JUPITER\(^1\) Trial Overview

**Rosuvastatin Vs Placebo For Primary Prevention In Low-Moderate Risk Older Adults With Normal LDL, \(\uparrow\) hs-CRP**

- **Trial:** n=17,802; 1.9 years median follow-up; a prospective, randomized, double-blind, placebo controlled international multi-center Astra-Zeneca funded trial completed Mar/08

- **Screening:** 72,088 of 89,890 people \((13/03-12/06)\) were ineligible for trial due to: LDL >3.4mmol/L (52%) & hs-CRP >2mg/L (36%)

- **Treatment studied:** rosvastatin CRESTEN: 20mg po daily \(\mu\) vs placebo \(\mu\); both arms used a 4 week placebo run-in to select compliant patients

- **Included:** LDL <3.4mmol/L & hs-CRP<2mg/L Baseline data (median): LDL 2.8mmol/L HS C-reactive protein 4.2mg/L, A1C 5.7%, PG 5.2mmol/L

- **Excluded:** previous or current lipid lowering therapy, current use of HRT, hepatic dysf-ALT>2xULN, \(\uparrow\) CRP >5xULN, \(\uparrow\) Scr >1.7mmol/L, diabetes, uncontrolled BP SBP>160 or DBP>100 or hypothyroidism or 
  
  - \(\uparrow\) TSH >10xULN, cancer (within 5yrs before trial, except breast or cutaneous-carcinoma of the skin), recent history of alcohol or drug abuse, inflammatory conditions (eg. RA, lupus, IBD), or if on immunosuppressants

- **CV Risk Population studied:** \(~50\%\) more moderate risk using the Framingham risk score (eg. >10%): \((\geq 550 \text{yr} \text{d}; \geq 350 \text{yr} \text{f}; \geq 38 \text{yr} \text{m} \text{w} ~66\%\)), BMi >28

- **Metabolic Syndrome**: no diabetes/CV disease/stroke, BP >134/80mm Hg; History of: Smoking 16%, Family history of premature CHD <12%; ASA used primarily in only 17%

### Table 1: Jupiter Results (Rosuvastatin 20mg daily vs Placebo)

<table>
<thead>
<tr>
<th>Endpoints</th>
<th>Rosuvastatin (n=8,901)</th>
<th>Placebo (n=8,901)</th>
<th>HR (95% CI)</th>
<th>NNT / yr</th>
<th>p value</th>
<th>Absolute risk ↓ 0.59 / 100 person-yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI, stroke, arterial revascularization, hospitalization for unstable angina or death from CV causes *(^1) (hard &amp; soft CV events)</td>
<td>0.77</td>
<td>142 events (14.4%)</td>
<td>1.36</td>
<td>251 events</td>
<td>0.56 (0.46-0.69)</td>
<td>82 CI:61-127</td>
</tr>
<tr>
<td>2° Myocardial Infarction (fatal or non-fatal)</td>
<td>0.17</td>
<td>31 events</td>
<td>0.37</td>
<td>68 events</td>
<td>0.46 (0.3-0.7)</td>
<td>241</td>
</tr>
<tr>
<td>2° Stroke (fatal or non-fatal)</td>
<td>0.18</td>
<td>33 events</td>
<td>0.34</td>
<td>64 events</td>
<td>0.52 (0.34-0.79)</td>
<td>288</td>
</tr>
<tr>
<td>2° Arterial Revascularization or Unstable Angina</td>
<td>0.41</td>
<td>76 events</td>
<td>0.77</td>
<td>143 events</td>
<td>0.53 (0.4-0.7)</td>
<td>133</td>
</tr>
<tr>
<td>2° Combined MI, Stroke or Death from CV causes *</td>
<td>0.45</td>
<td>83 events ((0.47))</td>
<td>0.85</td>
<td>157 event ((1.84))</td>
<td>0.53 (0.4-0.69)</td>
<td>120</td>
</tr>
<tr>
<td>2° Death from Any Causes</td>
<td>1</td>
<td>108 events ((2.5))</td>
<td>1.25</td>
<td>247 events ((2.8))</td>
<td>0.8 (0.67-0.97)</td>
<td>182</td>
</tr>
<tr>
<td>2° LDL mmol/L</td>
<td>1.4</td>
<td>1.6</td>
<td>1.4 (0.50%)</td>
<td>2.8</td>
<td></td>
<td>(&lt;0.01)</td>
</tr>
<tr>
<td>2° CR-protein (high sensitivity) mg/L</td>
<td>2.2</td>
<td>2.3</td>
<td>1.23</td>
<td></td>
<td></td>
<td>(&lt;0.01)</td>
</tr>
</tbody>
</table>

*Similar core CV clinical endpoints to previous statin trials. (CV death: NS by itself) Other Surrogate Results: eHDL 1.3 vs 1.3, ↓Triglycerides 1.3→1.1 (17% decrease), ↓A1C 5.7→5.9%.

### Table 2: Adverse Events Results (AE): Rosuvastatin 20mg daily vs Placebo

<table>
<thead>
<tr>
<th>Adverse Events % (# of events)</th>
<th>Rosuvastatin (n=8,901)</th>
<th>Placebo (n=8,901)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate of serious adverse events (SAE)</td>
<td>15.2% (1,552)</td>
<td>15.4% (1,377)</td>
<td>• Well tolerated &amp; similar to placebo in general.</td>
</tr>
<tr>
<td>Myopathy</td>
<td>0.1% (10)</td>
<td>0.1% (9)</td>
<td>• Muscle complaints in ~15% for each group.</td>
</tr>
<tr>
<td>Muscle weakness, stiffness or pain</td>
<td>16% (1,421)</td>
<td>15.4% (1,375)</td>
<td>• Short term trial inadequate for assessing long-term / lifelong potential adverse events. (Some AEs may only be seen in longer trial. Muscle &amp; liver SE’s are known to occur with statins. Cancer data reassuring (ca death 0.4% vs 0.7% p=0.12).</td>
</tr>
<tr>
<td>Creatinine (&gt;100% ↑ from baseline)</td>
<td>0.2% (16)</td>
<td>0.1% (10)</td>
<td>• New Onset Diabetes: not adjudicated by the end point committee. NNT=165 (Real or Type 1 error? Potential in long term for replacing 1 risk factor for another. )</td>
</tr>
<tr>
<td>Renal –glomerular filtration rate (ml/min/1.73m(^2))</td>
<td>66.8</td>
<td>p&lt;0.01</td>
<td>66.6</td>
</tr>
<tr>
<td>ALT &gt;3xULN (alanine aminotransferase)</td>
<td>0.3% (23)</td>
<td>0.2% (17)</td>
<td>• CRP should not be measured for initiation of statins during times of known inflammatory conditions. A repeat test after 1 month would be prudent before assigning a lower-risk patient to a lifelong statin. (Cost per test: ~$20)</td>
</tr>
<tr>
<td>Glycemia</td>
<td>0.4% (36)</td>
<td>0.4% (32)</td>
<td>• What we know and the additional results to add to our knowledge:</td>
</tr>
</tbody>
</table>
| Intracranial hemorrhage | 0.07% (6) | 0.1% (9) | • Statins not only lower LDL but have proven benefit in ↓ morbidity & mortality. Higher risk patients benefit most; even for Jetpack:
  - **2° prevention trial:** LIPID, LIPID-2, \(\uparrow\) HDL, \(\uparrow\) coronary death, CARE, \(\uparrow\) coronary death, \(\uparrow\) hs-CVD/total fatal vascular event, TNT high dose in stable coronary pts ideal dose after MI
  - **1° prevention trial:** CARDIS \(\uparrow\) in CHD event in diabetes, ASCOT \(\uparrow\) in diabetes death in high risk hypertensives, WOSCOPS \(\uparrow\) in diabetes death in high risk Scottish male, \(\uparrow\) in CV event

  Treaty: low risk 1° prevention patients: prevents CV events (RR 47%, but because low rate of CV events ~1%/yr, the absolute benefit is small NNT=120/1.9yr.)

  All-cause mortality: 4S trial \(\uparrow\) high risk secondary prevention NNT=30 over 5.4yr; JUPITER \(\uparrow\) lower risk primary prevention NNT=182 over 1.9yr (or projected to be 64 over 5.4yr)

  WOSCOPS trial \(\uparrow\) prevention NNT=111 \(\uparrow\) over 4.9yr; or 101 over 5.4yr. (Some reviewers caution on extrapolation from short 1.9yr trial.)

  Generalizability is a concern with only 1 out of 5 screened patients enrolled in this trial. (Likely few placebo patients taking non-study statins, unlike other trials) HPS1/2Allstat

### Questions remaining:

Statins generally do more good than harm in moderate/high risk patients, but when do we offer lower risk patients?

- Who should have a CRP level (select intermediate/moderate risk patients only)? Would different results be expected in patients with various CRP levels?
- To truly test a hs-CRP hypothesis, the trial would need to test a high hs-CRP group against a low hs-CRP group.
- What is the long-term 10-20year risk/benefit of being treated with a statin to an LDL of 1.4mmol/L? Would a lower dose have offered benefit?
- What about “exclusively, real-life” patients? Will benefits & risks balance out for those with comorbidities, \(\uparrow\) age, \(\uparrow\) renal function, Asians & on \(\uparrow\) meds?
- How would other statins compare? (If simvastatin 40mg/d equally effective, the cost would be $100,000/generation to prevent 1 CV event based on an NNT=120/1.9yr.)
- Would lifestyle (diet, exercise, smoking cessation) interventions & increased ASA use, be as effective? (Lifestyle is not as effective that mufflers to reduce diabetes CRP use facile.)
- Should we focus less on LDL targets & more on treating with a fixed statin dose based on global cardiovascular risk assessment of the patient?

### Take Home:

Rosuvastatin joins other statins: atorvastatin, simvastatin in showing clinical outcome benefits! Primary major CV event prevention in low-risk moderate-risk pts with rosvastatin in older adults with low LDL <3.4mmol/L & hs-CRP<2mg/L offers benefit (↓ MI, stroke, or CV death: NNT=120/1.9yr; estimated drug cost = ~$73,000 June/12 generic; long-term AEs unknown). CV death only: NNT=89/1 yr, other AEs: Weigh benefits, risk, tolerability, patient preferences and cost when considering statins for lower risk patients. Long-term benefit vs safety is not established for high dose statins, or low risk patients who may end up receiving for 20-40+ years. Role of hs-CRP testing will be debated. Don’t forget lifestyle interventions!
JUPITER Pears:

- Statins, including rosuvastatin offer benefit to patients at increased CV risk. Rosuvastatin joins the "statin hard outcome club"!
- A threshold-to-treat LDL may not be as important as identifying patients at risk.
- Rosuvastatin 20mg/day appears well tolerated in the relatively short term of 2-4 years. (Some cautions not withstanding e.g. ↑ diabetes)
- Statin therapy resulting in an LDL of 1.4 mmol/L appears safe in the short term; long-term benefits or harms of such a low LDL are uncertain
- For CV reduction in normotensive patient, a statin may offer a greater CV risk reduction than ACE/ARB JUPITER, HOPE, TRANSCEND.

JUPITER Cautions:

- Primary endpoint includes softer CV endpoints than most previous statin trials (e.g. arterial revascularization, hospitalization for unstable angina).
- The NNT=25-54years is commonly quoted for the 1st endpoint. When evaluating this NNT remember: 1) it is a composite that includes clinical CV endpoints softer than previous trials, 2) it is extrapolated & more than twice the 1.9 year average duration of intervention in the trial, and 3) comes from the 4 year point assessment of the Kaplan Meier curves which is of limited value due to the low number of patients assessed at the 4 year time point (only n=1,092 patients out of the total (n=17,802) in the trial).
- While approach trials discussions on a possible CRP threshold for statin therapy, note that this approach has not yet been tested.
- Consider the types of patients excluded from trial. (Also, if screened for 1 eligible for treatment, CRP cost would be $100 or $200 if CRP repeated x1) to find 1 person eligible for treatment.
- Don’t use the “achieved LDL” which is very low in JUPITER to justify ultra-low LDL targets that require much more aggressive drug therapy or combinations than have been studied.
- Remember that JUPITER patients had about 2X the risk of all-cause death seen in some other primary prevention trials, so overall patient risk should be considered to be higher than WOSCOPS, etc.
- Limits of Surrogate Association; e.g. homocysteine has been associated with stroke; however lowering homocysteine does not confer benefit. (HOPE 2: did not reduce the primary endpoint of major CV events, but did ↓ stroke.)
- Consider limitations of trial stopping early for benefit.
- Who might not be a good candidate for rosuvastatin 20mg/day? Caution for: 1) elderly, 2) renal impaired, 3) Asians, the liver or muscle challenged

All Cause Death NNTs from some other Statin trials (raw event data; extrapolated ~5 years):

| 1st or 2nd | Trial | NNT/5yr | NNT/5yr Baseline Mortality Rate in Placebo Group |
|------------|-------|---------|--|---|
| 3rd        | 4S    | 3N      | 10.6% / 5yr |
| 2nd & 1st  | HPS:  | NNT57   | 14.6% / 5yr |
| 1st        | WOSCOPS| NNT109;N=0.051 | 4.2% / 5yr |
| 1st        | JUPITER| NNT70   | 7.4% / 5yr |

Based on baseline control group mortality rate, the patients in JUPITER appear to be at higher overall mortality risk compared to WOSCOPS & other primary prevention trials such as AFCAPS, ASCOT. Caution: it should be noted that projecting the results of a 1.9year trial to 5 years carries assumptions that may not be valid. Benefits and risks do not always occur in a linear fashion.

References:

3. Zacho J, Tybjaerg-Hansen A, Jensen JS, Grande P, Sillesen H, Nordestgaard BG. Genetically elevated C-reactive protein and ischemic vascular disease. N Engl J Med. 2008 Oct 30;359(18):1897-908. Polymorphisms in the CRP gene are associated with marked increases in CRP levels and thus with a theoretically predicted increase in the risk of ischemic vascular disease. However, these polymorphisms are not in themselves associated with an increased risk of ischemic vascular disease.


Ogawa H, Nakayama M, Morimoto T, et al. for the Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes (J-PAAD) Trial Investigators. Low-Dose Aspirin for Primary Prevention of Atherosclerotic Events in Patients With Type 2 Diabetes: A Randomized Controlled Trial. JAMA. 2008 Nov 9. In this study of patients with type 2 diabetes, low-dose aspirin as primary prevention did not reduce the risk of cardiovascular events.


Ridker PM, MacFayden DG, Nordestgaard BG, et al. Rosuvastatin for primary prevention among individuals with elevated high-sensitivity C-reactive protein and 5% to 10% and 10% to 20% 10-year risk. Circ Cardiovasc Qual Outcomes. 2010; DOI:10.1161/circoutcomes.109.881188.


Sever PS, Faergeman O, Chang CL, et al. on behalf of the IDEAL Investigators. Evaluation of C-reactive protein prior to and on-treatment as a predictor of benefit from atorvastatin: observations from the Anglo-Scandinavian Cardiac Outcomes Trial - Eure Heart J. 2011 Jul 28.


Transcend: The Telmarin Randomised Assessments Study in ACE-in tolerant subjects with Cardiovascular Disease (TRANSCEND) Investigators. Effects of the angiotensin-receptor blocker telmisartan on cardiovascular events in high-risk patients intolerant to angiotensin-converting enzyme inhibitors; a randomised controlled trial. Lancet. 2008 Aug 29. [Epub ahead of print]

Vidit G, Ridsdon PM, Monypil JF, et al. Longitudinal Assessment of Estimated Glomerular Filtration Rate in Apparently Healthy Adults: A Post hoc Analysis From the JUPITER Study (Justification for the Use of Statin in Prevention: An Intervention Trial Evaluating Rosuvastatin). Clinical Therapeutics, Volume 33, Issue 6, June 2011, Pages 717-725, ISSN 0149-2918, DOI: 10.1016/j.clinthera.2011.05.004.


Copyright 2008 – RxFiles, Saskatoon Health Region (SHR) www.RxFiles.ca

Lifestyle articles:


Disclaimer: The content of this newsletter represents the research, experience and opinions of the authors and not those of the Board or Administration of Saskatoon Health Region (SHR). Neither the authors nor Saskatoon Health Region nor any other party who has been involved in the preparation or publication of this work warrants or represents that the information contained herein is accurate or complete, and they are not responsible for any errors or omissions or for the result obtained from the use of such information. Any use of this newsletter shall entail acknowledgment of this disclaimer and release any responsibility of SHR, its employees, servants or agents. Readers are encouraged to consult the information contained herein with other sources. Additional information and references online at www.RxFiles.ca