muscle). LDL generated from LPL action can enter the vessel wall, where its oxidation and uptake by macrophages leads to foam cell formation, a key step in atherogenesis. Nascent HDL secreted from the liver play an important role in reverse cholesterol transport

■ Hepatic Pathway (Fig. 6-3):

- Coordinates the transport of TG and cholesterol between the liver and target peripheral tissues
- Hepatocytes package TG with Apo B100 to form VLDL
- In the circulation, VLDL interacts with HDL to [1]: acquire additional lipoproteins (Apo C and E), and [2] exchange TG for CE
- Like CM, VLDL undergoes lipolysis by LPL to produce FFA
- VLDL hydrolysis yields IDL, which undergoes further hydrolysis by hepatic lipase to form LDL, the main courier of FC and CE
- LDL is taken by the liver, a process mediated by the LDL receptor (LDL-R)
- LDL modification in the vessel wall and uptake by macrophages leads to foam cell formation, a key step in atherogenesis

LIPOPROTEIN DISORDERS AND CHD RISK

- Several lipid and lipoprotein variables have been reported to confer an increased risk of CHD:
  - Elevated total cholesterol (TC) and LDL cholesterol (LDL-C) [6, 7]
  - Low HDL-C and high TG [6, 8]
  - Elevated non-HDL cholesterol (a measure of the total burden of Apo-B containing atherogenic lipoprotein particles) [9]
  - Apo B lipoprotein levels [9]
  - Elevated Lp(a) [10]
  - Small, dense LDL particles [11]
- NCEP-ATPIII guidelines identify LDL-C as the primary lipid target for intervention [4, 5]
- A continuous log-linear relationship exists between LDL-C and CHD risk [5]:
  - a decrease of 1 mg/dL in LDL-C results in a 1 % decrease in CHD relative risk
  - a given mg/dL change in LDL-C produces the same change in relative risk of CHD at any level of LDL-C
- Although LDL-C is the primary lipid target, other parameters such as low HDL-C, non-HDL-C, and Apo B appear to be stronger predictors of CHD risk [9, 12, 13]
- An increase of 1 mg/dL in HDL-C is associated with a 2–3 % decrease in CHD risk [8], but to date there is no RCT to support targeting HDL-C
- ATPIII identified non-HDL-C, a surrogate marker of Apo B levels, as a secondary target in patients with TG > 200 mg/dL (Non-HDL-C = TC - HDL-C)
- NCEP ATPIII guidelines did not recommend routine testing for emerging lipid risk markers

DIAGNOSIS AND SCREENING

- The most common lipoprotein disorders encountered clinically are related to age, physical inactivity, diet, obesity, and lifestyle factors (smoking)
- Recent classification systems from WHO and NCEP focus on thresholds and cut points for serum lipoprotein lipids to diagnose and treat lipoprotein disorders (Table 6-3)
- Plasma levels of lipids (cholesterol and triglycerides) and lipoprotein cholesterol (LDL-C and HDL-C) define three general patterns of lipoprotein disorders commonly encountered in clinical settings:
  - Hyperlipidemia refers to an elevation in LDL-C (and TC)
  - Hypertriglyceridemia refers to an elevation in TG
  - Dyslipidemia refers to a combination of hypertriglyceridemia and low HDL-C with either a normal or elevated TC or LDL-C (commonly seen in insulin resistant states)
- Fasting lipid profile (FLP), which provides direct measurement of TC, TG, HDL-C and calculated LDL-C, is the preferred initial test, rather than measurement of non-fasting TC and HDL-C alone.

TABLE 6-3

SERUM LIPID CONCENTRATIONS

LIPID	OPTIMAL (MG/DL)	BORDERLINE ELEVATION (MG/DL)	ELEVATED/HIGH RISK (MG/DL)
TC	<200	200–239	>240
LDL-C	<100 (100–129-near optimal)	130–159	>160
HDL-C	≥60	40–59 (men) 50–59 (women)	<40 (men) <50 (women)
TG	<150	150–199	>200

- The Friedewald formula [14] (below) is used to calculate LDL-C, because direct measurement of LDL-C is time consuming and costly

$$\text{LDL-C} = \text{TC} - (\text{HDL} + \text{TG}/5)$$

- The LDL-C calculated from the Friedewald formula is inaccurate at higher TG levels [15], and direct measurement of LDL should be considered if TG > 400 mg/dL [4, 15]
- ATP III screening guidelines: FLP at least once every 5 years for individuals older than 20 years of age, with consideration for more frequent testing in older individuals with risk factors [4]
- Significant elevations in LDL-C (> 190 mg/dL) can indicate a genetic disorder that warrants further consideration and family testing
- Patients admitted with MI should have a FLP within 24 h of admission (levels drawn later will be spuriously low due to hepatic stress response or medications)

MANAGEMENT OF LIPOPROTEIN DISORDERS

Drugs that Modulate Lipid Metabolism

Hyroxymethylglutaryl-Coenzyme A Reductase Inhibitors (Statins)

- Statins inhibit HMG-CoA reductase, the rate-limiting enzyme in sterol synthesis
- Statins increase expression of LDL-R and decrease CE formation, leading to enhanced LDL-C clearance from plasma and reduced VLDL production
- Statins are the drugs of choice for reducing LDL-C (20–55 % reduction)
- Statins also modestly decrease TG (5–30 %) and increase HDL-C (2–10 %)
- Data support efficacy of statins in primary and secondary prevention across age groups, in men and women, and in type 2 diabetes (T2D) [3, 4]
- Starting statin dose should be sufficient to decrease the LDL-C by 30–40 % [4] (Table 6-4)
- Doubling the dose of any of the statins yields a further 6 % decrease in LDL-C
- Starting doses should be lower in smaller patients, the elderly, and patients of East Asian ancestry, in whom starting doses of rosuvastatin should be 5 mg
- Statins are relatively safe with low rates of liver toxicity (1.4 %) and myopathy (0.2 %) [3]
- The risk of myopathy is significantly higher with 80 mg of simvastatin and doses higher than 40 mg of simvastatin should be avoided
- The risk of myositis is increased if statins are used with niacin or fibrates (especially gemfibrozil)
- Lower doses of potent statins (atorvastatin and rosuvastatin) are associated with lower rates of myositis and transaminitis
- Lovastatin, simvastatin, and atorvastatin are metabolized by CYP 3A4 and should be used with caution with other drugs that are metabolized using the same pathway

TABLE 6-4

DOSES OF AVAILABLE STATINS REQUIRED TO ATTAIN 30–40 % REDUCTION IN LDL-C

STATIN	DOSE (MG/DL)	LDL-C REDUCTION (%)
Fluvastatin	40–80	25–35
Lovastatin	40	31
Pravastatin	40	34
Simvastatin	20–40	35–41
Atorvastatin	10	39
Rosuvastatin	5–10	39–45
Pitavastatin[a]	2–4	38–45

[a]Most recently approved statin (FDA approval in 8/2009)

(macrolides, antifungals, cyclosporine, verapamil, amlodipine, ranolazine, or large quantities of grapefruit juice)
- Statins are contraindicated in pregnancy (Class X for known teratogenic effects) and other alternatives such as bile acid sequestrants (Class B) and fibrates (Class C) should be used

Fibrates
- Fibrates activate peroxisome proliferator-activated receptor alpha (PPARα) which increases apo A-I and represses apo B and VLDL production
- Lower TG 20–35 % and increase HDL-C by 6–18 % with modest effect on LDL-C (~20 % reduction)
- Drugs of choice for severe hypertriglyceridemia
- Helsinki Heart Study [16] and VA-HIT [17] trials showed fibrate monotherapy reduces CV events
- However the recent FIELD [18] and ACCORD [19] trials raise questions regarding clinical benefits of combined fibrate therapy in T2D patients with modest TG and HDL-C abnormalities
- ATPIII recommends considering adding fibrates to statins in high risk patients with TG and HDL-C abnormalities [4], although trial data for this strategy is lacking
- Gemfibrozil can inhibit glucurodination and elimination of statins, thereby significantly increasing the risk of statin-myotoxicity

Niacin
- Niacin has multiple effects including suppression of lipolysis, reduced hepatic synthesis of TG and VLDL secretion, increased apo B degradation, and decreased catabolism of HDL
- Most potent HDL-raising agent (10–35 %) that also lowers TG (20–30 %) and LDL-C (10–25 %)
- The CDP (coronary drug project) [20] showed niacin monotherapy decreased CV events by ~30 %
- ATPIII guidelines recommend addition of Niacin to statins in high risk patients with low HDL-C and high TG to address residual risk [4], although trial data for this strategy is lacking
- Recent AIM-HIGH trial investigating addition of niacin to patients on simvastatin and controlled LDL showed no benefit [21]
- Side effects include cutaneous flushing, hyperuricemia, transaminitis, and hyperglycemia

Bile Acid Sequestrants
- Interrupt reabsorption of cholesterol-containing bile acids
- Mainly used as an adjunctive therapy in patients with severe elevations in LDL-C
- Modest decreases in LDL-C (15–30 %) and small increases in HDL-C (5–15 %)
- Frequent GI side effects and occasionally results in hypertriglyceridemia

Cholesterol Absorption Inhibitors (Ezetimibe)
- Inhibits intestinal cholesterol absorption via cholesterol transport interference
- Reduces LDL-C (10–25 %) but may have beneficial effects on TG, apo B, and HDL-C
- Addition of ezetimibe to statins decreases LDL-C by an additional 25–30 %
- ENHANCE trial showed that addition of ezetimibe to simvastatin did not affect the surrogate marker of carotid intimal thickness [22]
- SHARP trial showed simvastatin/ezetimibe safely reduced LDL-C and CV events in patients with CKD compared to placebo [23] (Table 6-5)

Core concepts from NCEP ATPIII treatment guidelines

- Risk assessment and categorization using non-LDL risk factors (RF) and risk modifiers (Table 6-6) and Framingham Risk Score (FRS) are the first steps
- Evaluation of secondary causes of lipoprotein disorders
- Individualized LDL-C goals (primary target) and non-HDL-C goals (secondary target if TG > 200) based on risk stratification (Table 6-7)
- Therapeutic lifestyle changes (TLC) for all patients
- Appropriate initiation and intensity of pharmacologic therapy based on risk
- Treatment of non-lipid risk factors and secondary causes of dyslipoproteinemia
- Management considerations in genetic disorders

TABLE 6-5

PRIMARY LIPID-MODIFYING DRUG CLASSES

DRUG CLASS	METABOLIC EFFECTS	CLINICAL CONSIDERATIONS
Statins	↓LDL-C 20–55 % ↑HDL-C 2–10 % [a] ↓TG 5–30 %	↓CV events, CHD deaths, need for PCI, CVA, total mortality Liver and muscle toxicity (monitor CK, LFTs) Potential drug interactions between some statins[b] and CYP450 3A4 inhibitors (macrolides, antifungals, cyclosporine, grapefruit juice) Use with caution with fibrates (avoid gemfibrozil) and niacin Avoid simvastatin at 80 mg (ok to continue if tolerated>1 year) Absolute contraindications: active or chronic liver disease Relative contraindications: concomitant use of some drugs
Fibrates: Gemfibrozil Fenofibrate	↓TG 20–35 % ↑HDL-C 6–20 % ↓TC/LDL-C 20–25 %[c]	Reduced CV events (monotherapy) in 1^0 and 2^0 prevention No benefit observed in statin-treated DM patients with dyslipidemia GI side effects, transaminitis, muscle injury, elevation in creatine (not related to reduction in GFR) Absolute contraindications: severe renal/hepatic disease Relative contraindications: statins (avoid gemfibrozil)
Nicotinic acid: Multiple OTCs Prescription: Slo-Niacin Niaspan	↓TG 20–30 % ↑HDL-C 10–35 % ↓LDL-C 10–20 %	Reduced CV events as monotherapy Recent trial data show no benefit in statin-treated patients with well controlled LDL-C and persistent low HDL-C Frequent side effects: cutaneous flushing, hyperuricemia, hypertriglyceridemia, hepatotoxicity, gastritis Absolute contraindications: hepatic disease, severe gout Relative contraindications: DM, hyperuricemia, Peptic ulcer disease
Bile acid sequestrants: Cholestyramine Colestipol Colesevam	↓LDL-C 15–25 %	Mainly used as adjunctive therapy for LDL-C lowering Frequent GI side effects and may increase TG Many potential drug interactions Interferes with absorption of other drugs (administer 1 h after or 3 h before other medications) Absolute contraindications: TG>400 mg/dL Relative contraindications: TG>200 mg/dL
Cholesterol absorption inhibitor: Ezetimibe	↓LDL-C 10–20 % ↓LDL-C additional 25 % with statin	Used primarily as adjunctive therapy with statin for LDL-C lowering No trial data to support incremental clinical benefit over statin alone Rarely causes myopathy

[a]Less consistent than LDL effects
[b]Lovastatin, simvastatin>atorvastatin
[c]May increase LDL-C in patients with elevated TGs ("beta-shift")

TABLE 6-6

MAJOR NON-LDL RISK FACTORS

Risk factor
1. Cigarette smoking
2. Hypertension (BP≥140/90 mmHg or treatment for hypertension)
3. Low HDL (< 40 mg/dL for men and<50 mg/dL for women)[a]
4. Family history of premature CAD[b]
5. Age (≥45 years for men and ≥55 years for women)

[a]HDL-C>60 mg/dL represents a protective factor (removes 1 risk factor)
[b]CHD in male 1st degree relative<55 years and female 1st degree relative<65 years

TABLE 6-7

LDL-C AND NON-HDL-C GOALS BASED ON RISK STRATIFICATION

RISK CATEGORY	LDL-C GOAL (MG/DL)	NON-HDL-C[A] GOAL (MG/ DL)	DRUG THERAPY FOR LDL-C (MG/DL)
High risk: CHD or CHD equivalents (10-years risk>20 %) (<100 mg/dL-consider drugs)	<100 <70 (for very high risk)[b]	<130	≥100
Moderately-high risk: 2+ RF (10 years-risk 10–20 %)	<130	<160	≥130
Moderate risk: 2+ RF (10 years-risk <10 %)	<130	<160	≥160
Low risk: 0–1 RF (10 years-risk <10 %)	<160	<190	≥190

[a]Non-HDL-C=TC-HDL-C
[b]Optional target for very high risk patients: established CHD and (1) history of ACS, (2) T2D or MetS, (3) multiple RF, (4) severe or poorly controlled RF

■ Step 1- Risk assessment:

- ATPIII recommends classification of risk into four groups:
  1. High Risk (10 years risk >20 %)
  2. Moderately High Risk (2+ RF and 10 years risk 10–20 %)
  3. Moderate Risk (2+ RF and 10 years risk <10 %)
  4. Low risk (10 years risk >10 %)
- Classify patients with established CHD, other forms of atherosclerotic disease (peripheral and cerebrovascular disease, abdominal aneurysms), and T2D as "high risk"
- Classify CHD patients as "very high risk" if [1]: history of acute coronary syndrome (ACS) [2], multiple RF including T2D or metabolic syndrome (MetS), or [3] severe or poorly controlled RF
- If no established CHD or CHD equivalents, count major non-LDL risk RF (Table 6-6)
- If 0–1 RF, classify as low risk
- If 2+ RF, calculate FRS and classify patients as follows:
  1. FRS 10 years risk >20 % classify as "high risk"
  2. FRS 10 years risk 10–20 % classify as "moderately-high risk"
  3. FRS 10 years risk <10 % classify as "moderate risk"

■ Step 2: Rule out and treat secondary causes of lipoprotein disorders (T2D, thyroid disorders, drugs, nephrosis)

- Step 3: Establish LDL-C goal based on risk:
  - LDL-C is the primary target (Table 6-7)
  - For CHD and CHD equivalents, target LDL-C is <100 mg/dL (optional LDL-C goal of <70 mg/dL in very high risk patients)
  - For moderately-high risk and moderate risk patients, LDL-C goal is <130 mg/dL
  - For low risk patients, LDL-C goal is <160 mg/dL
  - If TG > 500 mg/dL (imminent risk of pancreatitis), treat hypertriglyceridemia first
- Step 4: Establish secondary goals (non-HDL-C and MetS):
  - Non-HDL-C is a marker of the total burden of atherogenic TG-rich lipoproteins
  - Non-HDL-C is a secondary goal when TG >200 mg/dL
  - Non-HDL-C goals are 30 mg/dL higher than LDL-C goals for each risk group
  - Interventions to decrease non-HDL-C include:
    1. Increase statin dose
    2. Add second agent (fibrate/niacin)
    3. TLC
  - ATPIII also identifies MetS as a secondary target for aggressive treatment
- Step 5: Initiate TLC in all patients and pharmacologic therapy in selected patients (Table 6-7):
  - All patients with lipoprotein disorders should be encouraged to undertake TLC:
    1. Decrease intake of dietary saturated fats (< 7 % total calories) and cholesterol (< 200 mg/dL)
    2. Exercise
    3. Increase plant phytosterol (2 g/day) and fiber (10–25 g/day) intake
  - Initiating pharmacologic therapy in high risk patients:
    1. Statins are drugs of choice for LDL-C lowering in patients with hyperlipidemia and dyslipidemia
    2. Start drug therapy if LDL-C >100 mg/dL
    3. If baseline LDL-C <100 mg/dL, starting drug therapy to attain an LDL-C <70 mg/dL is a therapeutic option
    4. Initial statin dose should achieve a 30–40 % decrease in LDL-C
    5. If TG >200 mg/dL or HDL-C levels are low, consider niacin or fibrate
  - Initiating pharmacologic therapy in moderately-high risk patients:
    1. Start drug therapy if LDL-C >130 mg/dL
    2. Consider drug options if LDL-C is 100–130 mg/dL
    3. Initial statin dose should achieve a 30–40 % decrease in LDL-C
  - Initiating pharmacologic therapy in moderate risk patients:
    1. Start drug therapy if LDL-C >160 mg/dL
    2. Consider drug options if LDL-C is 130–160 mg/dL
  - Initiating pharmacologic therapy in low risk patients: recommended threshold LDL-C > 190 mg/dL (starting drug for LDL-C 160–190 mg/dL is an option)
- Follow-up after initiating therapy:
  - Repeat FLP 6 weeks after initiation of therapy and again at 6 weeks intervals until at goal (LDL-C and any appropriate secondary targets)
  - If LDL-C not at goal, consider increasing statin dose, switching to a more potent statin, or adding adjunctive agent (niacin, fibrate, bile acid sequestrant, ezetimibe)
  - After LDL-C is at goal, patients should be tested every 6–12 months

- Baseline LFTs should be checked prior to initiation of therapy with statin, niacin, or fibrate, and then again 3 months after start of treatment, and then every 6–12 months
- CKs should be checked if patient complains of myalgias

Management of Genetic Dyslipidemias

Familial Hypercholesterolemia (FH)

- Autosomal co-dominant disorder due to mutation in LDL-R
- Heterozygous form (prevalence 1 in 500 people) results in LDL-C twice normal (190–350 mg/dL)
- Homozygous form (prevalence 1 in 1.1 million) results in LDL-C in 400–1,000 mg/dL range
- Tendon xanthoma, corneal arcus senilis usually present
- Premature CHD is common in the third decade in men and in the fourth decade in women
- LDL- lowering therapy initiated in teenage years with statin (1st line), bile acid sequestrant, or multi-drug regimen
- Homozygous FH patients often need plasma apheresis
- Family testing indicated

Familial Defective apolipoprotein B (FDB)

- Autosomal dominant disorder due to mutation in Apo B100 gene (prevalence of 1 in 1,000)
- Results in 1.5–2 fold elevations in LDL-C (160–300 mg/dL)
- Xanthomas as well as premature CHD and aortic valve disease are common
- As with heterozygous FH, combination LDL-lowering therapy is effective
- Family testing indicated

Polygenic Hypercholesterolemia

- Due to complex interactions between environmental factors and multiple genetic factors
- LDL-C > 190 mg/dL but generally milder than heterozygous FH
- Relatively common (prevalence 1 in 20)
- Only ~10 % of 1st degree relatives of affected individuals have elevated LDL-C
- Increased risk of CHD but xanthomas are absent
- TLC, LDL-lowering therapy with statins or bile acid sequestrants or combination therapy are indicated

Familial Hypertriglyceridemia

- Genetic defect undefined
- Affected individuals have normal or mildly elevated TC and LDL-C, but significant hypertriglyceridemia (200–500 mg/dL fasting and greater than 1,000 mg/dL after meals)
- Xanthoma usually absent and the relationship with CAD is not as strong as with FH
- Treatment based on dietary modifications, exercise, and drug therapy

Familial Combined Hyperlipidemia (FCH)

- Common familial lipoprotein disorder (prevalence of 1 in 50 people)
- Lipid abnormalities in FCH include elevated TC and LDL-C (>190 mg/dL) and TG (>300 mg/dL)
- Few clinical signs are present, but there is an increased risk of premature CAD
- Management is similar to other genetic dyslipidemias: TLC and statin, and consideration for addition of niacin or fibrate if indicated

Genetic Disorders Affecting HDL

- Hypoalphalipoprotenemia-low HDL levels due to mutation of Apo A-1, but only a subset of these patients have an increased risk of CHD
- Tangier's Disease- Low HDL-C due to ABCA-1 mutation with no clear increased risk of CHD

- Lecithin cholesterolacyl transferase (LCAT) Deficiency– Absent LCAT activity leads to decreased CE formation in circulating HDL particles and low HDL-C, without a clear increase in CHD risk
- CETP Deficiency- Absence of CETP leads to accumulation of cholesterol in HDL, leading to high HDL-C levels but no clear protection against CHD

QUICK REVIEW

- Disorders of lipoproteins are important targets in primary and secondary prevention of CHD
- Recent classification systems from WHO and NCEP focus on cut points for serum and lipoprotein lipids to diagnose and treat lipoprotein disorders
- FLP is the initial screening test of choice
- NCEP ATPIII guidelines advocate a step-wise approach to the diagnosis and management of lipoprotein disorders (Fig. 6-4)
- LDL-C is the primary target, but non-HDL-C and MetS are secondary targets in select populations
- TLC should be encouraged in all patients with lipoprotein disorders
- Statins are drugs of choice for LDL-lowering therapy

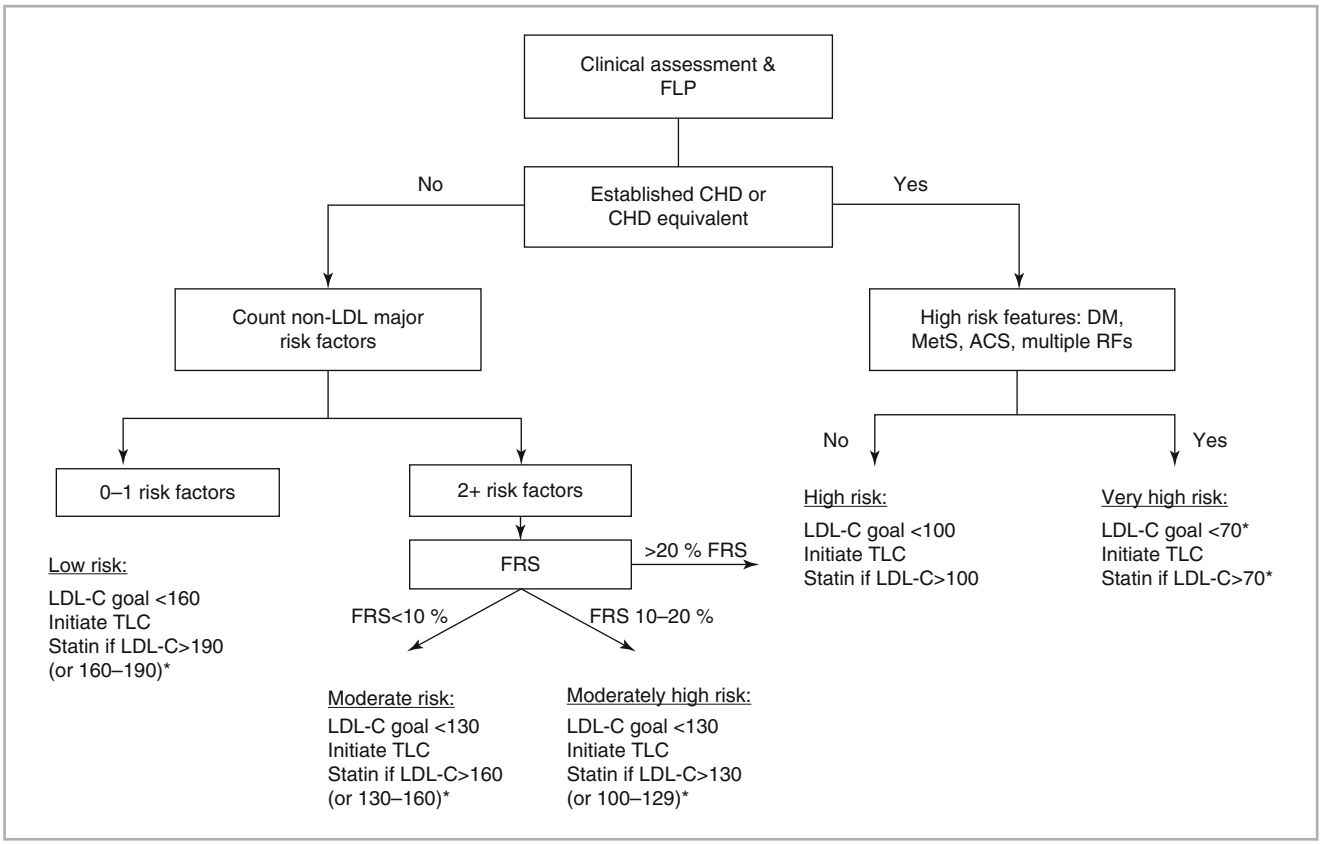

FIGURE 6-4

Summary of NCEP ATPIII guidelines for management of hyperlipidemia. Management strategy emphasizes individual risk assessment and establishing LDL-C (primary target) goals based on risk. * Optional targets based on 2004 ATPIII update

- Fibrates are most effective in treating hypertriglyceridemia, which should be the addressed first if TG elevations are severe (>500 mg/dL) and risk of pancreatitis is imminent
- Reassess FLP in 6 weeks intervals until LDL-C and secondary targets are at goal, then annually
- Marked elevations of LDL-C suggest a genetic disorder such as FH

REVIEW QUESTIONS

1. **A 58 year-old Asian man with no prior cardiac history presents to your office for evaluation. He has not seen in a doctor "in over 20 years." The patient smokes a half a pack of cigarettes daily and is not currently on any medications. He reports that his father suffered a heart attack at the age of 53. In the clinic, his BP is 154/93 with a HR of 78, and his BMI is 28. The patient's physical examination is notable only for the presence of an S4. An ECG shows sinus rhythm and evidence of LVH. A FLP and baseline labs show:**

Total cholesterol – 220 mg/dL	AST – 32 IU/L
Triglycerides – 286 mg/dL	ALT – 24 IU/L
HDL-C – 34 mg/dL	CK – 55 IU/L
LDL-C – 131 mg/dL	Fasting glucose – 103 mg/dL

You see the patient in follow-up 2 weeks later. At that time, his BP is 158/89. His Framingham 10-years risk score is 28 %. You initiate treatment for his HTN and outline a plan for dietary changes, exercise, and smoking cessation. The next best step in your management is:

(a) No further therapy is needed at this time
(b) Start 10 mg of lovastatin daily
(c) Start 80 mg of simvastatin daily
(d) Start 20 mg of atorvastatin daily
(e) Start 600 mg of gemfibrozil twice daily

2. **The above patient is seen in follow up 6 weeks later. He has quit smoking and his BP is now well controlled at 132/80. A repeat FLP shows the following:**

Total cholesterol – 188 mg/dL	Triglycerides – 268 mg/dL
HDL-C – 40 mg/dL	LDL-C – 94 mg/dL

The next best step in your management is:

(a) No further therapy is needed since LDL-C is less than 100 mg/dL
(b) Increase atorvastatin to 40 mg daily
(c) Discontinue atorvastatin and start gemfibrozil 600 mg twice daily
(d) Add eztimibe 10 mg to the current dose of atorvastatin
(e) Add gemfibrozil 600 mg twice daily to the current dose of atorvastatin

3. **A 17 year-old female is referred to your office for consultation after a recent abnormal fasting lipid panel. She is healthy and her family history is notable for hyperlipidemia and premature CHD in her father, who suffered an MI in his 30s. A screening fasting lipid panel showed the following:**

Total cholesterol – 267 mg/dL	Triglycerides – 90 mg/dL
HDL-C – 55 mg/dL	LDL-C – 194 mg/dL

In clinic, her BP is 118/67 and a HR of 66 with a BMI of 19. She was noted to have a nodular, mobile 0.5 cm mass over the right Achilles tendon. The ECG was within normal limits. The next best step in her treatment is to:

(a) Advise her to undertake therapeutic lifestyle modifications and defer drug therapy since statins are not safe in teenagers
(b) Calculate her 10 years risk score and start therapy if she is classified as moderate risk
(c) Calculate her 10 years risk score and start therapy if she is classified as high risk
(d) Calculate her 10 years risk score and start therapy if she is classified as very risk
(e) Initiate therapy with a statin after checking a pregnancy test

ANSWERS

1. (d) According to NCEP ATPIII, patients with two or more risk factors with a FRS 10 years risk score of > 20 % should be classified as high risk with a goal LDL-C of less than 100 mg/dL. Drug therapy is recommended for LDL-C levels greater than 130 mg/dL. This patient likely has metabolic syndrome with an atherogenic dyslipidemia characterized by mild elevations in TC and LDL-C, low HDL-C, and elevated triglycerides. Based on these issues and his baseline LDL-C, initiation of LDL-C lowering drug therapy is indicated. Although the Helsinki Heart Study [16] and VA-HIT [17] suggest that this patient would benefit from fibrate therapy, statins are considered the drugs of choice for LDL-lowering in patients with dyslipidemia. Starting doses of statins should be sufficient to lower LDL-C 30–40 %. Among the choices presented, 20 mg of atorvastatin represents the best selection. A dose of 10 mg of lovastatin is unlikely to achieve a 30–40 % reduction in LDL-C. Simvastatin 80 mg daily will likely decrease the LDL-C by >40 %; however, based on a recent FDA review, the 80 mg dose of simvastatin should not be started based on a significantly

higher risk of myotoxicity compared to other statins and lower doses of simvastatin. This is a particularly important issue in older patients and individuals of Asian ancestry.

2. (b) In patients with the atherogenic dyslipidemia of the metabolic syndrome and TG > 200 mg/dL, NCEP ATPIII recommends establishing a secondary non-HDL-C goal of <130 mg/dL. Non-HDL-C is a surrogate marker of apo B lipoprotein levels that predicts CV events and is calculated by subtracting HDL-C from TC. Although the LDL-C is at goal (<100 mg/dL), the non-HDL-C is still elevated at 148 mg/dL. Therefore, further intervention is required. NCEP ATPIII recommend two strategies to address non-HDL-C [1]: intensifying statin therapy and [2] adding either a fibrate or niacin to the statin. Based on current available evidence, intensifying statin therapy represents the best first option. This patient may not reach his non-HDL-C goal with just intensification of statin therapy, and at that time, it would be reasonable to consider addition of niacin or fibrates, but current evidence has not established that this offers additional clinical benefit [19, 21]. As discussed above, since LDL-C is the primary target, discontinuing atorvastatin in favor of fibrate monotherapy is not indicated.

3. **(**e) This patient likely has heterozygous familial hypercholesterolemia. The typical features in this patient include an LDL-C > 95th percentile for age (190–350 mg/dL), a 1st degree relative with severe hypercholesterolemia, and the Achilles tendon xanthoma. Patients with FH are at a risk for premature CHD and should be treated with LDL-C lowering therapy. Several studies demonstrate that statins, which are first line therapy for reducing LDL-C in these patients, are safe in children as young as 8 years of age [24, 25]. There is no role for the FRS calculation in the treatment-decision analysis in these patients because the expert consensus is that traditional risk scores significantly underestimate their CV risk.

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