

## Cholesterol and Lipid Management A Six-Step Approach

### *Objectives:*

1. Be able to define cardiac risk factors and risk equivalents.
2. Be able to estimate the 10 year cardiac risk for patients.
3. Be able to make rational lipid screening recommendations for all patients you encounter.
4. Be able to make treatment recommendations for patients with varying cardiac risks.
5. Be able to describe the therapeutic lifestyle changes as recommended by the NCEP and counsel a patient on how to implement them.
6. Be able to describe the mechanisms of action, contraindications, major side effects, and monitoring requirements of the major classes of lipid-lowering drugs.

### *Risk Assessment: The First Step*

- Patients with CHD, DM, symptomatic carotid artery disease, PAD, or CKD all fall into the category of secondary prevention with aggressive lipid control to be discussed later. (10 year cardiac risk >20% is also a cardiac risk equivalent.)
- Traditionally, the following have been described as major risk factors:
  - Age  $\geq$  45 in men, age  $\geq$  55 in women
  - Premature menopause (< 40) without HRT
  - Family history of premature CHD ( male 1<sup>st</sup> degree relative < 55 years and female < 65 years)
  - Cigarette smoking
  - HTN (BP > 140/90)
  - HDL < 40
  - LDL > 130
- HDL  $\geq$  60 is a negative risk factor
- Elevated apo B, small dense LDL, increase LDL particle number, triglycerides, and obesity are additional risk factors
- Old NCEP III scoring system classified 10 year risk as follows: >20% is high risk, 10%-20% is medium risk, and < 10% is low risk. (see appendix)
- 2013 ACC/AHA Guidelines recommended a different risk assessment (pooled cohort tool) and controversially recommended  $\geq$ 7.5% 10 year risk as the treatment threshold for primary prevention (> 20% is the European recommendation)

### *Making Screening Recommendations: The Second Step*

- ATP III recommends a full, fasting lipid profile as the preferred screening test. Testing is recommended every 5 years beginning at age 20. Follow-up testing depends on the levels but, in general, is every 1-2 years for borderline abnormal values. (There are new, still controversial, pediatric screening guidelines)

recommending screening start during childhood. This controversy will not be addressed on Internal Medicine.)

- The following table gives the screening recommendations from other prominent groups.

<p><b>Cholesterol Screening Criteria</b>  <b>National Cholesterol Education Program</b></p> <ul style="list-style-type: none"> <li>• Adults <math>\geq 20</math> yrs of age should have fasting lipid panel every 5 years</li> <li>• Follow up depends on risk factors and lipid levels</li> </ul> <p><b>U.S. Preventive Services Task Force</b></p> <ul style="list-style-type: none"> <li>• Screen men ages 35-65 years and women ages 45-65 years with total cholesterol and HDL every 5 years</li> <li>• Follow up depends on results</li> </ul> <p><b>Canadian Task Force on the Periodic Health Examination</b></p> <ul style="list-style-type: none"> <li>• Insufficient evidence to support routine screening; endorses case findings in men ages 30-59 years</li> </ul> <p><b>American College of Physicians</b></p> <ul style="list-style-type: none"> <li>• Appropriate but not mandatory but not mandatory in men ages 35-65 years and women ages 45-65 years</li> <li>• Not recommended in younger individuals unless they have multiple cardiac risk factors or suspected familial lipoprotein disorders</li> <li>• Insufficient evidence to screen between ages 65-75, but recommend against screening after age 75</li> </ul>
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### ***Establishing Therapeutic Goals: The Third Step***

If triglycerides are elevated (200-500), also calculate the non-HDL cholesterol (TC-HDL) and non-HDL cholesterol goals are those list below + 30. The table below gives the traditional cutoffs. However, the 2013 ACC/AHA emphasize a move away from treating to target and toward treating to risk. (The only exception is LDL  $\geq 190$ .)

<b>ATP III Classification of Lipid Levels (mg/dL)</b>	
<i>LDL Cholesterol</i>	
<70	Very high risk optimal*
< 100	Optimal
100-129	Near optimal
130-159	Borderline high
160-189	High
$\geq 190$	Very high
<i>HDL Cholesterol</i>	
< 40	Low
$\geq 60$	High
<i>Triglycerides</i>	
< 150	Normal
151-199	Borderline high
200-499	High
> 500	Very High
* 2004 ATP II update consideration	

### ***The Evaluation for Secondary Dyslipidemias: The Fourth Step***

- Any patient with elevated lipids should be assessed for the following conditions that can cause or exacerbate a dyslipidemia:
  - Diabetes (VLDL, TG)
  - Hypothyroidism (LDL, TC, TG, VLDL)

- Nephrotic syndrome (TC, LDL)
- Obstructive liver disease (LDL, TC)
- Chronic renal failure (TG, VLDL)
- Obesity (TG, VLDL)
- Drugs/supplements
  - o Anabolic steroids, progestins, protease inhibitors (LDL, TC)
  - o ETOH, corticosteroids, estrogen, OCP, protease inhibitors, thiazides, beta blockers (VLDL, TG)
- Primary dyslipidemias are reviewed on Table 1 of the appendix

***Therapeutic Lifestyle Changes (TLC): The Fifth Step***

- *All patients can benefit from TLC.* An individual's lipid levels and cardiac risk will determine how aggressive these changes should be and whether additional pharmacological intervention is required.
- The most significant change in the ATP III dietary recommendations is a loosening of the total fat restriction (very low fat diets can lower HDL) with increased emphasis on limiting *saturated* fats. (2013 AHA/ACC guidelines reference other guideline for lifestyle recommendations)
- An additional change to the ATP III dietary recommendations is the recommendation for the addition of plant stanol esters and/or soluble fiber as a means to lower LDL.

Nutrient	Recommended Intake
Saturated fat*	<7% of total calories
Polyunsaturated fat	Up to 10% of total calories
Monounsaturated fat	Up to 20% of total calories
Total fat	25%-35% of total calories
Carbohydrate†	50%-60% of total calories
Fiber	20-30 g/d
Protein	Approximately 15% of total calories
Cholesterol	<200 mg/d
Total calories‡	Balance energy intake and expenditure to maintain desirable body weight/prevent weight gain

\**Trans* fatty acids are another LDL-raising fat that should be kept at a low intake.  
 †Carbohydrates should be derived predominantly from foods rich in complex carbohydrates including grains, especially whole grains, fruits, and vegetables.  
 ‡Daily energy expenditure should include at least moderate physical activity (contributing approximately 200 kcal/d).

***Pharmacologic Therapy: The Sixth Step***

- The addition of lipid-lowering drugs does not negate the need to pursue TLC.
- In general, HMG CoA reductase inhibitors (LDL lowering 21-55%, TG 6-30%\*, raise HDL 2-10%\*) and nicotinic acids (LDL lowering 10-25%, TG 20-30%, raises HDL 10-35%) exert the strongest beneficial effects on all lipid parameters. Both have been shown to reduce all cause mortality in secondary prevention trials. \*At high doses, atorvastatin, rosvastatin
- 2013 ACC/AHA guidelines only recommend statins and in fixed doses (either high intensity or moderate intensity) rather than varying doses to treat to target lipid levels.

This is to reflect the way statins were used in the trials that showed mortality and morbidity benefits.

- Bile acid sequestrants are the only lipid-lowering drugs not contraindicated in patients with liver disease. They primarily exert their effect on LDL levels (15-25%). However, it is unclear whether they confirm benefit beyond lowering cholesterol numbers.
- Gemfibrozil primarily affects triglyceride levels (20-35% lowering) and is the first-line therapy for primary hypertriglyceridemia. It raises HDL levels 6-18%.
- The vast majority of patients can be optimally managed using a generic medication.
- Effects on lipids should be assessed 6-12 weeks after starting a medication or changing a dose.
- The following are the contraindications and monitoring recommendations for the major classes of lipid-lowering agents.
  - **Nicotinic acid.** *Contraindications:* active PUD, liver disease. *Relative contraindications:* gout, type 2 diabetes. *Monitor* LFTs, glucose. *Major side effects:* flushing, pruritus, hepatotoxicity (particularly sustained release form) UGI complaints, gout flares, hypotension.
  - **HMG CoA reductase inhibitors.** *Contraindications:* active liver disease, concomitant gemfibrozil, cyclosporine, or niacin is a *relative contraindication* (increased myopathy risk). *Monitoring:* LFTs no longer routinely recommended but should follow in patients with mild abnormalities. Check CPK if symptomatic myopathy (myalgias). *Major side effects:* transaminitis, myopathy, GI complaints.
  - **Bile acid sequestrants.** *Contraindications* severe constipation, severe diverticulosis, severe hypertriglyceridemia. *Drug interactions* include warfarin, phenobarbital, digitalis, and thiazides. *Monitor* appropriate drug levels.
  - **Fibrates (Gemfibrozil).** *Contraindications:* gallbladder disease, liver dysfunction, renal dysfunction, concomitant HMG CoA reductase inhibitor is *relative contraindication*. *Major side effects:* GI complaints.
  - **Zetia (Ezetimibe)-** blocks LDL absorption, often used with HMG CoA reductase inhibitors.

Table 7. Drugs Affecting Lipoprotein Metabolism\*

Drug Class, Agents, and Daily Doses	Lipid/Lipoprotein Effects	Side Effects	Contraindications	Clinical Trial Results
HMG-CoA reductase inhibitors (statins) <sup>†</sup>	LDL ↓ 18%-55% HDL ↑ 5%-15% TG ↓ 7%-30%	Myopathy; increased liver enzymes	Absolute: active or chronic liver disease Relative: concomitant use of certain drugs <sup>§</sup>	Reduced major coronary events, CHD deaths, need for coronary procedures, stroke, and total mortality
Bile acid sequestrants <sup>‡</sup>	LDL ↓ 15%-30% HDL ↑ 3%-5% TG No change or increase	Gastrointestinal distress; constipation; decreased absorption of other drugs	Absolute: dysbetalipoproteinemia; TG >400 mg/dL Relative: TG >200 mg/dL	Reduced major coronary events and CHD deaths
Nicotinic acid <sup>  </sup>	LDL ↓ 5%-25% HDL ↑ 15%-35% TG ↓ 20%-50%	Flushing; hyperglycemia; hyperuricemia (or gout); upper gastrointestinal distress; hepatotoxicity	Absolute: chronic liver disease; severe gout Relative: diabetes; hyperuricemia; peptic ulcer disease	Reduced major coronary events, and possibly total mortality
Fibric acids <sup>  </sup>	LDL ↓ 5%-20% (may be increased in patients with high TG) HDL ↑ 10%-20% TG ↓ 20%-50%	Dyspepsia; gallstones; myopathy; unexplained non-CHD deaths in WHO study	Absolute: severe renal disease; severe hepatic disease	Reduced major coronary events

\*HMG-CoA indicates 3-hydroxy-3-methylglutaryl coenzyme A; LDL, low-density lipoprotein; HDL, high-density lipoprotein; TG, triglycerides; ↓, decrease; ↑, increase; and CHD, coronary heart disease.

<sup>†</sup>Lovastatin (20-80 mg), pravastatin (20-40 mg), simvastatin (20-80 mg), fluvastatin (20-80 mg), atorvastatin (10-80 mg), and cerivastatin (0.4-0.8 mg).

<sup>‡</sup>Cholestyramine (4-16 g), colestipol (5-20 g), and colesevelam (2.6-3.8 g).

<sup>§</sup>Cyclosporine, macrolide antibiotics, various antifungal agents, and cytochrome P-450 inhibitors (fibrates and niacin should be used with appropriate caution).

<sup>||</sup>Immediate-release (crystalline) nicotinic acid (1.5-3 g), extended-release nicotinic acid (1-2 g), and sustained-release nicotinic acid (1-2 g).

<sup>¶</sup>Gemfibrozil (600 mg twice daily), fenofibrate (200 mg), and clofibrate (1000 mg twice daily).

## Selected References

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[www.ahcpr.gov/clinic/uspstfix.htm](http://www.ahcpr.gov/clinic/uspstfix.htm)

## Appendix

**Table 8. Clinical Identification of the Metabolic Syndrome**

Risk Factor	Defining Level
• Abdominal obesity* (waist circumference)†	
Men	>102 cm (>40 in)
Women	>88 cm (>35 in)
• Triglycerides	≥150 mg/dL
• High-density lipoprotein cholesterol	
Men	<40 mg/dL
Women	<50 mg/dL
• Blood pressure	≥130/≥85 mm Hg
• Fasting glucose	≥110 mg/dL

\*Overweight and obesity are associated with insulin resistance and the metabolic syndrome. However, the presence of abdominal obesity is more highly correlated with the metabolic risk factors than is an elevated body mass index (BMI). Therefore, the simple measure of waist circumference is recommended to identify the body weight component of the metabolic syndrome.

†Some male patients can develop multiple metabolic risk factors when the waist circumference is only marginally increased, eg, 94-102 cm (37-40 in). Such patients may have strong genetic contribution to insulin resistance and they should benefit from changes in life habits, similarly to men with categorical increases in waist circumference.

**Table 344-4: Characteristics of Common Hyperlipidemias**

Lipid Phenotype	Plasma Lipid Levels, mmol/L (mg/dL)	Lipoproteins		
		Elevated	Phenotype	Clinical Signs
<b>ISOLATED HYPERCHOLESTEROLEMIA</b>				
Familial hypercholesterolemia	Heterozygotes: total chol = 7-13 (275-500)	<u>LDL</u>	IIa	Usually develop xanthomas in adulthood and vascular disease at 30-50 years
	Homozygotes: total chol > 13(>500)	LDL	IIa	Usually develop xanthomas and vascular disease in childhood
Familial defective apo B100	Heterozygotes: total chol = 7-13 (275-500)	LDL	IIa	
Polygenic hypercholesterolemia	Total chol = 6.5-9.0 (250-350)	LDL	IIa	Usually asymptomatic until vascular disease develops; no xanthomas
<b>ISOLATED HYPERTRIGLYCERIDEMIA</b>				
Familial hypertriglyceridemia	TG = 2.8-8.5 (250-750) (plasma may be cloudy)	<u>VLDL</u>	IV	Asymptomatic; may be associated with increased risk of vascular disease
Familial lipoprotein lipase deficiency	TG > 8.5(>750) (plasma may be milky)	Chylomicrons	I, V	May be asymptomatic; may be associated with pancreatitis, abdominal pain, hepatosplenomegaly
Familial apo CII deficiency	TG > 8.5(>750) (plasma may be milky)	Chylomicrons	I, V	As above
<b>HYPERTRIGLYCERIDEMIA AND HYPERCHOLESTEROLEMIA</b>				
Combined hyperlipidemia	TG = 2.8-8.5 (250-750) Total chol = 6.5-13.0 (250-500)	VLDL, LDL	IIb	Usually asymptomatic until vascular disease develops; familial form may also present as isolated high TG or an isolated high LDL cholesterol
Dysbetalipoproteinemia	TG = 2.8-5.6 (250-500) Total chol = 6.5-13.0 (250-500)	VLDL, <u>IDL</u> ; LDL normal	III	Usually asymptomatic until vascular disease develops; may have palmar or tuberous xanthomas

NOTE: total chol, the sum of free and esterified cholesterol; LDL, low-density lipoprotein; TG, triglycerides; VLDL, very low density lipoproteins; IDL, intermediate-density lipoprotein.

10-year risk of CVD events	5-year NNT for CVD events	5-year NNT for myocardial infarction	5-year NNT for stroke	5-year NNT for mortality
5%	160	278	910	*
7.50%	108	186	606	*
10%	80	140	456	*
15%	54	94	304	334
20%	40	70	228	250

discontinuation of treatment due to adverse effect NNH 33  
 myalgia NNH 91  
 Elevated LFTs NNH 100  
 diarrhea NNH 142  
 newly diagnosed diabetes NNH 167