Expert Meeting on Large Simple Trials (LST´s)

Clinical Trials Transformation Initiative

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

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R&D Global Medicines Development

AstraZeneca
Definition of LST – was JUPITER an LST?

- Inclusion/exclusion criteria are unambiguous and easily applied
- Primary endpoint is unambiguous and directly related to the patient’s health and well-being (not a surrogate)
- Dosing, mechanism, and potentially adverse effects of intervention are generally well understood
- Sample size and statistical power to detect a modest but still clinically meaningful treatment effect
- Streamlined data collection and monitoring
GALAXY Program

Outcomes Program
- AURORA
- CORONA
- JUPITER

Atherosclerosis Program
- ORION
- ASTEROID
- METEOR

Lipid Program
- STELLAR
- MERCURY I
- MERCURY II
- DISCOVERY
- ECLIPSE
- ORBITAL
- COMETS
- LUNAR
- PLUTO
- POLARIS
- PULSAR
- EXPLORER
- CENTAURUS
- ARIES
- STARSHIP
- IRIS
- SOLAR

More than 55,000 Patients in 55 Countries
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.
Risk Factors for Future Cardiovascular Events: WHS

- Lipoprotein(a)
- Homocysteine
- IL-6
- TC
- LDL-C
- sICAM-1
- SAA
- Apo B
- TC: HDLC
- hsCRP
- hsCRP + TC: HDLC

Relative Risk of Future Cardiovascular Events

Inflammation, hsCRP, and Vascular Prevention

- Is there evidence that individuals with elevated levels of the inflammatory biomarker hsCRP are at increased vascular risk?

- Is there evidence that individuals identified at increased risk due to inflammation benefit from a therapy they otherwise would not have received?
Major inclusion criteria

- Men aged $\geq$ 55 years; women aged $\geq$ 65 years
- Fasting LDL-C levels $< 3.4$ mmol/L (130 mg/dL), CRP levels $\geq 2.0$ mg/L and TG levels $< 5.7$ mmol/L (500 mg/dL) on initial screening

Ridker PM. Circulation 2003; 108: 2292–2297
Major exclusion criteria

- Current use of statins or other lipid-lowering therapies

- Prior history of cardiovascular or cerebrovascular events, such as MI, unstable angina, prior arterial revascularisation or stroke, or CHD-risk equivalents

- Chronic inflammatory condition, such as severe arthritis, lupus or inflammatory bowel disease

Ridker PM. Circulation 2003; 108: 2292–2297
JUPITER – study endpoints

- **Primary**
  - time to the first occurrence of a major cardiovascular event (cardiovascular death, stroke, MI, unstable angina or arterial revascularisation)

- **Secondary**
  - Efficacy (incident diabetes mellitus, venous thromboembolic events, bone fractures)
  - Safety (total mortality noncardiovascular mortality, adverse events)
JUPITER: Inclusion and Exclusion Criteria, Study Flow

**Inclusion Criteria**
- Men ≥50 years
- Women ≥60 years
- No CVD, No DM
- LDL < 130 mg/dL
- hsCRP ≥2 mg/L

**Reason for Exclusion (%)**
- LDL>130 mg/dL 52
- hsCRP<2 mg/L 36
- Withdrew consent 5
- Diabetes 1
- Hypothyroid <1
- Liver disease <1
- TG >600 mg/dL <1
- Age out of range <1
- Current use of HRT <1
- Cancer <1
- Poor compliance/Other <1
JUPITER: Trial Structure

- **Independent Steering Committee:**
  - P Ridker (Chair), F Fonseca, J Genest, A Gotto, J Kastelein, W Koenig, P Libby, A Lorenzatti, B Nordestgaard, J Shepherd, J Willerson

- **Independent Academic Clinical Coordinating Center:**
  - P Ridker, E Danielson, R Glynn, J MacFadyen, S Mora (Boston)

- **Independent Academic Study Statistician:**
  - R Glynn (Boston)

- **Independent Data Monitoring Board:**
  - R Collins (Chair), K Bailey, B Gersh, G Lamas, S Smith, D Vaughan

- **Independent Academic Clinical Endpoint Committee:**
  - K Mahaffey (Chair), P Brown, D Montgomery, M Wilson, F Wood (Durham)
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

No Prior CVD or DM
Men ≥50, Women ≥60
LDL <130 mg/dL
hsCRP ≥2 mg/L

Rosuvastatin 20 mg (N=8901)
4-week run-in

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:
17,802 Patients; 1,315 Sites; 26 Countries

Total Randomized = 17,802
## JUPITER: 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 (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/dL</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 (2.69 mmol/L)]
JUPITER: Pre-specified Monitoring and Stopping Guidelines

- JUPITER was an event-driven trial designed to continue until accrual of 520 confirmed primary endpoints to attain 90% power to detect a 25% reduction in the rate of the primary endpoint.

- The monitoring plan specified interim efficacy analyses with O’Brien-Fleming stopping boundaries determined by the Lan-DeMets approach upon attainment of 37.5% and 75% of the targeted numbers of endpoints.

- The IDMB charter specified that an early stopping recommendation required proof beyond reasonable doubt that for all, or some specific types of patients, prolonged use of rosuvastatin is clearly indicated or clearly contraindicated based on the interim analyses or other sources which might reasonably be expected to influence clinicians’ management decisions for subjects in the study. On March 29, 2008 the IDMB voted to recommend termination of the trial after a median follow-up of 1.9 years (maximum 5.0).
JUPITER: Primary Endpoint

- **Rosuvastatin**: # of events 142 (1.6%)
- **Placebo**: # of events 252 (2.8%)

Cumulative Incidence, %

<table>
<thead>
<tr>
<th>Years</th>
<th>Number at risk Rosuvastatin</th>
<th>Number at risk Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>8901</td>
<td>8901</td>
</tr>
<tr>
<td>1</td>
<td>8412</td>
<td>8353</td>
</tr>
<tr>
<td>2</td>
<td>3892</td>
<td>3872</td>
</tr>
<tr>
<td>3</td>
<td>1352</td>
<td>1333</td>
</tr>
<tr>
<td>4</td>
<td>543</td>
<td>534</td>
</tr>
<tr>
<td>5</td>
<td>156</td>
<td>173</td>
</tr>
</tbody>
</table>

HR 0.56 (95% CI 0.46-0.69)
P<0.00001
## JUPITER: Individual Components of the Primary Endpoint

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Rosuvastatin</th>
<th>Placebo</th>
<th>HR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Endpoint</strong>*</td>
<td>142</td>
<td>252</td>
<td>0.56</td>
<td>0.46-0.69</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>22</td>
<td>62</td>
<td>0.35</td>
<td>0.22-0.58</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Any MI</td>
<td>31</td>
<td>68</td>
<td>0.46</td>
<td>0.30-0.70</td>
<td>&lt;0.0002</td>
</tr>
<tr>
<td>Non-fatal Stroke</td>
<td>30</td>
<td>58</td>
<td>0.52</td>
<td>0.33-0.80</td>
<td>0.003</td>
</tr>
<tr>
<td>Any Stroke</td>
<td>33</td>
<td>64</td>
<td>0.52</td>
<td>0.34-0.79</td>
<td>0.002</td>
</tr>
<tr>
<td>Revascularization or Unstable Angina</td>
<td>76</td>
<td>143</td>
<td>0.53</td>
<td>0.40-0.70</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>MI, Stroke, CV Death</td>
<td>83</td>
<td>158</td>
<td>0.52</td>
<td>0.40-0.68</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Adjudicated CV Death</td>
<td>35</td>
<td>44</td>
<td>0.80</td>
<td>0.51-1.24</td>
<td>0.32</td>
</tr>
<tr>
<td><strong>Total Mortality</strong></td>
<td>198</td>
<td>247</td>
<td>0.80</td>
<td>0.67-0.97</td>
<td>0.02</td>
</tr>
</tbody>
</table>

*Nonfatal MI, nonfatal stroke, revascularization, unstable angina, CV death

*NEJM 2008;359:2195 2207.*
JUPITER: Conclusions – Primary Endpoint

- Among apparently healthy men and women with elevated hsCRP but low LDL-C, rosvastatin reduced major cardiovascular events by 44%
- Benefits of rosvastatin were consistent regardless of age, sex, region or ethnicity
- Despite evaluating a population with lipid levels widely considered to be “optimal” in almost all current prevention algorithms, the relative benefit observed in JUPITER was greater than in almost all prior statin trials
JUPITER: Conclusions – Secondary Endpoints

- In this trial of low LDL/high hsCRP individuals who do not currently qualify for statin therapy, rosuvastatin significantly reduced all-cause mortality by 20 percent.

- Rosuvastatin allocation was associated with a 27 percent increase in investigator-reported diabetes.

- With regard to venous thromboembolism, rosuvastatin allocation was associated with a 43 percent reduction in deep vein thrombosis and/or pulmonary embolism.

- With regard to bone fracture, rosuvastatin allocation was not associated with an increase or decrease in events.
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