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>Hypertension</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></td>
<td></td>
<td></td>
<td>Caution: CHF (unstable CHF, bronchospasm, significant bradycardia); or in diabetes, asthma</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(use β1-selective), depression</td>
</tr>
<tr>
<td>Ca++-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 steatorrhea, gingivitis, laryngeal edema; cough (ACEI), taste, Flushing, dizziness</td>
</tr>
<tr>
<td>Diuretics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Low GFR, hypokalemia; hypokalemia; glucose intolerance</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, dizziness, 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, dizziness, headache, reflex tachycardia</td>
</tr>
</tbody>
</table>

Relative Risk for CHD vs Total Cholesterol

Abbreviations and Definitions (Lipids)

TG [Triglyceride] VLDL, IDL, CM

FFA [Free Fatty Acids] TG, primary energy source

C [Cholesterol] VLDL, IDL, LDL, HDL, CM

CE [Cholesterol ester] VLDL, IDL, LDL, HDL, CM
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]

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 TG ⇒ 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 Lecithin:Cholesterol Acyltransferase (HDL) takes up lipoprotein C and ⇒ 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).

Pathogenesis of Atherosclerosis
Cell Injury Cell Proliferation Plaque Formation
Atherosclerosis Timeline

- Foam Cells
- Fatty Streak
- Intermediate Atheroma
- 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

Surgical Treatment
(Coronary bypass, angioplasty, stents)

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%.

LDL Structure

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

Lipoprotein Metabolism I

Exogenous Pathway
- Intestine
- Liver
- HDL
- CMs
- CMRs

Endogenous Pathway
- Intestine
- Liver
- HDL
- CMs
- CMRs

Intestine → CMs → [LPL] → CMRs → Liver [non-ATH]
**Lipoprotein Metabolism II**

**Exogenous Pathway**
- Dietary Fat
- Liver
- Lipoprotein Lipase (LPL)
- VLDL
- IDL
- LDL
- HDL

**Endogenous Pathway**
- Liver
- VLDL
- IDL
- LDL
- HDL

Liver $\rightarrow$ VLDL $\rightarrow$ IDL $\rightarrow$ LDL $\rightarrow$ Tissues

**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
- 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).
Potency of Statins

<table>
<thead>
<tr>
<th>Statin dose required to lower LDL</th>
<th>30 to 35%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin [10 mg] = Rosuvastatin [10 mg]</td>
<td>&gt;</td>
</tr>
<tr>
<td>Simvastatin [20 mg] &lt; Pravastatin [40 mg]</td>
<td>=</td>
</tr>
<tr>
<td>Lovastatin [40 mg] &lt; Fluvastatin [80 mg]</td>
<td></td>
</tr>
<tr>
<td>Atorvastatin and Rosuvastatin are most potent statins</td>
<td></td>
</tr>
<tr>
<td>Best if taken evenings with food</td>
<td></td>
</tr>
</tbody>
</table>

Differences in dosages and expected effects of HMG CoA reductase inhibitors

<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></td>
<td>Maximum: 80 mg once</td>
<td>35-40%</td>
<td>247.80</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>Initial: 20 mg once</td>
<td>35-40%</td>
<td>112.20</td>
</tr>
<tr>
<td></td>
<td>Maximum: 80 mg once</td>
<td>45-50%</td>
<td>113.10</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>Initial: 20 mg once</td>
<td>25-32%</td>
<td>69.60</td>
</tr>
<tr>
<td></td>
<td>Maximum: 40 mg once</td>
<td>30-35%</td>
<td>112.50</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>Initial: 20 mg once</td>
<td>20-25%</td>
<td>41.40</td>
</tr>
<tr>
<td></td>
<td>Maximum: 40 mg b.i.d.</td>
<td>30-35%</td>
<td>82.80</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>Initial: 10 mg once</td>
<td>35-40%</td>
<td>57.30</td>
</tr>
<tr>
<td></td>
<td>Maximum: 80 mg once</td>
<td>50-60%</td>
<td>98.40</td>
</tr>
<tr>
<td>Cerivastatin</td>
<td>Initial: 0.4 mg once</td>
<td>34-38%</td>
<td>45.90</td>
</tr>
<tr>
<td></td>
<td>Maximum: 0.8 mg once</td>
<td>42-44%</td>
<td>68.40</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 VLDL by about 18%.
5. Increases LDL 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.

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

### Sites of Action

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

### 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

### 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

### 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.

### 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>Resins</th>
<th>HDL</th>
<th>LDL</th>
<th>TGs</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑ Bile reabsorption</td>
<td></td>
<td></td>
<td></td>
<td>Cholestyramine</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Statins</th>
<th>HDL</th>
<th>LDL</th>
<th>TGs</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>HMG-CoA reductase inh</td>
<td></td>
<td></td>
<td></td>
<td>Liver toxicity, myopathy, ↑mylination CI: pregnancy, children. ↑↑ LDL-Rec</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Niacin</th>
<th>HDL</th>
<th>LDL</th>
<th>TGs</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Nicotinic A. + Vit. B3)</td>
<td></td>
<td></td>
<td></td>
<td>Flushed face (Aspirin), GI, glucose intolerance, gout, liver toxicity, ulcer, diabetes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Fibrates</th>
<th>HDL</th>
<th>LDL</th>
<th>TGs</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipoprotein lipase stim.</td>
<td></td>
<td></td>
<td></td>
<td>Nausea, skin rash, headache, ↑ statin myopathy, gallstones. ↑ LDL synthesis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ezetimibe</th>
<th>HDL</th>
<th>LDL</th>
<th>TGs</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inh. Cholesterol absorp.</td>
<td></td>
<td></td>
<td></td>
<td>Newest class: No major adverse effects noted</td>
</tr>
</tbody>
</table>

Adult Treatment Guidelines (2001)

<table>
<thead>
<tr>
<th>Lipid</th>
<th>Desirable mg/dl</th>
<th>Borderline mg/dl</th>
<th>High mg/dl</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;160mg/dl with coronary disease or more than 2 risk factors</td>
</tr>
<tr>
<td>LDL Cholesterol</td>
<td>&lt;130</td>
<td>130-199</td>
<td>&gt;160</td>
<td>Optimal &lt;100mg/dl</td>
</tr>
<tr>
<td>HDL Cholesterol: Men</td>
<td>&gt; 40</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDL Cholesterol: Women</td>
<td>&gt; 50</td>
<td></td>
<td></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

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>none</td>
</tr>
<tr>
<td>VLDL</td>
<td>low sugar &amp; fat ↑PUFAs</td>
<td>Niacin</td>
<td>Fibrates</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>Drugs</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>↑PUFAs</td>
<td>Statins</td>
<td>Statins + NA/Fenofibrate</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/Fenofibrate</td>
</tr>
<tr>
<td>No Gemfibrozil</td>
<td>↑PUFAs</td>
<td>Resins</td>
<td>Resins + NA/Fenofibrate</td>
</tr>
<tr>
<td>with Statins</td>
<td></td>
<td>Statins</td>
<td>Gemfibrozil</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Niacin</td>
<td>Resins + Statins and</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fibrates</td>
<td>+NA/Fenofibrate</td>
</tr>
</tbody>
</table>