



JUPITER¹ 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_{mmol/L}, **HS C-reactive protein** 4.2_{mg/L}, A1C 5.7%, PG 5.2_{mmol/L}
- ♦ **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. ^{Aaron'08}

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
1° MI, stroke, arterial revascularization, hospitalization for unstable angina or death from CV causes (hard & soft CV endpoints)	0.77 142 events (↓44%) Absolute risk ↓ 0.59 / 100 person-yrs	1.36 251 events	0.56 (0.46-0.69)	82 CI: 61-127	<0.00001
2° Myocardial Infarction (fatal or non-fatal)	0.17 31 events	0.37 68 events	0.46 (0.3-0.7)	241	0.0002
2° Stroke (fatal or non-fatal)	0.18 33 events	0.34 64 events	0.52 (0.34-0.79)	288	0.002
2° Arterial Revascularization or Unstable Angina	0.41 76 events	0.77 143 events	0.53 (0.4-0.7)	133	<0.00001
2° Combined MI, Stroke or Death from CV causes *	0.45 83 events 0.9% (↓47%)	0.85 157 event 1.8%	0.53 (0.4-0.69)	120	<0.00001
2° Death from Any Causes	1 198 events 2.2%	1.25 247 event 2.8%	0.8 (0.67-0.97)	182	0.02
2° LDL mmol/L @ 12months	1.4 (↓50%)	2.8			<0.01
2° C-reactive protein (high sensitivity) mg/L @ 12months	2.2 (↓37%)	3.5			<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)	15.2% (1352)	15.4% (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)	0.2% (16)	0.1% (10)	♦ New Onset Diabetes: not adjudicated by the end point committee. NNH=165 (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 ²)	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	3% (270) p=0.01	2.4% (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 trial². 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 risk³, 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. ^{see subgroup plots.}
- ♦ **2° prevention trials:** 4S^{↓total mortality}, **LIPID**^{↓cardiac death}, **CARE**^{↓MI/cardiac death}, **HPS**^{↓fatal/non-fatal vascular event}, **TNT**^{high dose in stable coronary pts}, **Ideal**^{high dose after MI}
- ♦ **1° prevention trials:** **CARDS**^{↓1st CHD event in diabetics}, **ASCOT**^{↓MI/cardiac death in high risk hypertensives}, **WOSCOPS**^{↓MI/cardiac death in higher risk Scottish males}, & **AFCAPS**^{↓1st CV event}
- ♦ 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 ^{NNT=120/1.9yr}
- ♦ 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) ^{HPS>Allhat}

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). ^{CV death only: NS} 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 _{7NS; p=0.051}	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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