



The JUPITER Trial: *Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin*

I. ADDITIONAL STUDY DETAILS:

Study question: Whether apparently healthy persons with levels of LDL cholesterol below current treatment thresholds but with elevated levels of hsCRP might benefit from statin therapy.

<u>Inclusion criteria</u>	<u>Exclusion Criteria</u>
<ul style="list-style-type: none"> ▪ Men ≥ 50 years old ▪ Women ≥ 60 years old ▪ No prior history of CV disease ▪ LDL < 130 mg/dl; TG < 500 mg/dl ▪ Hs CRP ≥ 2.0 mg/l 	<ul style="list-style-type: none"> ▪ Prior use of lipid lowering drugs ▪ On HRT (estrogen raises CRP) ▪ ALT ≥ 2x ULN ▪ CPK ≥ 3x ULN ▪ Cr > 2.0 mg/dl ▪ Diabetes ▪ Uncontrolled HTN (>190/>100) ▪ Cancer within 5 years (except skin CA) ▪ TSH ≥ 1.5 x ULN ▪ Inflammatory condition – arthritis, lupus, IBD ▪ On immunosuppressants

<u>Study Population</u>	<u>Most Pertinent Baseline Characteristics</u>
<ul style="list-style-type: none"> ▪ Median age 66 yo ▪ 38% women ▪ 71% Caucasian ▪ 12.5% Black ▪ 12.5% Hispanic ▪ 3.5% other 	<ul style="list-style-type: none"> ▪ LDL 108 ▪ HDL 49 ▪ TG 118 ▪ TC 185 ▪ Glucose 94 ▪ Metabolic Syndrome: 41% on Crestor; 41.8% on placebo ▪ hsCRP: 4.2% on Crestor; 4.3% on placebo ▪ Family Hx: 11.2% on Crestor; 11.8% placebo ▪ Smokers: 15.7% on Crestor; 16% on placebo ▪ FBS: 94 mg/dl for both ▪ Glycated Hgb: 5.7% for both GFR: 73.3 on Crestor, 73.6 on placebo

On treatment lab values at 1 year (12 months) – median values			
	Crestor	Placebo	% difference (Crestor v. Placebo)
Hs CRP	2.2	3.5	37% lower
LDL	55	110	50% lower
HDL	52	50	4% higher
TG	99	119	17% lower



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OUTCOMES

Endpoint	Crestor # of patients	Placebo # of patients	Hazard Ratio	P value	Relative Risk Reduction
Primary endpoint	142	251	0.56	<0.00001	44%
Non-fatal MI	22	62	0.35	<0.00001	65%
Any MI	31	68	0.37	0.0002	63%
Non-fatal Stroke	30	58	0.52	0.003	48%
Any Stroke	33	64	0.52	0.002	48%
Arterial revascularization	71	131	0.71	<0.0001	29%
Hospitalization for unstable angina (UA)	16	27	0.59	<0.09	41%
Revascularization or hospitalization for UA	76	143	0.53	<0.0001	47%
MI, Stroke, or death from CV causes	83	157	0.53	<0.0001	47%
Death from any cause, death on known date	190	235	0.81	<0.03	
Any death	198	247	0.80	<0.02	20%

ADVERSE EVENTS

The total number of reported serious adverse events was similar in the Rosuvastatin (1352) and the placebo group (1377). Though these events may not be clinically relevant, events that were statistically different indicated in bold.

Muscle Related	Crestor	Placebo	P value
Muscle weakness, stiffness and pain	1421 (16%)	1375 (15.4%)	0.34
Myopathy no (%)	10 (0.1%)	9 (0.1%)	0.82
Rhabdomyolysis no (%)	* 1 (<0.1%)	0	--
* This one event occurred after the trial in a 90 yr. old man with flu/pneumonia & trauma.			
LIVER			
Hepatic disorder	216 (2.4%)	286(2.1%)	0.13
ALT>3xULN consecutive visits – no (%)	23 (0.3%)	17 (0.2%)	0.34
RENAL			
Renal disorder – no (%)	535 (6.0%)	480(5.4%)	0.08
Creatinine, >100% increase from baseline	16 (0.2%)	10 (0.1%)	0.24
GFR at 12 months – ml/min/1.73 m²	66.8	66.6	0.02
CANCER			
Newly diagnosed cancer – no (%)	298 (3.4%)	314(3.5%)	0.51
Death from cancer – no (%)	35 (0.4%)	58 (0.7%)	0.02
GLUCOSE			
Glycated Hgb at 24 mo - %	5.9	5.8	0.0001
Fasting Glucose at 24 mo. - mg/dl	98	98	0.12
>Trace glucose in urine at 12 mo.,no(%)	36 (<0.5%)	32 (2.4%)	0.64
Newly diagnosed DM (physician reported) - no (%)	270 (3.0%)	216 (2.4%)	0.01
Hemorrhagic stroke – no (%)	6 (0.1%)	9 (0.1%)	0.44



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There were no significant differences between the two study groups with regard to muscle weakness, newly diagnosed cancer or disorders of the hematologic, GI, hepatic or renal system. High dose statin therapy in STROKE patients (SPARCL trial with Lipitor) was associated with a slight but significant increase in hemorrhagic stroke. In this study, with median LDLs of 55, no increase in hemorrhagic stroke was seen (6 on Crestor, 9 in the placebo group). But this was not a trial in stroke patients.

The results of this trial are remarkable. The press has made more of a fuss over C-reactive protein than the actual treatment. The author did develop the high sensitivity essay and does have a conflict of interest. But the results are what they are. hsCR DOES give us a means to identify higher risk patients. Keep in mind though, that AGE is one of the strongest risk factors for CV events. Nowhere is the title of the paper or in the front page abstract does the paper mention AGE as a risk. Not until "inclusion criteria" is AGE mentioned. Even in the baseline characteristics, the author excludes age as an "ATP risk factor" He does state in footnotes, "ATP risk factors other than age" but age accounts for the majority of risk in the Framingham risk score analysis. The beginning of the paper leads the reader (and most of our patients), to believe anyone with a high CRP should be on treatment. The press and the people on TV have also stated that any statin would provide benefit, but it is unlikely that weaker statins would provide the same benefit. It took 4-5 years for Pravastatin and Simvastatin to show a significant benefit. Crestor is one of the safest statins for the amount of LDL reduction. I hardly think that a statin that lowers LDL 30% would provide the same benefit that Crestor provided, with it 50% reduction in LDL..

The data clearly supports that the better the LDL reduction with statins, the better the benefit. Unfortunately, the currently available generic statins simply don't provide the same LDL reduction as non-generic Lipitor and Crestor. 80mg of Simvastatin does not lower the LDL as much as 10mg of Crestor, and 80mg of Simvastatin is one of the most dangerous lipid treatments available. The result of the SEARCH trial were also reported at AHA. Patients with prior MI were treated with Simvastatin 20mg vs. 80mg. After 7 (seven) years! there was no significant difference in CV events, since the difference in LDL reduction was only 14mg/dl. There were, however, 53 cases of myopathy with high dose simva vs. 3 cases with low dose simva. Enclosed is a copy of increases in CPK and LFTs with different doses. Yes, all statins provide benefit – the amount of benefit is based on the amount of LDL reduction. And the number of adverse events is based on the dose of statin – moderate vs. high.

So, should we screen all of our patients or at least men ≥ 50 yr and women ≥ 60 yr for hsCRP? The number of patients who would need to be treated with Crestor for 2 years to prevent the occurrence of one primary end point is 95; for 4 years, the NNT's 31, for 5 years NNT is 25 (projected). Use your judgment as always, but this study provides compelling evidence to do so. If patients have documented disease or they are already at high risk, screening is not necessary – we're going to treat. But, if age is the only risk factor, or if the patient has only one risk factor to this then age, then screening with hsCRP seems reasonable.