Statins, Inflammation and Atherosclerosis
*Past, Present and Future*

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**Presenter Disclosure Information**

*Antonio M. Gotto, Jr., MD, DPhil*

The following relationships exist related to this presentation:

<table>
<thead>
<tr>
<th>Category</th>
<th>Name of Commercial Interest</th>
<th>Level of Relationship</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advisory Board</td>
<td>Vatera Capital</td>
<td>Significant</td>
</tr>
<tr>
<td>Board of Directors</td>
<td>Aegerion Pharmaceuticals, Arisaph Pharmaceuticals</td>
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<td>Consultant</td>
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<td>Health Advisory Board</td>
<td>DuPont</td>
<td>Modest</td>
</tr>
</tbody>
</table>
Statins, Inflammation and Atherosclerosis

- The lipid hypothesis and “lower is better”
- Strategies to manage dyslipidemia
- Inflammation in atherosclerosis
- Future of cardiovascular prevention

Relation of Serum Cholesterol to Mortality (25-yr follow-up of Seven Countries Study)

(Adapted from Verschuren et al., JAMA 1995;274:131-6. Following the work of Ancel Keys in 1955)
Framingham: Low HDL-C and Elevated LDL-C Are Independent Predictors of CHD Risk


Multiple Lipid Factors Are Associated With CHD Risk

The Liver and the Intestine Are Key Organs Involved in Cholesterol Homeostasis

Cholesterol homeostasis is maintained by a complex balance between:

- Cholesterol synthesis
- Dietary intake
- Cholesterol absorption
- Excretion of cholesterol


The Liver Synthesizes Cholesterol Endogenously, Takes It Up From the Circulation and Excretes It to the Intestine Via the Biliary System

Intestine

Liver

Blood

Atheroma

Extra Hepatic Tissues
- CNS
- Skin
- Muscle
- Adrenal
- Ovary

Michael Brown and Joseph Goldstein

Image on right from Encyclopedia Britannica online.

The Small Intestine Helps Maintain Cholesterol Balance by Regulating Absorption and Excretion of Dietary and Biliary Cholesterol

Isolation of HMG-CoA Reductase Inhibitor from Fungi

In 1976 biochemist Akira Endo demonstrated that compactin/mevastatin derived from *Penicillium citrinum* competitively inhibits HMG-CoA reductase, the rate-limiting step in cholesterol biosynthesis.

Image from Lasker Foundation, www.laskerfoundation.org
Scandinavian Simvastatin Survival Study (4S)

- Secondary prevention
- 4444 patients
- Cholesterol: 272 ± 23 mg/dL
- Simvastatin 20 mg/d
  - 40 mg/d in 37%
- LDL-C reduced 38%
- Survival and events
  - 30% decreased death rate
  - 34% decreased CHD events
- Subsequent secondary prevention trials

Survival and events

Survival and events

Years Since Randomization

Simvastatin

Placebo

p=0.0003


AFCAPS/TexCAPS: First Acute Major Coronary Event

37% Risk Reduction

(ρ = 0.00008)

### CTT Meta-analysis

For every 1.0 mmol/L (39 mg/dL) reduction in LDL-C...

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Treatment (45054)</th>
<th>Control (45002)</th>
<th>RR (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-fatal MI</td>
<td>2001 (4-4%)</td>
<td>2769 (6-2%)</td>
<td>0.74 (0.70-0.79)</td>
</tr>
<tr>
<td>CHD death</td>
<td>1548 (3-4%)</td>
<td>1960 (4-4%)</td>
<td>0.81 (0.75-0.87)</td>
</tr>
<tr>
<td>Any major coronary event</td>
<td>3337 (7-4%)</td>
<td>4420 (8-8%)</td>
<td>0.77 (0.74-0.80)</td>
</tr>
<tr>
<td>CABG</td>
<td>713 (1-6%)</td>
<td>1006 (2-2%)</td>
<td>0.75 (0.69-0.82)</td>
</tr>
<tr>
<td>PTCA</td>
<td>510 (1-1%)</td>
<td>688 (1-5%)</td>
<td>0.79 (0.69-0.80)</td>
</tr>
<tr>
<td>Unspecified</td>
<td>1397 (3-1%)</td>
<td>1770 (3-9%)</td>
<td>0.79 (0.69-0.84)</td>
</tr>
<tr>
<td>Any coronary revascularisation</td>
<td>2620 (5-6%)</td>
<td>3434 (7-4%)</td>
<td>0.76 (0.73-0.80)</td>
</tr>
<tr>
<td>Haemorrhagic stroke</td>
<td>105 (0-2%)</td>
<td>99 (0-2%)</td>
<td>1.05 (0.78-1.41)</td>
</tr>
<tr>
<td>Presumed ischaemic stroke</td>
<td>1235 (2-8%)</td>
<td>1518 (3-4%)</td>
<td>0.81 (0.74-0.89)</td>
</tr>
<tr>
<td>Any stroke</td>
<td>1240 (3-0%)</td>
<td>1617 (3-7%)</td>
<td>0.83 (0.78-0.88)</td>
</tr>
<tr>
<td>Any major vascular event</td>
<td>6354 (14-4%)</td>
<td>7994 (17-8%)</td>
<td>0.79 (0.77-0.81)</td>
</tr>
</tbody>
</table>


### 1:1 Relationship of LDL-C Reduction and CHD Risk

Reduction Maintained between Statin and Non-Statin Trials

- MI = myocardial infarction.

This relation is consistent with a large body of epidemiologic data available from clinical trials of LDL-lowering therapy.

These data suggest that for every 30-mg/dL change in LDL-C, the relative risk for CHD is changed in proportion by about 30%.

The relative risk is set at 1.0 for LDL-C = 40 mg/dL.

Where Do We Stand?

- Atherosclerosis was once thought to be an irreversible, inevitable consequence of aging.

- The recognition of dyslipidemia as a major modifiable risk factor introduced the possibilities of both treatment and prevention.

- The “lipid hypothesis” is now confirmed. Over the last decade, research has exposed new areas involving other lipoprotein fractions and inflammation, raising new opportunities.

Statins, Inflammation and Atherosclerosis

- The lipid hypothesis and “lower is better”

- Strategies to manage dyslipidemia

- Inflammation in atherosclerosis

- Future of cardiovascular prevention
Risk Assessment

- Obtain fasting lipid profile (every 5 years in adults ≥ 20 yr)
- Determine presence/absence of CHD and CHD risk equivalents
  - Other atherosclerotic disease (PAD, AAA, carotid artery disease)
  - Diabetes
  - At least 2 major risk factors with 10-year risk for CHD >20%
- Identify major risk factors other than LDL-C

Major CHD Risk Factors
(Exclusive of LDL-C)

- Cigarette smoking
- Hypertension (BP ≥140/90 mmHg or on antihypertensive medication)
- Low HDL cholesterol (<40 mg/dL)†
- Family history of premature CHD
  - CHD in male first-degree relative <55 years
  - CHD in female first-degree relative <65 years
- Age (men ≥45 years; women ≥55 years)

† HDL cholesterol ≥60 mg/dL counts as a “negative” risk factor; its presence removes one risk factor from the total count.
Risk Stratification

- Patients with CHD or CHD risk equivalents are high risk
- For patients with at least 2 risk factors, calculate Framingham risk score to identify 10-yr risk for CHD
  - Online version (at NHLBI website) and cell phone apps are available
- Patients with 0-1 risk factor are low risk


Lifestyle and Emerging Risk Factors

- Obesity
- Physical inactivity
- Atherogenic diet
- Lipoprotein(a)
- CRP
- Prothrombotic factors
- Impaired fasting glucose (100-125 mg/dL)
- Evidence of subclinical atherosclerosis

Encourage lifestyle changes

Can use to guide treatment decisions

LDL-C is the Primary Target

- Primary and secondary prevention focuses on achieving LDL-C goals first
  - Exception: TG ≥500 mg/dL
- Therapeutic lifestyle changes (TLC) are essential to lipid management
- Note: rule out possible causes of secondary dyslipidemia in individuals with elevated LDL-C
  - Diabetes, hypothyroidism, obstructive liver disease, chronic renal failure, medications

# ATP 2004 Update: LDL-C Therapy by Risk Categories

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>LDL-C Goal</th>
<th>Initiate Therapeutic Changes (TLC)</th>
<th>Consider Drug Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High risk</strong>: CHD or CHD risk equivalents (10-year risk &gt;20%)</td>
<td>&lt;100 mg/dL</td>
<td>≥100 mg/dL</td>
<td>≥100 mg/dL</td>
</tr>
<tr>
<td><strong>Very high risk</strong></td>
<td>Optional: &lt;70 mg/dL</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Moderately high risk</strong>: ≥2 risk factors (10-year risk 10%–20%)</td>
<td>&lt;130 mg/dL (Optional: &lt;100 mg/dL)</td>
<td>≥130 mg/dL</td>
<td>≥130 mg/dL (consider drug if LDL-C 100–129 mg/dL)</td>
</tr>
<tr>
<td><strong>Moderate risk</strong>: ≥2 risk factors (10-year risk &lt;10%)</td>
<td>&lt;130 mg/dL</td>
<td>≥130 mg/dL</td>
<td>&gt;160 mg/dL</td>
</tr>
<tr>
<td><strong>Low risk</strong>: ≤1 risk factor</td>
<td>&lt;160 mg/dL</td>
<td>≥160 mg/dL</td>
<td>≥190 mg/dL (consider drug if LDL-C 160–189 mg/dL)</td>
</tr>
</tbody>
</table>


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# Characteristics of the Metabolic Syndrome (A Secondary Target)

<table>
<thead>
<tr>
<th>Risk Factor (≥3)</th>
<th>Defining Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal obesity</td>
<td>Waist circumference*</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>≥150 mg/dl</td>
</tr>
<tr>
<td>HDL-C</td>
<td>&lt;40 mg/dl in men; &lt;50 mg/dl in women</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>≥130/≥85 mm Hg</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>≥110 mg/dl</td>
</tr>
</tbody>
</table>

*In US: men >40 in (102 cm); women >35 in (88 cm)

AHA Dietary and Lifestyle Guidelines

- Balance calorie intake and exercise (≥30 min/d on most days) to maintain desirable weight
- Include a variety of fruits, vegetables, whole grains, low-fat or nonfat dairy products, fish, legumes, poultry, lean meats
- Limit excess consumption of salt, added sugars, and alcohol
- Limit foods high in saturated fat (<7% of calories), trans fat (<1%), and cholesterol (<300 mg/d)


Steps in TLC
(if not immediately initiating drug therapy)

Visit 1
- Begin TLC
- 6 wks

Visit 2
- Evaluate LDL Response
- If LDL goal not achieved, intensify TLC
- 6 wks

Visit 3
- Evaluate LDL Response
- If LDL goal not achieved, consider drug therapy
- Every 4-6 mo

Visit N
- Monitor Adherence to TLC

- Emphasize ↓ saturated fat and cholesterol
- Encourage moderate exercise
- Consider referral to dietitian

- Reinforce ↓ saturated fat and cholesterol
- Consider plant stanol/sterol
- Increase fiber
- Consider referral to dietitian

- Initiate therapy for Met Syn
- Intensify weight mgmt and exercise
- Consider referral to dietitian

## Effects of Drug Classes on Serum Lipids

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>TC</th>
<th>LDL</th>
<th>HDL</th>
<th>TG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resins</td>
<td>↓ 20%</td>
<td>↓ 15%–30%</td>
<td>↑ 3%–5%</td>
<td>Variable</td>
</tr>
<tr>
<td>CAI</td>
<td>↓ 13%</td>
<td>↓ 19%</td>
<td>↑ 3%</td>
<td>↓ 8%</td>
</tr>
<tr>
<td>Nicotinic acid</td>
<td>↓ 25%</td>
<td>↓ 5%–25%</td>
<td>↑ 15%–35%</td>
<td>20%–50%</td>
</tr>
<tr>
<td>Fibrates</td>
<td>↓ 15%</td>
<td>Variable</td>
<td>↑ 10%–20%</td>
<td>20%–50%</td>
</tr>
<tr>
<td>n-3 fatty acids</td>
<td>&lt;---</td>
<td>&lt;---</td>
<td>&lt;---</td>
<td>↓ 35-50%</td>
</tr>
<tr>
<td>Statins</td>
<td>↓ 15%–60%</td>
<td>↓ 18%–60%</td>
<td>↑ 5%–15%</td>
<td>↓ 7%–30%</td>
</tr>
</tbody>
</table>

Combination Therapy

Consider combination therapy if:

- LDL-C goals are not achieved (ezetimibe, resin)
  - Ezetimibe as add-on to statin reduces LDL-C additional 25%
- Higher statin doses are not tolerated (ezetimibe, resin)
- A high-risk patient has high triglycerides (≥200 mg/dL) or low HDL-C (<40 mg/dL)
  - May add nicotinic acid or fibrate to statin
  - Caution: can increase risk of myotoxicity


Other Lipid Targets

- Non-HDL-C in high-risk patients with TG ≥200 mg/dL
  - Target is 30 mg/dL higher than corresponding LDL-C goal
  - Add fibrate or nicotinic acid to statin
- TG ≥500 mg/dL - must treat immediately
  - Nicotinic acid, fibrates, prescription omega-3 fatty acids
- HDL-C – no specific target
- Metabolic Syndrome
  - Weight reduction and physical activity will improve underlying risk factors

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Inflammatory Response to Atherogenic Lipoproteins

ICAM1 = intercellular adhesion molecule 1; oxLDL = oxidized low-density lipoprotein; VCAM1 = vascular cell adhesion molecule 1.

Atherosclerosis is an Inflammatory Disorder

Key points

– Inflammation is involved in atherogenesis
– Inflammatory cells (leukocytes, mediators) are critical in development of atheroma
– Microbial infection may play a role
– Benefits of anti-inflammatory agents (except ASA) in therapy of atherosclerosis remains speculative

JUPITER Trial Design

**JUPITER**

*Multi-National Randomized Double Blind Placebo Controlled Trial of Rosuvastatin in the Prevention of Cardiovascular Events Among Individuals With Low LDL and Elevated hsCRP*

- No Prior CVD or DM
- Men ≥50, Women ≥60
- LDL <130 mg/dL
- hsCRP ≥2 mg/L
- 4-week run-in
- Rosuvastatin 20 mg (N=8901)
- Placebo (N=8901)
- MI, Stroke, Unstable Angina, CVD Death, CABG/PTCA

Argentina, Belgium, Brazil, Bulgaria, Canada, Chile, Colombia, Costa Rica, Denmark, El Salvador, Estonia, Germany, Israel, Mexico, Netherlands, Norway, Panama, Poland, Romania, Russia, South Africa, Switzerland, United Kingdom, Uruguay, United States, Venezuela

JUPITER
Primary Trial Endpoint: MI, Stroke, UA/Revascularization, CV Death

HR 0.56, 95% CI 0.46-0.69
P < 0.00001

Number Needed to Treat (NNT5) = 25

- 44%

Placebo 251 / 8901
Rosuvastatin 142 / 8901

Ridker et al NEJM 2008

JUPITER
LDL reduction, hsCRP reduction, or both?

Placebo
- LDL>70mg/dL, hsCRP>2 mg/L: 1384, 1.11
- LDL<70mg/dL, hsCRP>2 mg/L: 2921, 0.62
- LDL>70mg/dL, hsCRP<2 mg/L: 726, 0.54
- LDL<70mg/dL, hsCRP<2 mg/L: 2685, 0.38

Rosuvastatin
- LDL>70mg/dL, hsCRP>2 mg/L: 1874, 0.95
- LDL<70mg/dL, hsCRP>2 mg/L: 4662, 0.56
- LDL>70mg/dL, hsCRP<1 mg/L: 236, 0.64
- LDL<70mg/dL, hsCRP<1 mg/L: 944, 0.24

P < 0.001
P < 0.001

Better
Worse
**JUPITER**

Primary Endpoint – Understudied or “Low Risk” Subgroups

<table>
<thead>
<tr>
<th>Understudied Subgroups</th>
<th>N</th>
<th>HR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td>6,801</td>
<td>0.54 (0.37-0.80)</td>
</tr>
<tr>
<td>Age &gt; 70</td>
<td>5,695</td>
<td>0.61 (0.46-0.82)</td>
</tr>
<tr>
<td>Black, Hispanic, Other</td>
<td>5,117</td>
<td>0.63 (0.41-0.98)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>“Low Risk” Subgroups</th>
<th>N</th>
<th>HR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Framingham Risk &lt; 10%</td>
<td>8,882</td>
<td>0.56 (0.38-0.83)</td>
</tr>
<tr>
<td>LDLC &lt; 100 mg/dL</td>
<td>6,269</td>
<td>0.66 (0.47-0.92)</td>
</tr>
<tr>
<td>BMI &lt; 25 mg/m2</td>
<td>4,073</td>
<td>0.59 (0.40-0.87)</td>
</tr>
<tr>
<td>No Hypertension</td>
<td>7,586</td>
<td>0.62 (0.44-0.87)</td>
</tr>
<tr>
<td>No metabolic Syndrome</td>
<td>10,296</td>
<td>0.49 (0.37-0.65)</td>
</tr>
<tr>
<td>Elevated hsCRP Only</td>
<td>6,375</td>
<td>0.63 (0.44-0.92)</td>
</tr>
<tr>
<td>All Participants</td>
<td>17,802</td>
<td>0.56 (0.46-0.69)</td>
</tr>
</tbody>
</table>

**New Indication for Rosuvastatin**

For primary prevention “in individuals without clinically evident coronary heart disease but with an increased risk of cardiovascular disease based on age ≥50 years old in men and ≥60 years old in women, hsCRP ≥ 2 mg/L, and the presence of at least one additional CVD risk factor”

**Plan to Widen Use of Statins Has Skeptics**

Cholesterol Pills Aimed at Healthy People

By DUFF WILSON

With the government’s blessing, a drug giant is about to expand the market for its blockbuster cholesterol-lowering medication: Crestor to a new category of customers: as a preventive measure for millions of people who do not have cholesterol problems.

**New York Times**
Front page
March 31, 2010
Statins, Inflammation and Atherosclerosis

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Mechanisms of HDL Protection

Adapted from Barter, 2004
PCSK9 Alleles Decrease LDL-C by 28% in African Americans and 15% in Caucasians

Coronary Heart Disease (%)  
8  4  12

Hypertension - 55%  
Smoking - 30%  
Diabetes - 15%

- Y142X or C679X

African Americans  
Hazard ratio = 0.11  
(CI: 0.02-0.8, p = 0.03)

- R46L

Caucasians  
Hazard Ratio = 0.5  
(CI: 0.32-0.79, p = 0.003)

* p = 0.008

n=3,364

Coronary Heart Disease (%)  
8  4  12

Hypertension - 25%  
Smoking - 23%  
Diabetes - 8%

* p = 0.003

n=9,524

Genome-Wide Association Studies Link Chromosome 9p21 to Increased CHD Risk

- ~20-25% of population are homozygotes
  - ~30-40% increased CHD risk (McPherson et al)
  - ~1.64 times increased MI risk, ~2.02 times increased early-onset MI risk (Helgadottir et al)
- Heterozygotes (50% of population) associated with ~15-20% increased CHD risk (McPherson et al)

- Replicated in 3 separate studies (n>45,000) with Caucasian subjects
- Risk allele not associated with major risk factors
- Chromosomal locus of risk not associated with any known genes
- Adjacent to tumor suppressor genes CDKN2A and CDKN2B

Conclusion

- The development of statins has helped confirm the lipid hypothesis and has revolutionized the field of cardiovascular prevention.
- LDL-C is the primary target of therapy.
- CRP helps target otherwise low-risk patients who would benefit from lipid-lowering therapy.
- The specific roles of inflammation, HDL-C, and other non-HDL-C components (VLDL, IDL, chylomicron remnants) in CV prevention and treatment remains to be determined.