Reducing Cardiovascular Risk: Evidence-based Strategies for Managing Dyslipidemia
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Reducing Cardiovascular Risk: Evidence-based Strategies for Managing Dyslipidemia

A G E N D A

6:15 a.m. – 6:45 a.m.  Registration and Breakfast

6:45 a.m. – 6:50 a.m.  Welcome – Introductory Remarks
Joseph Saseen, Pharm.D., FASHP, FCCP

6:50 a.m. – 7:40 a.m.  Reducing Cardiovascular Risk: Evidence-based Strategies for Managing Dyslipidemia

7:40 a.m. – 7:45 a.m.  Questions & Answers

F A C U L T Y

Joseph Saseen, Pharm.D., FASHP, FCCP
Professor and Vice Chair
Department of Clinical Pharmacy
Professor
Department of Family Medicine
University of Colorado
Aurora, Colorado
Reducing Cardiovascular Risk: Evidence-based Strategies for Managing Dyslipidemia

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Joseph Saseen, Pharm.D., FASHP, FCCP

Dr. Saseen declares that he has no relationships pertinent to this activity.

Joel C. Marrs, Pharm.D., FNLA, BCPS (AQ-Cardiology), CLS

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Erika Thomas, M.B.A., B.S.Pharm.

Ms. Thomas declares that she has no relationships pertinent to this activity.

Kristi N. Hofer, Pharm.D.

Dr. Hofer declares that she has no relationships pertinent to this activity.

ASHP staff has no relevant financial relationships to disclose.
Reducing Cardiovascular Risk: Evidence-based Strategies for Managing Dyslipidemia

ACTIVITY OVERVIEW

In the United States, it is estimated that coronary heart disease (CHD) causes more than 385,000 deaths and costs $108.9 billion annually. Dyslipidemia is a major risk factor for coronary heart disease (CHD).

Statin-based therapy is prescribed for chronic use, based on extensive evidence that demonstrates a reduction in cardiovascular events in patients with CHD risk factors. Since millions of patients are treated with these agents chronically, data regarding safety is continually emerging. Moreover, certain patient populations require careful risk and benefit analysis when statin-based therapy is considered. Recently, the Food and Drug Administration (FDA) has approved important safety label changes for statins. Updated National Cholesterol Education Program (NCEP) ATP 4 guidelines will be released for public opinion sometime in the near future. Therefore, clinicians will soon have several guidance documents from which to devise evidence-based strategies for managing patients with dyslipidemia.

This symposium will discuss trends in the prevalence and the treatment of dyslipidemia in the United States. New FDA recommendations regarding the safety of statin-based therapy along with supporting evidence will be reviewed. The risk and benefit of statin-based therapy in primary prevention patients will also be outlined using a case study to illustrate development of evidence-based management strategies.

ACTIVITY OBJECTIVES

At the conclusion of this application-based educational activity, participants should be able to

- Recommend therapy for treating patients with dyslipidemia as recommended by the NCEP guidelines.
- Review the revised FDA statin label regarding safety, including data supporting the development of incident diabetes.
- Identify patients who are candidates for primary prevention, taking into account the benefits versus risks of statin therapy for the management of dyslipidemia.
Reducing Cardiovascular Risk: Evidence-based Strategies for Managing Dyslipidemia

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 activity provides 1.0 hour (0.1 CEU) of continuing pharmacy education credit (ACPE activity #0204-0000-12-440-L01-P).

Attendees must complete a Continuing Pharmacy Education Request online and may immediately print their official statements of continuing pharmacy education credit at the ASHP CE Center at http://ce.ashp.org following the activity.

Complete instructions for receiving your statement of continuing pharmacy education online are found at the front of the CE in the Mornings handout booklet. Be sure to record the SESSION CODE beginning with “A” announced during the activity.

Your educational opportunities extend beyond today’s symposium…

A live webinar to be conducted March 7, 2013, where Joseph Saseen, Pharm.D., FASHP, FCCP, BCPS will explore issues raised by participant questions in today’s symposium (1 hour of CPE).

E-Newsletters featuring tips for incorporating information from this symposium into practice, as well as updates on emerging information.

Web-based activity based on today’s live symposium (1 hour of CPE, but please note that individuals who claim CPE credit for the live symposium are ineligible to claim credit for the web-based activity).

For more information and to sign up to receive e-mail updates, visit

www.cemornings.com
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Joseph Saseen, Pharm.D., FASHP, FCCP, BCPS, is Professor of Clinical Pharmacy, Vice Chair of the Department of Clinical Pharmacy, and a clinical pharmacy specialist at the University of Colorado A.F. Williams Family Medicine Center in Denver, Colorado. He is also Professor, Department of Family Medicine at the university. Dr. Saseen is Board-Certified Pharmacotherapy Specialist, certified Clinical Lipid Specialist, and Fellow of the American Society of Health-System Pharmacists (ASHP) and American College of Clinical Pharmacy.

Dr. Saseen received his Bachelor of Science in pharmacy and Doctor of Pharmacy degrees from the State University of New York at Buffalo and then completed a fellowship in ambulatory care research at the University of Illinois at Chicago and University of Colorado Health Sciences Center. In his current position, Dr. Saseen is chairman of the curriculum committee at the University of Colorado Skaggs School of Pharmacy and Pharmaceutical Sciences. He serves on the board of directors of the National Lipid Association and is the incoming Chair of the Board of Pharmacy Specialties. His professional efforts include national recognition of pharmacists as healthcare providers, post-graduate pharmacy residency training, and specialty board certification.

Dr. Saseen participates in research related to hypertension, dyslipidemia, and rheumatoid arthritis. He has published pharmacotherapy review articles and textbook chapters related to the management of cardiovascular diseases. He is also the recipient of the University of Colorado Anschutz Medical Campus Chancellor’s Teaching Recognition Award in May of 2011.
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Learning Objectives

• Recommend therapy for treating patients with dyslipidemia as recommended by the NCEP guidelines.
• Review the revised FDA statin label regarding safety, including data supporting the development of incident diabetes.
• Identify patients who are candidates for primary prevention, taking into account the benefits versus risks of statin therapy for the management of dyslipidemia.

American Heart Association (AHA)
Heart Disease and Stroke Statistics—2012 Update

82.6 Million Americans have Cardiovascular Disease

* Total cholesterol ≥ 240 mg/dL.
Atherosclerosis

LDL = low-density lipoprotein  
VLDL = very low-density lipoprotein  
CM = chylomicrons

Monocytes  
Macrophages  
Foam Cells  
Platelets

Trends in Lipids and Lipoproteins in US Adults, 1988-2010

- Three US cross-sectional NHANES:
  - 1988-1994 (n=16,573)
  - 1999-2002 (n=9,471)
  - 2007-2010 (n=11,766)

Mean Value (mg/dL)

*Geometric mean value used for triglycerides


Prevalence of Lipid-Lowering Medication Use

Population Surveyed (%)


3.4 9.3 15.5

P<0.001 for Linear Trend, 1988-1994 to 2007-2010  
P<0.001 for Comparison of 1999-2002 and 2007-2010

Clinical Case…

RA, a 65 year old woman with hypertension, “prediabetes” who smokes is seen for her annual medical examination.

- Current medications: benazepril/amlodipine 10/40 mg daily
  metformin 100 mg twice daily
- Vitals: BP 130/84 mm Hg, HR 70 beats/min
- Fasting Labs: Total cholesterol 200 mg/dL
  HDL-cholesterol 45 mg/dL
  LDL-cholesterol 120 mg/dL
  Triglycerides 150 mg/dL
  glucose 110 mg/dL
- Other Labs: A1C 6.3%
  high sensitivity CRP 1.0 mg/L (normal)
  Other labs are normal
- Framingham risk 10-year score is 14%

Polling Question #1...

- This patient should be treated with statin therapy because benefits outweigh risks.
  - I agree
  - I disagree
  - I am not certain

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National Cholesterol Education Program (NCEP)
Adult Treatment Panel 3 (ATP 3)
Lipoprotein Subclasses

<table>
<thead>
<tr>
<th>Diameter (nm)</th>
<th>Density (g/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-10</td>
<td>1.20</td>
</tr>
<tr>
<td>10-20</td>
<td>1.10</td>
</tr>
<tr>
<td>20-40</td>
<td>1.06</td>
</tr>
<tr>
<td>40-60</td>
<td>1.06</td>
</tr>
<tr>
<td>60-80</td>
<td>1.02</td>
</tr>
<tr>
<td>80-1000</td>
<td>1.02</td>
</tr>
</tbody>
</table>

TRIGLYCERIDES

Chylomicrons

VLDL

LDL

HDL

Non-HDL Cholesterol

Triglycerides

LDL Cholesterol

HDL Cholesterol

Density (g/mL)

Diameter (nm)

Targets of Treatment in Dyslipidemia

Primary Target: 
LDL-C

Secondary Target: 
Non-HDL-C

(Only when LDL-C goal is met and if TG ≥200 mg/dL)

• EXCEPTION: Triglyceride lowering is an immediate target of therapy if ≥500 mg/dL

### NCEP ATP III Goals & Cutpoints

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>LDL-C Goal (mg/dL)</th>
<th>Non-HDL-C Goal (mg/dL)</th>
<th>Initiate TLC (mg/dL)</th>
<th>Consider Drug Treatment (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High Risk: CHD or CHD Equivalent (10 y risk &gt; 20%)</td>
<td>&lt;100 (optional Goal &lt;70)</td>
<td>&lt;130</td>
<td>≥100</td>
<td>≥100 for high risk patients</td>
</tr>
<tr>
<td>Moderately High Risk: 2+ Risk Factors (very risk 10-20%)</td>
<td>&lt;130 (optional Goal &lt;100)</td>
<td>&lt;160</td>
<td>≥130</td>
<td>100 – 129; consider to achieve LDL-C goal of &lt;100</td>
</tr>
<tr>
<td>Lower Risk: 0-1 Risk Factors (very risk &lt; 10%)</td>
<td>&lt;160 (optional Goal &lt;100)</td>
<td>&lt;190</td>
<td>≥190</td>
<td>160 – 189; LDL-C Lowering Drugs Optional</td>
</tr>
</tbody>
</table>

*For very high risk patients


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### NCEP ATP III: LDL-C Goal Values

**AVD or Diabetes**

- Yes
- No

**>2 major CV risk factors**

- Yes
- No

10-year CHD risk: Framingham Score

- >20%
- 10-20%
- <10%

- High Risk <100 mg/dL
- Moderate High Risk <130 mg/dL
- Moderate Risk <130 mg/dL
- Lower Risk <160 mg/dL

*Major risk factors: Age (>45yrs men, >55yrs women), hypertension, smoking, family history of premature CHD, HDL-C <40 mg/dL


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### Polling Question #2...

A patient with untreated dyslipidemia has an LDL-C of 150 mg/dL. Their goal is < 100 mg/dL. Which of the following statin regimens is most appropriate?

- Atorvastatin 10 mg daily
- Pravastatin 10 mg daily
- Simvastatin 10 mg daily
ATP III: 2004 Update
Standard Statin Doses to Attain 30-40% LDL-C Reductions

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

Pitavastatin (not available in 2004) 1-2 mg/day attains 30-40% LDL-C reductions.


Lipid-Lowering Therapies

<table>
<thead>
<tr>
<th></th>
<th>LDL-C</th>
<th>HDL-C</th>
<th>TG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statins (atorvastatin, fluvastatin, lovastatin, pravastatin, simvastatin)</td>
<td>↓ 18-63%</td>
<td>↑ 5-15%</td>
<td>↓ 7-30%</td>
</tr>
<tr>
<td>Bile acid sequestrants (colesevelam, cholestyramine, colestipol)</td>
<td>↓ 15-30%</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>Fibric acid derivatives (gemfibrozil, fenofibrate)</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 fatty acids (life strength)</td>
<td>?</td>
<td>↑ 9%</td>
<td>↓ 45%</td>
</tr>
</tbody>
</table>


Clinical Scenarios

<table>
<thead>
<tr>
<th>Primary Target: Elevated LDL-C</th>
<th>Monotherapy Options</th>
<th>Combination Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Statin</td>
<td></td>
<td>Statin + Bile Acid Sequestrant</td>
</tr>
<tr>
<td>• Niacin</td>
<td></td>
<td>Statin + Ezetimibe</td>
</tr>
<tr>
<td>• Bile Acid Sequestrant</td>
<td></td>
<td>Statin + Niacin</td>
</tr>
<tr>
<td>• Ezetimibe</td>
<td></td>
<td>Others</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Secondary Target: Elevated non-HDL-C</th>
<th>Monotherapy Options</th>
<th>Combination Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Statin (high-dose)</td>
<td></td>
<td>Statin + Fibrate</td>
</tr>
<tr>
<td>• Niacin</td>
<td></td>
<td>Statin + Niacin</td>
</tr>
<tr>
<td>• Ezetimibe</td>
<td></td>
<td>Statin + Omega-3 Fatty Acids</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other: Very high TG</th>
<th>Monotherapy Options</th>
<th>Combination Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Fibrate</td>
<td></td>
<td>Fibrate + Omega-3 Fatty Acids</td>
</tr>
<tr>
<td>• Omega-3 Fatty Acid</td>
<td></td>
<td>Fibrate + Niacin</td>
</tr>
<tr>
<td>• Niacin</td>
<td></td>
<td>Niacin + Omega-3 Fatty Acids</td>
</tr>
</tbody>
</table>
FDA Updates to Statin Labeling

Statins

- Acetyl CoA
- HMG CoA Reductase (Inhibitors)
- Mevalonate
- Cholesterol production

- HMG CoA Reductase Inhibitors (Statins)
- Competitive Inhibition
- Expression of LDL receptors
- LDL, VLDL, and IDL particles
- Cholesterol production lowering
- LDL-C Lowering

Landmark Statin-based Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Statin Treatment (mg/day)</th>
<th>LDL-C (mg/dL)</th>
<th>Primary Endpoint/ CV Event Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4S</td>
<td>Simvastatin 20-40 mg</td>
<td>188</td>
<td>Baseline 122 Statin 28.0 Placebo 19.4</td>
</tr>
<tr>
<td>LIPID</td>
<td>Pravastatin 40 mg</td>
<td>150</td>
<td>Baseline 112 Statin 15.0 Placebo 13.3</td>
</tr>
<tr>
<td>CARE</td>
<td>Pravastatin 40 mg</td>
<td>139</td>
<td>Baseline 98 Statin 13.2 Placebo 10.2</td>
</tr>
<tr>
<td>HPS</td>
<td>Simvastatin 40 mg</td>
<td>132</td>
<td>Baseline 93 Statin 24.4 Placebo 19.9</td>
</tr>
<tr>
<td>PROSPER</td>
<td>Pravastatin 40 mg</td>
<td>147</td>
<td>Baseline 97 Statin 16.2 Placebo 14.5</td>
</tr>
<tr>
<td>WOSCOPS</td>
<td>Pravastatin 40 mg</td>
<td>152</td>
<td>Baseline 159 Statin 7.5 Placebo 5.3</td>
</tr>
<tr>
<td>AFCAPS</td>
<td>Lovastatin 20-40 mg</td>
<td>150</td>
<td>Baseline 115 Statin 5.5 Placebo 3.5</td>
</tr>
<tr>
<td>ARCOT-LLA</td>
<td>Atorvastatin 10 mg</td>
<td>133</td>
<td>Baseline 90 Statin 3.0 Placebo 1.9</td>
</tr>
<tr>
<td>CARDS</td>
<td>Atorvastatin 10 mg</td>
<td>118</td>
<td>Baseline 77 Statin 9.0 Placebo 5.8</td>
</tr>
<tr>
<td>JUPITER</td>
<td>Rosuvastatin 20 mg</td>
<td>108</td>
<td>Baseline 55 Statin 2.5 Placebo 1.6</td>
</tr>
</tbody>
</table>

FDA Drug Safety Communication: Important safety label changes to cholesterol-lowering statin drugs

Safety Announcement [2-28-2012]

• Monitoring Liver Enzymes
  – Removed the need for routine periodic monitoring of liver enzymes
• Adverse Event Information
  – Added potential for generally non-serious/reversible cognitive side effects (e.g., memory loss, confusion)
  – Added reports of increased blood glucose and glycosylated hemoglobin (HbA1c) levels

FDA continues to believe that the CV benefits of statins outweigh the small increased risks


Hepatotoxicity with Statin Therapy

• National Lipid Association:
  – Evidence does not support routine monitoring of liver biochemistries in asymptomatic patients receiving statins
  – Irreversible liver damage is exceptionally rare; is likely idiosyncratic
  – No data show that routine monitoring of liver biochemistries identifies the very rare individual who may develop significant liver injury
• Adverse Event Reporting System (2000-2009):
  – Serious liver injury extremely low (≤2 per one million patient-yrs)
  – Despite increased statin use, there has not been a detectable increase in the annual rates of fatal or severe liver injury cases


FDA Conclusions:
Hepatotoxicity with Statin Therapy

• Monitoring LFTs prior to initiating therapy and then only when clinically indicated:

  “serious liver injury with statins is rare and unpredictable in individual patients and that routine periodic monitoring of liver enzymes does not appear to be effective in detecting or preventing serious liver injury”

Statin and Risk of Diabetes

- 2010 meta-analysis of 13 trials (n=91,140)
  - 4,278 developed diabetes (2,226 with statins vs. 2,052 with control) over a mean 4 yrs
    - 9% increased risk (p<0.05)
    - NNH was 255 patients
- 2011 meta-analysis of 5 trials (n=32,752)
  - 2,749 developed diabetes (1,449 with intensive-dose statin vs. 1,300 with moderate-dose statin) over a mean 1.9 yrs
    - 12% increased risk (p<0.05)
    - NNH was 498; NNT for CV events was 155


Benefits and Diabetes Risk in JUPITER

- 17,603 patients, randomized to placebo or rosvastatin 20 mg for up to 5 years
  - Stratified based on presence of major risk factors for developing diabetes*

<table>
<thead>
<tr>
<th># of Diabetes Risk Factors</th>
<th>Placebo vs. Rosuvastatin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td># Primary CV Endpoints</td>
</tr>
<tr>
<td>0 (n=6,095)</td>
<td>91 vs. 44 (p&lt;0.0001)</td>
</tr>
<tr>
<td>≥ 1 (n=11,508)</td>
<td>157 vs. 96 (p&lt;0.0001)</td>
</tr>
</tbody>
</table>

*BMI ≥30 kg/m², metabolic syndrome, impaired fasting glucose, glycated hemoglobin A1c ≥6%


American Diabetes Association: Standards of Medical Care in Diabetes

Dyslipidemia:

- Statin therapy should be added to lifestyle therapy, regardless of baseline lipid levels, for diabetic patients with overt CVD, or without CVD if ≥40 yrs with ≥ 1 other CVD risk factors
- If targets not reached on maximal tolerated statin therapy, a reduction in LDL-C of 30-40% from baseline is an alternative
- Triglycerides <150 mg/dL and HDL-C >40 mg/dL in men and >50 mg/dL in women, are desirable; However, LDL-C-targeted statin therapy remains the preferred strategy
- If targets not reached on maximally tolerated doses of statins, combination therapy using statins and other agents may be considered

Polling Question #3...
Which of the following patients is at the highest risk for developing type 2 diabetes while on statin therapy?

- Obese patient with an A1C value of 6.3%
- Overweight patient with hypertension and low HDL-C

Dyslipidemia Treatment in Primary Prevention

Comparing Populations

Primary Prevention
• No history of established atherosclerotic vascular disease
• Risk for vascular event ranges from low to high and is dependent on the presence of other cardiovascular risk factors

Secondary Prevention
• Established atherosclerotic vascular disease, including coronary atherosclerosis (e.g., myocardial infarction) and non-coronary atherosclerosis (e.g., ischemic stroke)
• Risk for recurrent vascular events is considered high
Polling Question #4...

Which of the following primary prevention patients would benefit the most from statin therapy to manage dyslipidemia?

- 40 year old man with hypertension
- 50 year old woman with type 2 diabetes
- 70 year old man with a family history of heart disease

ASCOT-Lipid Lowering Arm

- Prospective, randomized, placebo controlled trial in 10,305 Primary prevention patients with hypertension

Comparing Benefits of Dyslipidemia Therapy

<table>
<thead>
<tr>
<th></th>
<th>Secondary Prevention: 4S</th>
<th>Primary Prevention: ASCOT-LLA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Endpoint Event Rates: Placebo vs. Statin</td>
<td>26.0 vs. 19.4%</td>
<td>3.0 vs. 1.9%</td>
</tr>
<tr>
<td>Relative Risk Reduction</td>
<td>31%</td>
<td>36%</td>
</tr>
<tr>
<td>Absolute Risk Reduction</td>
<td>8.6%</td>
<td>1.1%</td>
</tr>
<tr>
<td>Number Needed to Treat</td>
<td>11</td>
<td>91</td>
</tr>
</tbody>
</table>
Collaborative AtoRvastatin Diabetes Study (CARDS)

- Prospective, randomized, placebo controlled trial in 2838 primary prevention patients with type 2 diabetes

![Graph showing primary endpoint: major CV event (%) over years with Placebo and Atorvastatin 10 mg/day lines.](image)

- 37% relative risk reduction, p=0.001
- NNT = 31

Predicting Risk of CV Events in Primary Prevention

- Framingham risk scoring tool
  - Predicts 10-year risk of “hard coronary heart disease” which refers to non-fatal MI or fatal CHD
- Newer risk scoring tools
  - Predict risk of major vascular events: CHD, and other forms of major vascular events (e.g., stroke, revascularization procedures)
  - Can predict risk over 5 years
  - Some require additional risk markers (hs-CRP)

JUPITER Trial

- Randomized, controlled trial in 17,802 primary prevention patients randomized to rosuvastatin 20 mg daily or placebo
  - Men ≥ 50 years, women ≥ 60 years
  - LDL <130 mg/dL with hsCRP >2 mg/L
- Planned for 3.5 years, but stopped after 1.9 years
  - LDL-C at 12 months:
    - Placebo 110 mg/dL (94-125)
    - Rosuvastatin 55 mg/dL (44-72)
C-Reactive Protein (CRP) and Atherosclerosis

Localizes in atherosclerotic, but not normal, intima

Induces complement activation
Recruits monocytes into arterial wall
Induces production of tissue factor in monocytes
Blunts endothelial vasoreactivity
Mediates LDL uptake by macrophages

Induces cell adhesion molecule production
Induces PM-1 expression
Triggers LDL oxidation

NO = nitric oxide; PAI-1 = plasminogen activator inhibitor-1.


JUPITER Results

44% relative risk reduction
P<0.00001
NNT = 81

Primary Endpoint: Cumulative Incidence

JUPITER Results: Subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th># of Patients</th>
<th>Hazard Ratio (95% CI)</th>
<th>p-Value for Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>11,001</td>
<td>0.80</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>6,801</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤65 yr</td>
<td>8,541</td>
<td>1.00 (0.90-1.10)</td>
<td>0.32</td>
</tr>
<tr>
<td>&gt;65 yr</td>
<td>9,261</td>
<td>1.00 (0.90-1.10)</td>
<td>0.57</td>
</tr>
<tr>
<td>Race or Ethnic Group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>12,683</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonwhite</td>
<td>5,117</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.56 (0.46-0.68)</td>
<td></td>
</tr>
</tbody>
</table>

Cholesterol Treatment Trialists’ (CTT) Collaborators

- Meta-analysis of 22 randomized controlled trials (n=134,537), comparing statin to placebo with a median follow-up of 4.8 years
- Major vascular events assessed were major coronary events (i.e., non-fatal MI or coronary death), strokes, or coronary revascularizations
- Patients categorized based on baseline 5-year risk of a major vascular event risk:
  - <5%, ≥5% to <10%, ≥10% to <20%, ≥20% to <30%, ≥30%
  - Rate ratio (RR) estimated per 1.0 mmol/L LDL-C reduction


Cholesterol Treatment Trialists’ (CTT) Collaborators

- Results in all patients*:

<table>
<thead>
<tr>
<th>Major vascular event</th>
<th>Statin &gt; Placebo</th>
<th>LDL-C</th>
<th>Rate ratio (RR) estimated per 1.0 mmol/L LDL-C reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5%</td>
<td>387 (0.83)</td>
<td>314 (0.86)</td>
<td>0.01 (0.87-0.98)</td>
</tr>
<tr>
<td>≥5% to &lt;10%</td>
<td>604 (1.00)</td>
<td>514 (1.00)</td>
<td>0.03 (0.74-0.98)</td>
</tr>
<tr>
<td>≥10% to &lt;20%</td>
<td>435 (1.00)</td>
<td>339 (1.00)</td>
<td>0.03 (0.74-0.98)</td>
</tr>
<tr>
<td>≥20% to &lt;30%</td>
<td>214 (1.00)</td>
<td>191 (1.00)</td>
<td>0.03 (0.74-0.98)</td>
</tr>
<tr>
<td>≥30%</td>
<td>135 (1.00)</td>
<td>116 (1.00)</td>
<td>0.03 (0.74-0.98)</td>
</tr>
<tr>
<td>Overall</td>
<td>1220 (1.00)</td>
<td>1075 (1.00)</td>
<td>0.03 (0.77-0.98)</td>
</tr>
</tbody>
</table>

* Rate ratio (RR) estimated per 1.0 mmol/L LDL-C reduction


Cholesterol Treatment Trialists’ (CTT) Collaborators

- Results in primary prevention patients
  - Major vascular event RR 0.85 (0.77-0.95)
  - All-cause mortality RR 0.91 (0.85-0.97)
  - Proportional reductions were similar by baseline risk
  - No evidence of increased cancer incidence, cancer mortality, or other non-vascular mortality
- When 5-year risk was <10%:
  - 1 mmol/L reduction in LDL-C produced an absolute reduction in major vascular events of 11 per 1000 patients

Clinical Case...

RA, a 65 year old woman with hypertension, "prediabetes" who smokes is seen for her annual medical examination.

- Current medications: benazepril/amlopidine 10/40 mg daily
  metformin 100 mg twice daily
- Vitals: BP 130/84 mm Hg, HR 70 beats/min
- Fasting Labs: Total cholesterol 200 mg/dL
  HDL-cholesterol 45 mg/dL
  LDL-cholesterol 125 mg/dL
  Triglycerides 150 mg/dL
  glucose 110 mg/dL
- Other Labs: A1C 6.3%
  high sensitivity CRP 1.0 mg/L (normal)
  Other labs are normal
- Framingham risk 10-year score is 14%

Conclusions

- NCEP ATP 3 guidelines recommend lipid-lowering therapy based on risk of cardiovascular disease
- Revised FDA statin labeling removes the need for routine liver monitoring but highlights small risk of incident diabetes; benefits of statins typically outweigh this risk in most patients.
- Many primary prevention patients benefit from statin therapy to manage dyslipidemia.
Reducing Cardiovascular Risk: Evidence-based Strategies for Managing Dyslipidemia

SELECTED REFERENCES AND RESOURCES


Cohen DE, Anania FA, Chalasani N. An assessment of statin safety by hepatologists. Am J Cardiol 2006;97:77C-81C.


Reducing Cardiovascular Risk: Evidence-based Strategies for Managing Dyslipidemia


Reducing Cardiovascular Risk: Evidence-based Strategies for Managing Dyslipidemia

SELF–ASSESSMENT QUESTIONS

1. Which of the following choices is the primary therapeutic target in patients with dyslipidemia according to the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III guidelines?
   a. LDL-cholesterol.
   b. HDL-cholesterol.
   c. Non-HDL-cholesterol.
   d. Triglycerides.

2. Which of the following statements best explains why a statin regimen using a dose sufficient to reduce LDL-C by 30-40% is recommended by the NCEP guidelines?
   a. This approach has been shown to reduce the incidence of cardiovascular events.
   b. This approach is thought to reduce the risk of cardiovascular events.
   c. Side effects are extremely rare with this approach.
   d. There are no major drug interactions with this approach.

3. Which of the following patients has the lowest risk of incident (i.e., a new diagnosis of) diabetes after starting statin therapy?
   a. A normal weight patient with an A1C value of 6.2%.
   b. An overweight patient with metabolic syndrome.
   c. An overweight patient with an A1C value of 5.7%.
   d. An obese patient with elevated fasting glucose.

4. Lipid-lowering treatment in a patient with which of the following in his or her medical history is considered primary prevention of cardiovascular disease?
   a. Ischemic stroke.
   b. Myocardial infarction.
   c. Peripheral arterial disease.
   d. Hypertension.

Answers
1. a
2. a
3. c
4. d