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 triacyglycerol (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)

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.

Hypolipidemic drugs are important!

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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)

MAJOR RISK FACTORS FOR ATHEROSCLEROSIS	
Coronary heart disease = Diabetes mellitis	
Increasing age	Current cigarette smoking
Male gender	Hypertension
Family history of premature CHD	**HIGH SERUM LDL (hyperlipidemia)**
Genetic abnormalities	**LOW SERUM HDL (hypoalpha lipoproteinemia)**

Minor (and emerging) factors include: obesity, physical inactivity, athrogenic diet, lipoprotein (a), homocysteine, prothrombotic and proinflammatory factors, impaired fasting glucose.

FRAMINGHAM RISK ASSESSMENT

http://hin.nhlbi.nih.gov/atpiii/calculator.asp?usertype=prof

- 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

TOTAL CHOLESTEROL	≤200 mg/dL
LDL CHOLESTEROL	
No CHD, <2 RF	**≤160 mg/dL**
No CHD, >2 RF	**≤130 mg/dL**
CHD or diabetes = high risk	**<100 mg/dL**
Framington risk score >20% = very high risk	**<70 mg/dL**
HDL CHOLESTEROL	
Female	≥50 mg/dL
Male	≥40 mg/dL
TRIACYLGLYCEROLS	<150 mg/dL

TREATMENT DECISIONS (based on LDL cholesterol levels)

PATIENT CATEGORY	DIETARY THERAPY	DRUG TREATMENT	LDL GOAL
No CHD, <2 RF	**≥160 mg/dL**	**≥190 mg/dL**	**<160 mg/dL**
No CHD, ≥2 RF	**≥130 mg/dL**	**≥160 mg/dL**	**<130 mg/dL**
CHD or diabetes	**≥100 mg/dL**	**≥130 mg/dL**	**<100 mg/dL**
Very high risk			**<70 mg/dL**

TYPES OF HYPERCHOLESTEROLEMIA

	FEATURES	CAUSE	OTHER
TYPE I familial hyper**chylomicron**emia	↑↑↑ **serum TG**	**Lipoprotein lipase deficiency** **(no effective drug treatment)**	No ↑ in risk for CHD
TYPE IIA familial hypercholesterolemia	↑ **serum LDL**, normal TG	**↓ LDL receptors** **(limits usefulness of some drugs, esp. statins)**	**↑↑↑ CHD**
TYPE IIB familial combined (mixed) hyperlipidemia	**Same as IIA**, but with ↑ VLDL also	Overproduction of VLDL by liver	**Relatively common**
TYPE III familial dysbetalipoproteinemia	↑ IDL, causes **↑ TG and LDL**	Overproduction or underutilization of IDL due to **mutant apolipoprotein E**	Xanthomas, ↑ coronary and peripheral vascular disease
TYPE IV familial hypertriglyceridemia	↑ VLDL, normal or ↓ LDL, **↑↑↑ TG**	Overproduction and/or ↓ removal of VLDL	**Common** **↑ CHD**
TYPE V familial mixed hypertriglyceridemia	↑ VLDL and chylomicrons; normal or ↓ LDL, **↑↑↑ TG**	↑ production or ↓ clearance of VLDL and chylomicrons (**genetic defect**)	Most common in adults who are obese and/or diabetic

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

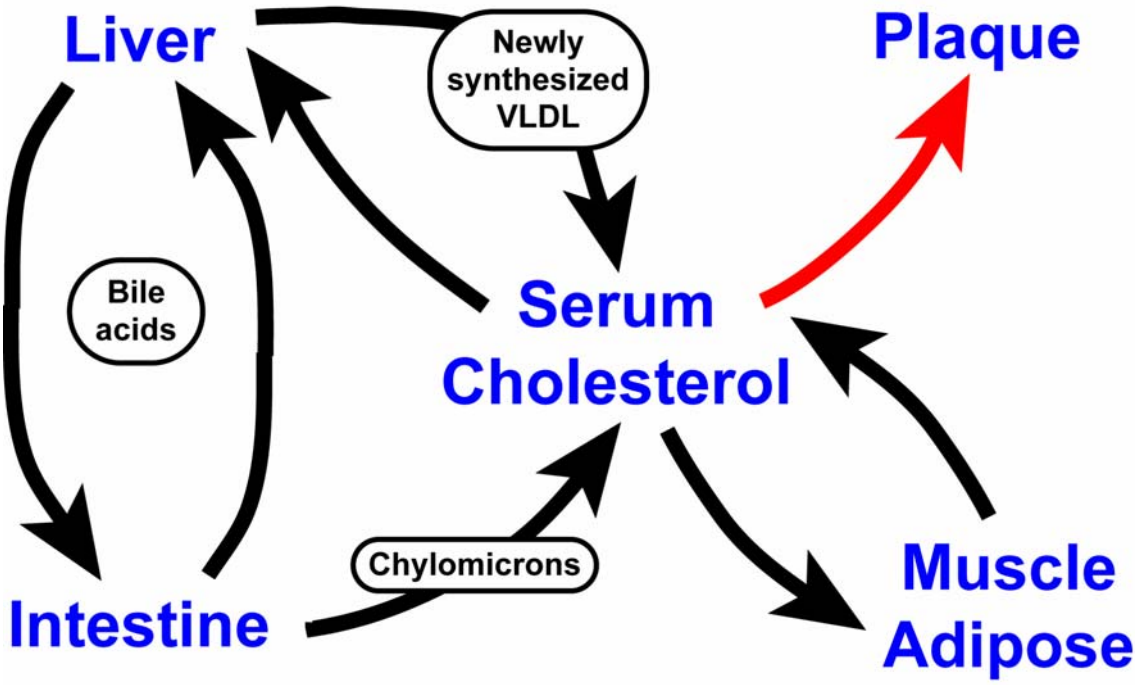
- interconversion of lipoproteins

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

Statins are the most effective agents for reducing LDL levels because they block cholesterol synthesis at is rate limiting step.

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**

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

SO, ARE ALL STATINS CREATED EQUAL?					
ATORVASTATIN	**FLUVASTATIN**	**LOVASTATIN**	**PRAVASTATIN**	**ROSUVASTATIN**	**SIMVASTATIN**
Extensive 1st pass effect CYP3A4	Extensive 1st pass effect CYP2C9	Extensive 1st pass effect CYP3A4	---	Extensive 1st pass effect CYP2C9	Extensive 1st pass effect CYP3A4
---	---	Metabolic activation	---	Higher bioavailability in Asian patients	Metabolic activation
Much longer $t_{1/2}$	---	---	---	--	--
			Excreted primarily in urine	90% excreted unchanged in stool	
May cause ↓ HDL				Definitely ↑ HDL	Definitely ↑ HDL
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. **↓ plasma LDL and total cholesterol**
2. Slight ↓ TG
3. Very slight ↑ 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 B_3 (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 triacyglycerol (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 **tumorgenesis** 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

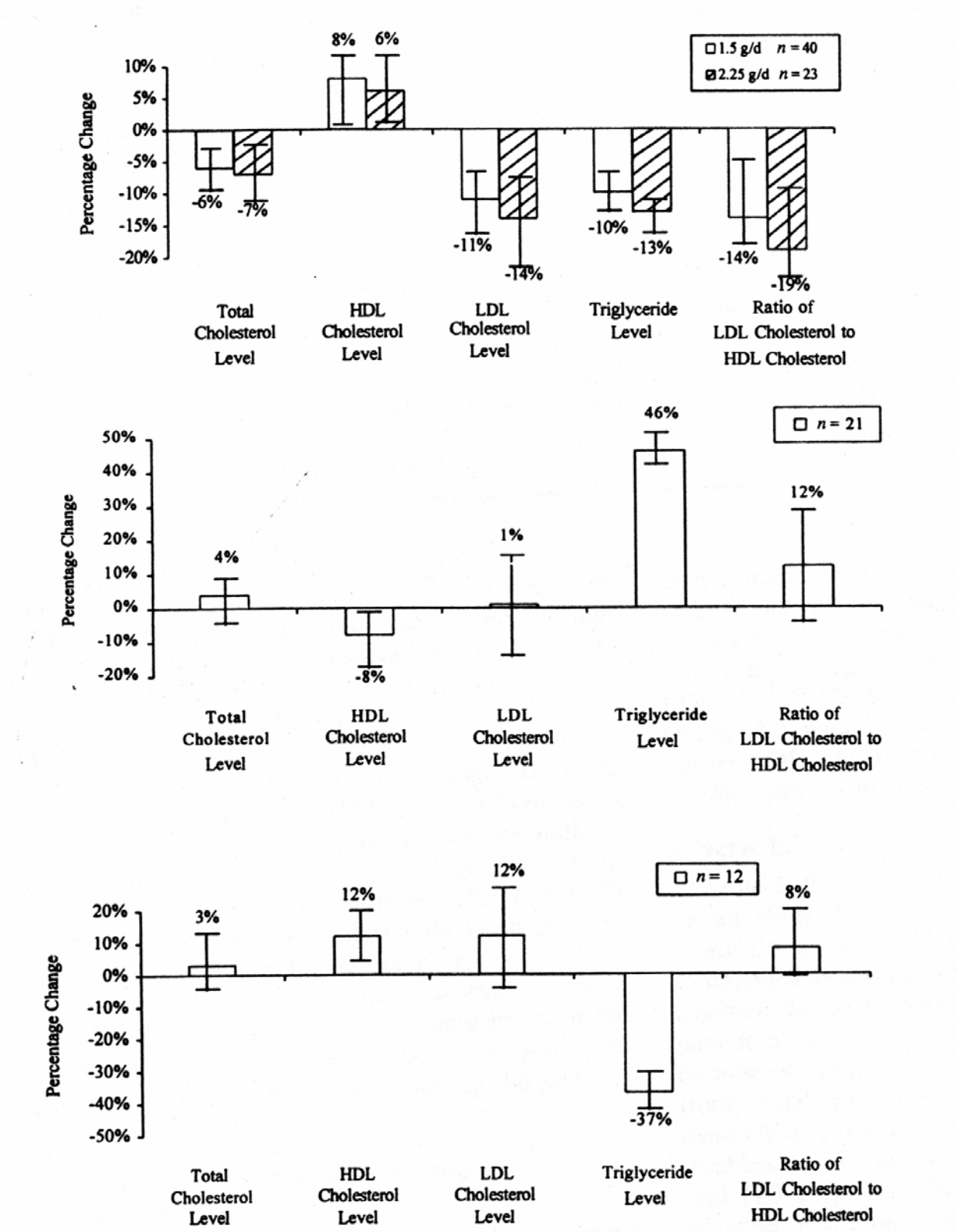
Hypolipidemic drugs are often used in combination, because of the severity of the underlying problem in many patients (remember, often the desired goal is to drop LDL levels more than 60%, and no single agent can do that). However, because of the complexity of the balance in the system, the effects of 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

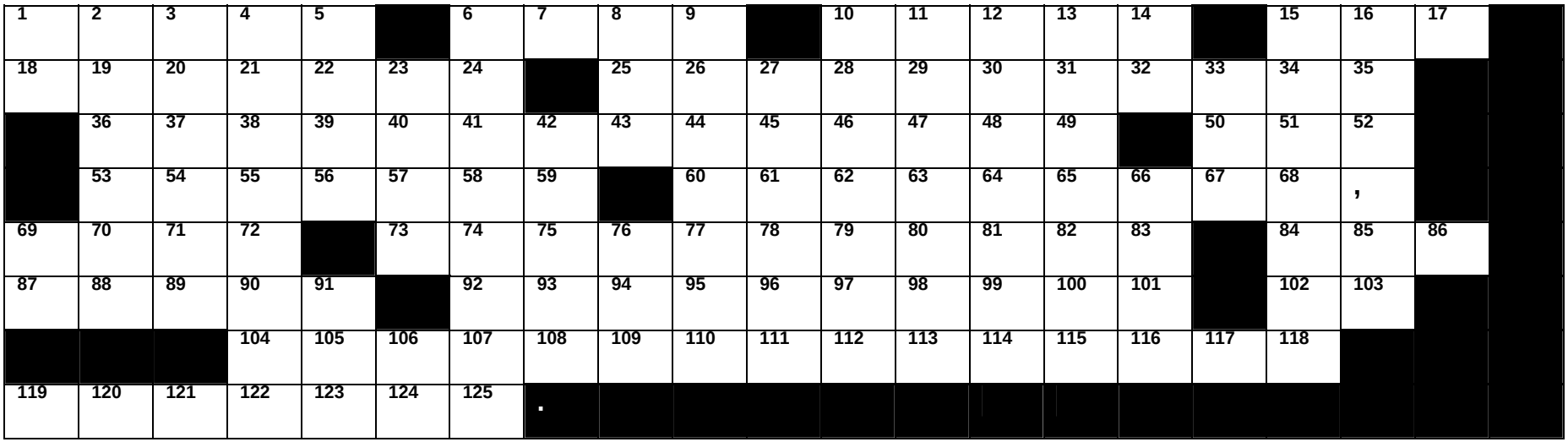
Common examples:

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


1.5 g/d n = 40
2.25 g/d n = 23
Percentage Change
10%
5%
0%
-5%
-10%
-15%
-20%
8%
6%
-6%
-7%
-11%
-14%
-10%
-13%
-14%
-19%
Total Cholesterol Level
HDL Cholesterol Level
LDL Cholesterol Level
Triglyceride Level
Ratio of LDL Cholesterol to HDL Cholesterol
n = 21
50%
40%
30%
20%
10%
0%
-10%
-20%
4%
-8%
1%
46%
12%
n = 12
20%
10%
0%
-10%
-20%
-30%
-40%
-50%
3%
12%
12%
-37%
8%

SUMMARY (modified from NCEP JAMA 285: 2486-2497, 2001)

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



WHY PRESCRIBE THESE DRUGS????

A.

120	34	73	31	53	114	67	105	91	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.

___	___	___	___	___	___	___	___	___	___	OF	___	___	___	DENSITY
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).