Lipid-Lowering Agents

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

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Hyper-tension</th>
<th>CHF</th>
<th>Arrhythmia</th>
<th>Angina</th>
<th>Contraindications/Cautions/Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-Blockers</td>
<td></td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>Caution: CHF (unstable CHF, bronchospasm, significant bradycardia); or in diabetes, asthma (use β1-selective), depression</td>
</tr>
<tr>
<td>Ca++-Channel blockers</td>
<td>3</td>
<td></td>
<td>3</td>
<td>3</td>
<td>CHF, Gingival hyperplasia, reflex tachycardia, constipation</td>
</tr>
<tr>
<td>ACEI / ARBs</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td></td>
<td>Low GFR, renal stenosis, glossitis, tetrogenic, cough (ACEI), taste, ↑renal mechanics</td>
</tr>
<tr>
<td>Diuretics</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td></td>
<td>Low GFR, hypokalemia → CG; glucose intolerance → diabetes</td>
</tr>
<tr>
<td>Cardiac glycosides</td>
<td></td>
<td></td>
<td></td>
<td>3</td>
<td>Many Rx interactions, low Ti, [K+] , important, low K+ → toxicity</td>
</tr>
<tr>
<td>Vasodilators</td>
<td>3</td>
<td>3</td>
<td></td>
<td></td>
<td>Flushing, dizziness, headache, reflex tachycardia, combo Rx</td>
</tr>
<tr>
<td>Na+ -Channel blockers</td>
<td>3</td>
<td></td>
<td>3</td>
<td></td>
<td>Effects enhanced in depolarized tissue, damaged tissue. Phase 0</td>
</tr>
<tr>
<td>Nitrates</td>
<td>3</td>
<td>3</td>
<td></td>
<td>3</td>
<td>Tolerance, flushing, dizziness, headache, reflex tachycardia</td>
</tr>
</tbody>
</table>

Leading Causes of Death in the U.S

Data NIH 2000
Relative Risk for CHD vs Total Cholesterol

Abbreviations and Definitions (Lipids)

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
<th>Metabolites</th>
</tr>
</thead>
<tbody>
<tr>
<td>TG</td>
<td>Triglyceride</td>
<td>VLDL, IDL, CM</td>
</tr>
<tr>
<td>FFA</td>
<td>Free Fatty Acids</td>
<td>TG, primary energy source</td>
</tr>
<tr>
<td>C</td>
<td>Cholesterol</td>
<td>VLDL, IDL, LDL, HDL, CM</td>
</tr>
<tr>
<td>CE</td>
<td>Cholesterol ester</td>
<td>VLDL, IDL, LDL, HDL, CM</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  [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

- Triglyceride
- Cholesterol

- HDL 5% TG 95% Chol
- LDL 10% TG 90% Chol
- IDL 50% TG 50% Chol
- VLDL 80% TG 20% Chol
- Chylomicron 95% TG 5% Chol
### Abbreviations and Definitions (Apoproteins)

<table>
<thead>
<tr>
<th>Apoprotein</th>
<th>Function</th>
<th>Lipoprotein Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>C&lt;sub&gt;II&lt;/sub&gt;</td>
<td>apoprotein C&lt;sub&gt;II&lt;/sub&gt;</td>
<td>lipoprotein lipase activator</td>
</tr>
<tr>
<td>A-1</td>
<td>apoprotein A-1</td>
<td>LCAT cofactor</td>
</tr>
<tr>
<td>E</td>
<td>apoprotein E</td>
<td>required for LP binding to receptors</td>
</tr>
<tr>
<td>B-48</td>
<td>apoprotein B-48</td>
<td>structural apo for CMs</td>
</tr>
<tr>
<td>B-100</td>
<td>apoprotein B-100</td>
<td>structural apo for VLDL, IDL, LDL</td>
</tr>
</tbody>
</table>

### Abbreviations and Definitions (Enzymes)

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Function</th>
<th>Lipoprotein Class</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LPL</strong></td>
<td>Lipoprotein [TG] Lipase</td>
<td>TG $\Rightarrow$ FFA</td>
</tr>
<tr>
<td><strong>HMG-CoA Reductase</strong></td>
<td>Rate limiting step C synthesis</td>
<td></td>
</tr>
<tr>
<td><strong>CETP</strong></td>
<td>Cholesterol ester transfer protein (HDL)</td>
<td>CE [HDL] exchanged for TG in lipoproteins</td>
</tr>
<tr>
<td><strong>LCAT</strong></td>
<td>Lecithin:Cholesterol Acyltransferase (HDL)</td>
<td>takes up lipoprotein C and $\Rightarrow$ CE for CETP</td>
</tr>
</tbody>
</table>
Atherosclerosis

Significance: Major cause of death in U. S.

Pathogenesis:
Injury/inflammation 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).

Pathogenesis of Atherosclerosis

1. LDL CHOLESTEROL
2. PLATELET
3. MONOCYTE

Cell Injury  Cell Proliferation  Plaque Formation
Atherosclerosis Timeline

Foam Cells  Fatty Streak  Intermediate Lesion  Atheroma Plaque  Fibrous Plaque  Complicated Lesion/Rupture

Endothelial Dysfunction

From First Decade  From Third Decade  From Fourth Decade

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

Coronary Occlusion

Plaque lining the artery

Coronary artery with partial occlusion

When a clogged artery keeps the heart from getting enough blood and oxygen, angina can occur.
Surgical Treatment
(Coronary bypass, angioplasty, stents)

Atherosclerosis

Risk Factors:
- Hypertension
- Diabetes
- Stress
- Family history

age  obesity
high fat diet  smoking
low HDL  lack of exercise
High levels of VLDL, IDL  and LDL.

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

- APOPROTEIN B100
- CHOLESTEROL
- PHOSPHOLIPID
- CHOLESTEROL ESTER
- TG, apo CII, E
- AI & B48

**Lipoprotein Metabolism I**

<table>
<thead>
<tr>
<th>Exogenous Pathway</th>
<th>Endogenous Pathway</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dietary Fat</td>
<td>LDL ( \rightarrow ) LDL Receptors</td>
</tr>
<tr>
<td>Intestine</td>
<td>Liver</td>
</tr>
<tr>
<td>Chylomorome</td>
<td>LDL Remnant Receptors</td>
</tr>
<tr>
<td>Remnant</td>
<td>LDL Receptors</td>
</tr>
<tr>
<td>Liver</td>
<td>HDL Cholesteryl</td>
</tr>
<tr>
<td>LDL ( \rightarrow ) LPL Lipoprotein Lipase</td>
<td>LDL ( \rightarrow ) LPL Lipoprotein Lipase</td>
</tr>
<tr>
<td>FFA</td>
<td>FFA</td>
</tr>
<tr>
<td>ADIPOSE TISSUE AND MUSCLE</td>
<td>ADIPOSE TISSUE AND MUSCLE</td>
</tr>
<tr>
<td>Intestine ( \rightarrow ) CMs</td>
<td>Intestine ( \rightarrow ) CMs</td>
</tr>
<tr>
<td>[LPL]</td>
<td>[LPL]</td>
</tr>
<tr>
<td>CMRs</td>
<td>CMRs</td>
</tr>
<tr>
<td>Liver</td>
<td>Liver</td>
</tr>
<tr>
<td>[non-ATH]</td>
<td>[non-ATH]</td>
</tr>
</tbody>
</table>

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

MAO of Resins and Statins

- Normal
- Cholestyramine
- Colestipol
- Colesevelam
- + Statins
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 (higher doses). Monitor liver function
- alanine aminotransferase (ALT)
- aspartate aminotransferase (AST)
Rhabdomyolysis potentiated with Gemfibrozil (avoid).

Caution: elderly, women (CI: pregnancy), children, hypothyroid, renal and liver dysfunction and drug interactions (reduced metabolism).
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 enhances 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.

MAO of Resins, Statins & Ezetimibe

- Normal
- Cholestyramine
- + Statins
- + Ezetimibe
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 acid secretion), diabetes and peptic ulcers

May produce liver injury

Fibrates - MOA

Gemfibrozil, Fenofibrate, Clofibrate

1. Increase VLDL (TG’s) clearance by increasing LPL activity (best agent).
2. Decrease VLDL production by inhibiting adipose tissue lipolysis
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.
Beneficial Effects of Gemfibrozil, Clofibrate & Fenofibrate

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

Adverse Effects of Fibrates

GI distress (discomfort), 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
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></td>
</tr>
<tr>
<td>↓ Bile reabsorption</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholestyramine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Statins</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HMG-CoA reductase inh.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atorvastatin, lovastatin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Niacin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Nicotinic A. + Vit. B3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>↓ VLDL release, ↓</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lipolysis in adipose</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Fibrates</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lipoprotein lipase stim.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clofibrate, Gemfibrozil</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Inh. Cholesterol absorp.</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ezetimibe</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Notes:
- LDL: ↓ decrease, ↑ increase
- HDL: ↓ decrease, ↑ increase
- TGs:
- Hate it, gritty, GI discomfort, constipation, ↑ LDL-Rec., ↑ VLDL, ↓ absorption of fat-sol. vitamins.
- Liver toxicity, myopathy, ↓ myelination C: pregnancy, children. ↑ ↑ LDL-Rec.
- Flushed face (↓ aspirin), GI, glucose intolerance, gout, liver toxicity, ulcer, diabetes.
- Nausea, skin rash, headache, ↑ statin myopathy, gallstones. ↑ LDL synthesis.
- Newest class: No major adverse effects noted.
**Adult Treatment Guidelines (2001)**

<table>
<thead>
<tr>
<th></th>
<th>Desirable mg/dl</th>
<th>Borderline to high</th>
<th>High</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Cholesterol</td>
<td>&lt; 200</td>
<td>200-239</td>
<td>&gt; 240</td>
<td>High if &gt;160 mg/dl with coronary disease or more than 2 risk factors</td>
</tr>
<tr>
<td>LDL Cholesterol</td>
<td>&lt; 130</td>
<td>130-159</td>
<td>&gt; 160</td>
<td>Optimal &lt;100 mg/dl</td>
</tr>
<tr>
<td>HDL Colestrol: Men Women</td>
<td>&gt; 40, &gt; 50</td>
<td></td>
<td>&gt; 60</td>
<td></td>
</tr>
<tr>
<td>Triglycerides</td>
<td>&lt; 120-150</td>
<td>120-199</td>
<td>&gt; 200</td>
<td></td>
</tr>
</tbody>
</table>

**Risk Factors:** age > 45 (male) and 55 (females), family history of early vascular disease or hyperlipidemia, current cigarette smoking, elevated blood pressure, obesity and low HDL

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**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, no alcohol</td>
<td>none</td>
<td>none</td>
</tr>
<tr>
<td>Chylomicrons</td>
<td>low fat, sugar &amp; alcohol, ↑PUFAs</td>
<td>Niacin</td>
<td>Fibrates</td>
</tr>
<tr>
<td>VLDL</td>
<td>low sugar &amp; ↑PUFAs</td>
<td>Niacin</td>
<td>none</td>
</tr>
<tr>
<td>IDL</td>
<td>low fat, ↑PUFAs</td>
<td>Niacin</td>
<td>Fibrates</td>
</tr>
</tbody>
</table>

### Primary Hypercholesterolemia

<table>
<thead>
<tr>
<th>Lipoproteins</th>
<th>Diet</th>
<th>Drug</th>
<th>Drug Combination</th>
</tr>
</thead>
<tbody>
<tr>
<td>VLDL + LDL</td>
<td>Low fat, ↑PUFAs</td>
<td>Fibrates</td>
<td>Statins + Ezetimibe</td>
</tr>
<tr>
<td>No Resins</td>
<td></td>
<td>Statins</td>
<td>Statins + NA/Fenib</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Niacin</td>
<td>Stat + Ezet + NA/FB</td>
</tr>
<tr>
<td>LDL</td>
<td>Low fat, ↑PUFAs</td>
<td>Resins</td>
<td>Statins + Ezet/Fenof</td>
</tr>
<tr>
<td>No Gemfibrozil with Statins</td>
<td></td>
<td>Statins</td>
<td>Resins + NA/Fenof/Gemfibrozil</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Niacin</td>
<td>Resins + Statins and +NA/Fenofibrate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fibrates</td>
<td></td>
</tr>
</tbody>
</table>
## Polyunsaturated fatty acids (PUFAs)

<table>
<thead>
<tr>
<th>Alpha-Linolenic Acid (Omega 3 family)</th>
<th>Linoleic Acid (Omega 6 family)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fish oils</td>
<td>Vegetables</td>
</tr>
<tr>
<td>Flaxseeds (ie. linseeds)</td>
<td>Fruits</td>
</tr>
<tr>
<td>Mustard seeds</td>
<td>Nuts (ie. Walnuts)</td>
</tr>
<tr>
<td>Pumpkin seeds</td>
<td>Grains</td>
</tr>
<tr>
<td>Soya bean</td>
<td>Seeds (ie. Sunflower)</td>
</tr>
<tr>
<td>Walnut oil</td>
<td>Corn</td>
</tr>
<tr>
<td>Green leafy vegetables</td>
<td>Soya</td>
</tr>
<tr>
<td>Grains</td>
<td>Pumpkin</td>
</tr>
</tbody>
</table>

**Atherosclerosis: An Inflammatory Disease**

- **Cell adhesion and migration**
- **Inflammation**
  - Endothelial injury
  - LDL
  - Monocyte
  - Cytokines
  - Necrosis
  - Smooth muscle cell proliferation

- **Plaque**
  - LDL
  - Macrophage
  - Foam cell

- **Proteolytic enzymes**
- **RBC**
- **Platelet**

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