LIPID-LOWERING AGENTS
(Anti- or Hypo-lipidemic Drugs)

Katzung (9th ed.) Chapter 35, especially Figures 35-1, 35-2
Basic Medical Biochemistry Chapters 32-34
especially Tables VI.I and 34.1, Figures VI.4, 32.13, 32.16, 33.2, 33.23, 33.24, 33.25, 34.12, 34.14, 34.22

CRITICAL FACTS

1. Hypolipidemic drugs are important!
   - They’re used to prevent the number one killer of North American men and women (coronary heart disease).
   - They’re among the most often prescribed drugs in the United States (over 120 million prescriptions for this class of drugs in 2004; ATORVASTATIN (Lipitor) was ranked #2 in prescriptions and #1 in sales).

2. The most effective agents for reducing LDL levels are the HMG-CoA reductase inhibitors ("statins"), because they block cholesterol synthesis at its rate limiting step.

3. EZETIMIBE is the newest hypolipidemic drug (approved in 2003). It is the first of a new class of agents that block cholesterol absorption, and it is typically given with a statin (EZETIMIBE + SIMVASTATIN = Vytorin).

4. The most effective use of Bile Acid Binding Resins (BABRs) is in the treatment of hypercholesterolemias (Type IIa and IIb) --- i.e., in patients that do not have elevated TGs.

5. NICOTINIC ACID has the “perfect” therapeutic profile (it significantly increases HDL while decreasing LDL, TGs and total cholesterol) but its adverse side effects can limit its usefulness because of decreased patient compliance.

6. GEMFIBROZIL and other fibrates are extremely useful in the treatment of patients with elevated triacylglycerol (TG) levels (i.e., Types III, IV and V), because they produce a 20-50% decrease in TGs.
7. Hypolipidemic drugs are often used in combination, because of the severity of the underlying problem in many patients (remember, the desired goal can be to drop LDL levels more than 60%, and no single agent can do that). However, because of the complexity of the balance in the system, the effects of combining agents can be unpredictable, and short-term vs. long-term results need to be considered.

**DRUGS YOU NEED TO KNOW:**
(in **BOLD** throughout the handout)

- **ATORVASTATIN** (Lipitor)
- **CHOLESTYRAMINE** (Questran)
- **CLOFIBRATE** (Atromid-S)
- **COLESTIPOL** (Colestid)
- **EZETIMIBE** (Zetia)
- **FENOFIBRATE** (Tricor)
- **FLUVASTATIN** (Lescol)
- **GEMFIBROZIL** (Lopid)
- **LOVASTATIN** (Mevacor)
- **NICOTINIC ACID** (Niacin, Nicobid, Nico-400, Nicolar)
- **PRAVASTATIN** (Pravachol)
- **PROBUCOL** (Lorelco)
- **ROSUVOSTATIN** (Crestor)
- **SIMVASTATIN** (Zocor)
- **NICOTINIC ACID**

**OBJECTIVES**

1. Be able to relate major risk factors for atherosclerosis to cholesterol goals and levels for initiating drug treatment (i.e., be able to apply the recommendations of NCEP ATPIII). From a mechanistic point of view, understand why specific lipid-lowering drugs are indicated (and others are not useful) for the treatment of specific types of hyperlipoproteinemias. Determine initial treatment strategies for hypothetical patients based on their lipoprotein profile.

2. Using summary diagrams, be able to relate the specific mechanisms of action of each class of hypolipidemic drugs to the important components of cholesterol metabolism and regulation.

3. Identify the basic mechanism of action, therapeutic effects and common adverse effects of each class of lipid-lowering agents. Be able to assign the hypolipidemic drugs to their classes.

4. **ATORVASTATIN** is the most widely prescribed HMG-CoA reductase inhibitor. Compare and contrast the properties of the other statins to those of **ATORVASTATIN**, with the goal of being able to identify patients who would benefit from treatment with specific reductase inhibitors.

5. List indications for combination therapy, and give examples of useful regimens.
GOALS OF DRUG THERAPY

1. Prevent **ATHEROSCLEROSIS** i.e., the presumptive cause of coronary heart disease and stroke. Although treatment of hyperlipidemia causes slow physical regression of plaques (over the course of years), there is a documented decrease in acute coronary events in the first few months following vigorous treatment that is thought to be chiefly due to decreased inflammatory activity of macrophages.

2. Prevent acute pancreatitis and retard development of xanthomas.

IDENTIFICATION OF AT-RISK PATIENTS

National Cholesterol Education Program (NCEP)
Adult Treatment Guidelines Panel III (ATPIII)
May 2001 (JAMA 285: 2486-2497)
2004 Modification (Circulation 110: 227-239)

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**MAJOR RISK FACTORS FOR ATHEROSCLEROSIS**

<table>
<thead>
<tr>
<th>Coronary heart disease = Diabetes mellitus</th>
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<tbody>
<tr>
<td>Increasing age</td>
</tr>
<tr>
<td>Male gender</td>
</tr>
<tr>
<td>Family history of premature CHD</td>
</tr>
<tr>
<td>Genetic abnormalities</td>
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</tbody>
</table>
Minor (and emerging) factors include: obesity, physical inactivity, athrogenic diet, lipoprotein (a), homocysteine, prothrombotic and proinflammatory factors, impaired fasting glucose.

**FRAMINGHAM RISK ASSESSMENT**


- uses data from the Framingham Heart Study to estimate 10-year risk for “hard” coronary heart disease outcomes (myocardial infarction and coronary death)
- designed for adults >20 years of age
- uses measures of risk (e.g. age, total cholesterol, HDL cholesterol, systolic blood pressure) to calculate the 10-year risk, which is reported as %

### CHOLESTEROL GOALS and TREATMENT STRATEGIES

Patients differ with respect to:

1. their cholesterol goals
2. when drug therapy should be initiated
   (lifestyle modifications should **ALWAYS** be the first line of treatment)

#### CHOLESTEROL GOALS FOR VARIOUS CHD RISK CATEGORIES

<table>
<thead>
<tr>
<th>TOTAL CHOLESTEROL</th>
<th>LDL CHOLESTEROL</th>
<th>HDL CHOLESTEROL</th>
<th>TRIACYLGLYCEROLS</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤200 mg/dL</td>
<td>No CHD, &lt;2 RF</td>
<td>No CHD, &gt;2 RF</td>
<td>≥50 mg/dL</td>
</tr>
<tr>
<td>≤160 mg/dL</td>
<td>CHD or diabetes = high risk</td>
<td>Framingham risk score &gt;20% = very high risk</td>
<td>&lt;150 mg/dL</td>
</tr>
<tr>
<td>≤130 mg/dL</td>
<td>&lt;100 mg/dL</td>
<td>&lt;70 mg/dL</td>
<td></td>
</tr>
<tr>
<td>≤100 mg/dL</td>
<td>&lt;70 mg/dL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;70 mg/dL</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### TREATMENT DECISIONS (based on LDL cholesterol levels)

<table>
<thead>
<tr>
<th>PATIENT CATEGORY</th>
<th>DIETARY THERAPY</th>
<th>DRUG TREATMENT</th>
<th>LDL GOAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>No CHD, &lt;2 RF</td>
<td>≥160 mg/dL</td>
<td>≥190 mg/dL</td>
<td>&lt;160 mg/dL</td>
</tr>
<tr>
<td>No CHD, ≥2 RF</td>
<td>≥130 mg/dL</td>
<td>≥160 mg/dL</td>
<td>&lt;130 mg/dL</td>
</tr>
<tr>
<td>CHD or diabetes</td>
<td>≥100 mg/dL</td>
<td>≥130 mg/dL</td>
<td>&lt;100 mg/dL</td>
</tr>
<tr>
<td>Very high risk</td>
<td></td>
<td></td>
<td>&lt;70 mg/dL</td>
</tr>
</tbody>
</table>
### Types of Hypercholesterolemia

<table>
<thead>
<tr>
<th>Type</th>
<th>Features</th>
<th>Cause</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type I</strong></td>
<td>Familial hyperchylomicronemia</td>
<td>Lipoprotein lipase deficiency</td>
<td>No ↑ in risk for CHD</td>
</tr>
<tr>
<td></td>
<td>↑↑↑ serum TG</td>
<td>(no effective drug treatment)</td>
<td></td>
</tr>
<tr>
<td><strong>Type IIA</strong></td>
<td>Familial hypercholesterolemia</td>
<td>↓ LDL receptors</td>
<td>↑↑↑ CHD</td>
</tr>
<tr>
<td></td>
<td>↑ serum LDL, normal TG</td>
<td>(limits usefulness of some drugs, esp. statins)</td>
<td></td>
</tr>
<tr>
<td><strong>Type IIB</strong></td>
<td>Familial combined (mixed) hyperlipidemia</td>
<td>Same as IIA, but with ↑ VLDL also</td>
<td>Relatively common</td>
</tr>
<tr>
<td></td>
<td>Overproduction of VLDL by liver</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Type III</strong></td>
<td>Familial dysbetalipoproteinemia</td>
<td>Overproduction or underutilization of IDL due to</td>
<td>Xanthomas, ↑ coronary and peripheral</td>
</tr>
<tr>
<td></td>
<td>↑ IDL, causes ↑ TG and LDL</td>
<td>mutant apolipoprotein E</td>
<td>vascular disease</td>
</tr>
<tr>
<td><strong>Type IV</strong></td>
<td>Familial hypertriglyceridemia</td>
<td>Overproduction and/or ↓ removal of VLDL</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>↑ VLDL, normal or ↓ LDL, ↑↑↑ TG</td>
<td></td>
<td>↑ CHD</td>
</tr>
<tr>
<td><strong>Type V</strong></td>
<td>Familial mixed hypertriglyceridemia</td>
<td>↑ production or ↓ clearance of VLDL and chylomicrons (genetic defect)</td>
<td>Most common in adults who are obese and/or diabetic</td>
</tr>
</tbody>
</table>
REVIEW OF PATHOPHYSIOLOGY AND BIOCHEMISTRY
(animation)

2/3 of cholesterol comes from endogenous sources (primarily via synthesis in the liver), while 1/3 is from exogenous sources (aka the diet), so understanding the regulation of liver cholesterol stores is the key to figuring out how hypolipidemic drugs alter plasma lipoprotein levels.

IMPORTANT SITES OF ACTION

1. Intestine
   - site of fatty acid, and cholesterol absorption via the cholesterol transporter
   - facilitated by bile salts (95% recirculated)
   - results in chylomicron formation

2. Liver
   - site of fatty acid, VLDL and cholesterol synthesis
   - rate limiting step in cholesterol synthesis is catalyzed by HMG-CoA reductase
   - bile salt formation
   - LDL receptor expression (ligand is B-100 found on VLDL and LDL)
   - in the liver, cholesterol is used to (among other things):
     a) regulate cholesterol synthesis
        (via feedback inhibition of HMG-CoA reductase)
     b) synthesize bile salts (required for fatty acid absorption)
     c) regulate LDL receptor expression (via regulation of transcription)
     d) generate VLDL

3. Muscle and 4. Adipose tissue
   - storage of cholesterol and fatty acids by lipoprotein lipase
5. Plaques
   - oxidation of LDL and incorporation into foam cells

6. Bloodstream
   - interconversion of lipoproteins

SELF STUDY EXERCISE
(answers are found on my Web site)

Using this diagram as a guide, identify: 1) the structure where the action will be mediated and 2) the effects of the following on the arrows in the diagram?

1. Inhibiting HMG-CoA reductase (reducing cholesterol synthesis)
2. Increasing LDL receptor expression
3. Preventing the reabsorption of bile acids from the small intestine
4. Inhibiting the cholesterol transporter in the small intestine
5. Increasing synthesis of lipoprotein lipase in muscle and adipose tissue
MECHANISMS OF ACTION OF HYPOLIPIDEMIC DRUGS

MAIN GOAL is to DECREASE LDL concentration
or INCREASE HDL concentration in plasma (OR BOTH)

Specific mechanisms:
A. Inhibit HMG-CoA reductase
B. Inhibit intestinal absorption of cholesterol
C. Bind bile acids
D. Inhibit VLDL synthesis and/or secretion
E. Stimulate lipoprotein lipase
F. Inhibit LDL oxidation

A. HMG-CoA REDUCTASE INHIBITORS (“statins”): ATORVASTATIN, FLUVASTATIN, LOVASTATIN, PRAVASTATIN, ROSUVASTATIN, SIMVASTATIN

Mechanism of Action
• **Competitive inhibitors** of cholesterol synthesis at the rate-limiting step
• Action is more complicated than simply reducing the amount of cholesterol synthesized
  ➢ **Compensatory induction of LDL receptors**
  ➢ Enhanced extraction of circulating LDL-CE from serum
• **Synergistic** with **bile acid binding resins (BABR)** and **EZETIMIBE**

Pharmacokinetics
• 30-90% oral absorption, 5-30% oral bioavailability
• **Evening dosing** (liver cholesterol synthesis is greatest between midnight and 2 am)
• Maximal effects in **one month** followed by slow regression of plaques as LDL is extracted
• Most have **extensive hepatic metabolism** (first pass effect) by **CYP3A4** and CYP2C9
• Excreted in bile and feces, with some renal excretion (degree varies among statins)
Therapeutic Effects

1. **↓ plasma LDL by 18-55%**

2. Slight **↑ in HDL** (depending upon the statin)

3. Modest **↓ VLDL, TG** (not shown to be of therapeutic benefit)

4. Other cardioprotective effects (vasorelaxation, stabilization of plaques, decreased inflammation and coagulation, decreased LDL oxidation)

5. **LOVASTATIN** and **SIMVASTATIN** may have osteogenic effect

6. 20% reduction in likelihood of cancer (particularly prostate and renal cancer)

Therapeutic Indications

- **All types** of hypercholesterolemia that are unresponsive to dietary management (although less effective in Type IIA and IIB due to the genetic deficiency in LDL receptors)

- Patients who have had or are at risk for **ischemic stroke** – statins may be unique among hypolipidemic drugs with respect to stroke reduction

Adverse Effects

- Promoted by drug and other interactions (N.B. grapefruit juice via CYP3A4)

- Are **not necessarily common to all drugs**
  i.e., a patient who cannot tolerate one drug may do fine on a different drug

- Liver and muscle function must be monitored throughout treatment - liver function is especially important (**PRAVASTATIN** may be a better choice in patients with liver disorders because of its renal excretion)

1. **Increases in liver and muscle enzyme activity** that can occur years later (must always monitor liver and muscle function):

   a) liver aminotransferase activity that is often intermittent and usually not associated with hepatic toxicity – in 2% of patients, changes may be 3X normal and persistently elevated, which indicates more severe hepatic toxicity; these patients present with malaise, anorexia and precipitous decreases in LDL

   b) serum creatinine kinase that is associated with generalized muscle pain and weakness - can progress to **rhabdomyelosis and other myopathies that can**
Lipid lowering drugs

cause fatal kidney problems - develops in <0.12% of patients who are not taking other drugs – risk doubles (0.22%) with interacting drugs

2. **Birth defects**: a 2004 study showed that 20/52 babies exposed to statins during the first trimester of pregnancy had central nervous system defects and limb deformities

3. **Hyperuricemia and gout**

4. **Drug interactions**: cyclosporine, itraconazole, erythromycin, GEMFIBROZIL, NICOTINIC ACID, BABR, cytochrome P450 inhibitors (warfarin)

5. Mild headache and GI disturbances (nausea, dyspepsia, diarrhea, cramps)

**CAUTION**: patients with hepatic and renal disorders, gout, diabetes mellitus, cardiac arrhythmias, pregnant women or pre-pubertal children

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**SO, ARE ALL STATINS CREATED EQUAL?**

<table>
<thead>
<tr>
<th>ATORVASTATIN</th>
<th>FLUVASTATIN</th>
<th>LOVASTATIN</th>
<th>PRAVASTATIN</th>
<th>ROSUVASTATIN</th>
<th>SIMVASTATIN</th>
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</thead>
<tbody>
<tr>
<td>Extensive 1&lt;sup&gt;st&lt;/sup&gt; pass effect CYP3A4</td>
<td>Extensive 1&lt;sup&gt;st&lt;/sup&gt; pass effect CYP2C9</td>
<td>Extensive 1&lt;sup&gt;st&lt;/sup&gt; pass effect CYP3A4</td>
<td>---</td>
<td>Extensive 1&lt;sup&gt;st&lt;/sup&gt; pass effect CYP2C9</td>
<td>Extensive 1&lt;sup&gt;st&lt;/sup&gt; pass effect CYP3A4</td>
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<tr>
<td>---</td>
<td>---</td>
<td>Metabolic activation</td>
<td>---</td>
<td>Higher bioavailability in Asian patients</td>
<td>Metabolic activation</td>
</tr>
<tr>
<td>Much longer t&lt;sub&gt;1/2&lt;/sub&gt;</td>
<td>---</td>
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<td>---</td>
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<td>---</td>
</tr>
<tr>
<td>May cause ↓ HDL</td>
<td>---</td>
<td>---</td>
<td>Excreted primarily in urine</td>
<td>90% excreted unchanged in stool</td>
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<tr>
<td>Approved in kids</td>
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</table>

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HDL    Definitely    Definitely    Definitely    -- --

Approved in kids

Osteogenic?    Osteogenic?
B. ABSORPTION INHIBITOR: EZETIMIBE

**EZETIMIBE** is the newest hypolipidemic drug (FDA approved in 2003). It is the first of a new class of agents that block cholesterol absorption, and it is typically given with a statin (**EZETIMIBE + SIMVASTATIN = VYTORIN**).

**Mechanism of Action**

- Following activation in the liver and small intestine, **EZETIMIBE** localizes to the brush border of the small intestine.
- **Selectively** inhibits the cholesterol transporter to prevent absorption of dietary cholesterol and reabsorption of cholesterol excreted in bile.
- Reduces cholesterol absorption by approximately 50%.
- Reduction in hepatic cholesterol stores causes increased cholesterol clearance from plasma.
- **Synergistic** with HMG-CoA reductase inhibitors.

**Pharmacokinetics**

- Oral administration; variable bioavailability (35-60%).
- Undergoes glucuronide conjugation in both the liver and the small intestine to form the active metabolite i.e., it is given as a prodrug.
- Biliary (stool) and renal excretion – plasma concentrations are increased when given with fibrates, and reduced when given with BABRs.

**Therapeutic Effects**

1. \(\downarrow\) plasma LDL and total cholesterol
2. Slight \(\downarrow\) TG
3. Very slight \(\uparrow\) HDL

**Therapeutic Indications**

- Has primarily been investigated in hypercholesterolemias (Type IIA and B).
Adverse Effects

- Better tolerated than **bile acid binding resins**
- **EZETIMIBE** does not affect absorption of other compounds, such as fat-soluble vitamins

1. **Drug – drug interactions:** can potentiate HMG-CoA reductase-related headache, muscle ache; **increases the frequency and magnitude** of increases in serum transaminase and serum creatinine kinase **activity when co-administered with statins**

2. GI effects: diarrhea, abdominal pain

3. Infection and respiratory system disorders: sinusitis, pharyngitis, viral infections, coughing

C. **BILE ACID BINDING RESINS:** **CHOLESTYRAMINE, COLESTIPOL**

Mechanisms of Action

- Bind intestinal bile acids (not absorbed from GI tract) → indirect decrease in cholesterol absorption
  - shift dynamics of cholesterol stores in liver
  - ↑ LDL receptor density → removal of LDLs from plasma

Pharmacokinetics

- Dry, gritty powders suspended in fluids taken just before or with meals
- Oral administration; excreted in feces (obviously!)
- Frequently prescribed in combination with other agents due to synergistic effect

Therapeutic Effect

1. ↓ plasma LDL and cholesterol
2. May cause a transient ↑ in TG and VLDL (limits usefulness in Type III, IV and V)
Therapeutic Indications

The most effective use of BABRs is in the treatment of hypercholesterolemias (Type IIa and IIb) --- i.e. in patients that do not have elevated TGs.

Adverse Effects

1. May ↑ TGs
2. Frequent “untoward” GI effects: nausea, discomfort, heartburn, indigestion, constipation, aggravation of hemorrhoids; can cause weight loss
3. Impaired intestinal absorption of concurrently administered drugs and fat-soluble vitamins: thiazide diuretics, warfarin, digitoxin, PRAVASTATIN, FLUVASTATIN, aspirin

D. VLDL SECRETION INHIBITOR (?): NICOTINIC ACID

- Actions are unrelated to vitamin B₃ (niacinamide) activity → must use NICOTINIC ACID form of niacin
- Vitamin requirements are 35 mg/day – for LDL/HDL control, doses are 1-2g, 3 x per day - when used in combination with a statin and/or BABR, doses can be reduced to 1-2 g/day

Mechanisms of Action (some are controversial)

1. ↓ clearance of apoA-1 → ↑ HDL
   (i.e., causes decreased catabolism of HDL, not increased synthesis)
2. Inhibition of VLDL secretion → ↓ LDL conversion
3. ↓ TG synthesis (liver) → ↓ VLDL synthesis
4. Inhibits intracellular lipase of adipose tissue via receptor-mediated signalling → ↓ flux of FFA to liver → ↓ VLDL synthesis BUT also increases liver lipase activity

Pharmacokinetics

- oral administration – converted to nicotinamide
- concentrates in liver
- excreted in urine
Therapeutic Effect

1. ↑ HDL (most potent of all drugs)
2. ↓ plasma VLDL, LDL (i.e. useful when both are elevated, ↓ VLDL more than LDL, TG and total cholesterol)
3. ↓ Lp(a)

Although NICOTINIC ACID has the “perfect” therapeutic profile (it significantly increases HDL while decreasing LDL, TGs and total cholesterol) but its adverse side effects can limit its usefulness because of decreased patient compliance.

Therapeutic Indications

- Treatment of simple and mixed hypertriglyceridemias (Type IIB, IV and V)
- Frequently combined with BABRs for treating mixed hyperlipoproteinemias (IIB)

Adverse Effects

1. **Intense cutaneous flush and pruritus** (affect >90% of patients) which decrease dramatically after 2 weeks
   - treat with 300 mg aspirin to dramatically reduce severity, limit intake of hot beverages and alcohol
2. **Vomiting, diarrhea, flatulence and dyspepsia** (>90%) – taking NICOTINIC ACID with a meal decreases these effects
3. **Hyperuricemia and gout** (20%)
4. Hepatotoxicity - cholestatic jaundice, hyperglycemia, glucose intolerance
5. In diabetics, can cause severe hyperglycemia (requiring insulin) and acanthosis nigricans
6. Reversible toxic amblyopia (patients should be instructed to report blurring of distance vision)
7. Potentiates action of antihypertensive drugs (doses should be adjusted)

**CAUTION:** patients with diabetes, hepatic disorders, gout, cardiac arrhythmias, hypertension; pregnant women or pre-pubertal children
E. LIPOPROTEIN LIPASE STIMULANTS ("fibrates"):
CLOFIBRATE, FENOFIBRATE, GEMFIBROZIL

- Actual mechanism of action is unknown – much greater clinical effect than would be predicted on the basis of cholesterol lowering

Mechanisms of Action
- known to be a ligand for a specific nuclear transcription receptor: peroxisome proliferator-activated receptor-alpha (PPAR-α)

1. In brown adipose tissue, ↑ LPL synthesis → ↑ clearance of TG’s (may transiently ↑ LDL)
2. In liver:
   a) inhibit hepatic synthesis of VLDL apoprotein CIII → ↓ VLDL
   b) ↑ apoA-I and II synthesis → ↑ HDL

Pharmacokinetics
- Rapid, near complete oral absorption
- Extensively (99%) bound in plasma (albumin)
- Extensive biotransformation, excreted in urine

Therapeutic Effect
1. Significant decrease in TGs, VLDL and LDL
2. ↑ in HDL
3. Variable effects on LDL, cholesterol (may ↑ as TGs ↓)

GEMFIBROZIL (and other fibrates) are extremely useful in the treatment of patients with elevated triacylglycerol (TG) levels (i.e., Types III, IV and V), because they produce a 20-50% decrease in TGs.
Therapeutic Indications

- Effective against Type III hyperlipidemia (dysbeta-lipoproteinemia) and Type IV or Type V hypertriglyceridemia that are unresponsive to diet or other drugs i.e., anything but I and II
- Recommended in patients with hypertriglyceridemia at high risk of MI and not responsive to dietary changes or NICOTINIC ACID

Adverse Effects (seen in <5% of patients)
1. **GI effects:** cholecystolithiasis, nausea, diarrhea, dyspepsia, flatulence, weight gain
2. May **increase mortality** in patients with pre-existing coronary atherosclerotic disease
3. Flu-like symptoms and **tumorigenesis** are common with CLOFIBRATE (GEMFIBROZIL and FENOFIBRATE have much lower mortality due to malignancy)
4. **Myositis** (may potentiate myopathy when combined with statins)
5. Hypersensitivity to GEMFIBROZIL
6. Drug interactions: warfarin, sulfonylureas, statins

**CAUTION:** Contraindicated in hepatic or renal failure and in pregnant or lactating women

F. **INHIBITOR OF LDL OXIDATION:** PROBUCOL

- Natural antioxidants (e.g. vitamin C and tocopherol) may have a similar function

Mechanisms of Action
- Inhibits oxidation of LDL

Therapeutic Indications
- Reserved solely for treating severe hypercholesterolemias when all else fails

Adverse Effects
1. **↓ HDL** more than LDL
2. May be **pro-arrhythmic** (lengthens QT interval); should not be administered in conjunction with digitalis, quinidine, sotalol, astemizole or terfenadine
COMBINATION THERAPY

Single drug therapy should be evaluated before drug combinations are used

Hypolipidemic drugs are often used in combination, because of the severity of the underlying problem in many patients (remember, often the desired goal is to drop LDL levels more than 60%, and no single agent can do that). However, because of the complexity of the balance in the system, the effects of combining agents can be unpredictable, and short-term vs. long-term results need to be considered.

Indications:
1. In very high risk patients with high TGs or low HDL in addition to high LDL, combine fibrate or NICOTINIC ACID with a statin
2. VLDL levels are significantly increased during treatment of hypercholesterolemia with a bile acid-binding resin
3. LDL and VLDL levels are both elevated initially
4. LDL or VLDL levels are not normalized with a single agent
5. Elevated levels of Lp(a) coexist with other hyperlipidemias

Common examples:
1. HMG-CoA Reductase Inhibitor + Nicotinic Acid
   • more effective than either agent alone in treating type IIa (familial hypercholesterolemia) and type IIb (familial mixed hypercholesterolemia)
2. Reductase Inhibitor + Ezetimibe or Bile Acid-Binding Resin
   • highly synergistic
   • BABR regimen may not control VLDL in some patients with type III (familial combined hyperlipoproteinemia)
   • must be sure to take statin 1 hour before BABR to ensure absorption
3. Nicotinic Acid + Bile Acid-Binding Resin
   • effective when both VLDL and LDL are increased
4. Bile Acid-Binding Resin, Nicotinic Acid, and Reductase Inhibitor
Lipid lowering drugs
### SUMMARY (modified from NCEP JAMA 285: 2486-2497, 2001)

<table>
<thead>
<tr>
<th>DRUG CLASS</th>
<th>EFFECTS</th>
<th>MAJOR SIDE EFFECTS</th>
<th>CONTRAINDICATIONS</th>
<th>RESULTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HMG-CoA Reductase Inhibitors</strong></td>
<td>LDL ↓ 18-55%</td>
<td>1. Myopathy</td>
<td>Absolute: early pregnancy liver disease</td>
<td>↓ major coronary events, CHD deaths, need for coronary procedures, stroke and total mortality</td>
</tr>
<tr>
<td>atorvastatin, fluvastatin</td>
<td>HDL ↑ 5-15%</td>
<td>2. Increased liver enzymes</td>
<td>Relative: concomitant use of various antifungal agents, macrolide antibiotics, cyclosporine, or cytochrome P450 inhibitors</td>
<td></td>
</tr>
<tr>
<td>lovastatin, pravastatin</td>
<td>TG ↓ 7-30%</td>
<td>3. Birth defects</td>
<td></td>
<td></td>
</tr>
<tr>
<td>rosuvastatin, simvastatin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ABSorption INHIBITOR</strong></td>
<td>LDL ↓ 15-20%</td>
<td>Potentiates side effects of statins</td>
<td></td>
<td>Unknown</td>
</tr>
<tr>
<td>ezitimibe</td>
<td>HDL ↑ 1-2%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>TG ↓ 5-10%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Bile Acid BINDING RESINS</strong></td>
<td>LDL ↓ 15-30%</td>
<td>1. GI distress</td>
<td>Absolute: TG&gt;400 mg/dL dysbetalipoproteinemia</td>
<td>↓ major coronary events, CHD deaths</td>
</tr>
<tr>
<td>cholestyramine</td>
<td>HDL ↑ 3-5%</td>
<td>2. ↓ absorption of other drugs and vitamins</td>
<td>Relative: TG&gt;200 mg/dL</td>
<td></td>
</tr>
<tr>
<td>colestipol</td>
<td>TG No change</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>or increase</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>NicotINIC AcId</strong></td>
<td>LDL ↓ 5-25%</td>
<td>1. Flushing and pruritus</td>
<td>Absolute: chronic liver disease; severe gout diabetes; hyperuricemia; peptic ulcer disease</td>
<td>↓ major coronary events and (maybe) total mortality</td>
</tr>
<tr>
<td></td>
<td>HDL ↑ 15-35%</td>
<td>2. Hyperuricemia (gout)</td>
<td>Relative:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TG ↓ 20-50%</td>
<td>3. upper GI distress</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>FibrIC AcIDs</strong></td>
<td>LDL ↓ 5-20%</td>
<td>1. GI distress</td>
<td>Absolute: severe liver disease; severe renal disease</td>
<td>↓ major coronary events</td>
</tr>
<tr>
<td>clofibrate</td>
<td>HDL ↑ 10-20%</td>
<td>2. myopathy;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>fenofibrate</td>
<td>TG ↓ 20-50%</td>
<td>3. unexplained non-CHD deaths</td>
<td></td>
<td></td>
</tr>
<tr>
<td>gemfibrozil</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
WHY PRESCRIBE THESE DRUGS????

A. 120 34 73 31 53 114 67 105 81 101 25 22 29 121 21 57

Enzyme that is stimulated by CLOFIBRATE and GEMFIBROZIL. (2 words)

B. 26 58 118 30 107 44 79 13 1 110 13 95 89 63

36 54 113 84 32 46 20 124 99 41 51 49 19

Transient adverse effect of an HMG-CoA reductase inhibitor. (4 words)

C. 119 14 64 56 8 110 32 44 105 22 38

HMG-CoA inhibitor that is eliminated to a greater extent in urine.
D. 46 35 59 124 80 42 117 83 33

Site of action of bile acid binding resins.

E. 18 24 49 73 93 27 97 66 8

GI disturbance associated with both FLUVASTATIN and GEMFIBROZIL.

F. 15 75 56 51 125 65 104 6 99 85

Another example of an HMG-CoA reductase inhibitor.

G. 47 34 1 88 6 117 100 41

PROBUCOL prevents this from happening to LDL lipoproteins.

H. 17 55 66 4 106 45 76 64 81 83

Occasional adverse effect of CLOFIBRATE and GEMFIBROZIL. (2 words)

I. 40 116 108 104 36 23 46 71 48 112 16 72

LIPOPROTEINS FROM PLAQUES

One result of inhibited cholesterol synthesis is?

J. 62 33 122 123 26 74 40 86

Metabolic activation of LOVASTATIN and SIMVASTATIN is ____________ in order to generate the active compound.

K. 22 68 7 117 99 23 69

Niacin ____________ VLDL synthesis.
L. 52 113 104 2 112 24 87 16 63 53 10 96 9 57

Oral absorption of **CLOFIBRATE** is... (2 words)

M. 94 19 63 103 46 43 109 34 10

Lipid lowering drug that has hypersensitivity as an adverse effect.

N. 121 42 28 77 56 84 98 116 88 59 26 52

HMG-CoA reductase inhibitor with the longest half-life.

O. 4 61 3 45

You should use caution in prescribing **NIACIN** to patients with this condition.

P. 60 78 101 16 103 22 92 8 105 124

Newest of the "**FIBRATE**" class of drugs.

Q. 20 66 39 11 9 117 48 81 50 8 111 81 86

Hypolipidemic drug that can cause an intense cutaneous flush.

R. 65 115 36 37 119 106 78 54 102 15

Naturally occurring antioxidant that may function in a similar manner to **PROBUCOL**.

S. 5 70 82 12

Following initiation of treatment with lipid lowering drugs, the physical regression of atherosclerotic lesions is ___________ (at least relative to the decrease in acute coronary events).