Biochemical Surrogates: Are They Valuable for Risk Stratification?

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Research Support: AstraZeneca, Asahi-Kasei, Eli Lilly
Biochemical Surrogates: Are They Valuable for Risk Stratification?

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Harvard Medical School
Brigham & Women’s Hospital

*The following slides are not prepared by AstraZeneca*
Acute Coronary Syndrome
Plaque Rupture

Defining a Biochemical Surrogate

- A biochemical surrogate of a clinical trial is a laboratory measurement that is used as a substitute for a clinical endpoint.

- The validity of using the biochemical surrogate is such that the effect of an intervention on the biochemical surrogate must reliably predict and capture the net effect of the intervention, in part or whole, on the clinical endpoint.
Recent Evidence from Statin Trials Suggests Lower LDL-C Levels Are Better

Time to Benefit in Lipid Lowering Trials: \(\downarrow\) LDL-C to \(\downarrow\) CHD Risk

LRC-CPPT (7.4 yrs)

4S (Simvastatin) (5 yrs)

POSCH (9.4 yrs)

WOSCOPS

CARE

Pravastatin (4.5 yrs)

% Reduction in Risk of Nonfatal MI or CHD

% LDL-C Reduction

Time to Benefit in Lipid Lowering Trials: Superiority of Statin Therapy

Atherosclerosis: 2-Hit Hypothesis?

Characteristics of Useful Surrogate Markers

- Consistent with the pathophysiology of the disease
- Sufficiently prevalent in patient populations
- Changes in markers meaningfully correlate with changes in patient outcomes
- Reproducible test and retest characteristics over multiple assessments to allow monitoring of disease
- Extensive clinical availability to support their use

Is a biochemical marker of inflammation such as hsCRP, a useful surrogate marker for cardiovascular disease?

hs-CRP and Risk of Future MI in Apparently Healthy Men

<table>
<thead>
<tr>
<th>Quartile of hs-CRP (Range, mg/L)</th>
<th>Relative Risk of MI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 &lt;0.55</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>2 0.56–1.14</td>
<td>1.15–2.10</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>3 1.15–2.10</td>
<td>2</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>4 &gt;2.11</td>
<td>1</td>
<td>P&lt;0.001</td>
</tr>
</tbody>
</table>

P Trend <0.001

# Association of CRP With Other Risk Factors

<table>
<thead>
<tr>
<th>Increased CRP</th>
<th>Decreased CRP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>Alcohol</td>
</tr>
<tr>
<td>BMI</td>
<td>consumption</td>
</tr>
<tr>
<td>Obesity</td>
<td>Physical activity</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Weight loss</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td>Medications</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
</tr>
</tbody>
</table>
CRP Adds Prognostic Information at All Levels of LDL-C and Framingham Risk Score

Is CRP a useful surrogate marker, which when combined with lipid evaluation, provides an improved method to target statin therapy in primary prevention?
First Acute Major Coronary Event: AFCAPS/TexCAPS

Years of Follow-Up

Cumulative Incidence

Placebo
Lovastatin

37% Risk reduction
$P = 0.00008$

Inflammation Discriminates Between Patients with Low Cholesterol Levels in Primary Prevention Trial

Inflammation, Pravastatin and the Risk of Coronary Events after MI in Patients with Average Cholesterol Levels (CARE)*

Inflammation = both CRP and SAA levels > 90th percentile

Randomized pravastatin assignment. N = 708


Relative Risk of Recurrent CAD Events

- Inflammation Absent
  - Statin: 25% ↓
  - Placebo: 0%

- Inflammation Present
  - Statin: 54% ↓
  - Placebo: 0%

↓ LDL-C: -40.3 mg/dL vs. -44.7 mg/dL, p=0.358*

p - trend = 0.005

Inflammation = both CRP and SAA levels ≥90th percentile
Randomized pravastatin assignment. N = 708
1. hsCRP assay is optimal inflammatory marker thus far

2. CRP may be useful in estimating risk of future cardiovascular events in primary prevention, particularly in persons at intermediate risk based on other risk factors

<table>
<thead>
<tr>
<th>hsCRP concentration</th>
<th>Risk Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1 mg/L</td>
<td>Low</td>
</tr>
<tr>
<td>1-3 mg/L</td>
<td>Medium</td>
</tr>
<tr>
<td>&gt;3 mg/L</td>
<td>High</td>
</tr>
</tbody>
</table>

Clinical Testing:

Standardized assay

hsCRP should be measured twice 2 weeks apart and averaged

If hsCRP > 10 mg/L, evaluate for obvious source of infection and repeat in 2 weeks
## Effects of CV Therapeutics on CRP

<table>
<thead>
<tr>
<th>CV Therapeutics</th>
<th>Reduction in CRP</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASA</td>
<td>-10%</td>
</tr>
<tr>
<td>Fibrates</td>
<td>-10%</td>
</tr>
<tr>
<td>Niacin</td>
<td>-15%</td>
</tr>
<tr>
<td>PPAR Agonists</td>
<td>-20%</td>
</tr>
<tr>
<td>ACE Inhibitors</td>
<td>-25%</td>
</tr>
<tr>
<td>ARB</td>
<td>-25%</td>
</tr>
<tr>
<td>Ezetimibe</td>
<td>+5%</td>
</tr>
<tr>
<td>Statins</td>
<td>-30-50%</td>
</tr>
</tbody>
</table>
Is there a relationship between change in LDL and change in CRP?

Change in LDL (mg/dl)

-0.04 -0.03 -0.02 -0.01 -0.005 0

20-30 30-40 40-50 50-60 60 +

Change in CRP (mg/dl)

* pravastatin treated patients only

Albert et al, JAMA 2001
Cardiovascular Protective Effects of Statin Therapy

- Lipid-lowering
- Pleiotropic effects
  - Improved endothelial function
  - Anti-inflammatory effects
  - Plaque stabilizing effects
  - Antioxidative effects
  - Anti-thrombotic effects
  - Pro-angiogenic effects
Advantages of Statin vs. Ezetimibe in Endothelial Function


% Change of LDL-cholesterol

Simvastatin group: 15.6%
Ezetimibe group: 15.4%

Flow-dependent dilation (percent change of diameter)

Statin group: Baseline 4 weeks
Ezetimibe group: Baseline 4 weeks

P<0.01
P=n.s.

P=n.s.
Advantages of Mono vs. Dual Therapy in Endothelial Function

A = atorvastatin; S = simvastatin; E = ezetimibe

## Clinical Outcomes Studies with Combination Therapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Objectives</th>
<th>Study Groups</th>
<th>Patient Type</th>
<th>N</th>
<th>Duration (yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ENHANCE</strong></td>
<td>To evaluate effects of aggressive lipid lowering on carotid artery IMT</td>
<td>Ezetimibe 10 mg/ Simvastatin 80mg Simvastatin 80mg</td>
<td>Hypercholesterolemia</td>
<td>725</td>
<td>≥2</td>
</tr>
<tr>
<td><strong>SEAS</strong></td>
<td>To assess whether aggressive lipid lowering in patients with moderate AS slows the progression of AS and reduces the number of valve replacements and incidence of CVD outcomes</td>
<td>Ezetimibe 10 mg/ Simvastatin 40mg Placebo</td>
<td>Aortic stenosis (AS)</td>
<td>1,400</td>
<td>≥4</td>
</tr>
<tr>
<td><strong>SHARP</strong></td>
<td>To assess the effects of aggressive lipid lowering on vascular events</td>
<td>Ezetimibe 10 mg/ Simvastatin 20mg Placebo</td>
<td>Chronic kidney disease</td>
<td>9,000</td>
<td>&gt;4</td>
</tr>
<tr>
<td><strong>IMPROVE IT</strong></td>
<td>To evaluate the effect of aggressive lipid lowering on reduction in risk of death and major coronary events</td>
<td>Ezetimibe 10 mg/ Simvastatin 40mg Simvastatin 40mg</td>
<td>Acute coronary syndrome</td>
<td>10,000</td>
<td>4</td>
</tr>
</tbody>
</table>

ENHANCE=Ezetimibe and simvastatin in Hypercholesterolemia enhances atherosclerosis regression; IMT=intima media thickness; SEAS=Simvastatin and Ezetimibe in Aortic Stenosis; SHARP=Study of Heart And Renal Protection; IMPROVE IT=IMProved Reduction of Outcomes; Vytorin™ Efficacy International Trial
ENHANCE Trial:
Ezetimibe Does Not Slow Atherosclerosis Progression Despite Further Reduction in LDL

Statins as Anti-inflammatory Agents?
**PROVE-IT/TIMI 22:** Pravastatin 40 mg vs Atorvastatin 80 mg

**No. of Patients**

<table>
<thead>
<tr>
<th></th>
<th>Pravastatin</th>
<th>Atorvastatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pravastatin</td>
<td>1973</td>
<td>2003</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>1844</td>
<td>1856</td>
</tr>
<tr>
<td></td>
<td>1761</td>
<td>1758</td>
</tr>
<tr>
<td></td>
<td>1647</td>
<td>1645</td>
</tr>
<tr>
<td></td>
<td>1445</td>
<td>1461</td>
</tr>
<tr>
<td></td>
<td>1883</td>
<td>1910</td>
</tr>
</tbody>
</table>

**Time of Visit**

- Baseline
- 30 Days
- 4 Mo
- 8 Mo
- 16 Mo
- Final

**LDL Cholesterol (mg/dL)**

- **40 mg of pravastatin**: 95
- **80 mg of atorvastatin**: 62

PROVE-IT/TIMI 22: Pravastatin 40 mg vs Atorvastatin 80 mg


Pravastatin 40mg
- Median LDL-C reduction 10%
- LDL-C achieved 95 mg/dL
- Event rate 26.3%

Atorvastatin 80mg
- Median LDL-C reduction 42%
- LDL-C achieved 62 mg/dL
- Event rate 22.4%

P = 0.005
16% RR
(p = 0.005)

No. at Risk
- Pravastatin: 2063, 1688, 1536, 1423, 810, 138
- Atorvastatin: 2099, 1736, 1591, 1485, 842, 133
Median CRP Levels According to Treatment Arm Over Duration of Study: PROVE-IT

Minimal Relationship Between LDL and CRP After Initiation of Statin Therapy

Clinical Relevance of LDL and CRP After Treatment with Statin Therapy

Follow-Up (years)

Clinical Relevance of LDL and CRP After Treatment with Statin Therapy

MIRACL: Intensive Statin Therapy Reduces Early Events After ACS

NS = not significant; RR = risk reduction.

Adapted from de Lemos et al. *JAMA*. 2004;292:1307, with permission.
Adapted from Schwartz et al. *JAMA*. 2001;285:1711, with permission.
Schwartz and Olsson. *Am J Cardiol*. 2005;96(suppl):45F.
# A-to-Z and MIRACL: CRP Appears To Be Correlated With The Early Time To Benefit With Intensive Statin Therapy

<table>
<thead>
<tr>
<th></th>
<th>A-to-Z</th>
<th>MIRACL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients randomized</td>
<td>4497</td>
<td>3086</td>
</tr>
<tr>
<td>Early* LDL achieved on treatment, mg/dL</td>
<td>62</td>
<td>72</td>
</tr>
<tr>
<td>Early* LDL cholesterol differential, mg/dL</td>
<td>62</td>
<td>63</td>
</tr>
<tr>
<td>CRP differential, %</td>
<td>17</td>
<td>34</td>
</tr>
<tr>
<td>Early event reduction, %</td>
<td>0*</td>
<td>16*</td>
</tr>
</tbody>
</table>

* Measured 120 days after randomization.

CRP = C-reactive protein.

Adapted from Nissen. JAMA. 2004;292:1365, with permission.
## PROVE IT-TIMI 22 And MIRACL: CRP Appears To Be Correlated With The Early Time To Benefit With Intensive Statin Therapy

<table>
<thead>
<tr>
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<th>A-to-Z</th>
<th>MIRACL</th>
<th>PROVE IT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients randomized</td>
<td>4497</td>
<td>3086</td>
<td>4162</td>
</tr>
<tr>
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<td>62</td>
</tr>
<tr>
<td>Early* LDL cholesterol differential, mg/dL</td>
<td>62</td>
<td>63</td>
<td>33</td>
</tr>
<tr>
<td>CRP differential, %</td>
<td>17</td>
<td>34</td>
<td>38</td>
</tr>
<tr>
<td>Early event reduction, %</td>
<td>0*</td>
<td>16*</td>
<td>18†</td>
</tr>
</tbody>
</table>

* Measured 120 days after randomization.
† Measured 90 days after randomization.

Adapted from Nissen. *JAMA*. 2004;292:1365, with permission.
JUPITER Study Design

4 Week Placebo Run-in

No History of CVD
Men ≥50 years;
Women ≥60 years
LDL-C < 130 mg/dL,
hsCRP levels ≥ 2.0 mg/L

Rosuvastatin 20 mg (n=8901)

Placebo (n=8901)

3-4 Years

Screening Visit

Randomization Visit

Safety Visit

Bi-Annual Visit

Final Visit

LDL-C
hsCRP

Lipids
hsCRP
LFTs
HbA\textsubscript{1C}

Lipids
hsCRP

Lipids
hsCRP

Lipids
hsCRP
HbA\textsubscript{1C}

## JUPITER: Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Race, %</strong></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>71.3</td>
</tr>
<tr>
<td>Black</td>
<td>12.5</td>
</tr>
<tr>
<td>Asian</td>
<td>1.6</td>
</tr>
<tr>
<td>Hispanic</td>
<td>12.7</td>
</tr>
<tr>
<td>Other</td>
<td>2.0</td>
</tr>
<tr>
<td><strong>Body mass index (range), kg/m²</strong></td>
<td>28.4 (25.3-32.0)</td>
</tr>
<tr>
<td><strong>Blood pressure (range), mmHg</strong></td>
<td>134 (124-145)/80 (75-87)</td>
</tr>
<tr>
<td><strong>Female, %</strong></td>
<td>38.2</td>
</tr>
<tr>
<td><strong>Age (range), years</strong></td>
<td>66.3 (60.9-71.8)</td>
</tr>
<tr>
<td><strong>Smoker, %</strong></td>
<td>15.8</td>
</tr>
</tbody>
</table>

All values are percent or median (interquartile range)

## JUPITER: Baseline Laboratory Parameters

**Randomized (n=17,802)**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>185 (169-200)</td>
</tr>
<tr>
<td>LDL-C, mg/dL</td>
<td>108 (94-119)</td>
</tr>
<tr>
<td>HDL-C, mg/dL</td>
<td>49 (40-60)</td>
</tr>
<tr>
<td>Non-HDL-C, mg/dL</td>
<td>134 (118-147)</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>118 (85-169)</td>
</tr>
<tr>
<td>hsCRP, mg/L</td>
<td>4.3 (2.8-7.1)</td>
</tr>
<tr>
<td>Glucose, mg/dL</td>
<td>94 (88-102)</td>
</tr>
<tr>
<td>HbA$_{1c}$, %</td>
<td>5.7 (5.5-5.9)</td>
</tr>
</tbody>
</table>

Values expressed as median (interquartile range). For hsCRP, values are the mean of the screening and randomization visits.

LDL-C=low-density lipoprotein cholesterol; HDL-C=high-density lipoprotein cholesterol; hsCRP=high sensitivity C-reactive protein; HbA$_{1c}$=glycosylated hemoglobin

AstraZeneca Disclosure
Regarding the JUPITER Study

- On March 31, 2008, AstraZeneca announced that the JUPITER study will be stopped early based on a recommendation from the Independent Data Monitoring Board and the JUPITER Steering Committee, which met on March 29, 2008.

- The recommendation to stop the trial is based on unequivocal evidence of a reduction in cardiovascular morbidity and mortality among patients who received rosuvastatin when compared to placebo.

- No further information is available at this time.
Current Concepts Regarding Surrogate Markers and Risk Stratification

- Aggressive lipid lowering is beneficial in the secondary prevention of cardiovascular disease or in patients at high risk.

- Some of the beneficial effects of statin therapy may be due to its non-cholesterol lowering or pleiotropic effects on inflammation.

- Inflammation is an important component of atherosclerosis and cardiovascular disease. Cardiovascular risk reduction with statin therapy depends not only on achieved LDL-C levels, but also on achieved CRP levels.

- Prospective primary prevention trial in patients with low LDL and systemic inflammation (JUPITER) suggests that hsCRP may be a useful surrogate marker in identifying patients who may benefit from statin therapy.