“Hypercholesterolemia: Pathophysiology and Therapeutics”

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Drug Treatment

Anti-hyperlipidemic Agents

- HMG-CoA Reductase Inhibitors: STATINS
- Fibrates (gemfibrozil, fenofibrate)
- Niacin (immediate vs. sustained release)
- Cholesterol Absorption Inhibitors (Ezetimibe)
- Omega 3- Fatty Acids
- Combination agents

HMG-CoA Reductase Inhibitors  "Statins"

Agents
1. Lovastatin - Mevacor® (Merck)
2. Pravastatin - Pravachol® (BMS)
3. Simvastatin - Zocor® (Merck)
4. Fluvastatin - Lescol® (Novartis)
5. Atorvastatin - Lipitor® (Pfizer)
6. Rosuvastatin - Crestor® (Astra-Zeneca)

MOA
- Block the rate limiting step in cholesterol synthesis (HMG-CoA→mevalonate)
- Increase LDL-C receptor density
- Other (pleiotropic) effects

Statins Approved in the U.S.

<table>
<thead>
<tr>
<th>Statin</th>
<th>Recommended starting dose (mg)</th>
<th>Max daily dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
<td>10 - 20</td>
<td>80</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>20 – 40</td>
<td>80</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>20 – 40</td>
<td>80</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>10 – 80</td>
<td>80</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>5 – 40</td>
<td>40</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>20 – 40</td>
<td>80</td>
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</tbody>
</table>

Pharmacologic Therapy: Statins

- Inhibit cholesterol synthesis
- Beneficial effects on all lipid parameters
  - LDL-C ↓ 22%-63%
  - HDL-C ↑ 5%-16%
  - TG ↓ 7%-30%
- 24%-40% relative reduction in coronary events
- Potential side effects: myopathy, ↑ liver enzymes
- Contraindications: liver disease, pregnancy
- Precautions: use with certain drugs

Pleiotropic Effects of Statins

- Endothelial function (NO regulation)
- Atherosclerotic plaque stabilization
- Inhibition of LDL-C oxidation
- Effects on VSMC growth
- Platelet inhibition and anti-thrombosis
- Reduced leukocyte adhesiveness
- Effects on circulatory clotting factors
  - Tissue factor
  - Fibrinogen
  - hs-CRP
  - PAI-1(Lp(a))
- Effects on blood viscosity and flow
- BP effects
- Reduced ischemia-reperfusion injury (cardiac and cerebral)
- Enhanced angiogenesis

References
**Recommendations From ATP III**

When LDL-C lowering drug therapy is employed, intensity of therapy should be sufficient to achieve AT LEAST a 30-40% reduction in LDL-C levels.

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**Pharmacologic Therapy: Statins—Rule of 6**

Majority of LDL-C Reduction Is Achieved With Starting Dose

- 3-Step Titration
- Statin – starting dose
  - 1st Doubling: 5%–6%
  - 2nd Doubling: 5%–6%
  - 3rd Doubling: 19%–45%

- Mean % Change in LDL-C
- Daily Fluvastatin Lovastatin Pravastatin Simvastatin Atorvastatin Rosuvastatin
- Dose (mg): 20 40 80 10 20 40 80
- Adapted from Package insert data reviewed 06/07

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**Statins: Effect on LDL-C:**

Package Insert Data

- Mean % Change in LDL-C
- Daily Fluvastatin Lovastatin Pravastatin Simvastatin Atorvastatin Rosuvastatin
- Dose (mg): 20 40 80 10 20 40 80
- Adapted from Package insert data reviewed 06/07

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**Statins: General Effects on HDL-C:**

- Mean % Change in HDL-C
- Daily Fluvastatin Lovastatin Pravastatin Simvastatin Atorvastatin Rosuvastatin
- Dose (mg): 20 40 80 10 20 40 80
- Adapted from Package insert data reviewed 06/07

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**Major Endpoint Lipid Trials**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Drug</th>
<th>Statin Dose</th>
<th>LDL-C Δ</th>
<th>Placebo CHD Risk</th>
<th>CHD Risk Reduction</th>
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</thead>
<tbody>
<tr>
<td>LRC-CPPT</td>
<td>SAB</td>
<td>10mg</td>
<td>200-175</td>
<td>9.8%</td>
<td>-19%</td>
</tr>
<tr>
<td>MRCAPS</td>
<td>Pravastatin 40mg</td>
<td>-25%</td>
<td>130-142</td>
<td>3.3%</td>
<td>-30%</td>
</tr>
<tr>
<td>TocAFAPS</td>
<td>Lovastatin 20-40mg</td>
<td>-20%</td>
<td>130-115</td>
<td>5.5%</td>
<td>-40%</td>
</tr>
<tr>
<td>ARCTIC</td>
<td>Atorvastatin 10mg</td>
<td>-34%</td>
<td>132-87</td>
<td>9.4%</td>
<td>-30%</td>
</tr>
</tbody>
</table>

- CHD and CHD Risk Equivalent
- 4S: Simvastatin 40mg
  - LDL-C Δ: -15% | 186-171 | 21.6% | -34%
- PROSIT: Surgery
  - LDL-C Δ: -25% | 162-170 | 30.5% | -35%
- LIPID: Pravastatin 40mg
  - LDL-C Δ: -25% | 130-112 | 15.9% | -24%
- CARE: Pravastatin 40mg
  - LDL-C Δ: -32% | 138-96 | 12.3% | -24%
- FAME-CABG: Lovastatin/GC
  - LDL-C Δ: -28% | 132-92 | 13.5% | -24%
- HPS: Simvastatin 40mg
  - LDL-C Δ: -26% | 131-89 | 11.8% | -24%
- PROVE-IT: Atorvastatin 80mg
  - LDL-C Δ: -35% | 95-62 | 8.3% | -16%
- A to Z: Simvastatin 40/60mg
  - LDL-C Δ: -19% | 81-66 | 14.4% | -11%

- AT1: Atorvastatin 80mg
  - LDL-C Δ: -34% | 181-127 | 9.3% | -20%

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**Statins-Safety: Myopathy and Hepatotoxicity**

- **Myopathy:** Muscle pain, tenderness or weakness (myositis) with CK>10X ULN (0-150 U/L) (CK= creatinine kinase)
  - Myopathy may take the form of rhabdomyolysis with or without ARF (acute renal failure), 2o to myoglobinuria
  - Risk of myopathy from clinical studies is dose related and ranges from 0.02% (20mg S) to 0.3% (80mg S), <0.1% prava, < 0.5% lova, 0.1% rosuva
  - Risk of these events increases with dose escalation or in combination with fibrates or niacin
  - **Perspective:** In 4S, 4444 pts on simvastatin 20-40mg for 5.4yrs the frequency of >1 occurrence of >3xULN for ALT (or AST) is <1.2% prava, 0.2-2.3% for atorva, <1.5% Lova

- **Hepatotoxicity:** LFT's (liver function tests such as ALT - Alanine aminotransferase) are monitored usually at baseline, 12 weeks, then periodically thereafter
  - Usual Incidence of >1 occurrence of >3xULN for ALT (or AST) is <1.2% prava, 0.2-2.3% for atorva, <1.5% Lova
  - **Perspective:** In 4S, 4444 pts on simvastatin 20-40mg for 5.4yrs the frequency of >1 occurrence of LFT>3xULN was the same for Simva as Placebo (0.7 vs 0.6%)
Occurrence of CK Elevations > 10x ULN as a Function of Dose and LDL-C Reductions

- Cerivastatin (0.2, 0.3, 0.4, 0.8 mg)
- Atorvastatin (10, 20, 40, 80 mg)
- Pravastatin (20, 40 mg)
- Rosuvastatin (10, 20, 40 mg)
- Simvastatin (40, 80 mg)

Note: the data for this analysis were derived from prescribing information, summary basis of approvals, clinical trials, and other sources. Prospectively designed comparative clinical trials were not utilized in this analysis and results should be interpreted with caution.

Selected NLA Recommendations to Health Care Professionals Regarding Muscle Safety With Statin Use

1. “Whenever muscle symptoms or an increased CK level is encountered in a patient receiving statin therapy, health professionals should attempt to rule out other etiologies, because these are most likely to explain the findings. Other common etiologies include increased physical activity, trauma, falls, accidents, seizure, shaking chills, hypothyroidism, infections, carbon monoxide poisoning, polymyositis, dermato myositis, alcohol abuse, and drug abuse (cocaine, amphetamines, heroin, or PCP).”

2. “Obtaining a pretreatment, baseline CK level may be considered in patients who are at high risk of experiencing a muscle toxicity (ie, older individuals or when combining a statin with an agent known to increase myotoxicity), but this is not routinely necessary in other patients.”

3. “It is not necessary to measure CK levels in asymptomatic patients during the course of statin therapy, because marked, clinically important CK elevations are rare and are usually related to physical exertion or other causes.”

4. “Patients receiving statin therapy should be counseled about the increased risk of muscle complaints, particularly if the initiation of vigorous, sustained endurance exercise or a surgical operation is being contemplated; they should be advised to report such muscle symptoms to a health professional.”

5. “CK measurements should be obtained in symptomatic patients to help gauge the severity of muscle damage and facilitate a decision of whether to continue therapy or alter doses.”

6. “In patients who develop intolerable muscle symptoms with or without a CK elevation and in whom other etiologies have been ruled out, the statin should be discontinued. Once asymptomatic, the same or different statin at the same or lower dose can be restarted to test the reproducibility of symptoms. Recurrence of symptoms with multiple statins and doses requires initiation of other lipid-altering therapy.”

7. “In patients who develop tolerable muscle complaints or are asymptomatic with a CK 10 the ULN, statin therapy may be continued at the same or reduced doses and symptoms may be used as the clinical guide to stop or continue therapy.”

8. “In patients who develop rhabdomyolysis (a CK > 10,000 IU/L or a CK 10 times the ULN with an elevation in serum creatinine or requiring IV hydration therapy), statin therapy should be stopped. IV hydration therapy in a hospital setting should be instituted if indicated for patients experiencing rhabdomyolysis. Once recovered, the risk vs benefit of statin therapy should be carefully reconsidered.”

Hepatic-Related Adverse-Event Profile With Statins

- Fluvastatin (20, 40, 80 mg)
- Rosuvastatin (10, 20, 40 mg)
- Lovastatin (20, 40, 80 mg)
- Atorvastatin (10, 20, 40, 80 mg)
- Simvastatin (40, 80 mg)

Note: the data for this analysis were derived from prescribing information, summary basis of approvals, clinical trials, and other sources. Prospectively designed comparative clinical trials were not utilized in this analysis and results should be interpreted with caution.
Regarding Hepatic Safety With Statin Use

1. “During the routine general evaluation of patients being considered for statin and other lipid-lowering therapy, it is advisable to obtain liver transaminase levels. If these tests are found to be abnormal, further investigation should be performed to elicit the etiology of the abnormal test results.”

2. “Until there is a change in the FDA-approved prescribing information for statins, it is appropriate to continue to measure transaminase levels before starting therapy, 12 weeks after initiating therapy, after a dose increase, and periodically thereafter. However, routine monitoring of liver function tests is not supported by the available evidence and the current recommendation for monitoring needs to be reconsidered by the FDA.”

3. “The clinician should be alert to patient reports of jaundice, malaise, fatigue, lethargy, and related symptoms in patients taking statin therapy as a signal of potential hepatotoxicity. Evidence for hepatotoxicity includes jaundice, hepatomegaly, increased indirect bilirubin level and elevated prothrombin time (rather than simple elevations in liver transaminase levels).”

4. “The preferred biochemical test to ascertain significant liver injury is fractionated bilirubin, which, in the absence of biliary obstruction, is a more accurate prognosticator of liver injury than isolated aminotransferase levels.”

5. “Should the clinician identify objective evidence of significant liver injury in a patient receiving a statin, the statin should be discontinued. The etiology should be sought and, if indicated, the patient referred to a gastroenterologist or hepatologist.”

6. “If an isolated asymptomatic transaminase level is found to be elevated 1–3 times the ULN, there is no need to discontinue the statin.”

7. “If an isolated asymptomatic transaminase level is found to be > 3 times the ULN during a routine evaluation of a patient administering a statin, the test should be repeated and, if still elevated, other etiologies should be ruled out. Consideration should be given to continuing the statin, reducing its dose, or discontinuing it based on clinical judgment.”

8. “According to the Expert Liver Panel, patients with chronic liver disease, nonalcoholic fatty liver disease, or nonalcoholic steatohepatitis may safely receive statin therapy.”

Drug-Drug Interactions Resulting from Impaired (Liver) Metabolism of Statins

Drug-Drug Interactions CYP Inhibition

Other Lipid-lowering Medications

Effects of Itraconazole on Serum Concentrations of Simvastatin and Pravastatin

Other Lipid-lowering Medications

Generic Tradell Recommended starting dose Max daily dose
Fibrates
Gemfibrozil Lopid
Fenofibrate Tricor (Others)
Nicotinic acid (375 mg capsules)
Resins
Cholestyramine Questran
Colestipol Colestid
Colestipol (565 mg tablets)
Other:
Ezetimibe Zetia 10mg/day 10mg/day
Other: ezetimibe/simvastatin Vytorin 10mg/40mg/80mg

$^*$ Titrated up over a 3-6 week period.
Fibrates (Gemfibrozil, Fenofibrate)

**Actions:**
- Lowers Trigs (approx 25% for Gem, 30-50% for fenofibrate)
- Moderately lowers total and LDL (0-4% for Gem, up to 20% for fenofibrate*)
- Raises HDL (approx. 8% for Gem, 1-34% for fenofibrate)

**Dosing:**
- Gemfibrozil: 600mg BID, 30 minutes before meals
- Fenofibrate: Multiple formulations: eg. 145mg/day with meals (available as 48mg for use in renal impairment)
- Dosage adjustment may be necessary with reduced renal function
- 5.3% increase in ALT/AST >3x ULN (vs. 1.1% PL)

* Depending on initial LDL this may be as low as 20% or – ve (ie raising of LDL-C say 14-45% if Trigs 300-500 or >500mg/dL)

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Adverse effects:
- Dyspepsia, abdominal pain, rash, cholelithiasis, preexisting gallbladder disease and diarrhea

Comments:
- Caution in patients also taking a “statin” gemfibrozil due to CYP inhibition (+/- fenofibrate)
- Caution with warfarin administration (→ incr. INR)
- Fenofibrate is a uricosuric in most patients

Studied:
- Helsinki Heart Disease Trial (gemfibrozil, 1st prev.) 34% reduction in CHD (p<0.02) (Frick NEJM 1987;317:1237-45)
- VA-HIT trial (NEJM 1999;341:410-418): Reduction in CVD death + NFMI (in men with normal LDL-C (<140) and low HDL-C (<40), TG <300mg/dL
- FIELD (Fenofibrate group: HR=0.89 (95%CI 0.75-1.05, p=0.16) for any CV event, NFMI HR=0.76, (95% CI 0.62-0.94, p=0.01) coronary heart disease mortality 1.19 (95% CI 0.9-1.57, p=0.22)
- Other findings, less albuminuria progression (p=0.002), retinopathy needing laser Tx (p=0.003) sign, in increase in pancreatitis and PE

VA-HIT Lipid Profile and End Point Results

<table>
<thead>
<tr>
<th>TC</th>
<th>HDL-C</th>
<th>LDL-C</th>
<th>TG</th>
<th>CHD Death/ Nonfatal MI</th>
</tr>
</thead>
<tbody>
<tr>
<td>175</td>
<td>111</td>
<td>161</td>
<td>32</td>
<td></td>
</tr>
</tbody>
</table>


Gemfibrozil for the Secondary Prevention of Coronary Heart disease in Men with Low Levels of HDL-C (VA-HIT) NEJM 1999;341:410-418

- Purpose: Gemfibrozil for secondary prevention: would raising HDL-C reduce coronary events?
- Subjects: 2531 men (<74 yo, median 64 yo) with HDL-C <40mg/dL, LDL <140mg/dL and Trigs <300mg/dL (actual BL LDL-C 111, HDL 32 and TG 160mg/dL)
- Design: Double-blind PL-controlled for 5.1 years gemfibrozil 1200mg/d vs PL
- Primary end point: CHD death/nonfatal MI

Conclusions:
- For CHD patients whose primary lipid abnormality is low HDL-C, therapy that increases HDL-C, reduces risk of major CV events
- The magnitude of coronary risk reduction approximates that of large statin trials in patient with elevated LDL-C

Gemfibrozil for the Secondary Prevention of Coronary Heart disease in Men with Low Levels of HDL-C (VA-HIT) NEJM 1999;341:410-418

Effects of Long-term Fenofibrate Therapy on CV Events in 9795 People with Type 2 DM (The FIELD Study) Lancet 2005;366:1849-1861

- Purpose: Fenofibrate for primary prevention in T2DM
- Subjects: 9795 men and women (50-75 yo) not taking statins at entry and total-C/HDL-C ratio of >4.0 or TG of 87-443mg/dL (Only 38% had TG>150 and HDL <40/50mg/dL for men/women)
- Design: Randomized, controlled study for 5 years of either fenofibrate 200mg/d vs PL
- Primary end point: CHD death/nonfatal MI
Effects of Long-term Fenofibrate Therapy on CV Events in 9795 People with Type 2 DM (The FIELD Study) 
Lancet 2005;366:1849-1861

• Results: Fenofibrate was associated with the following:
  - HR;0.89 (95%CI 0.75-1.05, p=0.16) for any coronary event (primary outcome)
  - HR;0.76, (95%CI 0.62-0.94, p=0.01) for NFMI
  - HR;1.19 (95% CI 0.9-1.57, p=0.22) in coronary heart disease mortality
  - HR;0.89 (95% CI 0.8-0.99, p=0.035) total CV disease events (included coronary revascularization)
  - Less progression to albuminuria (p=0.002)
  - Less retinopathy needing laser treatment (p=0.0003)
  - Fewer patients who commenced statins (8% vs 17%, p<0.0001)

• Interpretation:
  - Fenofibrate did not significantly reduce primary outcome
  - Higher rate of statin use in PL group may have masked a treatment benefit
    (adjustment for new lipid-lowering therapy indicated fenofibrate reduced the risk of CHD by 19% (p=0.01) and total CVD events by 15% (p=0.04))

Nicotinic Acid

Agents
- Niacin (OTC -generic), niacin SR, niacin extended release

MOA
- inhibits lipolysis, decreases hepatic esterification of trigs reduced production of Apo B

Actions
- Lows total, LDL (up to 17%) and TRG (up to 35%)
- Raises HDL (substantially, up to 26% cf. statins)

Nicotinic Acid

Dosing
  - Start low (eg. Immediate release 50 mg TID) and titrate upward (Sustained release usually bid, extended release Niaspan® qd)
  - Maximum 6 grams / day (Niaspan® max 2g/day)
  - Niaspan® :begin with 4 weeks @500mg/day, then up to 1000mg/d for another 4 weeks (taken before bed), usually up to 2 g/day

Adverse effects:
  - Mostly dose related, pruritis, GI intolerance (caution with PUD history) may take ASA 30' before dose-may help to reduce flushing,
  - Hyperglycemia, (caution in diabetics) and hyperuracemia
  - Liver toxicity (monitor as with statins, esp sustained release)
  - Cautiously combined with statins for (Trig and HDL-C effects)

Nicotinic Acid

Comments:
- Hepatic toxicity mostly related to SR products however experience with extended release formulation (Niaspan®) challenges this point
- Alcohol and hot drinks may increase dose related side effects (flushing etc.)
- HDL raising qualities may be beneficial for those who have maximized exercise (three E's)

Studies:
- CDP (niacin 2o prev.) non sign. Reduction in recurrent MI at 6 yrs, but 15 year follow up 11% reduction over placebo in all cause mortality (p<0.001) (Canner JACC1986;8:1245-55)
- Stockholm Ischemic Heart Disease 2o prev. Trials niacin + clofibrate reduced total mortality vs. placebo (p=0.05) if baseline TG>133mg/dL

Role: Elevations in HDL-C, Reductions in Trigs with modest needs for lowering LDL-C or combination with statins if high trigs (>400mg/dL),

Eg. Niacin (as Niaspan®) Efficacy 
(Goldberg Am J Cardiol 1998;82:35U-38U)
Omega-3 Fatty Acids

- Proposed mechanism of action
  - Increased intracellular degradation of Apo B-100 inhibits the secretion and synthesis of VLDL-C but enhanced conversion of VLDL-C to LDL-C
- Potential adverse effects
  - Increased levels of LDL-C and potentially increased oxidizability of LDL-C
  - Increased bleeding time due to interference with platelet function
  - Common AEs: eructation, flu-like syndrome, dyspepsia, fishy taste
  - Monitor ALT and LDL-C levels

Summary of AHA Recommendations for Omega-3 Fatty Acids

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>No CHD</td>
<td>Eat a variety of fatty fish &gt; twice/wk Include Oils and other foods rich in alpha-linolenic acid (flaxseed, canola and soybean oils; walnuts)</td>
</tr>
<tr>
<td>CHD present</td>
<td>1 g/day of EPA + DHA, preferably from fatty fish; use supplements after consulting a physician</td>
</tr>
<tr>
<td>High triglyceride levels</td>
<td>2-4 g/day of EPA + DHA under physician’s care</td>
</tr>
</tbody>
</table>

Goals and Recommendations for Clinical Management of Metabolic Syndrome : Non Drug Considerations

(Lifestyle Risk Factors:
- Abdominal Obesity
  - Reduce body weight by 7-10% during year 1 of therapy. Continue to extend possible to achieve desirable wt (BMI<25kg/m²)
  - How? Consistently encourage wt. maintenance/reduction -> balance physical activity, caloric intake, and behavioral modification programs to achieve maintain waist circumference of <40"(M) and <35" (F)
  - Atherogenic Diet
    - Reduce intake of saturated fat, trans fat, cholesterol
    - How? Recommend: saturated fat <7% of total calories, reduce trans fat: dietary cholesterol <200mg/d; total fat 25% to 35% of total calories, most fat should be unsaturated, simple sugars should be limited
Goals and Recommendations for Clinical Management of Metabolic Syndrome: Non Drug Considerations
(Grundy Circulation 2005;112:2735-2752)

Lifestyle Risk Factors:
- Physical Inactivity
  - Regular moderate-intensity physical activity: at least 30" (preferably 60") continuous or intermittent 5 d/wk, but preferably daily
  - How?
  - With CVD, assess risk to guide exercise advice, encourage 30-60" activity (walking to gardening) and some resistance training 2d/wk)

Summary
- Pharmacologic management of secondary targets such as the metabolic syndrome and non-HDL-C were reviewed
- Major drug therapy for TG lowering and HDL-C raising may involve niacin, fibrates and omega-3 FAs
- These goals should be achieved in light of the weight of evidence supporting their proven outcomes (relative to LDL-C and statins)
- Non-drug therapy to manage components of the metabolic syndrome are offered
- Emphasis remains on LDL-C first, but clinicians must go beyond LDL-C to include non-HDL, TG and HDL-C, and other components of the metabolic syndrome

Bile Acid Sequestrants

Agents
1. Cholestyramine - Questran®, Questran Light®, Prevalite®
2. Colestipol - Colestid®
3. Colesevlam HCl- Welchol®

MOA
- Bind with bile acids forming an insoluble complex which is excreted in the stool
- Increased loss of bile acids causes increased oxidation of cholesterol into bile acids

Bile Acid Sequestrants

Actions
- Lowers total and LDL-C (little effect on HDL)
- Raises trigs (problem for those with high Trigs)

Dosing
- Cholestyramine: initial 4 grams BID
- Colestipol: initial 5 grams BID
- Colesevlam: 3 tabs bid or 6-7 tabs qd

Adverse effects
- Mostly GI

Comments
- Drug and vitamin interactions (binding) (available data suggests this is not a problem for a limited number of incident drugs (digoxin, etc.)
- Safe for children and in very effective if combined with statins
- Poor compliance (gritty, GI issues, cost)

Colestyramine HCl

*Non-absorbed lipid lowering resin agent
*Indication: Alone or in combination with HMG-CoA inhibitors to lower LDL-C
*Dose: 6 tabs (3 bid) with food or fluids or 6 tabs qd. (max 7)
*Available: 625mg Tablets
*Role: Like other resins:
  1) For patients intolerant or unable to take statins (eg. pregnancy, children, liver problems)
  2) Combination with other agents

Unlike other resins:
  1) Apparently no binding to limited drugs tested to date
Ezetimibe (Zetia®) and Statins — Complementary Mechanisms

• ZETIA reduces the delivery of cholesterol to the liver (acts at brush border of small intestine and inhibits cholesterol absorption → decreased delivery of cholesterol to liver and reduced hepatic cholesterol stores → increased clearance from blood)

• The distinct mechanism of ZETIA is complementary to that of statins which reduce cholesterol synthesis in the liver¹

• The effects of ZETIA, either alone or in addition to a statin, on cardiovascular morbidity or mortality have not been established


ZETIA™ (ezetimibe) — Drug Interactions

• No clinically significant pharmacokinetic interactions with
  - statins (including atorvastatin, simvastatin, pravastatin, lovastatin, and fluvastatin)
  - Warfarin, digoxin, ethinyl estradiol, levonorgestrel, glipizide, tolbutamide

• ZETIA is neither an inhibitor nor an inducer of these CYP1A2, 2D6, 2C8/9, and 3A4 isozymes

• Fibrates: co-administration of ZETIA with fibrates is not recommended - co-admin with fenofibrate or gemfibrozil → 1.5 to 1.7 fold increase in ezetimibe

• Cyclosporine: ZETIA increased 12-fold in 1 renal transplant patient receiving multiple medications, including cyclosporine
  - Patients who take both ZETIA and cyclosporine should be carefully monitored

Pathways Affecting Cholesterol Balance*

Plasma Cholesterol Comes Continuously From Both Production and Absorption

Clinical Studies for ZETIA™ (ezetimibe) Monotherapy

Pooled Results From 2 Multicenter, Double-Blind, Placebo-Controlled, 12-Week Studies in 1,719 Patients With Primary Hypercholesterolemia

• Experience in non-Caucasians is limited and does not permit a precise estimate of the magnitude of the effects of ZETIA

*P<0.01 vs placebo.

ZETIA™ (ezetimibe) — Provided Additional Reduction in LDL-C When Added to Ongoing Statin Therapy

Statin Monotherapy¹

After Adding Placebo or ZETIA

139 mg/dL 138 mg/dL

After 12-Week Treated Baseline

Statin + Placebo (n=390) Statin + ZETIA (n=379)

P=0.001 for ZETIA + statin vs placebo + statin.


VLDL = very-low-density lipoprotein, IDL = intermediate-density lipoprotein, TG = triglyceride.
ZETIA™ (ezetimibe) Added to Ongoing Statin — Triglycerides and HDL-C Results

-3% 3%* 1%
–14% 3%† 0%
–30% –25% –20%
–15% –10% 5%
–5% 0%

HDL-C (mean) Triglycerides (median)

*P<0.001 for ZETIA + statin vs statin alone.
†P<0.05 for ZETIA + statin vs statin alone.

ZETIA™ (ezetimibe) — Added LDL-C Reduction With Any Atorvastatin Dose

Atorva 80 mg (n=62)
ZETIA + Atorva 80 mg (n=63)
Atorva 40 mg (n=66)
ZETIA + Atorva 40 mg (n=65)
Atorva 20 mg (n=60)
ZETIA + Atorva 20 mg (n=62)
Atorva 10 mg (n=60)
ZETIA + Atorva 10 mg (n=65)

Mean % Change in LDL-C From Unreated Baseline

–55%*,† –60%* –52%*,†
–54%* –54%* –53%
–50% –40% –30%
–20% –10% 0%

*P<0.01 for ZETIA + statin vs statin alone.
†P<0.001 for ZETIA + statin vs next highest dose of simvastatin monotherapy.

VYTORIN™ (ezetimibe/simvastatin) Lowered LDL-C by 52% at the Starting Dose

• VYTORIN lowered LDL-C more than simvastatin across the dosage range.
• Simvastatin lowered LDL-C by 34% at the 20-mg dose, 41% at the 40-mg dose, and 49% at the 80-mg dose.

VYTORIN™ (ezetimibe/simvastatin) Lowered LDL-C by 52% at the Starting Dose

Combination Drug Therapy for Hypercholesterolemia

• Useful for mixed dyslipidemias
• Optimizes effects on relevant lipid fractions of interest
• Selection may be complex based on tolerance, drug interactions and cost
• Unknown outcome as of yet
• Experience with some combinations are limited

Anti-hyperlipidemic Drug Combinations

• Statin+ Fibrate (gemfibrozil, fenofibrate)
  - increased likelihood of LFT increases, myopathy
• Statin+ Ezetimibe
  - augmented LDL, HDL and TG response with no need to increase monitoring (above statin rec.)
• Statin+ Niacin (Advicor as single entity)
  - augmented LDL, HDL and TG response with some need to increase monitoring (diabetics, SEs))
• Statin+ resin (Welcol or others)
  - augmented LDL, modest HDL and indifferent or worse TG response)
  - no need to increase monitoring

Phase III Combination Therapy: Ezetimibe Plus Simvastatin—Efficacy

Placebo (n=70)
Ezetimibe 10 mg (n=61)
Simvastatin (pooled, n=263)
Ezetimibe 10 mg + simvastatin (pooled, n=274)

*P<0.03 vs simvastatin.
†P<0.001 for VYTORIN vs each corresponding dose of simvastatin.
‡P<0.001 for VYTORIN vs next highest dose of simvastatin monotherapy.
Bays ACC 2004

### Clinical Event Trials Using Statins

**Secondary**
- **4S**
  - Simvastatin
  - LDL-C: 188 to 117 mg/dL
  - HDL-C: 45.3 to 48.9 (8%)
  - CHD Events: 25.5 to 16.4%

- **LIPID**
  - Pravastatin
  - LDL-C: 150 to 112 mg/dL
  - HDL-C: 36 to 37.8 (6%)
  - CHD Events: 18.7 to 12.3%

- **CARE**
  - Pravastatin
  - LDL-C: 139 to 98 mg/dL
  - HDL-C: 36 to 39 (6%)
  - CHD Events: 13.2 to 10.2%

**Primary**
- **WOSCOPS**
  - Pravastatin
  - LDL-C: >2 RF
  - CHD Events: LDL-C: 192 to 142 mg/dL
  - HDL-C: 44 to 46.2 (5%)
  - CHD Events: 7.9 to 5.5%

- **AFCAPS/TexCAPS**
  - Lovastatin
  - LDL-C: <2 RF
  - CHD Events: LDL-C: 156 to 115 mg/dL
  - HDL-C: 38 to 39 (6%)
  - CHD Events: 5.6 to 3.3%

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  - Simvastatin
  - LDL-C: 188 to 117 mg/dL
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  - CHD Events: 5.6 to 3.3%

### Selected Major Trials of Statins

**Effects on Cardiac Events**

- **4S**
- **CARE**
- **LIPID**
- **WOSCOPS**

**CV events Percent**

**LDL-C levels (mg/dL)**

- **Primary prevention**
  - Rx
  - Placebo

- **Secondary prevention**
  - Rx
  - Placebo

**Key Studies and Therapeutic Options**

- **Key (older landmark) Studies:**
  - Historically, 4S, CARE, LIPID and WOSCOPS, AFCAPS

Five Major (Newer) Trials With Clinical End Points

- Heart Protection Study (HPS)
- Prospective Study of Pravastatin in the Elderly at Risk (PROSPER)
- Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)
- Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT-LLA)
- Pravastatin or Atorvastatin Evaluation and Infection Trial (PROVE-IT)

Advances Which Have Taken Place in Recent Literature

1) Evidence for aggressive optional targets
   - HPS suggestive that treatment with statins in patients with LDL <100mg/dL → outcome benefits
   - PROVE-IT confirms LDL<70mg/dL in ACS patients → outcome benefits (vs. LDL=100mg/dL)
   - TNT extends above findings to patients with chronic CAD
   - Safety of statin therapy to these lower targets appears acceptable

2) Statins are effective among special populations:
   - ASCOT LLT- moderate to high risk- low dose statin
   - CARDS- diabetic specific trial –low dose statin

3) Other agents – combinations of agents are another means for attaining these aggressive goals

The Heart Protection Study (HPS)

- Randomized, PL-controlled of effects of simvastatin and antioxidant vitamins on morbidity and mortality

Patients
- >20,536 men and women 40-80 yr at incr. risk of CHD due to prior disease with total-C >135 mg/dL*

Treatment
- 3.5 yr Simvastatin (40 mg/d) vs placebo
- 3.5 yr Vitamins (600 mg E, 250 mg C, 20 mg beta-carotene) vs placebo

Primary
- The effect of simvastatin on total and cause-specific mortality, secondary-cause specific morbidity and mortality

*Increased risk of CHD due to prior disease defined as MI or prior CHD, occlusive disease of noncoronary arteries, diabetes, or treated hypertension.


Heart Protection Study Results: Risk Reduction

<table>
<thead>
<tr>
<th>Baseline feature</th>
<th>Statin (n=10,269)</th>
<th>Placebo (n=10,267)</th>
<th>Risk ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior MI or other CHD</td>
<td>617 (16.2%)</td>
<td>846 (22.5%)</td>
<td></td>
</tr>
<tr>
<td>Any CHD or Risk Equivalent</td>
<td>1459 (21.6%)</td>
<td>1941 (27.3%)</td>
<td></td>
</tr>
<tr>
<td>No prior CHD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CVD (1830)</td>
<td>173 (19.7%)</td>
<td>212 (23.8%)</td>
<td>↓24% (p&lt;0.0001)</td>
</tr>
<tr>
<td>PVD (2791)</td>
<td>327 (24.7%)</td>
<td>428 (30.5%)</td>
<td></td>
</tr>
<tr>
<td>Diabetes (3562)</td>
<td>276 (16.1%)</td>
<td>367 (18.6%)</td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>2033 (19.8%)</td>
<td>2595 (25.2%)</td>
<td></td>
</tr>
</tbody>
</table>

Heart Protection Study Results: Lipids

<table>
<thead>
<tr>
<th>Baseline LDL-C (mg/dL)</th>
<th>Statin (n=10,269)</th>
<th>Placebo (n=10,267)</th>
<th>Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;100</td>
<td>282 (16.4%)</td>
<td>350 (21.9%)</td>
<td>Statin Better</td>
</tr>
<tr>
<td>100-129</td>
<td>668 (19.3%)</td>
<td>871 (24.7%)</td>
<td>Statin Worse</td>
</tr>
<tr>
<td>210-239</td>
<td>1063 (21.6%)</td>
<td>1336 (28.3%)</td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>2033 (19.2%)</td>
<td>2595 (25.2%)</td>
<td>↓24% (p&lt;0.0001)</td>
</tr>
</tbody>
</table>

HPS: Main Conclusions

- After allowance for non-compliance, 40mg daily simvastatin safely reduces the risk of heart attack, of stroke, and of revascularization by about one-third
- 5 years of statin treatment typically prevents these “major vascular events” in about:
  - 100 of every 1000 people with previous MI
  - 80 “ “ “ other CHD
  - 70 “ “ “ cerebrovascular disease
  - 70 “ “ “ other arterial disease
  - 70 “ “ “ diabetes (age 40+)
  - irrespective of cholesterol level (or age, or sex, or other treatments)

Comparison of Intensive and Moderate Lipid Lowering with Statins after Acute Coronary Syndromes (PROVE-IT TIMI-22)
(Cannon et al NEJM:2004;350 1495-1504)

Background: Optimal level of LDL-C is unknown
Methods: Enrolled 4162 hospitalized for ACS within 10 days; 40mg Prav vs. 80mg Atorvastatin (Median baseline: LDL=106, HDL=39, TG=154, 78% males)
Endpoint: composite of death from any cause, MI, UA requiring re-hospitalization, PCI within 30 days and stroke
Design: to establish non-inferiority of Pravastatin vs. Atorvastatin follow-up mean 24 months

Results:
- Median LDL-C was 95mg/dL for Pravastain vs. 62mg/dL for Atorvastatin (P<0.01)
- Estimates primary endpoint were 26.3% fro P vs. 22.4% for A (16% reduction, p=0.005;95%CI5-26%)
- met the criteria for superiority of atorvastatin

Conclusions: Patients with recent ACS, intensive lipid lowering statin provides greater protection. Substantial lowering of LDL-C

Comments: Safety-elevations in AST were 1.1% pravastain vs. 3.3% for atorvastatin (P<0.001), myalgias or muscle aches or elevations in CK were 2.7 vs. 3.3% for P vs. A (NS)

PROVE-IT
Death or Major CV Event

<table>
<thead>
<tr>
<th>Time</th>
<th>RR</th>
<th>Pravastatin</th>
<th>Atorvastatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 days</td>
<td>1.9%</td>
<td>2.2%</td>
<td></td>
</tr>
<tr>
<td>90 days</td>
<td>5.3%</td>
<td>7.7%</td>
<td></td>
</tr>
<tr>
<td>180 days</td>
<td>12.2%</td>
<td>14.1%</td>
<td></td>
</tr>
</tbody>
</table>

TNT: Results- Outcomes

Outcome | RR | P
--- | --- | ---
First major CV event | -22% | <0.001
CHD death or nonfatal MI | -20% | 0.002
Fatal or nonfatal stroke | -25% | 0.02

TNT Results: Safety

<table>
<thead>
<tr>
<th>Treatment-related AEs (%)</th>
<th>Atorvastatin 10mg (n=5006)</th>
<th>Atorvastatin 80mg (n=4995)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment-related myalgia (%)</td>
<td>234 (4.7)</td>
<td>241 (4.8)</td>
</tr>
<tr>
<td>Rhabdomyolysis* (%)</td>
<td>3 (0.06)</td>
<td>2 (0.04)</td>
</tr>
</tbody>
</table>

AST/ALT elevated >3x ULN (%) | 9 (0.2) | 60 (1.2) |

*No cases were considered by the investigator with direct responsibility for the patient to be causally related to ATORVASTATIN, and none met ACC/AHA/NHLBI criteria for rhabdomyolysis
**TNT: Conclusion**

- Intensive lipid-lowering therapy with 80mg/d of atorvastatin in patients with stable CHD provides significant reduction in first major CV event beyond that afforded by treatment with 10mg of atorvastatin per day.
- This outcome is achieved at the expense of increased LFT’s and no overall change in all-cause mortality.


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**High-Sensitivity C-reactive Protein (hs-CRP) and CVD Risk**

- Acute-phase reactant produced by the liver in response to interleukin-6 and other cytokines.
- Epidemiologic studies suggest hs-CRP is a strong independent risk for myocardial infarction (MI), stroke, and PVD in CHD and CHD-free subjects.
- Strongly associated with increased CHD events in patients with unstable angina, stable angina, and history of MI.
- Levels >0.38 mg/dL independently predictive of vascular risk.


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**When to Measure hs-CRP**

- Measure hs-CRP when it influences decision to use lipid-lowering treatment:
  - Primary prevention with moderate risk (10%-20% 10-y CHD risk).
  - Primary prevention in young individuals with strong family history.
  - Secondary prevention with LDL-C <100 mg/dL, non-HDL-C <130 mg/dL.
- No need to measure in:
  - Secondary prevention and type 2 diabetes with LDL-C >100 mg/dL or non-HDL-C >130 mg/dL.


---

**Cut points of risk for hs-CRP**

<table>
<thead>
<tr>
<th>Risk level</th>
<th>hs-CRP (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Average</td>
<td>1.0 - 3.0</td>
</tr>
<tr>
<td>High</td>
<td>&gt;3.0</td>
</tr>
</tbody>
</table>

Summary

- NCEP ATP III guides us to address LDL-C first, then issues of HDL-C, TG, non-HDL and the metabolic syndrome.
- New studies re-affirm role of statins in elderly, women, diabetics and possibly those with CHD regardless of starting cholesterol values (?)- they also suggest lower optional targets for select patients.
- New agents open door for further consideration of novel combinations with statins for those not tolerating high dose statins.

CRP and Risk Assessment – 2003

- hs-CRP adds prognostic information to the Framingham Risk Score.
- As hs-CRP and LDL-C tend to detect somewhat different high-risk groups, a combined screening approach using both bio-markers is superior to the use of either alone.
- In primary prevention, high-hs-CRP/low-LDL-C individuals are at higher absolute risk than low-hs-CRP/high-LDL-C individuals, yet only the latter group is currently recommended for statin therapy.
- However, modulating hs-CRP has not yet been shown to affect cardiovascular risk.
