Objectives

- Review screening for lipid disorders
- Review cardiovascular disease risk stratification
- Review LDL and non-HDL targets
- Review therapeutic lifestyle changes
- Review pharmacotherapy

Screening Recommendations

- The National Cholesterol Education Program (NCEP) ATP III recommends:
  - fasting lipid panel Q 5 years in adults age 20 years or older
- The American College of Physicians and the USPSTF recommend routine screening of:
  - men age 35 years or older
  - women aged 45 years or older
  - If other risk factors present, routine screening should be initiated at age 20

ATP III Cholesterol Classification

- **LDL Cholesterol**
  - <100 Optimal
  - 100-129 Near Optimal
  - 130-159 Borderline High
  - 160-189 High
  - >190 Very High
ATP III Cholesterol Classification

- Total Cholesterol
  - <200: Desirable
  - 200-239: Borderline High
  - >240: High

- HDL Cholesterol
  - <40: Low
  - >60: High

Causes of Secondary Dyslipidemia

- Diabetes
- Hypothyroidism
- Obstructive liver disease
- Chronic renal failure
- Drugs that raise LDL cholesterol and lower HDL cholesterol (progestins, anabolic steroids, and corticosteroids)

CHD Risk Factors

- Cigarette smoking
- Hypertension (>140/90) or on anti-hypertensive medication
- Low HDL (<40mg/dL) (>60 is a negative risk factor)
- Age (men >/=45, women >/=55)
- Family Hx premature CHD (1st degree relative, male <55 and women < 65)

Risk Assessment

- The intensity of risk-reduction therapy should be adjusted to a person’s absolute risk

  **Count major risk factors**

- For patients with 2 or more risk factors (excluding elevated LDL)
  - Perform 10-year risk assessment
- For patients with 0–1 risk factor
  - 10 year risk assessment not required
  - Most patients have 10-year risk <10%
Risk Assessment

- NCEP/ATP III created a rapid assessment tool to calculate a person’s 10-year risk of myocardial infarction or coronary death (“hard” CHD endpoints) utilizing Framingham Study data.
- The NCEP recommends this risk assessment be performed every 5 years.

CHD Risk Equivalents

- New to the ATP III is the inclusion of diabetes mellitus to a CHD risk equivalent.
- Multiple studies have shown that a 7 to 10 year history of DM is a very significant risk factor for future CHD events.
- Two out of three people with DM die from MI or CVA.
Risk Categories and LDL Goals

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>LDL Goal (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD and CHD risk equivalents</td>
<td>&lt;100</td>
</tr>
<tr>
<td>2+ risk factors</td>
<td>&lt;130</td>
</tr>
<tr>
<td>0-1 risk factor</td>
<td>&lt;160</td>
</tr>
</tbody>
</table>

Outcomes with LDL-Lowering Therapy

- **Primary prevention:** Reduction in
  - major coronary events (MI, revascularization)
  - trend towards reduction in overall mortality (WOSCOPS)
- **Secondary prevention:** Reduction in
  - total mortality
  - coronary mortality
  - major coronary events
  - coronary procedures
  - stroke

Treatment Modalities

- **Primary goal of treatment is to achieve LDL target.**
- Therapeutic lifestyle changes (TLC) are the foundation of all risk reduction
- Dietary: Reduced intake of saturated fat (<7% of total calories) and cholesterol (<200mg per day)
- Increased physical activity
- Weight control

TLC Therapy

- A TLC diet with increased physical activity should be initiated on all patients with LDL levels above goal
- LDL response should be assessed after 6 weeks
- If LDL response is not at goal, viscous (soluble) fibers (oats, barley, soy beans) 10-25 grams/day and plant stanol/sterols 2 grams/day can be added
- If after 6 additional weeks, LDL not at goal, pharmacotherapy should be initiated
Pharmacotherapy

• ATP III recommends checking fasting cholesterol panel 6 weeks after initiation of statin therapy
• If goal achieved, no adjustment necessary.
• If goal not achieved, intensify therapy with increased dose of statin or by addition of another class of medication (nicotinic acid, fibrate, etc.)

Drug Therapy

HMG CoA Reductase Inhibitors (Statins)

• Reduce LDL-C 18–55% & TG 7–30%
• Raise HDL-C 5–15%
• Major side effects
  – Myopathy
  – Increased liver enzymes
• Contraindications
  – Absolute: liver disease
  – Relative: use with certain drugs

Pharmacotherapy

• TLC diet and exercise program should always be continued
• The first priority of therapy is to achieve the LDL target
• Owing to their superior effect on LDL, HMG CoA reductase inhibitors (statins) are the first line therapy in most cases
• Initiate statin therapy at a dose adequate to achieve goal LDL reduction, no need to start at lowest dose

Table 5: LDL Cholesterol Goals and Outcomes for Therapeutic Lifestyle Changes (TLC) and Drug Therapy in Different Risk Categories.

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>LDL Goal</th>
<th>LDL Level at Which to Initiate Therapeutic Lifestyle Changes (TLC)</th>
<th>LDL Level at Which to Consider Drug Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD or CHD Risk Equivalents (10-year risk &gt;20%)</td>
<td>&lt;100 mg/dL</td>
<td>≥100 mg/dL</td>
<td>≥130 mg/dL (100-129 mg/dL: drug optional)*</td>
</tr>
<tr>
<td>2+ Risk Factors (10-year risk ≤20%)</td>
<td>&lt;130 mg/dL</td>
<td>≥130 mg/dL</td>
<td>10-year risk 10-20%: ≥130 mg/dL</td>
</tr>
<tr>
<td>0-1 Risk Factor†</td>
<td>&lt;160 mg/dL</td>
<td>≥160 mg/dL</td>
<td>≥190 mg/dL (160-189 mg/dL: LDL-lowering drug optional)</td>
</tr>
</tbody>
</table>

* Some authorities recommend use of LDL-lowering drugs in this category if an LDL cholesterol >190 mg/dL cannot be achieved by therapeutic lifestyle changes. Others prefer use of drugs that primarily modify triglycerides and HDL, e.g., niacin and/or fibrate. Clinical judgment also may call for delaying drug therapy in this subcategory.
† Almost all people with 0-1 risk factor have a 10-year risk >20%, thus 10-year risk assessment in people with 0-1 risk factor is not necessary.

### HMG CoA Reductase Inhibitors (Statins)

<table>
<thead>
<tr>
<th>Statin</th>
<th>Dose Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lovastatin</td>
<td>20–80 mg</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>20–40 mg</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>20–80 mg</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>20–80 mg</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>10–80 mg</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>5–40 mg</td>
</tr>
</tbody>
</table>

### Demonstrated Therapeutic Benefits
- Reduce major coronary events
- Reduce CHD mortality
- Reduce coronary procedures (PTCA/CABG)
- Reduce stroke
- Reduce total mortality

### Drug Therapy
**Bile Acid Sequestrants**
- **Major actions**
  - Reduce LDL-C 15–30%
  - Raise HDL-C 3–5%
  - May increase TG
- **Side effects**
  - GI distress/constipation
  - Decreased absorption of other drugs
- **Contraindications**
  - Dysbetalipoproteinemia
  - Raised TG (especially >400 mg/dL)

### Bile Acid Sequestrants

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholestyramine</td>
<td>4–16 g</td>
</tr>
<tr>
<td>Colestipol</td>
<td>5–20 g</td>
</tr>
<tr>
<td>Colesevelam</td>
<td>2.6–3.8 g</td>
</tr>
</tbody>
</table>
Bile Acid Sequestrants (continued)

Demonstrated Therapeutic Benefits

• Reduce major coronary events
• Reduce CHD mortality

Drug Therapy

Nicotinic Acid

• Major actions
  – Lowers LDL-C 5–25%
  – Lowers TG 20–50%
  – Raises HDL-C 15–35%
• Side effects: flushing, hyperglycemia, hyperuricemia, upper GI distress, hepatotoxicity
• Contraindications: liver disease, severe gout, peptic ulcer

Nicotinic Acid

<table>
<thead>
<tr>
<th>Drug Form</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate release</td>
<td>1.5–3 g</td>
</tr>
<tr>
<td>(crystalline)</td>
<td></td>
</tr>
<tr>
<td>Extended release</td>
<td>1–2 g</td>
</tr>
<tr>
<td>Sustained release</td>
<td>1–2 g</td>
</tr>
</tbody>
</table>

Nicotinic Acid (continued)

Demonstrated Therapeutic Benefits

• Reduces major coronary events
• Possible reduction in total mortality
Drug Therapy

Fibric Acids

• Major actions
  – Lower LDL-C 5–20% (with normal TG)
  – May raise LDL-C (with high TG)
  – Lower TG 20–50%
  – Raise HDL-C 10–20%
• Side effects: dyspepsia, gallstones, myopathy
• Contraindications: Severe renal or hepatic disease

Fibric Acids

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gemfibrozil</td>
<td>600 mg BID</td>
</tr>
<tr>
<td>Fenofibrate</td>
<td>200 mg QD</td>
</tr>
<tr>
<td>Clofibrate</td>
<td>1000 mg BID</td>
</tr>
</tbody>
</table>

Fibric Acids (continued)

Demonstrated Therapeutic Benefits

• Reduce progression of coronary lesions
• Reduce major coronary events

Ezetimibe

• Blocks cholesterol absorption at the intestinal brush border
• Dose ranges from 5 to 20mg, typically 10mg
• Common side effects myalgias, headache, diarrhea
• Rarely causes significant elevations in AST or ALT
• Effect on cardiovascular morbidity and mortality not yet established
Ezetimibe

- EHNANCE trial: 2 yr study of patients with Heterozygous Fam. Hypercholesterolemia
  - simvastatin 80mg + placebo vs. simvastatin 80mg + 10mg ezetimibe
  - LDL lower in dual treatment group (statistically significant)
  - HOWEVER, no change in carotid intimal thickness (surrogate marker for atherosclerosis progression)

- Current recommendation: Use statins, fibrates, niacin, diet and exercise to lower LDL. Add ezetimibe only when other agents do not reach LDL goal.
- IMPROVE-IT study of CV events in 18,000 pts.
  - Due in 2011
  - 40mg simvastatin vs simvastatin 40mg + ezetimibe 10mg.

Omega 3 Fatty Acids

- ATPIII cites two potential uses for the n-3 fatty acids (Linolenic acid, DHA and EPA)
  - Alternative agent for treatment of hypertriglyceridemia
  - Secondary prevention of CHD
  - Doses generally 1-2grams/day as fish, fish oil supplements
  - Additional studies needed to make a stronger recommendation.

Initiation and Monitoring of Statins

- Baseline Screening: LFTS and creatine kinase (CK). Also assess for symptoms of muscle soreness
- Interval Screening: LFTs 12 weeks after initiating therapy, then annually
- Interval Screening: Assess muscle symptoms 6 to 12 weeks after initiation. Obtain follow-up CK when symptoms present
- LFT elevations occur in 0.5-2.0% of cases and are dose dependent
- LFT elevations <3x ULN are not contraindications to initiation, continuation or advancement of statin therapy
Adverse Effects and Discontinuation of Statin Therapy

- LFT elevations > 3x ULN are indication for dose reduction. If no improvement with dose reduction, statin should be discontinued.
- Progression to liver failure is extremely rare. LFT elevations frequently reverse with a reduction in dose.
- Myalgias (pain, soreness with normal CK) a common complaint.
- Myositis (pain, soreness with CK generally 10x>ULN) is an indication to stop statin therapy. Failure to stop can lead to rhabdomyolysis.

Adverse Effects with Combination Therapy

- Statins and fibrates both carry the risk of myositis.
- Nearly 600 persons have participated in controlled trials of statin and fibrate combination therapy:
  - 1% have experienced CK elevations >3xULN without symptoms.
  - 1% have withdrawn from therapy because of muscle symptoms.
  - No cases of rhabdomyolysis have been reported.

Pharmacotherapy

- Consultation with a lipid specialist may be considered for persons who fail to achieve goal LDL level despite intensive TLC and standard lipid-lowering therapy.
- When LDL goal has been reached, additional targets of therapy can be considered.
Secondary Targets

• Metabolic Syndrome: Controversial collection of metabolic risk factors which may confer an increased, synergistic risk of CHD when compared to the individual components

Secondary Targets: Metabolic Syndrome

• ATP III Criteria: Three of the following
  – Abdominal obesity (WC >102 cm in men, >88 cm in women)
  – Triglycerides > 150 mg/dL
  – Blood Pressure ≥ 130/85 mmHg
  – Fasting Glucose ≥ 100 mg/dL
  – HDL <40 mg/dL for men, <50 mg/dL for women

Metabolic Syndrome Management

• TLC diet
• Increased physical activity
• Treat LDL to goal based on risk assessment
• Control blood pressure
• Consider triglyceride lowering medication if above not successful at reaching goal <150 mg/dL

Specific Dyslipidemias: Very High LDL Cholesterol (≥190 mg/dL)

Causes and Diagnosis

• Genetic disorders
  – Monogenic familial hypercholesterolemia
  – Familial defective apolipoprotein B-100
  – Polygenic hypercholesterolemia
• Family testing to detect affected relatives
Hypertriglyceridemia

• Elevated triglycerides have been demonstrated to be an independent CHD risk factor
• Obesity, inactivity, high carbohydrate diets (>60% of energy intake), DM2, CKD, corticosteroids, estrogens, retinoids, high dose beta blockers and genetic disorders can all cause hypertriglyceridemia

Classification of Hypertriglyceridemia

• Normal TGs <150 mg/dL
• Borderline-high TGs 150-199 mg/dL
• High TGs 200-499 mg/dL
• Very high TGs >500 mg/dL

Hypertriglyceridemia Therapy

• **Borderline High**: Weight reduction and increased physical activity

• **High**: non-HDL cholesterol becomes a secondary target of therapy after LDL target reached

Non-HDL-C

• Non-HDL-C = TC - HDL=LDL+VLDL
• Non-fasting measurement
• Good estimate of the atherogenic lipoproteins in the serum (ApoB)
• As triglycerides rise, the estimation of LDL levels via the traditional equation becomes less accurate
• Non-HDL-C treatment targets are calculated by adding 30mg/dL to the LDL goals
• Secondary target of therapy when triglycerides ≥ 200 mg/dL
Management of Very High Triglycerides ($\geq 500$ mg/dL)

- Goal of therapy: prevent acute pancreatitis
- Very low fat diets ($\leq 15\%$ of caloric intake)
- Triglyceride-lowering drug usually required (fibrate or nicotinic acid)
- Reduce triglycerides before LDL lowering

Low HDL

- While a strong, independent predictor of CHD, there is insufficient evidence to specify a goal of therapy and the ATP III does not specify a goal for HDL raising
- Medications currently available do not significantly raise HDL levels (nicotinic acid and fibrates most effective)
- Increased physical activity, weight loss and smoking cessation are all important to improve HDL

Causes of Low HDL Cholesterol ($<40$ mg/dL)

- Elevated triglycerides
- Overweight and obesity
- Physical inactivity
- Type 2 diabetes
- Cigarette smoking
- Very high carbohydrate intakes (>60% energy)
- Certain drugs (beta-blockers, anabolic steroids, progestational agents)

Patients Hospitalized for Coronary Events or Procedures

- Measure LDL-C within 24 hours
- Discharge on LDL-lowering drug if LDL-C $\geq 130$ mg/dL
- Consider LDL-lowering drug if LDL-C is 100–129 mg/dL
- Start lifestyle therapies simultaneously with drug
Updates to ATP III

• Several high profile clinical trials were completed in the two years following release of the ATP III report, leading to a formal update

• **High-risk patients**: Overall LDL goal still <100 mg/dL but with therapeutic option to set goal of <70 mg/dL for very high-risk patients (recent MI, known CVD + DM, continued smoking or metabolic syndrome)

• **2+ risk factors** with a 10-20% risk: Consider LDL goal < 100 mg/dL and consider drug treatment if LDL 100-129 mg/dL.

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• **2+ risk factors** with a 10-20% risk: Consider LDL goal < 100 mg/dL and consider drug treatment if LDL 100-129 mg/dL.

• No change to moderate and low risk recommendations

NCEP Report, “Implications of Recent Clinical Trials for the NCEP ATP III,” Circulation, July 13, 2004
ATP IV: Possible Directions

• Due in 2009
• ACC and ADA Consensus Conference Report, March 2008
  – Lowering LDL still primary goal
  – Guiding therapy for patients on statins with measurements of apoB, apoB treatment goals
  – Possibly lowered LDL goals: Highest risk patients, LDL <70, High risk, LDL <100
  – non-HDL goals for everyone, not just secondary measure with high TGs.

References

• National Cholesterol Education Program Slide Show
• NCEP ATP III Guidelines At-A-Glance Quick Desk Reference