

Antiatherosclerotic Drugs

I. Introduction/Significance

Atherosclerosis

- Affects large and medium sized arteries.
- Focal plaques within the intima containing cholesterol and cholesterol esters (CE).
- Causes Coronary Heart Disease.

Hypercholesterolemia

- High serum cholesterol level
- Elevated LDL and triglycerides (TG) - associated with increased risk.
- Serum levels of HDL - inversely related to risk.

II. Regulation of cholesterol and triglyceride metabolism

A. Exogenous pathway: Route of uptake of dietary lipids.

- Chylomicrons (CM) - complexes of TG, CE and apoproteins.
- Chylomicron remnants - CM after removal of most TG.
- CM are degraded by lipoprotein lipase on endothelial cells of adipose tissue and muscle. After removal of TG for storage, the CM remnants are transported to the liver.
- Results: Dietary TG stored in adipose tissue and muscle. Cholesterol is stored in liver or excreted into the bile as cholesterol or bile acid.

B. Endogenous pathway: Route for distribution of CE from liver to target cells.

- VLDL - secreted by the liver to plasma and transported to adipose tissue and muscle where lipoprotein lipase extracted most TG. The remnant IDL is either taken up by the liver and circulated until the remaining TG are removed forming LDL particles which are rich in cholesterol.
- LDL is cleared from plasma through LDL receptor-mediated endocytosis.
- Results:
 - Transfer of TG from liver to target cells via VLDL;
 - Transfer of CE from liver to target cells via LDL;
 - Feedback regulation of cholesterol homeostasis by LDL receptor expression;
 - Creation of a steady-state LDL-CE reserve in plasma.

C. Reverse transport of cholesterol: Route for cholesterol recovery.

- As cell dies and the cell membrane turnover, free cholesterol is released into the

Anti-Atherosclerotic Drugs

plasma. It is immediately absorbed onto HDL particles, esterified with a long chain fatty acid by Lecithin:cholesterol acyltransferase (LCAT), and transferred to VLDL or IDL by a cholesteryl ester transfer protein in plasma. Eventually, it is taken up by the liver as IDL or LDL.

- Results: Recovery of cholesterol from cell membranes and reincorporation into LDL pool or return to liver.

D. De novo cholesterol biosynthesis

- Liver synthesizes 2/3 of cholesterol made by the body. The rate limiting enzyme is 3-hydroxy 3-methyl glutaryl (HMG)-CoA reductase.
- Results: Provide feedback regulation by cholesterol concentrations in cells.

E. Cholesterol excretion by enterohepatic circulation

- Bile salts are synthesized from cholesterol in the liver, released into the intestine, and recycled. A small amount of bile acid is excreted.
- Results: Conversion of liver cholesterol to bile salts for excretion.

III. Pathogenesis of atherosclerosis

- Current model of the formation of atherosclerotic plaque: chronic inflammatory response of the vascular wall to endothelial injury or dysfunction.
- Elevated LDL levels increases its probability to penetrate the endothelial lining of blood vessels. Oxidation of transmigrated LDL particles modifies apoproteins on LDL, and renders it recognizable to scavenger receptors of macrophages forming foam cells. Fatty streaks are made up largely of foam cells.
- Further responses: Proliferation of smooth muscle cells, platelet aggregation, deposition of extracellular matrix.

IV. Genetic defects of lipid metabolism

A. Monogenic

- Familial hypercholesterolemia (homozygous or heterozygous)
- Defect: inactive LDL receptor
- Familial lipoprotein lipase deficiency
- Defect: inactive lipoprotein lipase
- Familial combined hyperlipidemia
- Defect: unknown

B. Polygenic/multifactorial - commonly encountered

- Hypercholesterolemia
- Hypertriglyceridemia

V. Therapeutic strategy of atherosclerosis

A. Identify patients at risk

1. Routine screening of serum cholesterol
2. Assessment of contributing risk factors

B. Non-pharmacologic therapy

1. Diet modification
2. Lifestyle modification

C. Pharmacologic therapy

VI. Drug therapy of hyperlipidemia

1. Single drug therapy

A. Bile acid sequestrants (colestipol, cholestyramine)

- Taken orally.
- Actions: Anion exchange resins which bind negatively charged bile acids in the small intestine.
- Results:
 1. increased conversion of cholesterol to bile acid in hepatocytes;
 2. increased synthesis of cholesterol and LDL receptors in hepatocytes;
 3. decreased serum LDL and cholesterol levels.
- Advantages: clinically safe; effective; cost: \$500/year.
- Disadvantages: unpleasant GI effects; interference with GI drug absorption; may exacerbate hypertriglyceridemia (unknown mechanism).

B. Niacin (nicotinic acid)

- Actions: Decrease free fatty acid (FFA) available to the liver for synthesis of triglycerides. Inhibition of a hormone-sensitive lipase involved in lipolysis in adipose tissue.
- Results:
 1. decreased production and release of VLDL by liver;
 2. decreased serum levels of VLDL as well as LDL and TG;
 3. reduced the clearance of HDL or increased serum level of HDL;
 4. increased HDL/LDL ratio.
- Advantages: long clinical experience; effective; least expensive (\$50/year)

Anti-Atherosclerotic Drugs

- Disadvantage: evokes flushing, itchiness and GI discomfort; contraindicated for diabetic patients; adverse effects in hepatic disease and gout.

C. Lovastatin (aka "statins", HMG-CoA reductase inhibitors)

- Actions: competitively inhibits HMG-CoA reductase, the key enzyme for de novo cholesterol biosynthesis.
- Results: 1) cells express more LDL receptors; 2) decreased serum LDL levels; 3) suppresses production of VLDL in liver; 4) increased serum HDL levels; 5) increased HDL/LDL ratio.
- Advantages: specific; effective; well-tolerated.
- Disadvantages: safety unknown for long term use; most expensive (\$900/year)

D. Fibrates (U.S.: gemfibrozil; Europe: fenofibrate; prototype: clofibrate)

- Actions: stimulate lipoprotein lipase; increase the clearance of VLDL and reduces plasma triglyceride levels; decrease VLDL synthesis which also lower serum LDL levels; increase plasma HDL by increase synthesis and/or decrease clearance.
- Results: decreased serum TG and cholesterol; increased HDL/LDL ratio.
- Advantage: recent clinical data support safety and efficacy; well-tolerated; cost: \$375/year.
- Disadvantage: more effective in reducing TG than cholesterol; long-term effect not known. Clofibrate is not usable because of toxicity.

E. Probucol (lipophilic antioxidant)

- Action: Taken up by LDL particle and endothelial cells. Inhibits oxidation of LDL and prevents ingestion by macrophage foam cells. Decreases HDL production.
- Results:
 1. decreases atherosclerotic plaque formation;
 2. small reduction of serum LDL-cholesterol;
 3. greater reduction of serum HDL-cholesterol.
- Advantage: may be used in combination therapy with other drugs that lower serum LDL-cholesterol.
- Disadvantage: not effective in single drug therapy; no long term clinical data.

2. Combined drug therapy

- Advantages: Synergistic approach utilizes complementary mechanisms of drug

Anti-Atherosclerotic Drugs

action; reduces effective dose of single drug to prevent side effect.

- Hypercholesterol without hypertriglycerides:
 - Bile acid sequestrant plus nicotinic acid
 - Bile acid sequestrant plus lovastatin
 - Bile acid sequestrant plus lovastatin plus probucol
 - Bile acid sequestrant plus gemfibrozil (less common)
- Hypercholesterol plus hypertriglycerides:
 - Nicotinic acid plus lovastatin
 - Lovastatin plus gemfibrozil
 - Nicotinic acid plus lovastatin plus bile acid sequestrant

VII. Recommended readings:

1. Goodman and Gilman, 8th edition, Chapter 36, pp 874-896.
2. Report of the National Cholesterol Education Program Expert Panel on detection, evaluation, and treatment of high blood cholesterol in adults. *Arch. Intern. Med.* 148:36-39, 1988.

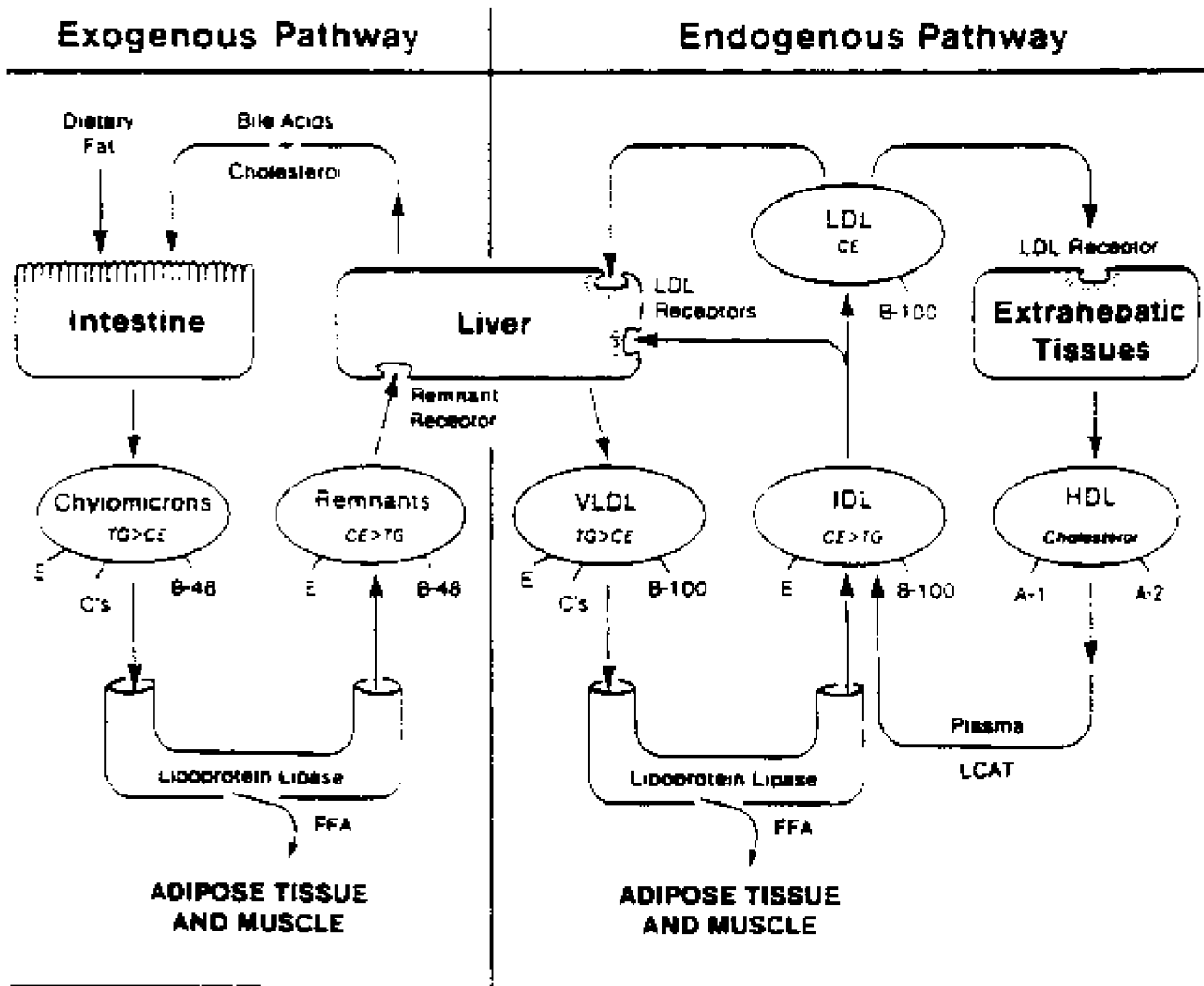


Figure 36-1. Model for the metabolism of plasma lipoproteins, showing the separate pathways for transport of endogenous and exogenous lipids

Anti-Atherosclerotic Drugs

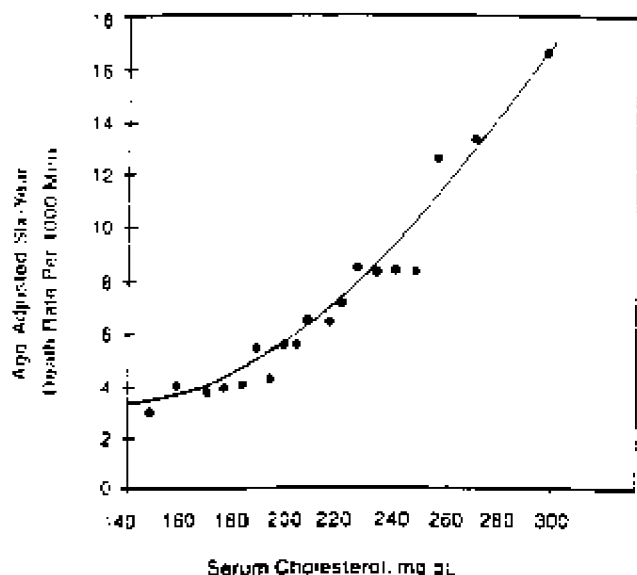


Fig. 1.—Relationship of serum cholesterol to coronary heart disease (CHD) death in 361 662 men 35 to 57 years of age during an average followup of six years. Each point represents median value for 5% of the population.⁸ Key points are as follows: (1) risk increases steadily, particularly above levels of 200 mg/dL; and (2) the magnitude of the increased risk is large, fourfold in the top 10% as compared with the bottom 10%.

Table 1.—Initial Classification and Recommended Followup Based on Total Cholesterol⁸

Classification, mg/dL	Desirable blood cholesterol
< 200	Desirable blood cholesterol
200 to 239	Borderline-high blood cholesterol
≥ 240	High blood cholesterol
Recommended followup	Repeat within five years
Total cholesterol < 200 mg/dL	
Total cholesterol 200-239 mg/dL	Dietary information and recheck annually
Without definite CHD or two other CHD risk factors (one of which can be male sex)	
With definite CHD or two other CHD risk factors (one of which can be male sex)	Lipoprotein analysis; further action based on LDL-cholesterol level
Total cholesterol ≥ 240 mg/dL	

⁸CHD indicates coronary heart disease; LDL, low density lipoprotein.

Table 2.—Classification and Treatment Decisions Based on LDL-Cholesterol⁹

Classification, mg/dL	Desirable LDL-cholesterol	Borderline-high-risk LDL-cholesterol	High-risk LDL-cholesterol	Initiation Level, mg/dL	Minimal Goal, mg/dL
< 130	Desirable LDL-cholesterol				
130 to 159	Borderline-high-risk LDL-cholesterol				
≥ 160	High-risk LDL-cholesterol				
Dietary treatment					
Without CHD or two other risk factors [†]				≥ 160	< 160
With CHD or two other risk factors [†]				≥ 130	< 130
Drug treatment					
Without CHD or two other risk factors [†]				≥ 190	< 150
With CHD or two other risk factors [†]				≥ 160	< 130

⁹LDL indicates low density lipoprotein; CHD, coronary heart disease.
[†]Patients have a lower initiation level and goal if they are at high risk because they already have definite CHD, or because they have any two of the following risk factors: male sex, family history of premature CHD, cigarette smoking, hypertension, low high density lipoprotein (HDL)-cholesterol, diabetes mellitus, definite cerebrovascular or peripheral vascular disease, or severe obesity.
[‡]Roughly equivalent to total cholesterol level of < 240 mg/dL or < 200 mg/dL.
[§]As goals for monitoring dietary treatment.

Table 4.—Risk Status Based on Presence of CHD Risk Factors Other Than LDL-Cholesterol

The patient is considered to have a high risk status if he or she has one of the following:
Definite CHD (the characteristic clinical picture and objective laboratory findings of either):
Definite prior myocardial infarction or
Definite myocardial ischemia, such as angina pectoris
Two other CHD risk factors:
Male sex [†]
Family history of premature CHD (definite myocardial infarction or sudden death before 55 years of age in a parent or sibling)
Cigarette smoking (currently smokes more than ten cigarettes per day)
Hypertension
Low HDL-cholesterol concentration (below 35 mg/dL, confirmed by repeated measurement)
Diabetes mellitus
History of definite cerebrovascular or occlusive peripheral vascular disease
Severe obesity (≥ 30% overweight)