**Cholesterol Management Guidelines - Current and Future**

Michael D. Shapiro
Oregon Health & Science University
Division of Cardiovascular Medicine
Assistant Professor of Medicine and Radiology
Director, Preventive Cardiology

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**Learning Objectives**

- Review current national guidelines for evaluation and management of hypercholesterolemia
- Discuss predicted changes to future guidelines
- Examine FDA safety label changes for statins, including the suggested link between statin use and risk of diabetes

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**Guidelines for Evaluation and Treatment of Hypercholesterolemia**

- ATP III – 2001
- Addendum to ATP III – 2004
- ATP IV – moving target

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**ATP III**

- Fasting lipids
- Determine the presence of risk factors and CHD equivalents
- Establish risk category and titrate LDL-C according to risk

*JAMA 2001; 285: 2486-2497*

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**Major ATP III Risk Factors**

1. Age
   - Male ≥ 45 years
   - Female ≥ 55 years
2. Family History
   - Male first degree relative < 55 years
   - Female first degree relative < 65 years
3. HDL-C < 40 mg/dL
4. Hypertension
5. Current Smoking

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**CHD Equivalents**

- Coronary Artery Disease (CAD)
- Diabetes Mellitus
- Abdominal Aortic Aneurysm
- Carotid Artery Disease (>50% stenosis)
- Prior CVA or TIA
- Peripheral Arterial Disease
- Framingham Score >20% 10 yr Risk
- CKD

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>LDL-C Goal</th>
<th>Consider Drug Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD or CHD risk equivalent</td>
<td>&lt;100 mg/dL</td>
<td>≥130 mg/dL*</td>
</tr>
<tr>
<td>≥2 Risk Factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10-yr risk 10–20%</td>
<td>&lt;130 mg/dL</td>
<td>≥130 mg/dL</td>
</tr>
<tr>
<td>10-yr risk &lt;10%</td>
<td>&lt;130 mg/dL</td>
<td>≥160 mg/dL</td>
</tr>
<tr>
<td>&lt;2 Risk Factors</td>
<td>&lt;160 mg/dL</td>
<td>≥190 mg/dL</td>
</tr>
</tbody>
</table>

**Goals for Therapy: 2004 Addendum**

- NCEP ATP III guidelines for LDL Therapy
- LDL-C <160 for 1 or less risk factors
- LDL-C <130 for 2+ risk factors (calculate FRS)
  - < 100 is a therapeutic option
- LDL-C <100 for CAD and CAD equivalents
  - <70 is option for very high risk patients
    1. CAD + multiple risk factors, especially diabetes
    2. CAD + severe or poorly controlled risk factor(s)
    3. CAD + metabolic syndrome
    4. Acute coronary syndrome
    5. CAD event despite baseline LDL-C < 100

**LDL-C Therapy**

- Therapeutic Lifestyle Change (TLC)
- Statins
- Bile Acid Sequestrants
- Ezetimibe
- Niacin
- Plant Stanols, Sterols

**Non-HDL-C**

- ATP III: Non-HDL-C is a secondary target of drug therapy when TG ≥ 200mg/dL
- Non-HDL-C = Total Cholesterol – HDL-C
- Represents all the triglyceride-rich lipoproteins – considered atherogenic
- Valid even if patient is non-fasting
- Cost-Effective

**Treatment of Low HDL**

- NCEP guidelines
  - For HDL < 40 mg/dl drugs such as nicotinic acid or fibrates have to be considered

**Treatment of Elevated Triglycerides**

- Primary aim of therapy is to reach LDL goal
- Intensify weight management
- Increase physical activity
- If triglycerides are ≥500 mg/dl, after LDL goal is reached, set secondary goal for non-HDL cholesterol (total – HDL)
  - 30 mg/dl higher than LDL goal.
- For high TG (200-499 mg/dl), non-HDL is the secondary target of therapy
  - Increase statin dose
  - Add fibrate/nicotinic acid/Omega-3s

**Treatment of Elevated Triglycerides**

- NCEP guidelines
  - For high TG (>500 mg/dl), triglyceride-rich lipoproteins are present
    - Very low-fat diet (≤11% of calories from fat)
    - Weight management and physical activity
    - Fibrates or nicotinic acid
    - Non-steady state TG ≥500 mg/dl, turn to LDL-lowering therapy
### Targets for Therapy after LDL-C Goal in Patients with TG ≥200 mg/dL

<table>
<thead>
<tr>
<th>Patient Category</th>
<th>LDL-C target (mg/dL)</th>
<th>Non-HDL-C target (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD or CHD risk equivalent</td>
<td>&lt;100</td>
<td>&lt;130</td>
</tr>
<tr>
<td>No CHD, 2+ RF</td>
<td>&lt;130</td>
<td>&lt;160</td>
</tr>
<tr>
<td>No CHD, &lt;2 RF</td>
<td>&lt;160</td>
<td>&lt;190</td>
</tr>
</tbody>
</table>


### Potential Goal Modifying Factors
- Lp(a)
- hs-CRP
- Metabolic Syndrome

### Current Paradigm
- **Count Risk Factors**
- **Estimate Risk for CV Event**
  - **Lifestyle Modifications**
  - **Medical Therapy**

### Magnitude of the Burden

<table>
<thead>
<tr>
<th></th>
<th>Deaths (thousands)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVD</td>
<td>950.2</td>
</tr>
<tr>
<td>Cancer</td>
<td>544.7</td>
</tr>
<tr>
<td>Accidents</td>
<td>93.8</td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td>32.7</td>
</tr>
</tbody>
</table>

*American Heart Association. Heart and Stroke Statistical Update*

### Magnitude of the Burden
- CVD leading cause of death in the U.S. and worldwide
- 1 in 2.9 deaths
- ~2,400 Americans die of heart disease each day
- >150,000 Americans killed by CVD <65 years old

*American Heart Association. Heart and Stroke Statistical Update*

### Heart Attack or Sudden Cardiac Death may be the Initial Presentation of Coronary Heart Disease

<table>
<thead>
<tr>
<th>Gender</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>82%</td>
</tr>
<tr>
<td>Women</td>
<td>12%</td>
</tr>
</tbody>
</table>

*Murabito et al, Circulation 1993*
Issues with Current Guidelines

Issue #1
More Precise Approaches to Risk Assessment are Needed

Issue #1
More Precise Approaches to Risk Assessment

• ATP-III recommends the 10-year FRS to predict future CV events
• FRS often inaccurate

Current Guidelines to Identify High Risk Patients

- NCEP, AHA, ACC recommend office-based assessment of all adults
- FRS is a risk prediction algorithm derived from the Framingham Heart Study
  - Age and gender
  - Total cholesterol
  - HDL-C
  - Blood pressure
  - Smoking

Example

- 60 yo woman
- TC 200 mg/dl
- HDL-C 45 mg/dl
- SBP 132 mmHg without therapy
- Not a smoker
- FRS – 2% risk of MI over 10 years

Example

- 60 yo woman
- TC 200 mg/dl
- HDL-C 45 mg/dl
- SBP 132 mmHg without therapy
- Not a smoker
- FRS – 2% risk of MI over 10 years
- If she had
  - Metabolic syndrome
  - stage II CKD
  - Mother with MI at age 64
  - Or sister with MI at age 61
  - ATP III categorizes her risk the same (2%)
**FRS Risk Categories**

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Low</th>
<th>Intermediate</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>10-yr event rate</td>
<td>&lt;10%</td>
<td>10-20%</td>
<td>&gt;20%</td>
</tr>
<tr>
<td>LDL &gt;190</td>
<td>LDL &gt;160</td>
<td>LDL &gt;100</td>
<td></td>
</tr>
<tr>
<td>% population</td>
<td>25</td>
<td>40</td>
<td>35</td>
</tr>
</tbody>
</table>

>50% of cardiac events occur in “Intermediate risk” patients

Do not qualify for the most intensive risk factor interventions

*Greenland P et al. Circulation 2001;104:1863*

**How Good Is NCEP III At Predicting MI?**

222 patients with 1st acute MI, no prior CAD men <55 y/o (75%), women <65 (25%), no DM

- 10% did not qualify for pharmacotherapy by FRS
- 82% F vs 59% M

*How would they be classified if they presented 1 day before their event?*

*Greenland P et al. Circulation 2001;104:1863*

**How Good Is NCEP III At Predicting MI?**

2969 men and women who presented with AMI and no previous history of CAD or lipid-lowering drugs

1. Only 15% categorized as high-risk by FRS
2. 69% did not meet criteria for drug therapy
3. Women more likely to NOT qualify for drug therapy (77% vs 66%)


**Of 136,965 patients hospitalized with CAD, 77% had normal LDL levels below 130 mg/dl**

*Modified from Sachdeva et al, Am Heart J 2009;157:111-7.e2*

**Atherosclerotic Plaque Development**

*Subclinical Atherosclerosis       Long Lag Time*
Assess Disease rather than Risk for Disease!!

**Issue #1**

More Precise Approaches to Risk Assessment

**Non-invasive Imaging**

- Coronary artery calcium score (CACS)
  - Measurement standardized
  - Small radiation dose
  - Direct assessment of disease itself and carries robust risk information
  - Hesitation of the full ATP III report that "testing is relatively expensive" is no longer true

- Carotid IMT (CIMT)
  - Measurement not standardized
  - If performed by experienced, precise technologist, may help reclassify risk

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Non-contrast Cardiac CT

**Coronary Artery Calcium Scoring**


\[ r = 0.90 \]
\[ p < 0.001 \]

Heart Scans from 3 Individuals Classified at Same CHD Risk According to FRS

Risk-Adjusted Survival by CAC

Shaw L, Raggi P, Berman D, Callister TQ. Radiology 2003

10,377 asymptomatic individuals
Age: 54±9 yrs
Follow-up: 5.0 years
249 Deaths
**St. Francis Heart Study**

Prospective study of 5,585 asymptomatic individuals
Predominantly Intermediate risk men and women

Follow up=4.3 years
CHD events=119

<table>
<thead>
<tr>
<th>CAC</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.0</td>
<td>1.0-1.0</td>
</tr>
<tr>
<td>1-99</td>
<td>1.9</td>
<td>0.8-4.2</td>
</tr>
<tr>
<td>100-399</td>
<td>10.2</td>
<td>4.8-21.6</td>
</tr>
<tr>
<td>&gt;400</td>
<td>26.2</td>
<td>12.6-53.7</td>
</tr>
</tbody>
</table>

Arad Y et al. J Am Coll Cardiol 2005

**Cooper Clinic Study**

10,782 Patients: 3.5 year follow-up

Nonfatal MI & CHD Death
Adjusted age, history of diabetes, hypertension, elevated cholesterol, over weight

Follow up=4.3 years
CHD events=119

<table>
<thead>
<tr>
<th>CAC</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>Ref</td>
<td>1.0-1.0</td>
</tr>
<tr>
<td>1-16</td>
<td>2.7</td>
<td>0.8-8.2</td>
</tr>
<tr>
<td>17-96</td>
<td>6.0</td>
<td>2.1-17</td>
</tr>
<tr>
<td>97-409</td>
<td>9.7</td>
<td>3.6-26</td>
</tr>
<tr>
<td>&gt;409</td>
<td>21.1</td>
<td>7.8-57</td>
</tr>
</tbody>
</table>


**MESA**

Median follow-up 3.8 years

Nonfatal MI & CHD Death

Adjusted age, history of diabetes, hypertension, elevated cholesterol, over weight

Follow up=3.8 years
Nonfatal MI & CHD Death

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<th>CAC</th>
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<th>95% CI</th>
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</thead>
<tbody>
<tr>
<td>None</td>
<td>Ref</td>
<td>1.0-1.0</td>
</tr>
<tr>
<td>1-16</td>
<td>4.3</td>
<td>2.4-8.1</td>
</tr>
<tr>
<td>17-96</td>
<td>10.0</td>
<td>5.0-21</td>
</tr>
<tr>
<td>97-409</td>
<td>14.1</td>
<td>6.0-34</td>
</tr>
<tr>
<td>&gt;409</td>
<td>24.1</td>
<td>9.4-67</td>
</tr>
</tbody>
</table>


**Long-term prognosis associated with CAC**

25,253 patients – median f/u 6.8±3 years

Budoff MJ et al. JACC 2007; 49:1860-70

**Coronary Artery Calcium Score and Risk Classification for Coronary Heart Disease Prediction**
CACS and Risk Classification for CHD Prediction

- CACS predicts future CHD events
- Extent to which adding CACS to traditional CHD risk factors improves classification of risk is unclear
- Used MESA cohort to determine whether adding CACS to TRFs improves classification of risk

Risk Stratification Capacity of the Model With and Without CACS

- Reclassification in 26% of the population (55% of intermediate risk patients)
- CACS appropriately identified a larger proportion of high risk patients

Polonsky et al. JAMA 2010;303:1610-16

EISNER Study

Impact of Coronary Artery Calcium Scanning on Coronary Risk Factors and Downstream Testing

Prospective RCT to compare the clinical impact of conventional risk factor modification to that associated with the addition of CACS

2,137 participants randomized to groups that either did or did not undergo CACs before risk factor counseling

CACs group showed a net favorable change in systolic blood pressure \((p=0.02)\), LDL \((p=0.02)\), LDL-C \((p=0.04)\), and waist circumference \((p=0.01)\), and tendency to weight loss among overweight subjects

Rise FRS in the no-scan group; FRS remained static in the scan group \((p=0.003)\)

Downstream medical testing and costs in the scan group were comparable to those of the no-scan group

lower and higher resource utilization for subjects with normal CAC scans and CAC scores 400

Rozanski A et al. J Am Coll Cardiol 2011;57:1622-32

EISNER Study

Findings

- Prospective RCT to compare the clinical impact of conventional risk factor modification to that associated with the addition of CACS
- 2,137 participants randomized to groups that either did or did not undergo CACS before risk factor counseling
- CACS group showed a net favorable change in systolic blood pressure \((p=0.02)\), LDL \((p=0.02)\), LDL-C \((p=0.04)\), and waist circumference \((p=0.01)\), and tendency to weight loss among overweight subjects
- Rise FRS in the no-scan group; FRS remained static in the scan group \((p=0.003)\)
- Downstream medical testing and costs in the scan group were comparable to those of the no-scan group
- lower and higher resource utilization for subjects with normal CAC scans and CAC scores 400

Rozanski A et al. J Am Coll Cardiol 2011;57:1622-32

EISNER Study

Conclusions

- CACS was associated with superior CAD risk factor control without increasing downstream medical testing

Rozanski A et al. J Am Coll Cardiol 2011;57:1622-32

Issue #2

Should hs-CRP be used to assess risk in primary prevention and should goals for LDL-C be lowered?
**Issue #2**

*Should hs-CRP be used to assess risk in primary prevention?*

- Medical therapy for secondary prevention unequivocally reduces future CHD events
- What is the data for primary prevention?
- Should hs-CRP be used as a risk stratifier in primary prevention?

**hs-CRP**

*What is it?*

- Protein found in the blood
- Levels rise in response to inflammation
- Atherosclerosis is an inflammatory disease
- CRP is general marker for inflammation and can be used as a rough proxy for heart disease risk
- A level >2.4 mg/l associated with 2X risk of a MI compared to levels below 1 mg/l


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**hs-CRP Adds Prognostic Information Beyond Traditional Risk Factors in All Major Cohorts Evaluated**

Meta-analysis of 54 Prospective Cohort Studies

Emerging Risk Factor Collaborators, Lancet 2010

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**Meta-analysis of 54 Prospective Cohort Studies**

Inflammation, Statin Therapy, and hs-CRP

Initial Observations

Emerging Risk Factor Collaborators, Lancet 2010
**PROVE-IT TIMI22**

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

- **LDL < 70 mg/dL, CRP > 2 mg/L**
- **LDL > 70 mg/dL, CRP > 2 mg/L**
- **LDL > 70 mg/dL, CRP < 2 mg/L**
- **LDL < 70 mg/dL, CRP < 2 mg/L**

**Why Consider Statins for Low LDL, high hsCRP Patients?**

**Rationale for JUPITER**

- Investigate whether rosuvastatin 20 mg compared to placebo would decrease the rate of first MACE among apparently healthy individuals with LDL < 130 mg/dL with increased inflammation (hs-CRP > 2 mg/L)

**JUPITER Trial**

- Investigate whether rosuvastatin 20 mg compared to placebo would decrease the rate of first MACE among apparently healthy individuals with LDL < 130 mg/dL with increased inflammation (hs-CRP > 2 mg/L)

**Baseline Clinical Characteristics**

<table>
<thead>
<tr>
<th>Rosuvastatin (N = 8901)</th>
<th>Placebo (n = 8901)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (IQR)</td>
<td>66.0 (60.0-71.0)</td>
</tr>
<tr>
<td>Female, N (%)</td>
<td>3,426 (38.5)</td>
</tr>
<tr>
<td>Ethnicity, N (%)</td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>6,358 (71.4)</td>
</tr>
<tr>
<td>Black</td>
<td>1,100 (12.4)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>1,121 (12.6)</td>
</tr>
<tr>
<td>Blood pressure, mm (IQR)</td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>134 (124-145)</td>
</tr>
<tr>
<td>Diastolic</td>
<td>80 (75-87)</td>
</tr>
<tr>
<td>Smoker, N (%)</td>
<td>1,400 (15.7)</td>
</tr>
<tr>
<td>Family History, N (%)</td>
<td>997 (11.2)</td>
</tr>
<tr>
<td>Metabolic Syndrome, N (%)</td>
<td>3,652 (41.0)</td>
</tr>
<tr>
<td>Aspirin Use, N (%)</td>
<td>1,481 (16.9)</td>
</tr>
</tbody>
</table>

**JUPITER**

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**

**Baseline Blood Levels (median, interquartile range)**

<table>
<thead>
<tr>
<th>Measure</th>
<th>Rosuvastatin (n = 8901)</th>
<th>Placebo (n = 8901)</th>
</tr>
</thead>
<tbody>
<tr>
<td>hsCRP, mg/L</td>
<td>4.2 (2.8 - 7.1)</td>
<td>4.3 (2.8 - 7.2)</td>
</tr>
<tr>
<td>LDL, mg/dL</td>
<td>108 (94 - 119)</td>
<td>108 (94 - 119)</td>
</tr>
<tr>
<td>HDL, mg/dL</td>
<td>49 (40 - 60)</td>
<td>49 (40 - 60)</td>
</tr>
<tr>
<td>Triglycerides, mg/L</td>
<td>118 (85 - 169)</td>
<td>118 (86 - 169)</td>
</tr>
<tr>
<td>Total Cholesterol, mg/dL</td>
<td>186 (168 - 200)</td>
<td>185 (169 - 199)</td>
</tr>
<tr>
<td>Glucose, mg/dL</td>
<td>94 (87 – 102)</td>
<td>94 (88 – 102)</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>5.7 (5.4 – 5.9)</td>
<td>5.7 (5.5 – 5.9)</td>
</tr>
</tbody>
</table>


**Primary Endpoint**

**MI, Stroke, UA/Revascularization, CV Death**

<table>
<thead>
<tr>
<th>Measure</th>
<th>Rosuvastatin</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR</td>
<td>0.56</td>
<td>0.69</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.46–0.69</td>
<td>0.46–0.69</td>
</tr>
<tr>
<td>P</td>
<td>&lt; 0.00001</td>
<td>0.46–0.69</td>
</tr>
</tbody>
</table>

NNT = 25

- 44 %

Number at Risk

<table>
<thead>
<tr>
<th>Follow-up (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosuvastatin</td>
</tr>
<tr>
<td>Placebo</td>
</tr>
<tr>
<td>8,901</td>
</tr>
<tr>
<td>8,631</td>
</tr>
<tr>
<td>8,412</td>
</tr>
<tr>
<td>6,540</td>
</tr>
<tr>
<td>3,893</td>
</tr>
<tr>
<td>1,958</td>
</tr>
<tr>
<td>1,353</td>
</tr>
<tr>
<td>983</td>
</tr>
<tr>
<td>544</td>
</tr>
<tr>
<td>157</td>
</tr>
</tbody>
</table>


**JUPITER**

**Primary Endpoint – Subgroup Analysis**

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>N</th>
<th>P for Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family HX of CHD</td>
<td>2,045</td>
<td>0.07</td>
</tr>
<tr>
<td>No Family HX of CHD</td>
<td>15,684</td>
<td>0.70</td>
</tr>
<tr>
<td>BMI &gt; 25 kg/m²</td>
<td>2,045</td>
<td>0.70</td>
</tr>
<tr>
<td>BMI 25-29.9 kg/m²</td>
<td>7,000</td>
<td>0.70</td>
</tr>
<tr>
<td>Metabolic Syndrome</td>
<td>7,275</td>
<td>0.14</td>
</tr>
<tr>
<td>No Metabolic Syndrome</td>
<td>10,296</td>
<td>0.51</td>
</tr>
<tr>
<td>Framingham Risk ≤ 10%</td>
<td>6,802</td>
<td>0.99</td>
</tr>
<tr>
<td>Framingham Risk &gt; 10%</td>
<td>6,041</td>
<td>0.99</td>
</tr>
<tr>
<td>hsCRP &gt; 2 mg/L Only</td>
<td>6,375</td>
<td>0.99</td>
</tr>
<tr>
<td>All Participants</td>
<td>17,802</td>
<td>0.99</td>
</tr>
</tbody>
</table>


**Secondary Endpoint – All Cause Mortality**

<table>
<thead>
<tr>
<th>Measure</th>
<th>Rosuvastatin</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR</td>
<td>0.80</td>
<td>0.80</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.67–0.97</td>
<td>0.67–0.97</td>
</tr>
<tr>
<td>P</td>
<td>0.02</td>
<td>0.02</td>
</tr>
</tbody>
</table>

- 20 %

Number at Risk

<table>
<thead>
<tr>
<th>Follow-up (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosuvastatin</td>
</tr>
<tr>
<td>Placebo</td>
</tr>
<tr>
<td>4,500</td>
</tr>
<tr>
<td>4,497</td>
</tr>
<tr>
<td>4,479</td>
</tr>
<tr>
<td>4,269</td>
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<td>3,665</td>
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<td>3,151</td>
</tr>
<tr>
<td>2,753</td>
</tr>
<tr>
<td>2,336</td>
</tr>
<tr>
<td>1,961</td>
</tr>
<tr>
<td>1,557</td>
</tr>
<tr>
<td>1,196</td>
</tr>
<tr>
<td>883</td>
</tr>
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<td>514</td>
</tr>
</tbody>
</table>

JUPITER
Event Reduction is Not Related to Baseline LDL-C

JUPITER
Absolute Risk Reduction Increases with Increasing Levels of hs-CRP

JUPITER
Achieved LDL-C, Achieved hs-CRP, or Both?

Issue #3
Narrow focus on LDL-C as the exclusive 1st therapeutic target

Issue #3
Narrow focus on LDL-C as the exclusive 1st therapeutic target
- Non-HDL-C, apoB, and LDL Particle Number Correlate Better to Risk for CVD

Cholesterol vs. Lipoproteins
Atherogenic (Apo B) Lipoproteins
LDL particles interacting at the artery wall initiate and promote atherosclerosis

Measurement of Cholesterol Concentration vs. Lipoprotein Particle Number

- LDL = Low Density Lipoprotein
- LDL-C = the amount of cholesterol contained in all LDL particles
- Non-HDL-C = TC – HDL-C
  - Non-HDL-C = LDL-C + (VLDL-C + IDL-C) + Lp(a)
- LDL-P = LDL particle number

Non-HDL-C is Superior to LDL-C in Predicting CHD Risk

- A strong positive and graded association between non-HDL-C and risk for CHD occurred within every level of LDL-C
- Non-HDL-C is a stronger predictor of risk than LDL-C

Non-HDL gives equal weight to each particle: LDL, VLDL, IDL, Lp(a)

- Not equal atherogenicity
- Example 1
  - TC=200, HDL=50, TG=200, non-HDL=150
- Example 2
  - TC=170, HDL=20, TG=500, non-HDL=150
  - Is risk equivalent for these 2 patients?

Considerable variance in the level of non–HDL-C for any given value of apoB

Anatomy of a Particle

- LDL-P vs. LDL-C
- This is an LDL Particle
- This is LDL Cholesterol
- A convenient analytic surrogate of LDL since 1972
Among Individuals At The Same LDL-C Level, the Number of LDL Particles Varies

100 mg/dL

Large LDL

Up to 70% More Particles

Small LDL

Cholesterol Balance

LDL Particle Number is Highly Heterogeneous Among Patients with Type 2 Diabetes Mellitus at LDL Cholesterol Target Goal <100 mg/dL

Am J Cardiol. 2006;98:1599-1602

Relationship between Elevated TGs, LDL-C, and LDL-P Number

Framingham Heart Study

Triglycerides (mg/dL)


LDL Particle Number Distribution in T2DM Subjects

Cromwell et al. Am J Cardiol. 2006;98:1599-1602

LDL Particle Number is Highly Heterogeneous Among Patients with Type 2 DM at LDL-C target goal <70 mg/dL

Relations of LDL Particle Number with CHD Outcomes

* Significant and independent after multivariate modeling (lipids and established risk factors)
CHD Event Associations of LDL-P versus LDL-C
Framingham Offspring Study (n=3,066)

Clinical Implications of Discordance Between Low-Density Lipoprotein Cholesterol and Particle Number
James D. Otvos, PhD, Samia Mora, MD, MHS, Irina Shalaurova, MD, Philip Greenland, MD, Rachel H. Mackey, PhD, MPH, David C. Goff, JR, MD, PhD.
Journal of Clinical Lipidology 2011;5:105-113

ADA/ACC Consensus Statement
A need for better lipoprotein Management

• “A more accurate way to capture the risk posed by LDL may be to measure the number of LDL particles”
• “Measurements of apoB or LDL particle number may more closely quantitate the atherogenic lipoprotein load”
• “ApoB and LDL particle number also appear to be more discriminating measures of the adequacy of LDL lowering therapy than are LDL cholesterol or non-HDL cholesterol”
Issue #4
10 year vs lifetime risk of CVD

Another potential explanation for the inability of FRS to predict risk accurately is related to 10 year time window.

Prediction of Lifetime Risk for Cardiovascular Disease by Risk Factor Burden at 50 Years of Age

Donald M. Lloyd-Jones et al

Circulation 2006;113:791-798

Lifetime Risk for CVD Increases With Greater Risk Factor Burden

Lifetime Risk of Death from CVD Among Black Men and White Men at 55 Years of Age

Lloyd-Jones DM et al. Circulation 2006;113:791-798

What can we expect from ATP-IV?

Predictions for ATP-IV
My own speculation

1. There will be a stronger statement on CACS and hs-CRP, but routine use in risk stratification or use as secondary target will not be specifically endorsed
2. The goals for LDL-C in primary prevention will be lowered
3. Non-HDL-C will be upgraded to a co-primary lipid target, but optional use of apo B or LDL-P will not be endorsed
4. A new risk calculator providing lifetime risk estimates will be provided

Statins and Risk of Diabetes

Impact of Statin Use on Major Vascular Events by Baseline Prognostic Factors

Impact of Statin Use on Major Vascular Events

WOSCOPS: Pravastatin and Reductions in Newly Diagnosed Diabetes

Statins and Risk of Diabetes

Freeman DJ et al. Circulation 2001;103:357-362
**JUPITER: Rosuvastatin and Newly Diagnosed Diabetes**

<table>
<thead>
<tr>
<th>Laboratory value</th>
<th>Rosuvastatin (14-200 mg)</th>
<th>Placebo (80 mg)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine, &gt;100 increase from baseline (n%)</td>
<td>14 (2.1)</td>
<td>10 (1.2)</td>
<td>.28</td>
</tr>
<tr>
<td>Microalbuminuria at baseline (mg/mmol)</td>
<td>20 (1.8)</td>
<td>25 (2.3)</td>
<td>.01</td>
</tr>
<tr>
<td>Median</td>
<td>66.6</td>
<td>66.6</td>
<td></td>
</tr>
<tr>
<td>Interquartile range</td>
<td>59.2-70.5</td>
<td>55.8-66.3</td>
<td></td>
</tr>
<tr>
<td>Average increase in fasting glucose (n%)</td>
<td>23 (1.3)</td>
<td>17 (1.2)</td>
<td>.8</td>
</tr>
<tr>
<td>Interquartile range</td>
<td>9.9-11.4</td>
<td>9.6-10.9</td>
<td></td>
</tr>
<tr>
<td>Fasting glucose at 24 mo (mg/dL)</td>
<td>97 (17)</td>
<td>96 (16)</td>
<td>.12</td>
</tr>
<tr>
<td>Median</td>
<td>65</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>Interquartile range</td>
<td>55-70</td>
<td>50-67</td>
<td></td>
</tr>
<tr>
<td>Air pressure at 24 mo (n, %)</td>
<td>12 (2.0)</td>
<td>16 (1.6)</td>
<td>.04</td>
</tr>
<tr>
<td>Excluding pravastatin (n, %)</td>
<td>258 (9)</td>
<td>286 (11)</td>
<td>.31</td>
</tr>
<tr>
<td>Percentage change (n, %)</td>
<td>0 (1.1)</td>
<td>9 (0.9)</td>
<td>.44</td>
</tr>
</tbody>
</table>

**Meta-analysis of Statin Trials for New-Onset Type 2 Diabetes During Follow-up**

All statins (n = 39,791) | 1.63 (0.89, 1.99)
Pravastatin (n = 13,911) | 0.84 (0.86, 1.49)
Rosuvastatin (n = 33,04) | 1.13 (0.86, 1.49)
Simvastatin (n = 14,573) | 1.14 (0.96, 1.33)
Atorvastatin (n = 77,713) | 1.14 (0.91, 1.42)
Excluding pravastatin (n = 25,860) | 1.14 (1.02, 1.28)

**Do Statins Increase New-Onset T2DM?**

<table>
<thead>
<tr>
<th>Statin</th>
<th>n</th>
<th>Event rate</th>
<th>OR (95% CI)</th>
<th>Weight (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosuvastatin</td>
<td>18,740</td>
<td>238</td>
<td>1.14 (0.89, 1.48)</td>
<td>10.8</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>10,679</td>
<td>280</td>
<td>1.11 (0.86, 1.45)</td>
<td>14.3</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>4,692</td>
<td>255</td>
<td>1.12 (0.87, 1.45)</td>
<td>12.4</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>10,921</td>
<td>271</td>
<td>1.19 (0.86, 1.65)</td>
<td>15.2</td>
</tr>
<tr>
<td>Lipid-lowering drugs</td>
<td>2,602</td>
<td>208</td>
<td>1.18 (0.89, 1.56)</td>
<td>8.4</td>
</tr>
<tr>
<td>Placebo</td>
<td>10,694</td>
<td>246</td>
<td>1.00 (0.70, 1.39)</td>
<td>10.0</td>
</tr>
</tbody>
</table>

**Statins Dose-Response T2DM and CVD**

<table>
<thead>
<tr>
<th>Statin dose comparisons</th>
<th>Diabetes: NNT = 498 pt-y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incident diabetes</td>
<td>Odds Ratio (95% CI)</td>
</tr>
<tr>
<td>PROVE IT-TIMI 22, 2004</td>
<td>2.0</td>
</tr>
<tr>
<td>A to Z, 2004</td>
<td>2.0</td>
</tr>
<tr>
<td>TNT, 2005</td>
<td>2.0</td>
</tr>
<tr>
<td>IDEAL, 2005</td>
<td>2.0</td>
</tr>
<tr>
<td>SEARCH, 2010</td>
<td>2.0</td>
</tr>
<tr>
<td>Incident CVD</td>
<td>Odds Ratio (95% CI)</td>
</tr>
<tr>
<td>PROVE IT-TIMI 22, 2004</td>
<td>2.0</td>
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<td>2.0</td>
</tr>
</tbody>
</table>

**Statin vs New-Onset Diabetes: Ongoing Studies**

**J-PREDICT**
- N = 1240, subjects with IGT
- Randomized Rx: lifestyle alone vs pitavastatin (1-4 mg/day) + lifestyle
- Endpoint: new-onset T2DM
- Study start date: April 2006
- Estimated study completion date: March 2013 (duration not specified)

**Thank You**

shapirmi@ohsu.edu