Part 2
Antianginal drugs
1 OVERVIEW

2 ANTIANGINAL DRUGS
   - Organic nitrates
   - $\beta$ -blockers
   - Calcium channel blockers

3 CLINICAL USE OF ANTIGANGINAL DRUGS
1.1 What is angina pectoris?

**Frequency:** in America, about 6.3 million people are estimated to experience angina. An estimated 350,000 new cases of angina occur every year. One million died of angina each year in China.

A comprehensive approach to diagnosis and to medical management of angina is an integral part of the daily responsibilities of physicians.
Leading Sources of Disease Burden*

- Ischemic Heart Disease
- Unipolar Major Depression
- Cardiovascular Disease
- Alcohol Use
- Traffic Accidents
- Lung and other cancers
- Dementia and Neurodegenerative Disorders

*based on DALY’s (Disability Adjusted Life Years, WHO) which measure lost years of healthy life due to premature death or disability
1.1 What is angina pectoris?

**Symptoms:** Sudden, uncomfortable pressure, fullness, squeezing or severe substernal pain, radiating to the left arm, shoulders, neck, etc.
1.2 How does angina pectoris happen?

Demand of the myocardium for oxygen

Oxygen delivery to the myocardium by the coronary circulation
Demand ↑
✓ Preload (venous return)
✓ Afterload (arteriolar resistance)
✓ Heart rate

Delivery ↓
✓ Atherosclerosis plaque
✓ Thrombus
✓ Spasm of coronary arteries
1.3 Classification of angina pectoris:

Stable angina pectoris

Unstable angina pectoris
- initial onset type
- accelerated type
- spontaneous type

Variant/Prinzmetal’s angina pectoris

Caused by spontaneous spasm of coronary arteries

Caused by atherosclerosis plaque and thrombus formation
Occurrence of stable and unstable angina pectoris

- Extreme weather
- Strong emotion
- Excessive food intake
- Exercise
- Excessive smoking

Variant/Prinzmetal’s angina: usually occur when a person is at rest between midnight and 8am
1.4 Strategy for angina treatment

- Dilating arteries, especially coronary arteries, including relieving spasm and opening collateral circulation
- Dilating veins
- Cardiac inhibition: decrease HR, contractility, tensility of myocardium
- Anti-platelet coagulation and thrombus formation

Decrease the oxygen demand and/or increase the delivery BY
1.5 Antianginal drugs

- Organic nitrates
- β-receptor blockers
- Calcium channel blockers
2. Antianginal drugs

2.1 Organic nitrates （硝酸酯类）

Nitroglycerin, Isosorbide dinitrate

A Actions

Dilate vessels --- pre- and after-load ↓
Redistribution of coronary blood flow --- subendocardial area ↑
preload, epicardial vessels, collateral circulation
Anticoagulation of platelets
B. Mechanisms of action

Nitrates (prodrug) $\rightarrow$ NO $\rightarrow$ GC activated

$\rightarrow$ cGMP $\uparrow$

\[
[\text{Ca}^{2+}]_i \downarrow
\]

Dephosphorylation of myosin light chain

$\rightarrow$ Vascular smooth muscle relaxation
$\rightarrow$ Anticoagulation of platelets
**C Pharmacokinetics**

**Nitroglycerin**
- **Time to peak effect**: 2 min
- **Duration of action**: 25 min
  - Sublingual

**Isosorbide dinitrate**
- **Time to peak effect**: 15 min
- **Duration of action**: 1 hour
  - Sublingual
D  Adverse effects

- Symptoms due to vasodilation: headache, increase of intraocular pressure, postural hypotension, facial flushing and tachycardia
- Allergy
- Methaemoglobinemia (at very high dose)
E Tolerance

- Provision of daily “nitrate-free interval”
- To supplement -SH

E Interactions with other drugs

- Antihypertensive drugs
- Alcohol and Viagra
Something’s Gotta Give
2. Antianginal drugs

2.2 β -blockers

Physiological effects of β receptors in the heart

- Catecholamine
- Na⁺ influx ↑ during phase 4
- Ca²⁺ influx ↑ during phase 0
- K⁺ efflux ↑ during repolarization
2. Antianginal drugs

2.2 β-blockers

Propranolol, metoprolol, atenolol

A. Actions

- Decrease myocardial oxygen consumption
- Improve myocardial metabolism (FFA ↓)
- Increase blood supply to ischemic area
- Increase oxygen supply to tissues
- Inhibit coagulation of platelets
2. Antianginal drugs

2.2 β receptor blockers

B Therapeutic uses:

- stable and unstable type, especially associated with hypertension or arrhythmias, even with myocardial infarction.

- not suitable for variant type.
2. Antianginal drugs

2.2 β receptor blockers

C Notices:
• Begin with small dose
• Withdraw gradually (rebound phenomenon)
• Better when combined with nitroglycerin
2. Antianginal drugs

2.3 Calcium channel blockers

A Functions of calcium in cardiovascular system:

- muscle contraction
- neurotransmitter release
- automaticity of SA node
- conductivity of AV node, etc.
2. Antianginal drugs

2.3 Calcium channel blockers

B Origin and elimination of intracellular calcium:

extracellular calcium influx

calcium store release

calcium pump and Na+-Ca2+ exchange
2. Antianginal drugs

2.3 Calcium channel blockers

C Types of calcium channels:

L, T, N, P, Q, R, and ligand gated types
2. Antianginal drugs

D Classes of calcium channel blockers:

Class I: blocking L type

a: phenylalkylamines (苯烷胺类): verapamil (维拉帕米)
b: benzothiazepines (苯硫卓类): diltiazem (地尔硫卓)
c: dihydropyridines (二氢吡啶类):
   - nifedipine (硝苯地平)
   - nimoldipine (尼莫地平)
   - amlodipine (氨氯地平)
d: tetrandrine (粉防己碱)
2. Antianginal drugs

D Classes of calcium channel blockers:

Class II blocking other types
- T type: phenytoin (苯妥英钠), mibefradil (米贝地尔)
- N type: conotoxins (芋螺毒素)
- P type: spider toxin

Class III non-selective agents
- prenylamine (普尼拉明), flunarizine (氟桂利嗪)
2. Antianginal drugs

Actions of calcium channel blockers:

- Heart

  - Negative inotropic action: excitation-contraction discoupling

  - Negative chronotropic and slowing conduction action: spontaneous depolarization in phase 4 and depolarization in phase 0 of slow reaction autonomic cells
2. Antianginal drugs

- **Smooth muscle**
  - **Vascular smooth muscle**: relax the tone of artery, especially coronary artery
  - **Others**
    smooth muscle of bronchus, gastrointestinal tract, ureter, uterus
2. Anti-anginal drugs

- **Anti-atherosclerosis**
  - Alleviate $\text{Ca}^{2+}$ overload
  - Inhibit proliferation of smooth muscle cells and protein production of arterial matrix
  - Inhibit lipid peroxidation
  - Decrease cholesterol level
2. Antianginal drugs

- **Erythrocyte and platelet**
  - Improve membrane stability of erythrocyte
  - Inhibit platelet activation

- **Kidney**
  - Increase the blood flow of kidney
2. Antianginal drugs

**Therapeutic uses of calcium channel blockers:**

- **Angina pectoris**
  - Stable angina: ver, dil
  - Variant angina: nif
  - Unstable angina: ver, dil, nif + β blockers
2. Antianginal drugs

Actions of calcium channel blockers contributing to antianginal effect:

- Decrease myocardial oxygen consumption
- Increase myocardial blood supply
- Protect ischemic myocardial cell
- Inhibit coagulation of platelets
2. Antianginal drugs

F Therapeutic uses of calcium channel blockers:
  - Arrhythmias:
    - Supraventricular tachycardia
    - Arrhythmias induced by triggered activity following after-depolarization (ver, dil)
2. Antianginal drugs

F Therapeutic uses of calcium channel blockers:

- Hypertension
  - Severe: nif
  - Mild to moderate: ver, dil
2. Antianginal drugs

**Therapeutic uses of calcium channel blockers:**

- **Cerebrovascular diseases:**
  transient ischemia attack, cerebral thrombosis, and cerebral embolism
- **Other diseases:** peripheral vascular spasmodic disease, arteriosclerosis, migraine
2. Antianginal drugs

G Adverse effects of calcium channel blockers:

- peripheral edema
- sympathetic excitation (nif)
- cardiac inhibition (ver, dil)
- hypotension (nif)
2. Antianginal drugs

H Contraindications of calcium channel blockers:
- hypotension
- severe heart failure
- sinus bradycardia
- atrioventricular block
3. Combination of antianginal drugs

<table>
<thead>
<tr>
<th>心肌氧供需决定因素</th>
<th>硝酸酯类</th>
<th>β受体阻断药</th>
<th>钙拮抗药</th>
</tr>
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<tbody>
<tr>
<td>室壁张力</td>
<td>↓</td>
<td>±</td>
<td>↓</td>
</tr>
<tr>
<td>心室容积</td>
<td>↓</td>
<td>↑</td>
<td>±</td>
</tr>
<tr>
<td>心室压力</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>心脏体积</td>
<td>↓</td>
<td>↑</td>
<td>±</td>
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<tr>
<td>心率</td>
<td>↑</td>
<td>↓</td>
<td>±</td>
</tr>
<tr>
<td>收缩性</td>
<td>↑</td>
<td>↓</td>
<td>±</td>
</tr>
<tr>
<td>心内外膜血流比率</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>侧枝血流量</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
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</table>
3. Combination of antianginal drugs

<table>
<thead>
<tr>
<th>作用</th>
<th>硝酸酯类</th>
<th>β受体阻断药</th>
<th>硝酸酯类 + β受体阻断药</th>
</tr>
</thead>
<tbody>
<tr>
<td>动脉压</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>心率</td>
<td>↑（反射性）</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>心肌收缩力</td>
<td>↑（反射性）</td>
<td>↓</td>
<td>抑制或不变</td>
</tr>
<tr>
<td>射血时间</td>
<td>↓</td>
<td>↑</td>
<td>不变</td>
</tr>
<tr>
<td>舒张期灌流时间</td>
<td>↓</td>
<td>↑</td>
<td>延长</td>
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<tr>
<td>左室舒张末压</td>
<td>↓</td>
<td>↑</td>
<td>不变或降低</td>
</tr>
<tr>
<td>心室容积</td>
<td>↓</td>
<td>↑</td>
<td>不变或缩小</td>
</tr>
</tbody>
</table>
3. Combination of antianginal drugs

Notice:

- Hypotension
- Cardiac low perfusion
Part 3   Agents Used in Hyperlipidemia
Outline

1. Introduction to hyperlipidemia
2. Agents managing hyperlipidemia
1. Introduction of hyperlipidemia

Lipids include:

- Triglyceride (TG)
- Cholesterol (TC)
- Others, like phospholipids and fatty acid
The Physiologic Role of Cholesterol

- Component of all cell membranes
- Precursor of other steroids
  - Cortisol
  - Progesterone
  - Estrogen
  - Testosterone
  - Bile acids
1. Cholesterol enters artery wall
2. LDL oxidation
3. Inflammation
4. HDL carries cholesterol to liver
5. Liver converts cholesterol into bile for removal from body

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LDL (low density lipoprotein)

• LDL is associated with increased heart disease “lousy cholesterol” “bad cholesterol”, the major carrier of cholesterol in the blood

The role of LDL is to transport cholesterol to peripheral tissues

Half-life for clearance is ~ 24 hrs (every day about half the circulating LDL is removed via receptor mediated endocytosis)
The LDL receptor is central to cholesterol homeostasis

When LDL binds to its receptor (via recognition of the apoprotein B100) the entire LDL molecule is taken up (engulfed) by the cell in clatherin coated pits → endosomes → lysosomes
Correlation Between Cholesterol Levels and CHD Death

Rule: For every 1% increase in LDL-C, there is a 1% increase in CHD events

Age-adjusted 6-year CHD death rate per 1000 men

n=325,000 men

HDL (high density lipoprotein)

HDL: secreted by the liver and intestine; Lipids of HDL come from CM and VLDL during lipolysis, or acquires cholesterol from peripheral tissues.
The role of HDL is keeping the cholesterol homeostasis of cells
Low HDL is an independent risk factor for CHD.
## Classification of hyperlipidemia

<table>
<thead>
<tr>
<th>Type</th>
<th>Elevated lipoprotein</th>
<th>Ch</th>
<th>TG</th>
<th>Risk of CHD</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>CM</td>
<td>+</td>
<td>+++</td>
<td>/</td>
</tr>
<tr>
<td>IIa</td>
<td>LDL</td>
<td>++</td>
<td>/</td>
<td>High</td>
</tr>
<tr>
<td>IIb</td>
<td>LDL+VLDL</td>
<td>++</td>
<td>++</td>
<td>High</td>
</tr>
<tr>
<td>III</td>
<td>β VLDL</td>
<td>++</td>
<td>++</td>
<td>Moderate</td>
</tr>
<tr>
<td>IV</td>
<td>VLDL</td>
<td>+</td>
<td>++</td>
<td>Moderate</td>
</tr>
<tr>
<td>V</td>
<td>CM+VLDL</td>
<td>+</td>
<td>++</td>
<td>/</td>
</tr>
</tbody>
</table>

Ch: cholesterol; TG: triglyceride; /: no change
## Simple Classification of Hyperlipidemias

<table>
<thead>
<tr>
<th></th>
<th>TC</th>
<th>TG</th>
<th>HDL</th>
</tr>
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<tbody>
<tr>
<td><strong>Hypercholesterolemia</strong></td>
<td></td>
<td>↑</td>
<td></td>
</tr>
<tr>
<td><strong>高胆固醇血症</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hypertriglyceridemia</strong></td>
<td></td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td><strong>高甘油三酯血症</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Mix Hyperlipidemia</strong></td>
<td>↑</td>
<td>↑</td>
<td></td>
</tr>
<tr>
<td><strong>混合型高脂血症</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>hypoalphalipoproteinemia</strong></td>
<td>↓</td>
<td>↓</td>
<td></td>
</tr>
<tr>
<td>** hypoalipoproteinemia**</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
2. Agents managing hyperlipidemia

------Drugs lowering TC
------Drugs lowering TG
2. Agents managing hyperlipidemia

HMG-CoA Reductase Inhibitors
(Statins)
Net Cholesterol Balance in Humans

Intestine
- Dietary cholesterol (300 mg/day)
- Biliary cholesterol/Bile acids
- Fecal sterols (1100 mg/day)

Liver
- VLDL
- LDL
- LDL-R
- SR-BI
- HDL
- Synthesized cholesterol (800 mg/day)

Extrahepatic tissues
- Chol
- Acetyl CoA

57
Acetyl CoA → HMG CoA → Mevalonate → IPP, DPP, GPP, FPP → Isoprenoids → Adhesion molecules, G-proteins, Cell proliferation

HMG CoA reductase

Statins

(甲羟戊二酸单酰辅酶A)

(甲羟戊酸)

(异戊二烯)

(鲨烯)

(胆固醇)
Mechanism of Statin Action

Structural analogs of the HMG-CoA intermediate, inhibit synthesis of Ch.

Increase in high-affinity LDL receptors

Increase catabolic rate of LDL and the liver's extraction of LDL precursors (VLDL remnants), thus reducing plasma LDL.

Due to the first pass hepatic extraction, the major effect is in liver.
## Summary of Pharmacological Properties of Statins

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Potency on enzyme IC$_{50}$ (nM)</th>
<th>Bioavailability</th>
<th>Elimination half life (h)</th>
<th>Hepatic metabolism by CYP3A4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosuvastatin</td>
<td>5.4</td>
<td>~20%</td>
<td>19</td>
<td>No</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>8.2</td>
<td>~14%</td>
<td>14</td>
<td>Yes</td>
</tr>
<tr>
<td>Cerivastatin</td>
<td>10.0</td>
<td>60%</td>
<td>2–3</td>
<td>Yes</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>11.2</td>
<td>&lt; 5%</td>
<td>1–2</td>
<td>Yes</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>27.6</td>
<td>24%</td>
<td>1–2</td>
<td>No</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>44.1</td>
<td>17%</td>
<td>1–2</td>
<td>No</td>
</tr>
</tbody>
</table>

Clinical Use of Statins

- Most Effective for ↓ LDL
- Some ↑ HDL and good ↓ VLDL
- Enhanced if taken with food (except for pravastatin – taken without food)
- Given in the evening
Why Should Statins Given Once Daily Be Taken at Bedtime?

Cholesterol synthesis is highest at night

It May be Necessary to Increase the Levels of Statin Drugs During the Course of Therapy. Why?

Induction of HMB-CoA Reductase gene in response to decreased cholesterol
Pooled Statin Trial Results

Total of 30,817 subjects in 3 secondary and two primary prevention trials

Mean age 59 years
Mean follow-up = 5.4 yrs

Reduction in TC:    -20%
Reduction in LDL-c: -28%
Reduction in TG:    -13%

Meta-analysis: LaRosa JC et al. JAMA. 1999;282:2340-2346
Pooled Statin Trial Results

Significant reduction in major coronary events & death ($P < 0.001$)

- Coronary events: -31% (CI. 26-36%)
- Fatal CHD: -29% (CI. 20-36%)
- Total mortality: -21%
- CV mortality: -27%
Statins – Adverse Effects

– Statins are pregnancy category X
– Rash, GI disturbances (dyspepsia, cramps, flatulence, constipation, abdominal pain)
– Myopathy (0.5% of pts)
  • Risk highest with lovastatin and especially in combination with Fibrates (苯氧酸类降脂药)
– Cyp3A4 or CYP2C9 drug interactions with many statins
– Hepatotoxicity
Risk Factors for Myopathy

Advanced age
  - > 80 yo
  - Women > men
Multisystem disease
  - diabetes, thyroid, liver
Perioperative period
Major trauma
Electrolyte imbalance

Metabolic acidosis
Hypoxia
Infection
Large quantities of grapefruit juice
  - > 1 qt./day
Alcohol abuse
Drug interactions

Davidson MH. Am J Cardiol 2002;90 (suppl):50K-60K
Statins – Adverse Effects

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– Myopathy (0.5% of pts)
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– Cyp3A4 or CYP2C9 drug interactions with many statins
– Hepatotoxicity
CYP Enzymes

(from Guengerich 2003)
CYP3A4

**Inducers**
- Glucocorticoids
- Rifampin
- Phenytoin
- Carbamazepine

**Inhibitors**
- Nefazodone
- Fluvoxamine
- Ketoconazole
- Itraconazole
- Erthyromycin
- Sertraline
- Grapefruit juice

http://medicine.iupui.edu/flockhart/table.htm
Lipid Lowering Drugs and Cytochrome P450 System

Statin

Inhibitors

Liver Cyp 450 Enzymes

3A4

2C9

2C8

2D6

1A2

Increased blood concentration of statin or active metabolite

Risk of Muscle Toxicity
Statins – Adverse Effects

- Statins are *pregnancy category X*
- Rash, GI disturbances (dyspepsia, cramps, flatulence, constipation, abdominal pain)
- Myopathy (0.5% of pts)
  - Risk highest with lovastatin and especially in combination with Fibrates
- Cyp3A4 or CYP2C9 drug interactions with many statins
- Hepatotoxicity
Hepatotoxicity?

Hepatic transaminase elevations: occur in 0.5-2% and are dose dependant

Progression to liver failure specifically due to statins is exceedingly rare, if it ever occurs

No evidence exists showing exacerbation of liver disease when statins are given to patients with cholestasis and active liver disease

Statins may actually improve transaminase elevations in individuals with fatty liver

CHOLESTEROL ABSORPTION INHIBITORS

Ezetimibe
(依折麦布)
Net Cholesterol Balance in Humans

**Intestine**
- Dietary cholesterol (300 mg/day)
- Biliary cholesterol/Bile acids
- Fecal sterols (1100 mg/day)

**Liver**
- LDL
- VLDL
- LDL-R
- SR-BI
- HDL

**Extrahepatic tissues**
- LDL-R
- Chol
- Acetyl CoA

**Synthesized cholesterol (800 mg/day)**
Cholesterol Absorption Inhibitor (ezetimibe)

**Mechanisms:**
- Blocks cholesterol absorption at the intestinal brush border
- No effect on absorption of lipid-soluble vitamins
## Pharmacotherapy: Effect on Serum Lipids

<table>
<thead>
<tr>
<th>Drug class</th>
<th>LDL-C (% Δ)</th>
<th>HDL-C (% Δ)</th>
<th>TG (% Δ)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ezetimibe</td>
<td>↓ 18</td>
<td>↑ 1</td>
<td>↓ 8</td>
</tr>
<tr>
<td>Fibrates</td>
<td>↓ 5-20</td>
<td>↑ 10-35</td>
<td>↓ 20-50</td>
</tr>
<tr>
<td>Niacin</td>
<td>↓ 5-25</td>
<td>↑ 15-35</td>
<td>↓ 20-50</td>
</tr>
<tr>
<td>Resins</td>
<td>↓ 15-30</td>
<td>↑ 3-5</td>
<td>↑ /Neutral</td>
</tr>
<tr>
<td>Statins</td>
<td>↓ 18-60</td>
<td>↑ 5-15</td>
<td>↓ 7-30</td>
</tr>
</tbody>
</table>


Cholesterol Absorption Inhibitor (ezetimibe)

**Pharmacology and clinical uses**

- High LDL
- Intestinal wall localization
- Interruption of enterohepatic circulation (肝肠循环)
- Minimal systemic exposure and very well tolerated
- Additive in combination with statin
Ezetimibe+ Statin vs. Statin Titration

- **1-STEP COADMINISTRATION**
  - Statin – starting dose
  - 1st
  - 2nd
  - 3rd
  - 5%-6% 5%-6% 5%-6%

- **3-STEP TITRATION**
  - Statin – starting dose + Zetia
  - 10 mg
  - Doubling
  - 15%-18%

% Reduction in LDL-C
Bile Acid-Binding Resins (RESINS)

- Colestipol (考来替泊)
- Cholestyramine (考来烯胺)
- Colesevelam (考来维仑)
**Resins**

**Mechanisms:**

Binds to bile acid in the intestines, interrupting enterohepatic circulation and increasing fecal excretion:

↑ LDL receptors

**Efficacy:**

LDL ↓ 20-30%
Resins

Cholestyramine

- Polymer Backbone
  - Hydrophobic Side Chain
  - Primary Amines
  - Bound Bile Acid
  - Quaternary Amine Side Chains

Colesevelam
Resins

**Indications:**

High LDL

Can be used to relieve pruritis in patients who have cholestasis and bile salt accumulation; and/or to relieve diarrhea in post-cholecystectomy patients

They bind digitalis glycosides, the resins may be useful in digitalis toxicity.
Resins – Adverse effects

- Constipation
- Bloating, indigestion, nausea
- Large doses may impair absorption of fats or fat soluble vitamins (A, D, E, and K)
- Drug Interactions
  - Resins bind digoxin, warfarin, thiazide diuretics, tetracycline, thyroxine, iron salts, pravastatin, fluvastatin, folic acid, phenylbutazone, aspirin, ascorbic acid (these agents should be given 1 hour before the resin or 4 hours after)
NICOTINIC ACID (NIACIN)

Acipimox
Mechanisms

Suppresses synthesis of VLDL, IDL, & LDL in the liver.

Increases clearance of VLDL via the LPL pathway, ↑ TG catabolism

May ↓ HDL catabolism
Nicotinic Acid

Decreased VLDL Production

Liver

Other sites

CONVERSION

Increased VLDL clearance through LPL
Nicotinic Acid (Niacin, Vitamin B₃)

**Efficacy:**
- TC ↓ 25%
- LDL ↓ 10-25%
- HDL ↑ 10-40%
- TG ↓ 20-50%

**Indications:**
- High LDL (and/or VLDL)
- Combined hyperlipidemia (including low levels of HDL--Niaspan®, approved for elevating HDL levels)
Niacin – Adverse Effects

- Flushing
  - Harmless cutaneous vasodilation, VERY uncomfortable
  - Occurs after drug is started or ↑ dose
  - Lasts for the first several weeks
  - Relieved by giving aspirin 30 minutes before dosing

- Pruritis, rashes, dry skin

- Nausea and abdominal discomfort
  - Peptic disease
Niacin – Adverse effects

- Hepatotoxicity
  - Rare true hepatotoxicity occurs
  - Monitor liver functions regularly
  - Liver injury is less likely with Niaspan
- Hyperuricemia
  - Occurs in about 1/5 of pts
  - Occasionally precipitates gout
- Carbohydrate tolerance may be moderately impaired (hyperglycemia)
  - Reversible
  - Can be given to diabetics receiving insulin
FIBRIC ACID DERIVATIVES (FIBRATES)

Gemfibrozil and fenofibrate
Mechanisms

- Act as PPARα ligands (peroxisome proliferator-activated receptor-α, 过氧化物酶体增殖物激活受体α)
  - a nuclear receptor that regulates lipid metabolism and glucose homeostasis
  - ↑ FA oxidation in muscle and liver
- Apo CIII is key to ↑ VLDL catabolism. ↑ LPL, ↓ Apo CIII
  - ↑ clearance of VLDL by ↑ action of lipoprotein lipase, VLDL production ↓
  - ↓ Intracellular lipolysis in adipose tissue
Fibrates

**Efficacy:**

- LDL ± 10%
- HDL ↑ 10-25%
- TG ↓ 40-55%

**Indications:**

- High TG and/or low HDL
Fibrates – Adverse effects

- Rashes
- GI upset
- Gallstones (upper abdominal discomfort, intolerance of fried food, bloating)
  - ↑ biliary cholesterol saturation
  - Use with caution in pts with biliary tract disease
Fibrates – Adverse effects

- Displaces warfarin from plasma albumin since drug is highly protein bound.
- Will increase risk of statin-induced myopathy when used together (rhabdomyolysis has occurred rarely)
- Avoided in patients with hepatic or renal dysfunction
# Pharmacotherapy: Effect on Serum Lipids

<table>
<thead>
<tr>
<th>Drug class</th>
<th>LDL-C (% Δ)</th>
<th>HDL-C (% Δ)</th>
<th>TG (% Δ)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ezetimibe</td>
<td>↓ 18</td>
<td>↑ 1</td>
<td>↓ 8</td>
</tr>
<tr>
<td>Fibrates</td>
<td>↓ 5-20</td>
<td>↑ 10-35</td>
<td>↓ 20-50</td>
</tr>
<tr>
<td>Niacin</td>
<td>↓ 10-25</td>
<td>↑ 10-40</td>
<td>↓ 20-50</td>
</tr>
<tr>
<td>Resins</td>
<td>↓ 15-30</td>
<td>↑ 3-5</td>
<td>↑ /Neutral</td>
</tr>
<tr>
<td>Statins</td>
<td>↓ 18-60</td>
<td>↑ 5-15</td>
<td>↓ 7-30</td>
</tr>
</tbody>
</table>

## Summary of Clinical Effects

### Lipid-lowering agents

<table>
<thead>
<tr>
<th>Drug</th>
<th>Effect on LDL “bad cholesterol”</th>
<th>Effect on HDL “good cholesterol”</th>
<th>Effect on triglycerides</th>
</tr>
</thead>
<tbody>
<tr>
<td>HMG-CoA reductase inhibitors</td>
<td>↓↓↓↓</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>(lovastatin, pravastatin, simvastatin, atorvastatin)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Niacin</td>
<td>↓↓</td>
<td>↑↑</td>
<td>↓</td>
</tr>
<tr>
<td>Bile acid resins (cholestyramine, colestipol)</td>
<td>↓↓</td>
<td>—</td>
<td>Slightly ↑</td>
</tr>
<tr>
<td>Cholesterol absorption blocker (ezetimibe)</td>
<td>↓↓</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>“Fibrates” (gemfibrozil, clofibrate, bezafibrate, fenofibrate)</td>
<td>↓</td>
<td>↑</td>
<td>↓↓↓↓</td>
</tr>
</tbody>
</table>
## Summary of Side Effects

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resins</td>
<td>Unpalatability, bloating, constipation, heartburn</td>
</tr>
<tr>
<td>Nicotinic acid</td>
<td>Flushing, nausea, glucose intolerance, abnormal liver function tests</td>
</tr>
<tr>
<td>Fibrates</td>
<td>Nausea, skin rash</td>
</tr>
<tr>
<td>Statins</td>
<td><strong>Myositis</strong>, myalgia, elevated hepatic transaminases</td>
</tr>
<tr>
<td>CAIs</td>
<td>Transaminitis, transient diarrhea</td>
</tr>
</tbody>
</table>

Non-pharmacologic measures for cholesterol reduction

<table>
<thead>
<tr>
<th>Dietary Component</th>
<th>Dietary change</th>
<th>LDL Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saturated Fat</td>
<td>&lt; 7% kcal</td>
<td>8-10%</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>&lt; 200mg/day</td>
<td>3-5%</td>
</tr>
<tr>
<td>Weight Reduction</td>
<td>Lose 10 lbs.</td>
<td>5-8%</td>
</tr>
<tr>
<td>Viscous Fiber</td>
<td>5-10g/day</td>
<td>3-5%</td>
</tr>
<tr>
<td>Sterol/stanol esters</td>
<td>2g/day</td>
<td>6-15%</td>
</tr>
<tr>
<td>Cumulative</td>
<td></td>
<td>20-30%</td>
</tr>
</tbody>
</table>
References


Lipincott’s illustrated reviews—pharmocology (2nd edition), 2002

《药理学》，杨世杰主编，人民卫生出版社，2005

《基础医学教程各论》，陈季强主编，科学出版社，2004