Pharmacotherapy of Dyslipidemia
KHOI NGUYEN LAM

<table>
<tr><td></td><td>Polygenic</td><td>Familial</td></tr>
<tr><td>Disease State Definition</td><td>• LDL above 160 or
• TG
• HDL below 40</td><td>• Autosomal dominant disorder
• Increase Tc, LDL
• Premature CAD
• Typically with first degree relative</td></tr>
<tr><td>Epidemiology</td><td>- 65 million quality for lifestyle changes
- 36 million for pharmacologic therapy</td><td>- 1/500 in US
- 1/67 Ashkenazi Jews
- 1/100 Afrikaners, South African Indians</td></tr>
<tr><td>Patho-physiology</td><td>- Susceptible genotype (no gene discovered)
- Aggravated by excessive saturated fat, trans fatty acid, cholesterol intake
- Elevated LDL production
- Decreased LDL cellular uptake
- Diet high in fat/cholesterol decrease LDL receptor on liver</td><td>- Absent or grossly malfunctioning LdL receptors
- Found on short arm of Chromosome 19
- 5 mutation types found</td></tr>
<tr><td>Clinical Presentation</td><td colspan="2">- None
- Premature Coronary artery disease (CAD)
- Metabolic Syndrome
o Abdominal obesity (♂ > 40”; ♀ > 35”)
o TG > 150
o BP > 135/85
o FPG > 110
o HDL (♂ < 40; ♀ <50)

- 2nd causes
o DM
o Hypothydoism
o Obstructive Liver Disease
o Chronic Renal Failure
o Drugs
▪ Progestin
▪ Steroids</td></tr>
<tr><td>Risk Factors</td><td colspan="2">- Of LDL
o Cigarette Smoking
o HTN (>140/90)
o HDL (< 40)
o Family Hx
o Age (♂ > 45; ♀ > 55)</td></tr>
<tr><td>Diagnosis</td><td colspan="2"><table>
<tr><td></td><td>Optimal</td><td>Above</td><td>Borderline High</td><td>High</td><td>Very High</td></tr>
<tr><td>LDL</td><td><100</td><td>100-130</td><td>130-160</td><td>160-190</td><td>>190</td></tr>
<tr><td>TG</td><td><150</td><td></td><td>150-200</td><td>200-500</td><td>>500</td></tr>
<tr><td>Total Chol</td><td><200</td><td></td><td>200-240</td><td>>240</td><td></td></tr>
<tr><td>HDL</td><td>>40</td><td colspan="3">LOW :: <40</td></tr>
</table></td></tr>
<tr><td>Desired Therapeutic Outcomes*

*Reference of Guidelines Used

(ATP 3)</td><td colspan="2"><table>
<tr><td>Risks</td><td>LDL Goal</td><td>When to Treat</td><td>When to Use Drugs</td></tr>
<tr><td>CHD,
CHD risks,
diabetes</td><td>100</td><td>> 100</td><td>> 130</td></tr>
<tr><td>2+ Risks Factors</td><td><130</td><td>> 130</td><td>> 130 (10-20% risk)
>160 (<10% risk)</td></tr>
<tr><td>0-1 Risk Factors</td><td><160</td><td>>160</td><td>>190</td></tr>
</table></td></tr>
</table>

Treatment Options** **(Non-drug and Drug Therapy – include all therapeutic classes/agents available and preferences per treatment guidelines)** *****See Treatment Options Table***	- Life Style Changes o Reduce Sat Fat o Eat Plant Stanols / Sterols (additive to margarines, salad dressin, mayonnaise) and Fiber o Wt Reduction o Increase physical activity - Statins (HMG-CoA Reductase Inhibitor o Lovastatin (Mevacor) o Atorvastatin (Lipitor) o Simvastatin (Zocor) o Cerivastatin (Baycol) d/c o Rosuvastatin (Crestor) o Fluvastatin (Lescol) o Pravastatin (Pravachol) - Nicotinic Acid o Niacin - Fibric Acid o Fenofibrate (Tricor) o Gemfibrozile (Lopid) o Clofibrate (d/c) - Bile Acid Sequestrates o Cholestyramine o Colestipol (Colestid) o Colesevelam (Welchol) - Ezetimibe - Combination Products o Lovastatin + Niacin (Advicor) o Atorvastatin + Amlodipine (Caduet) o Pravastatin + ASA (Pravigard Pac) o Simvastatin + Ezetimibe (Vytorin) o

Drugs	LDL	HDL	TG	Side Effects	ContraIndication	Results
Statins	55%	15%	30%	Myopathy ▲liver enzyme	chronic liver disease	▼CHD ▼mortality
Bile Acid Sequestrant	30%	5%	-	GI distress ▼ drug absorption	dysbeta-lipoproteinemia TG > 400	▼coronary events ▼CHD deaths
Nicotinic Acid	25%	35%	50%	flushing hyperglycemia hyperuricemia GI distress hepatotoxic	liver disease severe gout *diabetes* *hyperuricemia* *peptic ulcer*	▼coronary events ▼mortality
Fibric Acid	20%	20%	50%	Dyspepsia Gallstones Myopathy CHD death	renal disease hepatic disease	▼coronary events
2-azetidin	18%	±	8%	Diarrhea Fatigue Infection ▲liver enzyme	Liver disease	Unknown for mono therapy

Pharmacological Treatment Options for Dyslipidemia

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<table>
<tr><th></th><th>Statins</th><th>Fibric Acid</th></tr>
<tr><td>Product Availability Generic (Brand)</td><td>Lovastation (Mevacor, Altocor/Altoprave)
Simvastation (Zocor)
Atorvastatin (Lipitor)
Cerivastatin (Baycol)***d/c 2001
Rosuvastatin (Crestor)
Fluvastatin (Lescol)
Pravastatin (Pravachol)</td><td>Fenofibrate (Tricor)
Gemfibrozil (Lopid)
Clofibrate (d/c)</td></tr>
<tr><td>Mechanism of Action</td><td>• Analogue for cholesterol precursor (HMG CoA)
• Binds to HMG CoA Reductase and destroys it
• Gets lower LDL in blood stream
• By lowering LDL, increase LDL receptor on Liver
• More LDL is removed from plasma</td><td>• Binds to fat
• Block absorption
• Stops cholesterol synthesis
• Breaks down and remove chylomicron, VLDL</td></tr>
<tr><td>EFFICACY

(Indication/Use, Clinical Data Support)</td><td>• Decrease LDL (55%)
• Increase HDL (15%)
• Decrease TG (30%)
• Antiproliferation effects on smooth muscle cells
• Antioxidant
• Anti-inflammatory
<table><tr><th>@ Max Dose</th><th>@ 40mg</th></tr><tr><td>1. Crestor 40mg 63%
2. Lipitor 80mg 60%
3. Zocor 80mg 47%
4. Mevac 80mg 42% (BiD)
5. Altocor 60mg 41%
6. Pravachol 80mg 37 %
7. Lescol 80mg 36% (BiD)
8. Lescol XL 80mg 35%</td><td>1. Crestor 63%
2. Lipitor 50%
3. Zocor 41%
4. Altocor 36%
5. Pravachol 34%
6. Mevacor 31%
7. Lescol 25%</td></tr></table>
<table><tr><th></th><th>HDL (+)</th><th>TG</th><th>TC</th></tr><tr><td>Zocor</td><td>16%</td><td>33%</td><td>36%</td></tr><tr><td>Altocor</td><td>13%</td><td>25%</td><td>29%</td></tr><tr><td>Pravachol</td><td>12%</td><td>24%</td><td>27%</td></tr><tr><td>Lescol XL</td><td>11%</td><td>25%</td><td>25%</td></tr><tr><td>Lipitor</td><td>9%</td><td>37%</td><td>45%</td></tr><tr><td>Mevacor</td><td>9%</td><td>27%</td><td>34%</td></tr><tr><td>Lescol</td><td>9%</td><td>23%</td><td>27%</td></tr><tr><td>Crestor</td><td>4%</td><td>35%</td><td>46%</td></tr></table></td><td>• Decrease LDL (20%)
• Increase HDL (20%)
• Decrease TG (50%)</td></tr>
<tr><td>SAFETY

(Major Drug Interactions, Pre-cautions, Contra-indications, Adverse Effects, Pregnancy Risk Category)</td><td>• AE
o Rabdo myopathy (1/100K)
o Constipation, flatulence, dyspepsia, ab pain
o Blurred vision, angioedema
o Hepatitis, cholestasis, jaundice, cirrhosis, hep failure, pancreatitis.
o ED
o Infection, rhinitis, sinusitis, steve-johnson
• Interaction
o 3A4 substrate (amiodarone, barbiturates, St. John’s Wort, phenytoin, anti-retroviral protease inh, CaCB, fluconazole,
o 2C9 substrate for Fluvastatin (amiodarone, fluoxetine, zafirlukast, STI-571”Imatinib”, irbesartan “Avapro”,)
o Fluvastine (H2 antag, PPI)</td><td>• AE
o Dyspepsia 20%, ab pain 10%, diarrhea 7%, fatigue 4% (GEM)
o Similar to Placebo, abnormal LFT (FENO)
• Interaction
o Warfarin, increase INR (FENO)
o Antidiabetic agents, hypoglycemia, incr insulin sensitivity, decr glucagon secretion
o GEM, Bile Acid Seq, take two hours apart
o Cyclosporine, increase nephrotoxicity
o Ezetimibe, (w/GEM, ?, cause cholelithiasis)
o Statins, incr Rabdo
• Precaution
o EtOH
• Contraindication
o Hepatic disease</td></tr>
</table>

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<table>
<tr><th></th><th>Statins</th><th>Fibric Acid</th></tr>
<tr><td></td><td>

o Except Pravastatin, Rosuvastatin
o Antacid (decr plasma Conc)
o Bile Acid Seq (decr plasma Conc)
o Cyclosporin (Myopathy)
o Digoxin toxicity (80mg/QD strength)
o Erythomycin, Clarithromycin (Myopathy)
o Exenatide (AUC, Cmax decr, clinical relevance unknown)
o Fibric Acid (Myopathy)
o Other Statins
o Oral Contraceptives (Lipitor, Crestor)
o Glitazone (Lipitor)
o Repaglinide “Prandin” (Zocor) incr Prandin SE
o Warfarin (Lovastatin, Fluvastatin, Crestor, Zocor) inc INR
o GRAPEFRUIT
• Precaution

o EtOH
o Asians (Crestor) – 2X plasma
o DM (renal dx)
o Elderly
o Renal defficient
o Hepatic deficient

• Contraindication

o Alcoholism
o Hepatic Disease
o Manitol hypersensitivity (Baycol)

• Pregnancy = X

</td><td>

o Gallbladder (GEM, not strong w/FENO)
o Renal Dx
• Pregnancy :: C Fenofibrate
• Pregnancy :: B Gemfibrozil

</td></tr>
<tr><td>Dosage & Administration

(Include renal and/or hepatic adjustments)</td><td>
<table>
<tr><th></th><th>Dosages</th><th>Children</th><th>Renal</th><th>Hep</th></tr>
<tr><td>Lipitor</td><td>10, 20, 40, 80</td><td>>10, 20 max</td><td>--</td><td>NO</td></tr>
<tr><td>Baycol</td><td>0.2,0.4, 0.8</td><td>--</td><td>CrCl ≤ 60; 0.2-0.3</td><td>NO</td></tr>
<tr><td>Lescol</td><td>20, 40, 80</td><td>>10</td><td>--</td><td>NO</td></tr>
<tr><td>Mevacor</td><td>10, 20, 40, 80</td><td>>10, 40 max</td><td>CrCl < 30; 20 max</td><td>NO</td></tr>
<tr><td>Pravachol</td><td>10, 20, 40, 80</td><td>14-18, 40 max
8-13, 20 max</td><td>Start at 10</td><td>NO</td></tr>
<tr><td>Crestor</td><td>5, 10, 20, 40</td><td>--</td><td>CrCl < 30; 10 max</td><td>NO</td></tr>
<tr><td>Zocor</td><td>10, 20, 40, 80</td><td>>10, 40 max</td><td>CrCl ≤ 20, 5 w/ monit</td><td>NO</td></tr>
</table>
</td><td>
<table>
<tr><th></th><th>Dosages</th><th>Renal</th><th>Hep</th></tr>
<tr><td>Tricor</td><td>48, 54, 67, 134, 145, 160, 200</td><td>CrCL ≤ 10 = NO
CrCL 11-49 = 48-67mg</td><td>NO</td></tr>
<tr><td>Lopid</td><td>600</td><td>CrCL ≤ 10 = NO
CrCL 10-50 no recommended but use with caution</td><td>NO</td></tr>
</table>
</td></tr>
<tr><td>Monitoring</td><td>• LFT (prior, 12wks)</td><td>• Efficacy :: Lipids
• Toxicity :: CPK (creatine phoshokinase, LFTs, serum bilirubin</td></tr>
<tr><td>Patient Education</td><td>• Take 2 hr apart from antacid</td><td>• Tell your dr other medications you’re taking
• Cause blurred vision, dizziness (careful when driving)</td></tr>
<tr><td>Cost</td><td>Lipitor 40mg = $167.90
Lescol
Lovastatin 40mg = $62.90
Pravachol 40mg = $147.03
Crestor 40mg = $116.57
Zocor Simvastatin</td><td>Gemfibrozil = $49.57
Tricor = $162.00</td></tr>
<tr><td>References</td><td>• Clinical Pharmacology
• Drug Insert
ATP 3</td><td>• Clinical Pharmacology
• Drug Insert
ATP 3</td></tr>
</table>

Pharmacological Treatment Options for Dyslipidemia

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	2-azetidinone compound	Nicotinic Acid	Bile Acid Sequesterates
Product Availability Generic (Brand)	Ezetimibe (Zetia)	Niacin, B3, Niaspan, Slo-Niacin 60mg Tryptophan = 1mg Niacin	Cholestyramine Colestipol (Colestid) Colesevelam (Welchol)
Mechanism of Action	Inhibit dietary cholesterol from absorbing into small intestines Allows fat soluble Vits to absorb Synergistic with statins	Stops the breakdown of TG in adipose tissue Together with riboflavin and other micronutrients, convert fats and proteins to glucose	Binds to bile acids that the liver excrete out Prevents it's reabsorption Liver need to make more bile acids LDL receptors are upregulated More LDL are taken out of plasma
EFFICACY **(Indication/Use, Clinical Data Support)**	• Mono therapy • Decrease LDL (18%) • Increase HDL (±) • Decrease TG (8%)	• Decrease LDL (25%) • Increase HDL (35%) • Decrease TG (50%) • Increase blood flow • Dilate blood vessels	• Decrease LDL (30%) • Increase HDL (5%) • Decrease TG (0/+) • Clostridium difficile • Not absorbed, safer toxicity profile • Especially for women and children • Diarrhea • Digoxin overdose (colestipol)
SAFETY **(Major Drug Interactions, Pre-cautions, Contra-indications, Adverse Effects, Pregnancy Risk Category)**	• AE (20%>placebo, >2%) o Fatigue o Diarrhea o Viral infection o Sinusitis o Cholecystitis, choletithiasis, pancreatitis, thrombocytopenia (post market) • Not recommended co-admin o Clofibrate (cholelithiasis) o Gemfibrozil (cholelithiasis) o Bile Acid Sequestrants – decr (80%) conc o Cyclosporine – incr (50%) conc • Precaution o Hepatic Dx • Pregnancy Cat :: C •	• AE o Flush o HA/migraines o hyperglycemia o Hepatotoxicity o Hypotension o Hyperuricemia o Bleeding o GI • Contraindication o Bleeding o Hepatic dx o Peptic ulcer dx o Rhabdo o Alcoholics o Gallbladder dx • Not recommended co-admin o Antidiabetic agents o Statins o Warfarins o vasodilators • Precaution o People who receive vasodilators o DM (not take) o Anticoag therapy • Pregnancy Cat :: C	• AE o Decrease absorption of Vit A, D, E, K o Ab pain, anorexia, bleeding, constipation, GI obstruction, asthenia, • Contraindication o Biliary cirrhosis o Biliary obstruction o Cholelithiasis o GI obstruction o Phenylketonuria (cholestyramine) o Coagulation therapy (binds to Vit K) o Hypothyroidism (binds to thyroid) • Interaction o Decrease absorption (furosemide, penicillin, propranolol, tetracycline, Vit A, K, D, vancomycin, thiazide, glipizide, NSAIDs, digitoxin, ezetimibe, • Pregnancy Cat :: C • Pregnancy Cat :: B (Colesevelam, Cholestyramine)
Dosage & Administration	• Dosage o 10mg QD • Renal Dosing o none • Hepatic Dosing o none	• Dosage o 250mg QD → 1g TiD o Max = 6g/d (rapid release) o Max Niaspan 2g/d • Renal Dosing o Not available • Hepatic Dosing o Do not use	• Dosage o Cholestyramine 4g BiD (max 24g/d) o Colesevelam 625mg, 3Tabs BiD (max 7 tabs/d) o Colestipol 5g QD, increase 1-2 months (max 30g/d) • Renal Dosing :: none • Hepatic Dosing :: none

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Pharmacotherapy Presentation – Pharmaceutical Care Rotation
Happy Harry's Pharmacy Patient Care Center, Perryville, MD

	2-azetidinone compound	Nicotinic Acid	Bile Acid Sequesterates
Monitoring **(Efficacy and Toxicity Parameters)**	• Efficacy o LDL, HDL, Tc, TG • Toxicity o SE o LFTs o Myopathy	• Efficacy o LDL, HDL, Tc, TG • Toxicity o LFTs (Dose related) o More with sustained release o d/c if AST/ALT are 3x higher o FPG o Serum uric acid	• Efficacy o LDL, HDL, Tc, TG • Toxicity o LFTs o Serum creatinine o BUN
Patient Education	• Take ezetimibe >2 hrs before or 4 hrs after "resin" type meds (cholestyramine, colesevelam, colestipol)	• Notify if, DM, HTN, taking anticoag, have liver, gall bladder, GI Dx, • Stay away from EtOH • May have fainting spells, GI discomfort, flushing • Tell PCP if have yellow skin, fainting, palpitations, SoB	o Biliary cirrhosis o Biliary obstruction o Cholelithiasis o GI obstruction o Phenylketonuria (cholestyramine) o Coagulation therapy (binds to Vit K) o Hypothyroidism (binds to thyroid)
Cost	$94.20/30days (QD)		
References	• Clinical Pharmacology • Drug Insert • ATP 3	• Clinical Pharmacology • Drug Insert • ATP 3	• Clinical Pharmacology • Drug Insert • ATP 3

Table B1. Estimate of 10-Year Risk for Men (Framingham Point Scores)

Age	Points
20-34	-9
35-39	-4
40-44	0
45-49	3
50-54	6
55-59	8
60-64	10
65-69	11
70-74	12
75-79	13

Total Cholesterol	Points				
	Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79
<160	0	0	0	0	0
160-199	4	3	2	1	0
200-239	7	5	3	1	0
240-279	9	6	4	2	1
≥280	11	8	5	3	1

	Points				
	Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79
Nonsmoker	0	0	0	0	0
Smoker	8	5	3	1	1

HDL (mg/dL)	Points
≥60	-1
50-59	0
40-49	1
<40	2

Systolic BP (mmHg)	If Untreated	If Treated
<120	0	0
120-129	0	1
130-139	1	2
140-159	1	2
≥160	2	3

Point Total	10-Year Risk %
<0	< 1
0	1
1	1
2	1
3	1
4	1
5	2
6	2
7	3
8	4
9	5
10	6
11	8
12	10
13	12
14	16
15	20
16	25
≥17	≥ 30

Table B2. Estimate of 10-Year Risk for Women (Framingham Point Scores)

Age	Points
20-34	-7
35-39	-3
40-44	0
45-49	3
50-54	6
55-59	8
60-64	10
65-69	12
70-74	14
75-79	16

Total Cholesterol	Points				
	Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79
<160	0	0	0	0	0
160-199	4	3	2	1	1
200-239	8	6	4	2	1
240-279	11	8	5	3	2
≥280	13	10	7	4	2

	Points				
	Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79
Nonsmoker	0	0	0	0	0
Smoker	9	7	4	2	1

HDL (mg/dL)	Points
≥60	-1
50-59	0
40-49	1
<40	2

Systolic BP (mmHg)	If Untreated	If Treated
<120	0	0
120-129	1	3
130-139	2	4
140-159	3	5
≥160	4	6

Point Total	10-Year Risk %
<9	< 1
9	1
10	1
11	1
12	1
13	2
14	2
15	3
16	4
17	5
18	6
19	8
20	11
21	14
22	17
23	22
24	27
≥25	≥ 30