Modifying the Progression of Atherosclerosis

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Accreditation:
Pharmacists: 0788-0000-10-086-001-P
Pharmacy Technicians: 0788-0000-10-086-001-T
Nurses: N-635

Target Audience:
Pharmacists, Technicians & Nurses

Program Overview:
This program will review recent developments in the understanding of how statins modify the progression of atherosclerosis, describe the principles and limitations of statin therapy and outline the clinical evidence that has shaped today's concepts of lipid management. The participant must understand the potential of currently available therapies along with their probable results and possible side effects and play an active role in educating patients on their strategies for modifying the progression of atherosclerosis.

Objectives:
• Describe the epidemiology and etiology of atherosclerosis
• Outline the evidence and developments in the understanding of how statins modify the progression of atherosclerosis
• Describe the benefits and limitations of statin therapy to include mechanisms of action, efficacy, dose and duration of therapy
• Review the pharmacist’s role in counseling patients on lifestyle changes, drug treatment strategies and medication adherence to improve the quality of life and long-term maintenance of patients with atherosclerosis

The complications

› Myocardial infarction (MI)
› Stroke
› Peripheral vascular disease
› Kidney disease

Speaker:
Dr. Watson’s research interests include improving the care of heart failure patients and developing programs to improve medication appropriateness and adherence. She practices in the in-patient medicine and cardiology services at the University of Maryland Medical Center as well as at the heart failure clinic at the Veterans Administration Hospital.

Speaker Disclosure:
Dr. Watson has no actual or potential conflicts of interest in relation to this program.
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Risk factors

<table>
<thead>
<tr>
<th>Non-modifiable</th>
<th>Modifiable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Smoking</td>
</tr>
<tr>
<td>Gender</td>
<td>Obesity</td>
</tr>
<tr>
<td>Family history</td>
<td>Diabetes</td>
</tr>
<tr>
<td></td>
<td>High blood pressure</td>
</tr>
<tr>
<td></td>
<td>Cholesterol levels</td>
</tr>
<tr>
<td></td>
<td>Total cholesterol</td>
</tr>
<tr>
<td></td>
<td>Triglycerides</td>
</tr>
<tr>
<td></td>
<td>High-density lipoprotein (HDL)</td>
</tr>
<tr>
<td></td>
<td>Low-density lipoprotein (LDL)</td>
</tr>
</tbody>
</table>

Cholesterol and Cardiovascular Outcomes

- Triglycerides: elevated levels increase the risk of cardiovascular disease (CVD) by 14% in men and 37% in women
- Total cholesterol: 46% of CV-related deaths can be attributed to levels ≥ 180 mg/dL
- HDL: for every 1 mg/dL increase there is a 2–3% reduction in the risk of CV events

<table>
<thead>
<tr>
<th>LDL-cholesterol (mg/dL)</th>
<th>Age-adjusted 10 yr rate of CVD for Men</th>
<th>Age-adjusted 10 yr rate of CVD for Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 130</td>
<td>7.3%</td>
<td>2.3%</td>
</tr>
<tr>
<td>130–159</td>
<td>11.3%</td>
<td>6.5%</td>
</tr>
<tr>
<td>≥ 160</td>
<td>17.3%</td>
<td>10.6%</td>
</tr>
</tbody>
</table>

Stamler J JAMA 1986;256:2827–8
Modifying the Progression of Atherosclerosis

Accumulation of modified low-density lipoprotein (LDL) particles
Inflammatory cell migration
Inflammatory cell activation
Accumulation of macrophages and formation of "foam cells"
Formation of fatty streaks
Smooth muscle cell recruitment
Fibrous cap formation
Weakening/erosion of fibrous cap
Vulnerable plaque

Hansson GK. NEJM 2005;352:1685-95


Comparison of Effects on Lipoproteins*

<table>
<thead>
<tr>
<th>Class</th>
<th>High density lipoprotein (HDL)</th>
<th>Low density lipoprotein (LDL)</th>
<th>Total cholesterol</th>
<th>Triglycerides</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bile acid sequestrants</td>
<td>↑ 3–5%</td>
<td>↓ 15–30%</td>
<td>↓ 20%</td>
<td>No change or ↑ 3–10%</td>
</tr>
<tr>
<td>Cholesterol Absorption Inhibitors</td>
<td>↑ 0–5 %</td>
<td>↓ 18–20%</td>
<td>↓ 13–14%</td>
<td>↑ 5–11%</td>
</tr>
<tr>
<td>Fibric acid derivatives</td>
<td>↑ 10–20% (can increase if high triglycerides)</td>
<td>↓ 5–15%</td>
<td>↓ 9–19%</td>
<td>↓ 40–55%</td>
</tr>
<tr>
<td>HMG-CoA Reductase inhibitors (statins)</td>
<td>↑ 1–22%</td>
<td>↓ 21–63%</td>
<td>↓ 16–58%</td>
<td>↓ 6–53%</td>
</tr>
<tr>
<td>Nicotinic acid</td>
<td>↑ 15–35%</td>
<td>↓ 5–25%</td>
<td>↓ 20–25%</td>
<td>↓ 20–50%</td>
</tr>
</tbody>
</table>

*Pooled data regardless of indication

Poll Question 1

The primary target of cholesterol lowering therapy is:
A. No Answer
B. Triglycerides
C. High-density lipoprotein (HDL)
D. Low-density lipoprotein (LDL)
Modifying the Progression of Atherosclerosis

The Statins
Our first line defense against LDL

Mechanism of Action

Statins → HMG-CoA
Mevalonate
Mevalonate pyrophosphate
Isopentenyl pyrophosphate
Geranyl pyrophosphate
Farnesyl pyrophosphate
Squalene
Cholesterol

Is it just the cholesterol lowering benefits?
- Anti-inflammatory effects
- Plaque stabilization
- Reduction in plaque growth
- Increased nitric oxide bioavailability
- Improves endothelial dysfunction

Heart Protection Trial
- 20,536 adults aged 40 to 80 years at high risk for a CV event
- Simvastatin 40 mg daily vs. placebo
- Primary outcome: all-cause mortality
  - 12.9% simvastatin group and 14.7% placebo group
  - Mean duration of follow-up: 5 yrs

Heart Protection Study Collaborative Group Lancet 2002; 360: 7–22
Secondary Prevention

<table>
<thead>
<tr>
<th>Trial</th>
<th>Study design</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROVE-IT TIMI 22</td>
<td>Hospitalization for ACS randomized to Atorvastatin 80 mg/d vs. pravastatin 40 mg/d</td>
<td>Primary end point: all-cause death, MI, hospitalization for USA, revascularization &amp; stroke</td>
</tr>
<tr>
<td>(n=4162) Mean f/u = 24 mo.</td>
<td></td>
<td>prav 26.3 % vs. ator 22.4 % (HR 0.84; 95% CI 0.75–0.93, p=0.005)</td>
</tr>
<tr>
<td>The A to Z trial</td>
<td>Hospitalization for ACS</td>
<td>Primary end point: cardiovascular death, nonfatal MI, readmission for ACS, and stroke</td>
</tr>
<tr>
<td>(n=4497) Median f/u ~ 24 mo.</td>
<td></td>
<td>placebo + simv 16.7% vs 14.4% simvastatin only</td>
</tr>
<tr>
<td>TNT Trial</td>
<td>Stable coronary disease &amp; LDL &lt; 130 mg/d</td>
<td>Primary end point: first major cardiovascular event 80 mg group 8.7% vs. 10 mg group 10.9% (HR 0.89; 95% CI 0.76–1.04; p=0.14)</td>
</tr>
<tr>
<td>(n=10001) Median f/u ~4.9 yr</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ACS = acute coronary syndrome, CI= confidence interval, HR = hazard ratio, MI = myocardial infarction, USA = unstable angina

JUPITER Trial

- Randomized trial (rosuvastatin 20 mg/day vs. placebo) 17,802 apparently healthy men and women
  - LDL < 130 mg/dl and high-sensitivity C-reactive protein levels ≥2.0 mg/L
  - Primary end point of MI, stroke, arterial revascularization, hospitalization for unstable angina, or CV death
    - Rate of 0.77 and 1.36 events per 100 person-years of follow-up in the rosuvastatin and placebo groups, respectively (hazard ratio for rosuvastatin, 0.56; 95% confidence interval, 0.46 to 0.69; P<0.00001)
    - Mean follow-up ~2.2 years


Pharmacology and Pharmacokinetics

<table>
<thead>
<tr>
<th>Statin</th>
<th>Lipophilicity</th>
<th>Half-life</th>
<th>Metabolism</th>
<th>Excretion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
<td>Lipophilic</td>
<td>14 hrs</td>
<td>Extensive 3A4</td>
<td>Bilary</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>Hydrophilic</td>
<td>&lt; 3 hrs</td>
<td>Extensive 2C9,3A4</td>
<td>Feces</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>Lipophilic</td>
<td>3–4 hrs</td>
<td>Extensive 3A4</td>
<td>Bile</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>Lipophilic</td>
<td>12 hrs</td>
<td>Marginal 2C9–2C8</td>
<td>Feces</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>Hydrophilic</td>
<td>77 hrs</td>
<td>Extensive sulfation</td>
<td>Renal and hepatic</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>Lipophilic</td>
<td>Unknown</td>
<td>Extensive 3A4</td>
<td>Feces</td>
</tr>
</tbody>
</table>

Some other notable differences

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose considerations for renal insufficiency</th>
<th>LDL lowering effect</th>
<th>Generic formulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
<td>No</td>
<td>36–52%</td>
<td>No</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>No</td>
<td>22–36%</td>
<td>Yes</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>Yes</td>
<td>10–44%</td>
<td>Yes</td>
</tr>
<tr>
<td>Pitavastatin</td>
<td>No</td>
<td>32–45%</td>
<td>No</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>Yes</td>
<td>21–40%</td>
<td>Yes</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>Yes</td>
<td>45–63%</td>
<td>Yes</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>Yes</td>
<td>26–50%</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Atorvastatin

- Approved to reduce CV outcomes in select populations
- Dose range: 10–80 mg
- Considerations
  - Drug interactions
    - Digoxin
    - Rifampin
    - Oral Contraceptives
    - Cyclosporine: maximum dose 10 mg
    - Clarithromycin, itraconazole, ritonavir + saquinavir or lopinavir + ritonavir: caution exceeding > 20 mg

Fluvastatin

- Approved to reduce the risk of coronary revascularization in those with CV disease
- Dosing
  - Immediate release: 20–80 mg in one/two doses
  - XL formulations: 80 mg in one daily
  - Renal impairment: dose > 40 mg have not been studied in those with severe renal impairment
- Considerations
  - Drug interactions
    - Cholestyramine
    - Fluconazole
    - Glyburide
    - Phenytoin

Lovastatin

- Approved for primary prevention of cardiovascular disease and for use in those with CV disease
- Dosing
  - 10–80mg/day in one or two divided doses
  - Use caution with doses > 20mg if creatinine clearance (CrCl) < 30 ml/min
- Considerations
  - Drug interactions
    - Avoid use with: itraconazole, ketoconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, nefazodone or large amounts of grapefruit juice
    - Do not exceed 20 mg with: fibrates, ≥ 1g/day of niacin, cyclosporine, danazol
    - Do not exceed 40 mg with: amiodarone or verapamil


Livalo (pitavastatin) Package Insert. Kowa Pharmaceutical America, Montgomery, AL Jan 2010

Lipitor (Atorvastatin) Package Insert. Pfizer New York, NY June 2009


Mevacor (lovastatin) Package Insert. Merck & Co., Whitehouse Station, NJ May 2010
### Pitavastatin

**Dosing**
- Range 1–4 mg once daily
- Administer any time of the day, with or without food

**Considerations**
- Drug interactions: ritonivir, erythromycin, rifampin and fibrates

**Limitations**
- Effects on CV outcomes has not been determined
- Not studied in combination with protease inhibitors
- ↑ risk of severe myopathy with doses > 4 mg daily
- Renal impairment
  - GFR 30 – 60 mL/min/1.73m² and hemodialysis: Starting dose 1 mg/day; maximum dose 2 mg once daily
  - GFR < 30 mL/min/1.73m²: do not use

### Pravastatin

**Approved for primary and secondary prevention of CV events**

**Dosing**
- 10–80 mg daily
- Starting dose of 10 mg for those with significant hepatic or renal dysfunction

**Considerations**
- Bile–acid binding resins
- Cyclosporine: 10–20 mg/day

### Rosuvastatin

**Approved for use for primary prevention of CV disease**

**Dosing**
- 5–40 mg once daily
- CrCl < 30 mL/min (not on hemodialysis): starting dose 5mg/day and maximum dose 10 mg/day

**Considerations**
- Asian population: consider starting dose of 5 mg
- Drug interactions
  - 5 mg maximum dose with: cyclosporine
  - 10 mg maximum dose with: gemfibrozil, lopinavir/ritonavir or atazanavir/ritonavir
- Warfarin

### Simvastatin

**Approved for prevention of CV events in high risk individuals**

**Dosing**
- 5–80 mg
- Severe renal impairment: starting dose of 5 mg daily
- 80 mg dose
- Do not use in Chinese patients receiving niacin–containing products
- Monitor liver function test more frequently

**Drug interactions**
- Avoid use: itraconazole, ketoconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, nefazodone or large amounts of grapefruit juice
- 10 mg maximum dose: gemfibrozil, cyclosporine, danazol
- 20 mg maximum dose: amiodarone, verapamil
- 40 mg maximum dose: verapamil
- Warfarin

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**GFR = glomerular filtration rate**
**Livalo (pitavastatin) Package Insert. Kowa Pharmaceuticals America, Montgomery, AL Jan 2010**
**Pravastatin (Pravachol) Package Insert. Bristol-Myers Squibb, Princeton, NJ July 2010**
**Crestor (rosuvastatin) Package Insert. AstraZeneca Pharmaceuticals, Wilmington, DE June 2010**
**Zocor (simvastatin) Package Insert. Merck & Co Whitehouse Station, NJ May 2010**
Safety

¬ Elevated hepatic transaminases
  - Occurs in 0.5–2% of statin users
  - Progression to liver failure is rare
¬ Myopathy
  - Occurs in 1.5–10% of statin users
¬ Myositis
  - Muscle symptoms + creatine kinase > 10 x upper limit of normal
  - 0.27 to 2.37 cases per million prescriptions
¬ Rhabdomyolysis
  - Criteria for myositis + elevated serum creatinine
  - < 1 death/million prescriptions

Risk factors for Statin–Associated Myopathy

¬ Age > 80 years old (female > men)
¬ Small body frame/frail
¬ Multiple disease states
¬ Alcohol abuse
¬ Multiple medications
  - Amiodarone
  - Antifungals: azoles, itraconazole, ketoconazole
  - Cyclosporine
  - Erythromycin and clarithromycin
  - Fibrates (especially gemfibrozil)
  - HIV protease inhibitors
  - Macrolide antibiotics
  - Verapamil

Poll Question 2

How frequently should liver enzymes be monitored in most patients receiving statin therapy?

A. No answer
B. At baseline and then every 12 weeks
C. At baseline, 12 weeks and then semiannually
D. At baseline and then semiannually

Monitoring

¬ Headache, dyspepsia
¬ Muscle soreness, tenderness, or pain
¬ Alanine transferase/aspartate transferase (AST/ALT)
Special Populations

- Hepatic impairment
  - Use caution
  - Contraindicated in active liver disease
- Pregnancy/nursing mothers
  - Contraindicated

PROSPER Trial

- 5,804 pts aged 70–82 with vascular disease, smoking, hypertension or diabetes
- Pravastatin 40 mg vs. placebo
- Follow-up 3.2 years
- Primary endpoint: coronary death, non-fatal MI, and fatal or non-fatal stroke
  - 34% reduction in those treated with pravastatin
    (408 vs. 473 events, hazard ratio 0.85, 95% confidence interval 0.74–0.97, p = 0.014)

National Cholesterol Education Panel III and 2004 Update* Recommendations for LDL cholesterol

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>LDL Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD* or CHD risk equivalents ^ (10 year risk &gt; 20%)</td>
<td>&lt;100 mg/dl</td>
</tr>
<tr>
<td>Optional goal &lt; 70 mg/dl</td>
<td></td>
</tr>
<tr>
<td>2+ Risk Factors* (10 year risk &lt; 20%)</td>
<td>&lt;130 mg/dl</td>
</tr>
<tr>
<td>0-1 Risk Factor (10 year risk &lt; 20%)</td>
<td>&lt;160 mg/dl</td>
</tr>
</tbody>
</table>

* no difference in goals based on age; CHD = coronary heart disease
^ myocardial infarction, unstable angina, stable angina, coronary angioplasty or bypass surgery, or evidence of clinically significant myocardial ischemia.
¥ abdominal aortic aneurysm, and carotid artery disease, diabetes, peripheral arterial disease, transient ischemic attacks or stroke of carotid origin.
¥ cigarette smoking, hypertension, low HDL cholesterol, family history of premature cardiovascular disease and age (men 45 years; women 55 years).

Choosing a statin?

- Are there any contraindications to statin therapy?
- What is the indication for statin therapy and/or what percent LDL lowering effect is required?
  - Remember the RULE OF SIX
- Are there any notable patient related factors?
  - Renal dysfunction
  - Drug interactions
    - HIV protease inhibitors
    - Cyclosporine
    - Cost

www.nhlbi.nih.gov/guidelines/cholesterol
Patient Counseling

- Discuss the patient’s understanding of their cholesterol and need for therapy
  - Clarify the clinical benefits of therapy…it’s not just the LDL
  - Review the ACTUAL risk of adverse effects
- Set short- and long-term goals for cholesterol and therapeutic lifestyle changes
- Provide tips to help the patient to remember to take their medications
- Encourage support of family and friends

Therapeutic Lifestyle Changes

<table>
<thead>
<tr>
<th>Component</th>
<th>Recommendation</th>
<th>Approximate LDL reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-raising nutrients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saturated fats</td>
<td>&lt; 7% of total calories</td>
<td>8–10%</td>
</tr>
<tr>
<td>Dietary cholesterol</td>
<td>&lt; 200 mg/day</td>
<td>3–5%</td>
</tr>
<tr>
<td>Therapeutic options for LDL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>lowering</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plant sterols/stanols</td>
<td>2 grams per day</td>
<td>6–15%</td>
</tr>
<tr>
<td>Viscous (soluble) fiber</td>
<td>10–25 grams per day</td>
<td>3–5%</td>
</tr>
<tr>
<td>Weight loss</td>
<td>Adjust total caloric intake to</td>
<td>5–8%</td>
</tr>
<tr>
<td></td>
<td>maintain desirable body weight/</td>
<td></td>
</tr>
<tr>
<td></td>
<td>prevent weight gain</td>
<td></td>
</tr>
<tr>
<td>Physical activity</td>
<td>Moderate exercise, 30 minutes</td>
<td>3–4%</td>
</tr>
<tr>
<td></td>
<td>most days</td>
<td></td>
</tr>
</tbody>
</table>

Frequently Asked Questions

- Is this too high of a dose?
- Can statin therapy be discontinued?
- Can the dose be reduced in the future?
- Is statin therapy indicated even though LDL levels are at goal?
- Can too low of LDL cholesterol levels be harmful?

Prevention is Key!!

- Aspirin therapy
- Blood pressure control
- Diabetes control
- Diet, exercise and weight loss
- Smoking cessation
- Alcohol moderation
- Cholesterol management
Learning Objectives

- Describe the epidemiology and etiology of atherosclerosis
- Outline the evidence and developments in the understanding of how statins modify the progression of atherosclerosis
- Describe benefits and limitations of statin therapy to include mechanisms of action, efficacy, dose and duration of therapy
- Review the pharmacist’s role in counseling patients on lifestyle changes, drug treatment strategies and medication adherence to improve the quality of life and long-term maintenance of patients with atherosclerosis.