



## JUPITER<sup>1</sup> Trial Overview

### Rosuvastatin Vs Placebo For Primary Prevention In Low-Moderate Risk Older Adults With Normal LDL, ↑ 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 (Feb/03-Dec/06) were ineligible for trial due to: LDL ≥3.4mmol/L (52%) & hs-CRP <2mg/L (36%)
- ♦ **Treatment studied:** rosuvastatin **CRESTOR** 20mg po daily n=8901 vs placebo n=8901; (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 2.8<sub>mmol/L</sub>, HS C-reactive protein 4.2<sub>mg/L</sub>, A1C 5.7%, PG 5.2<sub>mmol/L</sub>
- ♦ **Excluded:** previous or current lipid lowering therapy, current use of HRT, hepatic dysfx ALT>2x ULN, ↑CK >3x ULN, ↑Scr >177umol/L, diabetes, uncontrolled BP SBP>190 or DBP>100 or hypothyroidism TSH >1.5x ULN, cancer within 5yrs before trial except basal or squamous-cell carcinoma of the skin, recent history of alcohol or drug abuse, inflammatory conditions (eg. RA, lupus, IBD) or if on immunosuppressants eg. cyclosporine, tacrolimus, azathioprine or steroids long term; (and of course those who did not pass the screening process)
- ♦ **CV Risk Population studied:** ~50% were moderate risk using the Framingham risk score (e.g. >10%); {≥50yr ♂, ≥60yr ♀ 38% female, age ~66yr, BMI~28, Metabolic Syndrome 41%, no diabetes/CV disease/stroke, BP ~134/80mm Hg; History of: Smoking 16%, Family history of premature CHD ~12%; ASA used previously in only 17%}

**Table 1: Jupiter Results (Rosuvastatin 20mg daily vs Placebo)** NNT below calculated based on raw patient event data as traditionally reported; article uses event based data which may exaggerate the treatment benefit. <sup>Aaron'08</sup>

Endpoints	Rosuvastatin (n = 8,901) Per 100 person yrs; (% reduction)	Placebo (n = 8,901) Per 100 person yrs	HR (95% CI)	NNT /1.9yr	p value
<b>1° MI, stroke, arterial revascularization, hospitalization for unstable angina or death from CV causes</b> (hard & soft CV endpoints)	<b>0.77</b> 142 events (↓44%) Absolute risk ↓ 0.59 / 100 person-yrs	<b>1.36</b> 251 events	<b>0.56</b> (0.46-0.69)	<b>82</b> CI: 61-127	<0.00001
2° Myocardial Infarction (fatal or non-fatal)	<b>0.17</b> 31 events	<b>0.37</b> 68 events	<b>0.46</b> (0.3-0.7)	<b>241</b>	0.0002
2° Stroke (fatal or non-fatal)	<b>0.18</b> 33 events	<b>0.34</b> 64 events	<b>0.52</b> (0.34-0.79)	<b>288</b>	0.002
2° Arterial Revascularization or Unstable Angina	<b>0.41</b> 76 events	<b>0.77</b> 143 events	<b>0.53</b> (0.4-0.7)	<b>133</b>	<0.00001
2° <b>Combined MI, Stroke or Death from CV causes</b> *	<b>0.45</b> 83 events 0.9% (↓47%)	<b>0.85</b> 157 event 1.8%	<b>0.53</b> (0.4-0.69)	<b>120</b>	<0.00001
2° <b>Death from Any Causes</b>	<b>1</b> 198 events 2.2%	<b>1.25</b> 247 event 2.8%	<b>0.8</b> (0.67-0.97)	<b>182</b>	0.02
2° LDL mmol/L @ 12months	<b>1.4</b> (↓50%)	<b>2.8</b>			<0.01
2° <b>C-reactive protein</b> (high sensitivity) mg/L @ 12months	<b>2.2</b> (↓37%)	<b>3.5</b>			<0.01

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

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

Adverse Events % (# of events)	Rosuvastatin (n = 8901)	Placebo (n = 8901)	Comments
Rate of serious adverse events (SAE)	<b>15.2%</b> (1352)	<b>15.4%</b> (1377)	♦ Well tolerated & similar to placebo in general.
Myopathy	0.1% (10)	0.1% (9)	♦ Muscle complaints in ~ 15% for each group.
Muscle weakness, stiffness or pain	16% (1421)	15.4% (1375)	♦ Short term trial inadequate for assessing long-term / lifelong potential adverse events. (Some AEs may only be seen in longer trial. Muscle & liver SE's are known to occur with statins. Cancer data reassuring (ca death 0.4% vs 0.7% p=0.02).)
Creatinine (>100% ↑ from baseline)	<b>0.2%</b> (16)	<b>0.1%</b> (10)	♦ <b>New Onset Diabetes:</b> not adjudicated by the end point committee. <b>NNH=165</b> (Real or Type 1 error? Potential in long term for replacing 1 risk factor for another. (PROVE-IT atorvastatin 80mg also had more diabetes.))
Renal -glomerular filtration rate (ml/min/1.73m <sup>2</sup> )	66.8 p=0.02	66.6	
ALT >3x ULN (alanine aminotransferase)	0.3% (23)	0.2% (17)	
Glycosuria	0.4% (36)	0.4% (32)	
Intracranial hemorrhage	0.07%(6)	0.1%(9)	
Diabetes- new onset physician reported	<b>3%</b> (270) p=0.01	<b>2.4%</b> (216)	

#### Of Note:

- ♦ **Efficacy:** First positive outcome trial for rosuvastatin (CORONA & Gissi-HF in heart failure patients showed no benefit on 1° outcome)
- ♦ **Safety:** No significant difference in overall adverse events. Of note: 1 rhabdomyolysis age 90, & more diabetes, however only a short 1.9 year trial.
- ♦ Similar positive results in all subgroups: for ≥65yr, for women, for lower risk patients, for blacks, & for Hispanics.
- ♦ Terminated early at 1.9 year trial vs the originally planned 4 year trial<sup>2</sup>. Risk vs benefit assessment in low risk would require longer term follow up.
- ♦ Those with CV risk >10% accounted for more events; therefore, absolute risk of patient correlates to absolute benefit. (Higher risk patients benefit most!)
- ♦ Trial design offers only limited indirect information about role of hs-CRP. {CRP shown not to affect CV risk<sup>3</sup>, but suggestion of benefit Reversal, WHI & Prove-IT. } CRP can be elevated with inflammatory conditions RA, lupus, IBD, sores, etc., infections & injuries. 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)

Note: Ridker (investigator) holds CRP testing patent.

#### What we knew and what these results add to our knowledge:

- ♦ **Statin not only lower LDL but have proven benefit in ↓ morbidity & mortality.** Higher risk patients benefit most; even for Jupiter. <sup>see subgroup plots.</sup>
- ♦ **2° prevention trials:** 4S<sup>↓total mortality</sup>, LIPID<sup>↓cardiac death</sup>, CARE<sup>↓MI/cardiac death</sup>, HPS<sup>↓fatal/non-fatal vascular event</sup>, TNT<sup>high dose in stable coronary pts</sup>, Ideal<sup>high dose after MI</sup>
- ♦ **1° prevention trials:** CARDS<sup>↓1st CHD event in diabetics</sup>, ASCOT<sup>↓MI/cardiac death in high risk hypertensives</sup>, WOSCOPS<sup>↓MI/cardiac death in higher risk Scottish males</sup>, & AFCAPS<sup>↓1st CV event</sup>
- ♦ Treating lower risk 1° prevention patients: prevents CV events ↓RR 47%, but because low rate of CV events ~1%/yr, the absolute benefit is small <sup>NNT=120/1.9yr</sup>
- ♦ All-cause mortality: 4S trial high risk secondary prevention NNT=30 over 5.4yr; JUPITER lower risk primary prevention NNT=182 over 1.9yr (or projected to be 64 over 5.4yr)
- ♦ WOSCOPS trial 1° prevention NNT=111 p=0.051 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) <sup>HPS>Allhat</sup>

#### Questions remaining: Statins generally do more good than harm in moderate/high risk patients, but when do we offer to 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?
  - o 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 "excluded, real-life" patients? Will benefits & risks balance out for those with comorbidities, ↑age, ↓renal function, Asians & on ↑meds?
- ♦ How would other statins compare? (If simvastatin 40mg/d equally effective, the cost would be \$110,000 generic 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 was more effective than metformin to reduce diabetes DPP-see references)
- ♦ 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 eg. atorvastatin, simvastatin in showing clinical outcome benefits! **Primary major CV event prevention** in low-moderate risk pts with rosuvastatin in older adults with low LDL <3.4mmol/L & high hs-CRP ≥2mg/L, offers benefit (↓ MI, stroke, or CV death: NNT=120/1.9yr; estimated drug cost = ~ \$185,000; long-term AEs unknown). <sup>CV death only: NS</sup> Weigh benefits, risk, tolerability, patient preferences and cost when considering statins in 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 Pearls:

- 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 notwithstanding 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 ACEI/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=25/5years is commonly quoted for the 1° 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}.
- Although trial prompts 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 5 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 stopping trial early for benefit. Bassler D, Montori VM, Briel M, Glasziou P, Guyatt G. Early stopping of randomized clinical trials for overt efficacy is problematic. *J Clin Epidemiol.* 2008 Mar;61(3):241-6.
- Who might not be a good candidate for rosuvastatin 20mg/day? Caution for: 1) elderly, 2) renal impaired, 3) Asians, 4) the *liver or muscle challenged*

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

1° or 2°	Trial	NNT/~5yr	Baseline Mortality Rate in Placebo Group (indicator of risk)
• 2°	4S:	NNT=33	10.6% / 5yr
• 2° & 1°	HPS:	NNT=57	14.6% / 5yr
• 1°	WOSCOPS	NNT=109 <sub>7NS; p=0.051</sub>	4.2% / 5yr
• 1°	JUPITER	NNT=70	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 1.9 year trial to 5 years carries assumptions that may not be valid. Benefits & risks do not always occur in a linear fashion.

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#### Lifestyle articles:

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