Panel Discussion: Literature that Should Have an Impact on our Practice: The JUPITER Study

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The JUPITER Trial: Will You Change Your Practice?

- In patients with hyperlipidemia, treatment with statins reduces cardiovascular risk, even in people without a history of cardiovascular disease. However, nearly half of all first cardiovascular events occur in people whose low-density lipoprotein (LDL) cholesterol levels are below current thresholds for lipid-lowering therapy. Therefore, recent research has sought to refine our ability to identify people who are at risk and to find interventions capable of reducing that risk.

JUPITER Primary Objectives

To investigate whether rosuvastatin 20 mg compared to placebo would decrease the rate of first major cardiovascular events among apparently healthy men and women with LDL < 130 mg/dL (3.36 mmol/L) who are nonetheless at increased vascular risk on the basis of an enhanced inflammatory response, as determined by hsCRP > 2 mg/L.

To enroll large numbers of women and individuals of Black or Hispanic ethnicity, groups for whom little data on primary prevention with statin therapy exists.

Justification for the Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin

Ridker et al NEJM 2008

The JUPITER Trial: The JUPITER Trial: Will You Change Your Practice? Will You Change Your Practice?

- In patients with hyperlipidemia, treatment with statins reduces cardiovascular risk, even in people without a history of cardiovascular disease. However, nearly half of all first cardiovascular events occur in people whose low-density lipoprotein (LDL) cholesterol levels are below current thresholds for lipid-lowering therapy. Therefore, recent research has sought to refine our ability to identify people who are at risk and to find interventions capable of reducing that risk.

JUPITER NEJM Poll

Do you believe, on the basis of the JUPITER trial results, that the approach to laboratory screening of apparently healthy adults should be changed?

- Yes, the trial results indicate that the approach to laboratory screening should be changed. 49%
- No, the trial results do not provide a basis for a change in the approach to laboratory screening. 51%

2553 total responses
JUPITER NEJM Poll

Do you believe, on the basis of the JUPITER trial results, that the therapeutic use of statins in apparently healthy adults should be changed?

- Yes, the trial results indicate that the therapeutic use of statins should be changed. 48%
- No, the trial results do not provide a basis for a change in the therapeutic use of statins. 52%

LDLC Levels in 136,905 Patients Hospitalized With CAD: 2000-2006

CTT meta-analysis: Proportional reduction in NON-FATAL MI or CHD DEATH versus absolute LDL-C reduction

The Acute-Phase Response Pathway

**CRP Epidemiology**

Is C-reactive protein (CRP) a causal factor in the pathogenesis of atherosclerosis?

If it is, implications could be far reaching for new approaches for the prevention and treatment of myocardial infarction and stroke.

**CRP Epidemiology**

Support for a role of CRP in the pathogenesis of atherosclerosis are from epidemiologic studies that have consistently observed an association between elevated plasma CRP levels and cardiovascular events.

**CRP: Chicken or the EGG?**

A

- Causation: the biomarker is causally involved in the disease process
- Reverse causation: the biomarker is increased by the disease process
- Confounding: other factors affect both the biomarker and the disease

**JUPITER**

Why Consider Statins for Low LDL, high hsCRP Patients?

However, while intriguing and of potential public health importance, the observation in AFCAPS/TexCAPS that statin therapy might be effective among those with elevated hsCRP but low cholesterol was made on a post hoc basis. Thus, a large-scale randomized trial of statin therapy was needed to directly test this hypotheses.

**JUPITER**

**Trial Design**

**MULTI-NATIONAL RANDOMIZED DOUBLE BLIND PLACEBO CONTROLLED TRIAL OF ROSUVASTATIN IN THE PREVENTION OF CARDIOVASCULAR EVENTS AMONG INDIVIDUALS WITH LOW LDL AND ELEVATED hsCRP**

**Baseline Clinical Characteristics**

<table>
<thead>
<tr>
<th></th>
<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>
<td>66.0 (60.0-71.0)</td>
</tr>
<tr>
<td>Female, N (%)</td>
<td>3,426 (38.5)</td>
<td>3,375 (37.9)</td>
</tr>
<tr>
<td>Ethnicity, N (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>6,358 (71.4)</td>
<td>6,325 (71.1)</td>
</tr>
<tr>
<td>Black</td>
<td>1,100 (12.4)</td>
<td>1,124 (12.6)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>1,121 (12.6)</td>
<td>1,140 (12.8)</td>
</tr>
<tr>
<td>No Prior CVD or DM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women &gt; 50, Women &gt; 60</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL &lt; 130 mg/dL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline LDLc</td>
<td>104 mg/dL</td>
<td>104 mg/dL</td>
</tr>
<tr>
<td>Baseline HDLc</td>
<td>49 mg/dL</td>
<td>49 mg/dL</td>
</tr>
<tr>
<td>Baseline hsCRP</td>
<td>4.2 mg/L</td>
<td>4.2 mg/L</td>
</tr>
<tr>
<td>Smoker, N (%)</td>
<td>1,400 (15.7)</td>
<td>1,420 (16.0)</td>
</tr>
<tr>
<td>Family History, N (%)</td>
<td>907 (10.2)</td>
<td>907 (11.5)</td>
</tr>
<tr>
<td>Metabolic Syndrome, N (%)</td>
<td>3,652 (41.0)</td>
<td>3,723 (41.8)</td>
</tr>
<tr>
<td>Aspirin Use, N (%)</td>
<td>1,481 (16.6)</td>
<td>1,477 (16.6)</td>
</tr>
</tbody>
</table>

All values are median (interquartile range) or N (%)

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

<table>
<thead>
<tr>
<th></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 (84-119)</td>
<td>108 (84-119)</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>

All values are median (interquartile range). [Mean LDL = 104 mg/dL]
JUPITER - Primary Endpoint

Time to first occurrence of a CV death, non-fatal stroke, non-fatal MI, unstable angina or arterial revascularization

Hazard Ratio 0.56
(95% CI 0.46-0.69)
P<0.00001


NNT for 2y = 95
5y* = 25

*Extrapolated figure based on Altman and Andersen method

JUPITER Predicted Benefit Based on LDL Reduction vs Observed Benefit

Mean LDL cholesterol difference between treatment groups (mmol/l)

JUPITER Predicted Benefit Based on LDL Reduction vs Observed Benefit

Proportional reduction in vascular event rate (95% CI)

Mean LDL cholesterol difference between treatment groups (mmol/l)

JUPITER Primary Endpoint – Subgroup Analysis II

P for Interaction

37% PCR reduction in JUPITER. Same magnitude as REVERSAL
JUPITER. Primary End Point


Benefits vs Adverse Events

NNH=166. That means:

More than a new--onset diabetes vs 2 prevented events

JUPITER: Caveats

Primary Prevention with Statins

Primary Prevention with Statins

JUPITER: Caveats. Study Stopped Earlier than planned

Overestimate the beneficial effects

Primary Prevention with Statins

Secondary Prevention

Lipids an IHD

A Comparative Study of Biomarkers in Acute Coronary Syndrome – Results of the SIESTA study

Biomarker levels (categorized in thirds) and the occurrence of the 360-day second study endpoint.

<table>
<thead>
<tr>
<th>Variable</th>
<th>No events</th>
<th>Events</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
<td></td>
</tr>
<tr>
<td>CRP, mg/L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st third, n</td>
<td>189 (34)</td>
<td>15 (27.8)</td>
<td>0.190</td>
</tr>
<tr>
<td>2nd third, n</td>
<td>188 (36)</td>
<td>15 (28.8)</td>
<td></td>
</tr>
<tr>
<td>3rd third, n</td>
<td>172 (32.2)</td>
<td>24 (44.4)</td>
<td></td>
</tr>
<tr>
<td>NT-ProBNP, ng/L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st third, n</td>
<td>154 (34.9)</td>
<td>7 (17.5)</td>
<td>0.030</td>
</tr>
<tr>
<td>2nd third, n</td>
<td>147 (33.3)</td>
<td>13 (32.5)</td>
<td></td>
</tr>
<tr>
<td>3rd third, n</td>
<td>140 (31.7)</td>
<td>20 (46.0)</td>
<td></td>
</tr>
<tr>
<td>Cystatin –C, mg/L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st third, n</td>
<td>183 (35)</td>
<td>6 (12)</td>
<td>0.135</td>
</tr>
<tr>
<td>2nd third, n</td>
<td>171 (32.7)</td>
<td>18 (36)</td>
<td></td>
</tr>
<tr>
<td>3rd third, n</td>
<td>169 (32.3)</td>
<td>26 (52)</td>
<td></td>
</tr>
<tr>
<td>Fibrinogen, mg/dL</td>
<td></td>
<td></td>
<td>0.002</td>
</tr>
<tr>
<td>1st third, n</td>
<td>183 (36)</td>
<td>6 (12)</td>
<td></td>
</tr>
<tr>
<td>2nd third, n</td>
<td>171 (32.7)</td>
<td>18 (36)</td>
<td></td>
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<td>169 (32.3)</td>
<td>26 (52)</td>
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</tbody>
</table>

1. Revised biomarker levels based on the study results of hsCRP < 2.0 mg/L to report acute myocardial infarction or death event rate.

Jupiter Study Limitations

- The study did not include anyone with hsCRP < 2.0 mg/L and therefore the trial does not inform whether people with normal, low, or no hsCRP values would have also benefited from the robust LDL-C lowering. So the ultimate value of hsCRP for selecting patients for treatment remains unknown.
- Principal investigator disclosed financial conflicts of interest as a co-inventor on patents that relate to the use of hsCRP in the evaluation of patients’ risk of cardiovascular disease.
- AstraZeneca, manufacturer of rosvastatin, sponsored the study.

Statins in Primary Prevention

Estimation of additional number to treat in U.S. with the selection criteria of JUPITER

JUPITER. Clinical Implications:

Is justified treat with statins a population (JUPITER) with normal LDL-cholesterol?

- Subgroups? YES
- Whom? Based on Global CV Risk
- Is necessary a population screening? NO
- Are these results extrapolable to other statins? Possibly NO
THE JUPITER TRIAL
A Consensus Statement for KP Health Care Providers from the Dyslipidemia Management Guideline Development Team

Recommendations
Apply ONLY to Patients for Primary Prevention

1. Do not measure hsCRP if decision for Rx already made
2. Determine Framingham 10-year risk status.
   For people at > 20% risk:
   • If baseline LDL-C is 100-159 mg/dL, initiate simvastatin 40 mg daily.
   • If baseline LDL-C is ≥ 160 mg/dL, initiate simvastatin 80 mg daily
   • If baseline LDL-C is < 100 mg/dL, it is optional to measure hsCRP in men > 50 years old and women > 60 years old, and if hsCRP is ≥ 2 mg/L, to initiate simvastatin 40 mg daily. (not fully EBM)
   • Target LDL-C is < 100 mg/dL.

FHS: Risk Assessment Tool for Estimating 10-year Risk of Developing Hard CHD (Myocardial Infarction and Coronary Death)

- Framingham Heart Study to estimate 10-year risk for “hard” coronary heart disease outcomes (myocardial infarction and coronary death). This tool is designed to estimate risk in adults aged 20 and older who do not have heart disease or diabetes.

1. Age: years
2. Gender: Female Male
3. Total Cholesterol: mg/dL
4. HDL Cholesterol: mg/dL
5. Smoker: No, Yes
6. Systolic Blood Pressure: mm/Hg
7. Currently on medication to treat high blood pressure. No, Yes

For people at Framingham 10-20% risk:
- If baseline LDL-C is 130-219 mg/dL, initiate simvastatin 40 mg daily.
- If baseline LDL-C is ≥ 220 mg/dL, initiate simvastatin 80 mg daily.
- If baseline LDL-C is < 130 mg/dL, it is optional to measure hsCRP in men ≥ 50 years old and women ≥ 60 years old, and if hsCRP is ≥ 2 mg/L, to initiate simvastatin 40 mg daily. (not fully EBM)
- Target LDL-C is < 130 mg/dL.
For people at <10% risk:

- If baseline LDL-C is 190-219 mg/dL, initiate simvastatin 40 mg daily.
- If baseline LDL-C is > 220 mg/dL, initiate simvastatin 80 mg daily.
- If baseline LDL-C is < 190 mg/dL, it is optional to measure hsCRP in men > 50 years old and women > 60 years old, and if hsCRP is > 2 mg/L, to initiate simvastatin 40 mg daily. (not fully EBM)
- Target LDL-C is <130 mg/dL.

Caveats of CRP Measurement

- Do not use hsCRP to monitor therapy.
- Information Regarding hsCRP Ordering and Interpretation
  - hsCRP should be ordered only in metabolically stable patients who are free of active infection, systemic inflammation*, recent trauma and are not on estrogen therapy, immunosuppressants or glucocorticoids.
  - If hsCRP is > 2 mg/L, repeat hsCRP two weeks later. Statin therapy contingent on hsCRP is only recommended if two hsCRP tests are both > 2 mg/L.
  - If hsCRP is > 10 mg/L, the patient should be evaluated for sources of infection or inflammation and the test repeated.
  - The standard CRP test is not useful for cardiac risk assessment and should not be ordered for this purpose. The correct test is the high-sensitivity CRP, sometimes called the “cardio CRP” or “wide range CRP.”