Evidence-based Strategies for the Management of Dyslipidemia: A Case Study Approach

Conducted during the 41st ASHP Midyear Clinical Meeting
Anaheim, California
CONTINUING EDUCATION ACCREDITATION

The American Society of Health-System Pharmacists is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. This program provides 1 hour (0.1 CEU) of continuing education credit (program number 204-000-06-439-H01). After successful completion of the CE post test, participants can print the CE statement online at www.ashpadvantage.com.
Evidence-based Strategies for the Management of Dyslipidemia:
A Case Study Approach

PROGRAM AGENDA

Introductory Remarks
Joseph Saseen, Pharm.D., BCPS, FCCP, Program Moderator

Overview of Atherogenesis and Goals of Pharmacotherapy
Barbara S. Wiggins, Pharm.D., BCPS

Case Studies in the Management of Dyslipidemia: Understanding Statin Myopathy and Avoiding Clinical Inertia
Joseph Saseen, Pharm.D., BCPS, FCCP

PROGRAM FACULTY

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University of Colorado Health Sciences Center
Denver, Colorado

Barbara S. Wiggins, Pharm.D., BCPS (AQ Cardiology)
Pharmacy Clinical Specialist – Cardiology
University of Virginia Health System
Clinical Assistant Professor in Internal Medicine
University of Virginia School of Medicine
Charlottesville, Virginia
PROGRAM DESCRIPTION

Cardiovascular disease is the number one killer of both men and women in the United States, and the disease has an enormous economic impact. Dyslipidemia is a major risk factor for cardiovascular disease. Epidemiologic data have demonstrated a correlation between low-density lipoprotein (LDL) cholesterol and the risk for coronary heart disease (CHD). Therefore, LDL cholesterol is the primary target of therapeutic interventions for patients with dyslipidemia. Other lipids, lipoproteins, and CHD risk factors are secondary targets. HMG-CoA reductase inhibitors, otherwise known as statins, are the agents of choice for lowering LDL cholesterol. Statins are also effective in lowering the risk of cardiovascular events. Intensive lipid-lowering therapy utilizing high-dose statins has been shown to provide greater clinical benefit than moderate-dose statin therapy for reduction of cardiovascular events in those patients at very high risk.

Some patients with dyslipidemia fail to achieve a target LDL-cholesterol goal despite pharmacotherapy with maximum recommended statin doses. Failure to achieve adequate LDL reduction can be costly and the use of combination drug therapy may be necessary to help patients achieve therapeutic goals. Some patients may also experience statin-associated side effects such as myopathy. Although these muscle-related side effects often decrease patient compliance, they do not always represent a serious adverse drug event.

This program will describe the rationale for targeting LDL cholesterol in patients with dyslipidemia. Three case studies will be used to illustrate the therapeutic decision-making process based on the results of current clinical trials and scientific evidence. Patient cases will be varied to illustrate evidence-based options available to pharmacists who manage drug therapy in this population. An interactive question-and-answer discussion will be held at the conclusion of the program.

LEARNING OBJECTIVES

At the conclusion of this presentation, participants should be able to:

- Characterize the relationship between LDL cholesterol and the risk for CHD, and identify the primary target and a secondary target for therapeutic intervention to reduce CHD risk in patients with dyslipidemia.
- Assess the lipid profile and other CHD risk factors in a patient hospitalized for acute coronary syndrome, and recommend non-drug as well as drug therapy to manage dyslipidemia.
- Evaluate the response to lipid-lowering drug therapy in a patient experiencing muscle pain and revise the therapeutic plan if the response is inadequate.
- Discuss the rationale and recommendation for managing a patient with diabetes and uncontrolled dyslipidemia.
- Identify common barriers to achieving therapeutic goals in patients with dyslipidemia and strategies for overcoming these barriers.
Case 1

- MG is a 75-yr-old male with DM, and no significant CAD Hx, who presents to the ER with a CC of chest pain. Patient is diagnosed with a STEMI and undergoes cardiac catheterization. He was on no medications prior to admission. His fasting lipid panel revealed the following:

  - Fasting Labs: TC = 188 mg/dL, HDL-C = 39 mg/dL
  - LDL-C = 123 mg/dL, TGs = 157 mg/dL

- Patient does not smoke or drink.

- Medications on discharge:
  - Aspirin 325 mg daily, clopidogrel 75 mg daily, metoprolol 50 mg twice daily, lisinopril 10 mg daily and atorvastatin 80 mg daily.

- MG now presents to clinic 4 weeks following hospital discharge and pertinent laboratory results are as follows:
  - AST = 110
  - ALT = 123
  - ALK Phos = 450

Reflective Questions

- What is this patient's LDL goal?

- What percentage reduction in LDL is needed?

- Is atorvastatin at 80 mg appropriate in this patient?

- Should the atorvastatin be discontinued?

- What medication changes if any should occur?
Case 2

- GG is a 56-yr-old man with a past medical history of hypertension and dyslipidemia.
- Smokes, is obese (waist circumference is 45”, BMI is 32 kg/m2), and Framingham Risk score is 18%
- Medications:
  - Simvastatin 40 mg daily at bedtime, aspirin 81 mg daily, lisinopril 10 mg daily, hydrochlorothiazide 25 mg daily
- Fasting Labs:  TC = 180 mg/dL, HDL-C = 39 mg/dL, LDL-C = 95 mg/dL, TGs = 180 mg/dL glucose 110 mg/dL
  - all other labs, including a TSH are within normal limits
- GG has recently read information from the internet about muscle-related statin side effects. He has had muscle soreness for many years now, but did not think it was a problem. He reported this to his physician, who then measured his creatine kinase; it was 400 IU/L (normal: 0-200). GG is now concerned about continuing his statin.

Reflective Questions

- What are his goals of therapy, and what is the benefit of statin therapy?

- Fear of myopathy is a barrier to treatment. Does simvastatin have to be stopped because of his muscle symptoms?

- What medication changes should be implemented?
Case 3

- RP is a 65-yr-old woman on atorvastatin 10 mg daily.
- Past medical history: type 2 diabetes, hypertension, dyslipidemia, and an ischemic stroke.
- Medications:
  - Atorvastatin 10 mg daily, aspirin 81 mg daily, losartan 100 mg daily, hydrochlorothiazide 25 mg daily, metformin 1000 mg twice daily, insulin glargine 30 U daily in the evening
- Fasting Labs: TC = 185 mg/dL, HDL-C = 45 mg/dL, LDL-C = 90 mg/dL, TGs = 250 mg/dL
  - A1C is 6.8 mg/dL (target < 7 mg/dL for diabetes)
  - all other labs, within normal limits

Reflective Questions

- What are her goals of therapy?
- Is single drug therapy as effective as combination drug therapy?
- “Clinical Inertia” is a barrier to treatment. What is the evidence supporting treatment of this type of patient?
Evidence-based Strategies for the Management of Dyslipidemia: 
A Case Study Approach

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Pharmacy Clinical Specialist – Cardiology
University of Virginia Health System
Clinical Assistant Professor in Internal Medicine
University of Virginia School of Medicine
Charlottesville, Virginia

Barbara S. Wiggins, Pharm.D., BCPS, is Clinical Assistant Professor in Internal Medicine at the University of Virginia School of Medicine, Clinical Instructor for the University of Virginia School of Nursing, and Pharmacy Clinical Specialist in Cardiology at the University of Virginia Health System Heart Center in Charlottesville, Virginia. Dr. Wiggins also holds an adjunct faculty appointment of Clinical Assistant Professor at Virginia Commonwealth University/Medical College of Virginia School of Pharmacy in Richmond, Virginia.

In 1996, Dr. Wiggins received her Doctor of Pharmacy degree from Virginia Commonwealth University/Medical College of Virginia in Richmond, Virginia, after which she completed a fellowship in Cardiology and Emergency Medicine. Some of Dr. Wiggins’ accomplishments include: Junior Alumni of the Year Award from St. Louis College of Pharmacy, Rho Chi Pharmacy Honor Society, Merck Award for Clinical Research, and board certification in pharmacotherapy with added qualifications in cardiology. Dr. Wiggins has published two book chapters and authored numerous articles in the fields of cardiology and emergency medicine. Dr. Wiggins is currently co-authoring a book entitled “A Pharmacists Guide to Lipid Management”.

Evidence-based Strategies for the Management of Dyslipidemia: A Case Study Approach

41st ASHP Midyear Clinical Meeting
Anaheim ~ Orange County, California

Overview of Atherogenesis and Goals of Pharmacotherapy

Barbara S. Wiggins, Pharm.D., BCPS
(AQ Cardiology)
Pharmacy Clinical Specialist
University of Virginia Health System
Charlottesville, Virginia

Pathogenesis of Atherosclerosis

- Atherosclerosis
  - Diffuse disease of medium and larger arteries
  - Progressive disease

Age 15  Age 40  Age 65
Pathogenesis of Atherosclerosis

- Intrinsic cells
  - Endothelium
  - Smooth muscle Cells
- Inflammatory Cells
  - Mast Cells
  - T-Lymphocytes
  - Macrophages

Mechanisms of Atherosclerosis

- Smooth Muscle Cells
- Macrophage
- T-Lymphocytes
Optical Coherence Tomogram of a Vulnerable Plaque

A, OCT image of a lipid-rich cartoid plaque showing a signal-poor lipid pool (L) with poorly delineated borders beneath a thin homogeneous band, corresponding to fibrous cap (arrow).

Atherosclerosis Timeline

Role of Lipid-Lowering Therapy

- Changes composition especially in vulnerable plaques
- Stabilizing plaques
- Reduces progression
- Partial regression
**Risk Factors**

- Low HDL < 35 mg/dL
- Hypertension
- Smoking
- Diabetes
- Age
- Family History

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**NCEP ATP III: 2004 Report**

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>LDL-C goal (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High Risk *</td>
<td>&lt; 100 (Optional &lt; 70)</td>
</tr>
<tr>
<td>CHD or equivalents (10-yr risk &gt; 20%)</td>
<td></td>
</tr>
<tr>
<td>Moderately High Risk *</td>
<td>&lt; 130 (Optional &lt; 100)</td>
</tr>
<tr>
<td>2+ risk factors (10-yr risk 10 to 20%)</td>
<td></td>
</tr>
<tr>
<td>Moderate Risk</td>
<td>&lt; 130</td>
</tr>
<tr>
<td>2+ risk factors (10-yr risk &lt; 10%)</td>
<td></td>
</tr>
<tr>
<td>Lower Risk</td>
<td>&lt; 160</td>
</tr>
<tr>
<td>0 to 1 risk factors</td>
<td></td>
</tr>
</tbody>
</table>

*Very high risk factors < 70 mg/dL.
*High risk or moderately high with lifestyle-related risk should be on therapeutic lifestyle changes regardless of LDL-C, and should achieve at least a 30 to 40% LDL-C reduction.
†10-yr risk of CHD based on Framingham Scoring.

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**Magnitude of the Disease**

- Number of killer of men and women in the U.S.
- Present in 13.2 million.
- Accounts for 37.3% of all adult deaths.
- Claims an average of 1 life every 35 seconds.

AHA Heart Disease and Stroke Statistics – 2006.
Case Study #1: Management of Statin-induced Transaminase Elevations

- MG is a 75-yr-old male with DM, and no significant CAD Hx who presents to the ER with a CC of chest pain. Pt. is diagnosed with a STEMI and undergoes cardiac cath. His fasting lipid panel revealed the following:
  - TC = 188 mg/dL, HDL-C = 39
  - LDL-C = 123, TGs = 157
- The patient is started on atorvastatin 80 mg

Case #1 Cont:

- The patient presents to clinic 1 month following hospital discharge and pertinent lab results are as follows:
  - AST = 110
  - ALT = 123
  - ALK Phos = 450
Case #1 Cont.

- What is this patient's LDL Goal?
- What percent reduction in LDL is needed?
- Is atorvastatin at 80 mg appropriate in this patient?
- Should the atorvastatin be discontinued?
- What medication changes if any should occur?

MIRACL

Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering

- Randomized, double-blind (n=3086)
- Tx = atorvastatin 80mg or placebo x 16 weeks
- Primary endpoint
  - Death, nonfatal acute MI, cardiac arrest with resuscitation, or recurrent symptomatic myocardial ischemia


MIRACL

- Results
  - Primary endpoint occurred in 14.8% in atorvastatin group vs 17.4% in Placebo (p=0.48)
  - Atorvastatin 80 mg reduces recurrent ischemic events (p=0.02)
  - LDL lowering 124 mg/dL to 72 mg/dL

**MIRACL**

Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering

- **Safety and Tolerability**
  - **Hepatotoxicity**
    - LFT’s > 3 x ULN 2.5% for atorvastatin 80 mg vs 0.6% for placebo (p<0.001)
  - **Myotoxicity**
    - no cases of myositis reported


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**PROVE IT – TIMI 22 RESULTS: All-Cause Death or Major CV Events in All Randomized Subjects**

![Graph showing event rates](image)

Cannon CP et al, NEJM 2004;350:1495-504

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**Clinical Relevance of Achieved LDL and Achieved CRP After Treatment with Statin Therapy**

![Graph showing event rates](image)

**PROVE-IT TIMI 22**

Safety and Tolerability

- LFT abnormalities
  - 1.1% in pravastatin group versus 3.3% in atorvastatin group (p<0.001)
- No cases of Rhabdomyolysis
- No significant difference in rate of myalgias


**Treating to New Targets (TNT)**

- 10,001 patients randomized to atorvastatin 80 mg versus atorvastatin 10 mg
- All patients had stable CAD
- Primacy Endpoint
  - Occurrence of first major CV event (death, non fatal MI, resuscitation after cardiac arrest, fatal or non-fatal stroke)

LaRosa JC et al. NEJM 2005;305.

**Treating to New Targets (TNT)**

- Results
  - Primary endpoint occurred in 8.7% of patients on atorvastatin 80 mg vs. 10.9% for atorvastatin 10 mg
  - P<0.001
  - 22% relative risk reduction (P<0.001)
  - No difference in overall mortality

LaRosa JC et al. NEJM 2005;305.
Treating to New Targets (TNT)

- Safety and Tolerability
  - LFT abnormalities
    - 0.2% for atorvastatin 10 mg
    - 2.2% for atorvastatin 80 mg
    - P < 0.001

  Rates of discontinuation
  - 5.8% for atorvastatin 10 mg
  - 8.1% for atorvastatin 80 mg
  - P < 0.001 LaRosa JC et al. NEJM 2005;305.

Risk Factors for Statin-Hepatotoxicity

- Advanced age
- Diabetes
- Obesity
- Interacting medications

Case #1

- MG is a 75-yr-old male with DM, and no significant CAD Hx who presents to the ER with a CC of chest pain. MG is diagnosed with a STEMI and undergoes cardiac catheterization. His fasting lipid panel revealed the following:
  - TC = 188 mg/dL, HDL-C = 39
  - LDL-C = 123, TGs = 157

- The patient is started on atorvastatin 80 mg
Case #1 Cont:

- The patient presents to clinic 6 weeks following hospital discharge and pertinent lab results are as follows:
  - AST = 110
  - ALT = 123
  - ALK Phos = 450

Case #1 Cont.

- What is this patient’s LDL Goal?
  - < 70 mg/dL
- What percent reduction in LDL is needed?
  - ~ 43%
- Is atorvastatin at 80 mg appropriate in this patient?
  - Probably not
- Should the atorvastatin be discontinued?
  - Not always necessary
- What medication changes if any should occur?
  - Reduce the dose to 40 mg and continue to monitor

Hepatotoxicity - Management

- Obtain baseline LFTs on all patients
- Monitor for symptoms of hepatic injury
- Identify etiology
- Transaminase levels > 3 x ULN
- Use in pre-existing liver dysfunction
Evidence-based Strategies for the Management of Dyslipidemia: A Case Study Approach

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Joseph Saseen, Pharm.D., BCPS, FCCP, is Associate Professor of Clinical Pharmacy and Family Medicine at the University of Colorado at Denver and Health Sciences Center. Dr. Saseen received his Bachelor of Science and Doctor of Pharmacy degrees from the State University of New York at Buffalo, and completed a fellowship in ambulatory care research at the University of Illinois/University of Colorado.

Dr. Saseen practices as Clinical Pharmacy Specialist in the Department of Family Medicine. He is a board-certified pharmacotherapy specialist with added qualifications in cardiology. Dr. Saseen is a member of the Board of Regents and is Fellow of the American College of Clinical Pharmacy. Dr. Saseen has published several articles and book chapters related to cardiovascular disease pharmacotherapy. He has received many teaching awards at the University of Colorado. In May 2006, Dr. Saseen was honored as the recipient of the President’s Excellence in Teaching Award.
Understanding Statin Myopathy and Avoiding Clinical Inertia

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(AQ Cardiology)
Associate Professor
Departments of Clinical Pharmacy & Family Medicine
University of Colorado at Denver Health Sciences Center
Denver, Colorado

Case #2

• GG is a 56-yr-old man with a past medical history of hypertension and dyslipidemia.
• Smokes, is obese (waist circumference is 45”, BMI is 32 kg/m²), and Framingham Risk score is 18%
• Medications:
  – Simvastatin 40 mg daily at bedtime, aspirin 81 mg daily, lisinopril 10 mg daily, hydrochlorothiazide 25 mg daily
• Fasting Labs:  TC = 180 mg/dL, HDL-C = 39 mg/dL
  LDL-C = 95 mg/dL, TGs = 180 mg/dL
  glucose 110 mg/dL
  – all other labs, including a TSH are within normal limits.

Case #2 cont.

• GG has recently read information from the internet about muscle-related statin side effects.
• He has had muscle soreness for many years now, but did not think it was a problem.
• He reported this to his physician, who then measured his creatine kinase; it was 400 IU/L (normal: 0-200).
• GG is now concerned about continuing his statin.
Case #2 Reflective Questions

- What are his goals of therapy, and what is the benefit of statin therapy?
- Fear of myopathy is a barrier to treatment. Does simvastatin have to be stopped because of his muscle symptoms?
- What medication changes should be implemented?

NCEP ATP III: 2004 Report

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$^f$ High risk or moderately high with lifestyle-related risk should be on therapeutic lifestyle changes regardless of LDL-C, and should achieve at least a 30 to 40% LDL-C reduction by 10-yr risk of CHD based on Framingham Scoring.

AHA/NHLBI Scientific Statement

Metabolic Syndrome Diagnostic Criteria

<table>
<thead>
<tr>
<th>Measure (3 of 5 constitutes diagnosis)</th>
<th>Cut Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated waist circumference (in)</td>
<td>≥ 40 (men), ≥ 35 (women)</td>
</tr>
<tr>
<td>Elevated TGs (mg/dL)</td>
<td>≥ 150 or drug therapy</td>
</tr>
<tr>
<td>Reduced HDL-C (mg/dL)</td>
<td>&lt; 40 (men), &lt; 50 (women) or drug therapy</td>
</tr>
<tr>
<td>Elevated BP (mm Hg)</td>
<td>≥ 130/85 or drug therapy</td>
</tr>
<tr>
<td>Elevated fasting glucose (mg/dL)</td>
<td>≥ 100 or drug therapy</td>
</tr>
</tbody>
</table>

Cholesterol Treatment Trialists’ Collaborators

- Meta-analysis, 14 randomized controlled trials (n=90,056)

**Major Vascular Events (per 1 mmol/L LDL-C reduction)**

<table>
<thead>
<tr>
<th>Event Rate (%)</th>
<th>Control</th>
<th>Statin</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>0.6</td>
<td>0.4</td>
</tr>
<tr>
<td>1.0</td>
<td>0.6</td>
<td>0.4</td>
</tr>
<tr>
<td>1.5</td>
<td>0.6</td>
<td>0.4</td>
</tr>
<tr>
<td>2.0</td>
<td>0.6</td>
<td>0.4</td>
</tr>
<tr>
<td>2.5</td>
<td>0.6</td>
<td>0.4</td>
</tr>
<tr>
<td>3.0</td>
<td>0.6</td>
<td>0.4</td>
</tr>
<tr>
<td>3.5</td>
<td>0.6</td>
<td>0.4</td>
</tr>
</tbody>
</table>

*p<0.001

ASCOT-Lipid Lowering Arm

- 10,305 primary prevention patients, multiple CV risk factors randomized to placebo or atorvastatin 10 mg daily for 3.3 yrs
- Mean baseline LDL-C 133 mg/dL decreased to 90 mg/dL

**Nonfatal MI & CHD Death (%)**

<table>
<thead>
<tr>
<th>Years</th>
<th>Placebo</th>
<th>Atorvastatin 10 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
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<tr>
<td>1.5</td>
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<tr>
<td>3.5</td>
<td>3.0</td>
<td>2.5</td>
</tr>
</tbody>
</table>

36% reduction *p<0.0005

ATP III: 2004 Update

**Doses that Attain 30-40% LDL-C Reductions**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (mg/d)</th>
<th>LDL-C reduction (%)</th>
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</thead>
<tbody>
<tr>
<td>Atorvastatin (Lipitor®)</td>
<td>10</td>
<td>39</td>
</tr>
<tr>
<td>Lovastatin (Mevacor®)</td>
<td>40</td>
<td>31</td>
</tr>
<tr>
<td>Pravastatin (Pravachol®)</td>
<td>40</td>
<td>34</td>
</tr>
<tr>
<td>Simvastatin (Zocor®)</td>
<td>20-40</td>
<td>35-41</td>
</tr>
<tr>
<td>Fluvastatin (Lescol®)</td>
<td>40-80</td>
<td>25-35</td>
</tr>
<tr>
<td>Rosuvastatin (Crestor®)</td>
<td>5-10</td>
<td>39-45</td>
</tr>
</tbody>
</table>

National Lipid Association (NLA) Statin Safety Assessment Task Force

• Definitions describing muscle findings in patients taking statins:
  – **Myopathy**
    • Complaints of myalgia (muscle pain or soreness), weakness, and/or cramps, plus
    • Elevation in serum CK >10 x ULN
  – **Rhabdomyolysis**
    • CK 10,000 > IU/L, or
    • CK >10 x ULN plus an elevation in serum creatinine or medical intervention with IV hydration

ACC/AHA/NHLBI Clinical Advisory Risk Factors for Statin Myopathy

• Advanced age (esp. > 80 yrs, women >men)
• Severe chronic kidney disease
• Impaired liver function
• Perioperative periods
• Alcohol abuse
• Large quantities of grapefruit juice (certain statins)
• Interacting medications
• Hypothyroidism

NLA Recommendations Muscle and Statin Safety

1. Rule out other etiologies of muscle symptoms or an increased CK level.
2. Consider a baseline CK in patients who are at high risk of experiencing a muscle toxicity.
3. Do not measure CK in asymptomatic patients.
4. Appropriate counsel patients about the increased risk of muscle complaints.
5. Measure CK in symptomatic patients to help gauge the severity and guide therapy.
### NLA Recommendations

**Muscle and Statin Safety**

6. **Intolerable** muscle symptoms stop statin therapy regardless of CK; once resolved restart the same/different statin at same/lower dose.

7. **Tolerable** muscle complaints or asymptomatic with a CK < 10 the ULN, continue statin therapy at the same or reduced doses.

8. **Rhabdomyolysis**, stop statin therapy and treat accordingly; once recovered, re-evaluate the risk vs benefit of statin therapy.

*Am J Cardiol 2006;97(suppl 8A):89C–94C.

### Statin Pharmacokinetic Profiles

<table>
<thead>
<tr>
<th>Statin</th>
<th>Half-life* (hr)</th>
<th>Hydrophilic</th>
<th>CYP Metabolism</th>
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<tbody>
<tr>
<td>Atorvastatin</td>
<td>14</td>
<td>No</td>
<td>3A4</td>
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<tr>
<td>Fluvastatin</td>
<td>&lt; 3, 9 (XL)</td>
<td>No</td>
<td>2C9</td>
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<tr>
<td>Lovastatin</td>
<td>3–4</td>
<td>No</td>
<td>3A4</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>77</td>
<td>Yes</td>
<td>None</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>19</td>
<td>Yes</td>
<td>2C9, 2C19</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>1.9</td>
<td>No</td>
<td>3A4</td>
</tr>
</tbody>
</table>

*Elimination half-life of drug and metabolites, if any

### CK Elevations and LDL-C Reduction

*Am J Cardiol 2006;97(suppl):44C–51C.
**Case #2 Reflective Questions**

- What are his goals of therapy, and what is the benefit of statin therapy?
  - LDL-C < 100 mg/dL: Will decrease risk of CV events
- Fear of myopathy is a barrier to treatment. Does simvastatin have to be stopped because of his muscle symptoms?
  - No.... It is neither myopathy nor rhabdomyolysis, and is not considered intolerable
- What medication changes should be implemented?
  - Continue dyslipidemia regimen and promote other risk reduction strategies (weight loss, smoking cessation)

**Case #3**

- RP is a 65-yr-old woman on atorvastatin 10 mg daily
- Past medical history: type 2 diabetes, hypertension, dyslipidemia, and an ischemic stroke
- Medications:
  - Atorvastatin 10 mg daily, aspirin 81 mg daily, losartan 100 mg daily, hydrochlorothiazide 25 mg daily, metformin 1000 mg twice daily, insulin glargine 30 U daily in the evening
- Fasting Labs:
  - TC = 185 mg/dL, HDL-C = 45 mg/dL
  - LDL-C = 90 mg/dL, TGs = 250 mg/dL
  - A1C is 6.8 mg/dL (target < 7 mg/dL for diabetes)
  - all other labs, within normal limits
- RP’s provider is not inclined to intensify therapy

**Case #3 Reflective Questions:**

- What are her goals of therapy?

- Is single drug therapy as effective as combination drug therapy?

- “Clinical Inertia” is a barrier to treatment. What is the evidence supporting treatment of this type of patient?
NCEP ATP III: 2004 Report

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>LDL-C goal (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High Risk *</td>
<td>&lt; 100 (Optional &lt;70)</td>
</tr>
<tr>
<td>Moderately High Risk *</td>
<td>&lt; 130 (Optional &lt; 100)</td>
</tr>
<tr>
<td>Moderate Risk</td>
<td>&lt; 130</td>
</tr>
<tr>
<td>Lower Risk</td>
<td>&lt; 160</td>
</tr>
</tbody>
</table>

* Very high risk favors < 70 mg/dL.
* High risk or moderately high with lifestyle-related risk should be on therapeutic lifestyle changes regardless of LDL-C, and should achieve at least a 30 to 40% LDL-C reduction.
¶ 10-yr risk of CHD based on Framingham Scoring.

Dyslipidemia Goal Values

- **Primary target:** LDL-C
- **Secondary target:** Non-HDL-C
  - Only if LDL-C goal met and if TG ≥ 200 mg/dL
  - Always 30 mg/dL higher than LDL-C goal
- **Tertiary target:** HDL-C
  - If Metabolic Syndrome and only after LDL-C and non-HDL-C goals are met
  - Raise HDL-C to extent possible with standard therapies to ≥ 40 mg/dL (men), ≥ 50 mg/dL (women)

Lipid-Lowering Therapies

<table>
<thead>
<tr>
<th>Therapy Type</th>
<th>LDL-C</th>
<th>HDL-C</th>
<th>TG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statins</td>
<td>↓ 15-30%</td>
<td>↑ 5-15%</td>
<td>↓ 7-30%</td>
</tr>
<tr>
<td>Bile Acid Sequestrants</td>
<td>↓ 15-20%</td>
<td>↑ 3-5%</td>
<td>0 or ↑</td>
</tr>
<tr>
<td>Nicotinic Acid</td>
<td>↓ 5-25%</td>
<td>↑ 15-35%</td>
<td>↓ 20-50%</td>
</tr>
<tr>
<td>Fibrin Acid Derivatives</td>
<td>↓ 5-20 or ↑</td>
<td>↑ 10-20%</td>
<td>↓ 20-50%</td>
</tr>
<tr>
<td>Cholesterol Absorption Inhibitor (ezetimibe)</td>
<td>↓ 18%</td>
<td>↑ 1%</td>
<td>↓ 7%</td>
</tr>
<tr>
<td>Omega-3-acid (prescription strength fish oil)</td>
<td>?</td>
<td>↑ 9%</td>
<td>↓ 45%</td>
</tr>
</tbody>
</table>
STEMLAR Trial
Statin Therapies for Elevated Lipid Levels compared Across doses to Rosuvastatin
- 6-week, parallel groups, open-label study (n=2431)

Ezetimibe Added to a Statin
- Double-blind, controlled trial
- 769 patients not at LDL goal while on statin monotherapy
- Randomized to placebo or ezetimibe 10 mg daily

Clinical Inertia in Diabetes
NHANES 1999-2002
The Heart Protection Study (HPS)

**VASCULAR EVENT by PRIOR DISEASE**

<table>
<thead>
<tr>
<th>Baseline Feature</th>
<th>STATIN (10,269)</th>
<th>PLACEBO (10,267)</th>
<th>Risk ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior coronary disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1469 (21.8%)</td>
<td>1841 (27.5%)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>574 (16.1%)</td>
<td>744 (20.8%)</td>
<td></td>
</tr>
<tr>
<td>Prior cerebrovascular</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>disease</td>
<td>406 (24.7%)</td>
<td>488 (29.8%)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1527 (19.9%)</td>
<td>2097 (24.3%)</td>
<td></td>
</tr>
<tr>
<td>Prior diabetes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>601 (20.2%)</td>
<td>748 (25.1%)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1432 (19.6%)</td>
<td>1837 (24.3%)</td>
<td></td>
</tr>
<tr>
<td>ALL PATIENTS</td>
<td>2033 (19.8%)</td>
<td>2585 (25.2%)</td>
<td></td>
</tr>
</tbody>
</table>

The Heart Protection Study (HPS): VASCULAR EVENT by PRIOR DISEASE


Collaborative AtoRvastatin Diabetes Study (CARDS)

- 2838 primary prevention patients with type 2 diabetes randomized to placebo or atorvastatin 10 mg daily for 3.9 yrs
- Mean baseline LDL 118 mg/dL decreased to 77 mg/dL

Placebo

Atorvastatin 10 mg

37% reduction p<0.001


Treat to New Targets (TNT) Trial

- Sub-analysis of 1501 patients with CHD and diabetes
- Randomized to atorvastatin 10 mg or 80 mg daily for 5 yrs

10 mg atorvastatin

Mean LDL = 99 mg/dL

25% RR reduction p<0.026

80 mg atorvastatin

Mean LDL = 77 mg/dL

Diabetes Care 2006;29:1220-1226.
Stoke Prevention by Aggressive Reduction in Cholesterol (SPARCL)

- 4731 patients with a history of stroke or TIA
- Randomized, double-blind, to placebo or atorvastatin 80 mg/day x 4.9 years
- Mean LDL-C (mg/dL):
  - placebo: 129
  - atorvastatin: 72

Primary Endpoint: Stroke

![Graph showing the comparison between placebo and atorvastatin 80 mg/day for primary endpoint (stroke)](JAMA 2006;355:549-559)

Case #3 Reflective Questions

- What are her goals of therapy?
  - LDL-C < 70 mg/dL
- Is single drug therapy as effective as combination drug therapy?
  - Depends on agents used... combination regimens can provide robust reductions in LDL-C
- "Clinical Inertia" is a barrier to treatment. What is the evidence supporting treating this type of patient?
- Lowering LDL-C further in diabetes and in ischemic stroke provides additional CV event risk reduction
REFERENCES


Evidence-based Strategies for the Management of Dyslipidemia: A Case Study Approach


Evidence-based Strategies for the Management of Dyslipidemia: A Case Study Approach

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