Lipid-Lowering Agents

Edward JN Ishac, Ph.D.

Department of Pharmacology and Toxicology
Medical College of Virginia
Campus of Virginia Commonwealth University
Richmond, Virginia, USA

Smith Building, Room 742
eishac@hsc.vcu.edu
828-2127

Agents used in the treatment of HT, CHF, Arrhythmia and Angina

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Hypertension</th>
<th>CHF</th>
<th>Arrhythmia</th>
<th>Angina</th>
<th>Contraindications/Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-Blockers</td>
<td>☑ ☑ ☑ ☑</td>
<td>☑</td>
<td>☑ ☑ ☑ ☑ ☑</td>
<td>☑ ☑ ☑</td>
<td>Caution: CHF (unstable CHF, bronchospasm, significant bradycardia), or in diabetes, asthma (use β1-selective), depression</td>
</tr>
<tr>
<td>Ca2+-Channel Blockers</td>
<td>☑ ☑ ☑ ☑ ☑</td>
<td>☑</td>
<td>☑ ☑ ☑ ☑ ☑</td>
<td>☑ ☑ ☑</td>
<td>CHF, Gingival hyperplasia, reflex tachycardia, constipation</td>
</tr>
<tr>
<td>ACEI / ARBs</td>
<td>☑ ☑ ☑ ☑</td>
<td>☑</td>
<td>☑ ☑ ☑ ☑ ☑</td>
<td>☑ ☑ ☑</td>
<td>Low GFR, renal failure, glosisitis, tetradenic, cough (ACEI), taste, Trenal mechanisms</td>
</tr>
<tr>
<td>Diuretics</td>
<td>☑ ☑ ☑ ☑</td>
<td>☑</td>
<td>☑ ☑ ☑ ☑ ☑</td>
<td>☑ ☑ ☑</td>
<td>Low GFR, hypokalemia → CHF; glucose intolerance → Diabetes</td>
</tr>
<tr>
<td>Cardiac glycosides</td>
<td>☑ ☑ ☑ ☑</td>
<td>☑</td>
<td>☑ ☑ ☑ ☑ ☑</td>
<td>☑ ☑ ☑</td>
<td>Many Rx interactions, low TI, K+, important, low K+ → toxicity</td>
</tr>
<tr>
<td>Vasodilators</td>
<td>☑ ☑ ☑ ☑</td>
<td>☑</td>
<td>☑ ☑ ☑ ☑ ☑</td>
<td>☑ ☑ ☑</td>
<td>Flushing, diazois, headache, reflex tachycardia, combo Rx</td>
</tr>
<tr>
<td>Na+-Channel blockers</td>
<td>☑ ☑ ☑ ☑</td>
<td>☑</td>
<td>☑ ☑ ☑ ☑ ☑</td>
<td>☑ ☑ ☑</td>
<td>Effects enhanced in depolarized tissue, damaged tissue: Phase 0</td>
</tr>
<tr>
<td>Nitrates</td>
<td>☑ ☑ ☑ ☑</td>
<td>☑</td>
<td>☑ ☑ ☑ ☑ ☑</td>
<td>☑ ☑ ☑</td>
<td>Tolerance, flushing, diazois, headache, reflex tachycardia</td>
</tr>
</tbody>
</table>

Leading Causes of Death in the U.S

<table>
<thead>
<tr>
<th>Cause</th>
<th>2000 Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart Disease</td>
<td>1,000,000</td>
</tr>
<tr>
<td>Cancer</td>
<td>750,000</td>
</tr>
<tr>
<td>Respiratory Disease</td>
<td>500,000</td>
</tr>
<tr>
<td>Accidents</td>
<td>250,000</td>
</tr>
<tr>
<td>Diabetes</td>
<td>250,000</td>
</tr>
<tr>
<td>Influenza</td>
<td>100,000</td>
</tr>
<tr>
<td>Alzheimer's Disease</td>
<td>100,000</td>
</tr>
</tbody>
</table>

Data NIH 2000

Relative Risk for CHD vs Total Cholesterol

Abbreviations and Definitions (Lipids)

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>TG</td>
<td>Triglyceride</td>
</tr>
<tr>
<td>FFA</td>
<td>Free Fatty Acids</td>
</tr>
<tr>
<td>C</td>
<td>Cholesterol</td>
</tr>
<tr>
<td>CE</td>
<td>Cholesterol ester</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>VLDL</td>
<td>Very Low Density Lipoprotein</td>
</tr>
<tr>
<td>IDL</td>
<td>Intermediate Density Lipoprotein</td>
</tr>
<tr>
<td>CM</td>
<td>Chylomicrons</td>
</tr>
<tr>
<td>LDL</td>
<td>Low Density Lipoprotein</td>
</tr>
<tr>
<td>HDL</td>
<td>High Density Lipoprotein</td>
</tr>
</tbody>
</table>

### Abbreviations and Definitions (Lipoproteins)

- **VLDL** [very-low-density lipoprotein] [TG / CE] Apo B-100 [ATH]
- **IDL** [intermediate-density lipoprotein] [TG / CE] Apo B-100 [very ATH]
- **LDL** [low-density lipoprotein] [TG / CE] Apo B-100 [very ATH]
- **HDL** [high-density lipoprotein] [C / CE] Apo A, C, E [non-ATH]
- **CM** [chylomicrons] [TG / CE] Apo B-48 [non-ATH]

### Relative size, density and TG/Chol ratio of different lipoproteins

- **Chylomicron**: 95% TG, 5% Chol
- **HDL**: 5% TG, 95% Chol
- **LDL**: 10% TG, 90% Chol
- **IDL**: 50% TG, 50% Chol
- **VLDL**: 80% TG, 20% Chol

### Abbreviations and Definitions (Apoproteins)

- **CII apoprotein CII**: lipoprotein lipase activator [HDL]
- **A-1 apoprotein A-1**: LCAT cofactor [HDL]
- **E apoprotein E**: required for LP binding to receptors [HDL]
- **B-48 apoprotein B-48**: structural apo for CMs
- **B-100 apoprotein B-100**: structural apo for VLDL, IDL, LDL

### Abbreviations and Definitions (Enzymes)

- **LPL**: Lipoprotein [TG] Lipase $\Rightarrow$ FFA [VLDL, CM]
- **HMG-CoA Reductase**: Rate limiting step C synthesis
- **CETP**: Cholesterol ester transfer protein (HDL) CE [HDL] exchanged for TG in lipoproteins
- **LCAT**: Lechitin:Cholesterol Acpyltransferase (HDL) takes up lipoprotein C and $\Rightarrow$ CE for CETP

### Atherosclerosis

**Significance:** Major cause of death in U. S.

**Pathogenesis:**
Injury to blood vessel and infiltration of LDL and platelets. Formation of foam cells when LDL (oxidized) is internalized. Blood vessel is narrowed by plaque and blood clot reduces blood flow to brain (stroke) and heart (heart attack).
Atherosclerosis Timeline

Adapted from Pepine CJ. *Am J Cardiol.* 1998;82(suppl 104).

Atherosclerosis

Risk Factors:
- Hypertension
- Age
- Obesity
- Diabetes
- High fat diet
- Smoking
- Stress
- Low HDL
- Lack of exercise
- Family history
- High levels of VLDL, IDL, and LDL.

Treatment: appropriate diet and drugs lowers mortality and morbidity 20 to 40%.

Lipoprotein Metabolism I

Apo CII & E on HDL
Transfer To CM & VLDL
↑ CMs
↑ CMRs

Intestine → CMs — [LPL] → CMRs → Liver [non-ATH]

Lipoprotein Metabolism II

Factors Increasing HDL Levels

Exercise
- Moderate Alcohol Intake
- Weight Reduction (overweight)
- Stop Smoking
- Lipid-lowering drugs
  (Resins, Statins, Fibrates, Ezitimibe & Niacin)

Increased HDL levels are antiatherogenic
HDL enhances the clearance of LPs and Cholesterol
Primary Hyperlipidemia (fasting blood sample)

Hypertriglyceridemia (TG 400-2,000 mg%) [PA= pro-atherosclerosis]
1. Increased CMs (low LPL), non-atherogenic
2. Increased CMs and VLDLs (low LPL & increased VLDL production) [PA]
3. Increased VLDL (increased VLDL production and decreased LPL) [PA]
4. Increased IDL & CM remnants (decreased clearance, low apo E) [PA]

Hypercholesterolemia (C 250-800 mg%)
1. Increased VLDL and LDL (increased VLDL production) [PA]
2. Increased LDL (increased LDL production and decreased LDL clearance) ↓ LDL receptors in genetic disorders, 50% heterozygote and 100% homozygote) [PA].

Secondary Hyperlipidemia

Hypertriglyceridemia (VLDL)
Diabetes, oral contraceptives (estrogen), hypothyroidism, hypopituitarism, high sugar diet and high alcohol intake (increased production and decreased clearance of VLDL).

Hypercholesterolemia (LDL)
High cholesterol (fat) diet, hypopituitarism and hypothyroidism (decreased LDL receptors).

Resins - MOA
Resins: Colestipol, Cholestyramine and Colesevelam
1. Bind bile salts and block enterohepatic cycle of bile acids.
2. Lower cellular cholesterol content by increasing bile acid synthesis.
3. Increase LDL receptors in liver.
4. Rise in receptor-mediated endocytosis of LDL lowers plasma LDL levels.
5. Increase in cholesterol biosynthesis (bad).
6. Increase in plasma VLDL levels (bad) [do not use in patients with elevated VLDL]
7. Modest increase in HDL levels (10%) [good]

MAO of Resins and Statins

Normal
Cholestyramine
Colestipol
Colesevelam + Statins

Beneficial Effects of Resins

Lower LDL levels about 15 to 25%
Increase HDL levels about 10%
Relatively safe drugs (no systemic absorption)
Good combo agents with statins
Decreases morbidity and mortality of CAD

Adverse Effects of Resins

Gritty bad taste, patients don’t like
Increase cellular cholesterol biosynthesis
Increase plasma VLDL levels (do not use in patients with ↑ VLDL).
GI: nausea, constipation, bloating (less with Colesevelam [Welchol])
Decreases absorption of other agents
- fat soluble vitamins A, D, E & K
- aspirin, thiazides, digoxin, phenobarbital
Statins - MOA
Statins: Fluvastatin, Rosuvastatin, Pravastatin, Lovastatin, Simvastatin and Atorvastatin.
1. Competitive inhibitors of HMG-CoA reductase which regulates cholesterol formation.
2. Decreased cellular cholesterol level increases LDL receptors.
3. Rise in receptor-mediated endocytosis of LDL lowers plasma LDL levels (15-50%)
4. Modest increase in HDL levels (10%)
5. Statins + Resins are good combination for lowering elevated LDL levels.
6. Atorvastatin and simvastatin also lower VLDL.

Beneficial Effects of Statins
Lower plasma LDL levels, best agents (15 to 50%)
Increase plasma HDL levels (10%)
Atorvasatin & Simvastatin also lower plasma VLDL
ComboRx with Resins to lower plasma LDL
Reduce morbidity and mortality of CAD

Adverse Effects of Statins
May produce headaches, rashes and myopathy (muscle damage)
May cause rhabdomyolysis (muscle wasting) and liver injury (high doses). Monitor liver function.
Rhabdomyolysis potentiated with Gemfibrozil (avoid).
Caution: elderly, women (Cl: pregnancy), children, hypothyroid, renal and liver dysfunction and drug interactions (reduced metabolism).

Potency of Statins
Statin dose required to lower LDL 30 to 35%
Atorvastatin [10 mg] = Rosuvastatin [10 mg] >
Simvastatin [20 mg] < Pravastatin [40 mg] =
Lovastatin [40 mg] < Fluvastatin [80 mg]
Atorvastatin and Rosuvastatin are most potent statins
Best if taken evenings with food

Differences in dosages and expected effects of HMG CoA reductase inhibitors¹

<table>
<thead>
<tr>
<th>Drug</th>
<th>FDA-approved dosage</th>
<th>Usual decrease in LDL-C</th>
<th>30 Day Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lovastatin</td>
<td>Initial: 10 mg once</td>
<td>25-30%</td>
<td>69.60</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>Initial: 20 mg once</td>
<td>35-40%</td>
<td>112.20</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>Initial: 20 mg once</td>
<td>25-32%</td>
<td>69.60</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>Initial: 20 mg once</td>
<td>20-25%</td>
<td>41.40</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>Initial: 10 mg once</td>
<td>35-40%</td>
<td>57.30</td>
</tr>
<tr>
<td>Cerivastatin</td>
<td>Initial: 0.4 mg once</td>
<td>34-38%</td>
<td>45.90</td>
</tr>
</tbody>
</table>

¹Drugs of Choice from Medical Letter, 14th Edition
**Ezetimibe - MOA**

1. Inhibits cholesterol absorption in intestinal cells.
2. Reduce cholesterol transport system in intestinal cell wall.
3. Reduces cholesterol absorption by more than 50%.
4. Reduces LDL by 18%.
5. Increases HDL by about 3%.
6. Ezetimibe enhanced the lipid-lowering effects of statins.
7. In combination with statins enhances the reductions in LDL and VLDL. Less statin required to significantly lower LDL and VLDL.
8. Dosage: 10 mg oral dose alone or combo with statins.

**Beneficial Effects of Ezetimibe**

- Reduces Plasma LDL (18%)
- Reduces Plasma VLDL (5%)
- Increases Plasma HDL (3%)
- Enhances the lipid-lowering effects of statins.
- No adverse effects identified (safe drug??)

**Niacin (Nicotinic Acid and Vitamin B3 )**

1. Decrease VLDL production by inhibiting adipose tissue lipolysis.
2. Increase VLDL clearance by increasing LPL activity.
3. Lowers IDL and LDL production and content.
4. Increases HDL levels (20-50%) best agent for increasing HDL.
5. Lipoproteins: Lowers VLDL, IDL and LDL

Dose: 2-6 g oral dose given daily in divided doses (start low) with meals.

**Beneficial Effects of Niacin**

- Lowers Plasma VLDL (primary), IDL and LDL.
- Increases Plasma HDL (20 to 50%) [best HDL stimulator]
- Reduces morbidity and mortality of CAD

**Adverse Effects of Niacin**

- GI distress, flushing (involves PG’s, reduced if aspirin taken just prior), rashes and itching
- Potentiates gout (decrease uric A. secretion), diabetes and peptic ulcers
- May produce liver injury
**Fibrates - MOA**

Gemfibrozil, Fenofibrate, Clofibrate

1. Decrease VLDL production by inhibiting adipose tissue lipolysis
2. Increase VLDL (TG’s) clearance by increasing LPL activity (best agent).
3. Lowers IDL and LDL production and content.
4. Increase HDL levels (20-30%).
5. Lipoproteins: Lowers VLDL (TG’s), IDL and LDL.

Dosage: oral dose 1 to 2 times per day gemfibrozil (600 mg) fenofibrate (67 mg), fenofibrate is more potent than gemfibrozil.

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**Beneficial Effects of Gemfibrozil, Clofibrate & Fenofibrate**

- **Lower Plasma VLDL (primary), IDL and LDL.**
- **Greatest decrease in plasma TG’s**
- **Increase Plasma HDL (20 to 30%)**
- **Reduces morbidity and mortality of CAD**
- **Fenofibrate is more potent than Gemfibrozil**

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**Adverse Effects of Fibrates**

- GI distress, rashes and headaches
- May produce liver injury
- Gemfibrozil potentiates myopathy with Statins, combination should be avoided
- Fenofibrate is safer to use with statins
- May increase risk of gallstones

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**MAO of Niacin, Gemfibrozil & Fenofibrate**

Inhibit fat cell lipolysis which decreases VLDL, IDL and LDL biosynthesis. Increases VLDL clearance by increasing LPL.

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**Lipid-Lowering Agents - Summary**

<table>
<thead>
<tr>
<th></th>
<th>LDL</th>
<th>HDL</th>
<th>TGs</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Resins</strong></td>
<td></td>
<td></td>
<td></td>
<td>Hate it, gritty, GI discomfort, constipation, ↑ LDL-Rec., ↑↑ LDL, ↓ absp. fat sol. Vits.</td>
</tr>
<tr>
<td><strong>Statins</strong></td>
<td></td>
<td></td>
<td></td>
<td>Liver toxicity, myopathy, ↓ mylination CII, pregnancy, children. ↑↑ LDL-Rec.</td>
</tr>
<tr>
<td><strong>Niacin</strong></td>
<td></td>
<td></td>
<td></td>
<td>Flushed face (&lt;aspirin&gt;), GI, glucose intolerance, gout, liver toxicity, ulcer, diabetes</td>
</tr>
<tr>
<td><strong>Fibrates</strong></td>
<td></td>
<td></td>
<td></td>
<td>Nausea, skin rash, headache, ↑ statin myopathy, gallstones. ↑ LDL synthesis</td>
</tr>
<tr>
<td><strong>Ezetimibe</strong></td>
<td></td>
<td></td>
<td></td>
<td>Newest class: No major adverse effects noted</td>
</tr>
</tbody>
</table>
Who Should Be Treated With Drugs?

LDL levels > 190 mg/dl and 0-1 risk factors.
LDL levels > 160 mg/dl and 2 or more risk factors.
CAD and LDL > 100 mg/dl.
Higher risk factors, more aggressive treatment

Risk Factors:
Smoking  obesity  diabetes
low HDL  family history of early CAD
hypertension  age

Primary Hypertriglyceridemia

<table>
<thead>
<tr>
<th>Lipoproteins</th>
<th>Diet</th>
<th>Drug</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chylomicrons</td>
<td>low fat</td>
<td>none</td>
<td>none</td>
</tr>
<tr>
<td>Cholumicrons &amp; VLDL</td>
<td>low fat, sugar &amp; alcohol, ↑PUFA</td>
<td>Niacin</td>
<td>none</td>
</tr>
<tr>
<td>VLDL</td>
<td>low sugar &amp; fat, ↑PUFA</td>
<td>Niacin none</td>
<td>Fibrates none</td>
</tr>
<tr>
<td>IDL</td>
<td>low fat, ↑PUFAs</td>
<td>Niacin</td>
<td>Fibrates none</td>
</tr>
</tbody>
</table>

Primary Hypercholesterolemia

<table>
<thead>
<tr>
<th>Lipoproteins</th>
<th>Diet</th>
<th>Drug</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>VLDL + LDL No Resins</td>
<td>Low fat ↑PUFAs</td>
<td>Fibrates Statsins + Ezetimibe</td>
<td>Statins + NA/Fenofibrate</td>
</tr>
<tr>
<td>VLDL No Gemfibrozil with Statins</td>
<td>Low fat ↑PUFAs</td>
<td>Resins Statins</td>
<td>Statins + NA/Fenofibrate</td>
</tr>
<tr>
<td>LDL</td>
<td>Low fat ↑PUFAs</td>
<td>Resins Statins</td>
<td>Statins + NA/Fenofibrate</td>
</tr>
<tr>
<td>LDL</td>
<td>Low fat ↑PUFAs</td>
<td>Resins Statins</td>
<td>Statins + NA/Fenofibrate</td>
</tr>
</tbody>
</table>

Atherosclerosis: An Inflammatory Disease

Apoproteins (Apolipoproteins)

A: a class of apolipoproteins, apo A-I, -II, -III, and -IV, that occur primarily in high-density lipoproteins (HDL) and in lesser amounts in chylomicrons; apo A-I is the activator of lecithin-cholesterol acyltransferase (LCAT), which forms cholesteryl esters in HDL.

B: a class of apolipoproteins recognized by specific cell-surface receptors that mediate endocytosis of lipoprotein particles; apo B-100 on very-low-density, intermediate-density, and low-density lipoproteins is recognized by LDL receptors on liver and extrahepatic cells; apo B-48 on chylomicrons is recognized by chylomicron remnant receptors on liver cells.

C: a class of apolipoproteins, apo C-I, -II, and -III, that occur in very-low-density and high-density lipoproteins and chylomicrons; apo C-II activates lipoprotein lipase, which hydrolyzes triglycerides for transfer from VLDL and chylomicrons to tissues.

D: now called A-III.

E: an apolipoprotein, apo E, that occurs in all classes of lipoproteins; it may be involved in the conversion of very-low-density to intermediate-density lipoprotein and its clearance from the circulation.

ApoA-1 (Milano)

The development of this investigational drug is an unusual story. About 30 years ago, researchers discovered 40 individuals in Limone Sul Garda in Northern Italy who appeared perfectly healthy, despite having very low levels of good cholesterol. Ordinarily, such people would have a high risk of heart disease, but these people did not. Intrigued, researchers wanted to find out why. Their studies revealed a variant in a protein known as Apolipoprotein A-I, which is a component of HDL. This variant was named ApoA-I Milano after the city of Milan, where the initial laboratory work was done.

ApoA-I Milano is being developed into a potential treatment for heart disease by Esperion Therapeutics Inc. (purchased by Pfizer). Esperion’s investigational treatment, designated ETC-216, is a recombinant version of ApoA-I Milano after the city of Milan, where the initial laboratory work was done. ApoA-I Milano is being developed into a potential treatment for heart disease by Esperion Therapeutics Inc. (purchased by Pfizer). Esperion’s investigational treatment, designated ETC-216, is a recombinant version of ApoA-I Milano combined with a phospholipid. After pre-clinical studies showed rapid removal of plaques from diseased arteries, scientists at Esperion came to Dr. Nissen to help them design a study to determine whether infusions of the ApoA-I Milano phospholipid complex could reverse coronary plaque buildup in patients with heart disease. All traced their origins to a common ancestor born in 1780.
Lipoprotein Subclasses

Cholesterol
Triglycerides
Chylomicrons
IDL
VLDL
Chylomicron Remnants
LDL
HDL2
HDL3
NON-HDL Cholesterol

Density (g/mL)

Diameter (nm)

5 10 20 40 60 80 1,000


Sites of Action

1. Resins
2. Statins
3. Niacin
4. Fibrates
5. Ezetimibe