Disclosure Information: Paul M Ridker, MD, FACC

Dr Ridker is listed as a co-inventor on patents held by the Brigham and Women's Hospital that relate to the use of inflammatory biomarkers in cardiovascular disease that have been licensed to Seimens and AstraZeneca. Dr Ridker is the Principal Investigator of JUPITER, an investigator initiated trial funded by AstraZeneca.

Dr Ridker has served as a consultant to AstraZeneca, Novartis, Merck, Schering Plough, ISIS, Vascular Biogenics (modest).

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CRP Reduction, LDL Reduction, and Cardiovascular Event Rates After Initiation of Rosuvastatin: The JUPITER Trial

Paul Ridker*, Eleanor Danielson, Francisco Fonseca*, Jacques Genest*, Antonio Gotto*, John Kastelein*, Wolfgang Koenig*, Peter Libby*, Alberto Lorenzatti*, Jean MacFadyen, Børge Nordestgaard*, James Shepherd*, James Willerson, and Robert Glynn*
on behalf of the JUPITER Trial Study Group

An Investigator Initiated Trial Funded by AstraZeneca, USA

** These authors have received research grant support and/or consultation fees from one or more statin manufacturers, including Astra-Zeneca. Dr Ridker is a co-inventor on patents held by the Brigham and Women's Hospital that relate to the use of inflammatory biomarkers in cardiovascular disease that have been licensed to Dade-Behring and AstraZeneca.*

JUPITER
Background and Prior Work

Current statin guidelines emphasize the need to achieve specific goals for LDLC to maximize clinical outcomes.

However, accumulating data indicates that statin therapy has greatest efficacy in the presence of inflammation and that statins reduce the inflammatory biomarker hsCRP in a manner largely independent of LDLC.

Further, in both the PROVE IT – TIMI 22 and A to Z trials of patients with acute coronary ischemia treated with statin therapy, the best clinical outcomes occurred among those who not only achieved LDLC < 70 mg/dL, but who also achieved hsCRP levels < 2 mg/L. In both of these trials, even greater clinical benefits accrued when hsCRP levels were further reduced below 1 mg/L.

JUPITER
Background and Prior Work

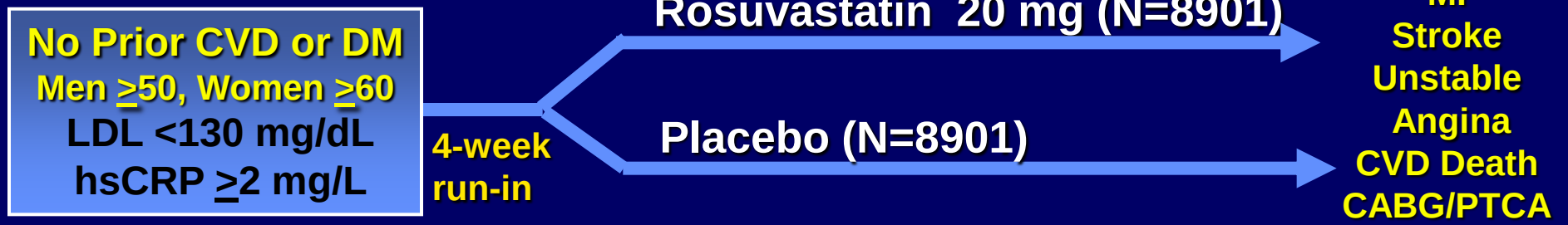
These prior data are consistent with the understanding that atherothrombosis is a disorder of both hyperlipidemia and inflammation, and that statins have anti-inflammatory as well as lipid-lowering properties.

Despite the consistency of these data, whether achieving lower levels of hsCRP after initiation of statin therapy is associated with improved clinical outcomes in a similar manner to that associated with achieving lower levels of LDLC remains highly controversial.

We prospectively tested this hypothesis in the large-scale JUPITER trial.

JUPITER

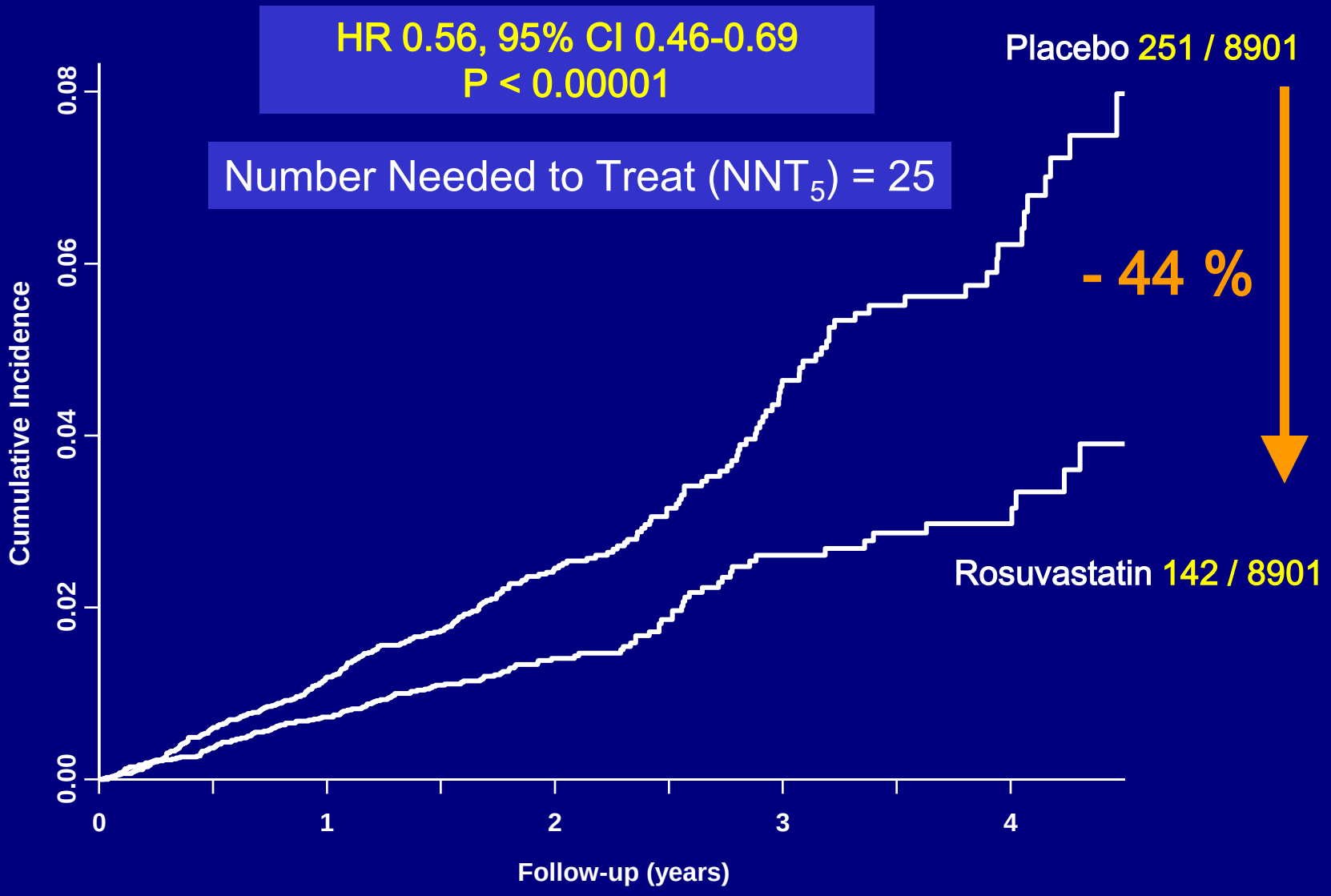
Multi-National Randomized Double Blind Placebo Controlled Trial of Rosuvastatin in the Prevention of Cardiovascular Events Among Individuals With Low LDL and Elevated hsCRP



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

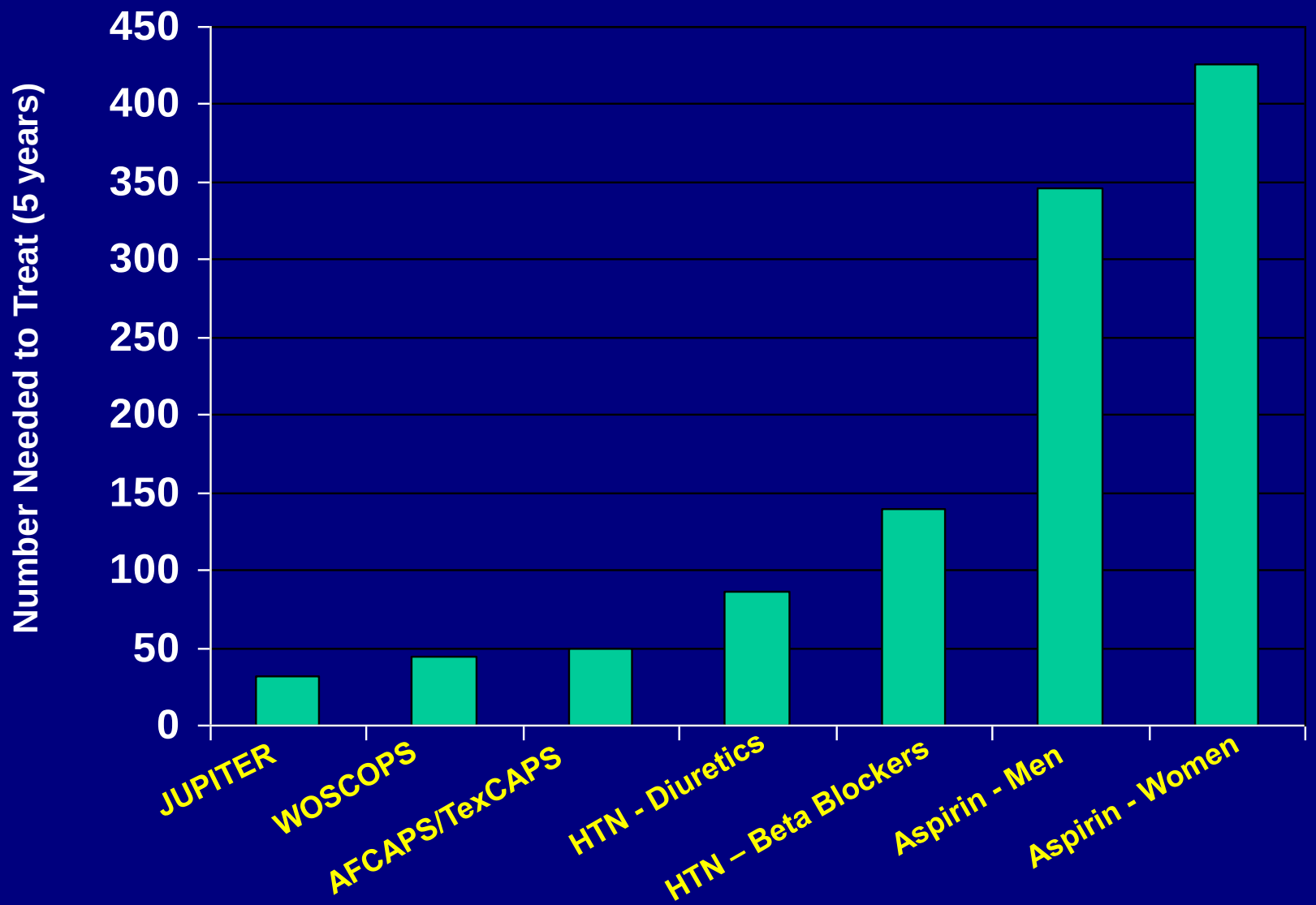
Primary Trial Endpoint：MI, Stroke, UA/Revascularization, CV Death



Ridker et al, NEJM 2008;359:2195-207

JUPITER

5-Year NNT Values for Primary Prevention of CVD



JUPITER
Achieved LDLC, Achieved hsCRP, or Both?

Objectives:

To compare clinical outcomes among JUPITER trial participants according to achieved levels of LDLC and hsCRP, *after adjustment for all available baseline clinical characteristics*, including entry levels of LDLC, HDLC, and hsCRP.

To evaluate whether clinical outcomes according to achieved lipid and hsCRP levels are altered by substituting ApoB or the ApoB:ApoA ratio for LDLC.

JUPITER
Achieved LDLC, Achieved hsCRP, or Both?

Methods:

In an analysis of 15,548 initially healthy men and women participating in the JUPITER trial (87% of the full cohort), we prospectively assessed the effects of rosuvastatin 20 mg vs placebo on rates of the trial primary endpoint during a maximum follow-up of 5 years (median 1.9 years) according to on-treatment concentrations of LDL-C ($\geq$ 70 or < 70 mg/dL) and on-treatment concentrations of hsCRP ($\geq$2 or < 2 mg/L). Pre-specified analyses were also performed using the more aggressive hsCRP target of $\geq$ or < 1 mg/L.

To ensure the validity of this *a-priori* approach, we also performed comparable analyses based on achieved reductions of both LDLC and hsCRP of $\geq$ or < 50 percent.

JUPITER – Achieved LDL, Achieved hsCRP Analysis
Baseline Clinical Characteristics (N=15,548)

	Placebo	Rosuvastatin			
		LDL≥70	LDL<70	hsCRP≥2	hsCRP<2
Age, (years)	66	65	66	66	66
BMI, (kg/m2)	28.4	27.8	28.5	29.0	27.7
Blood pressure					
Systolic	134	134	135	135	134
Diastolic	80	80	80	80	80
Smoker, (%)	15.6	17.9	14.5	17.2	13.3
Fam His, (%)	11.8	11.3	11.7	11.0	12.4
Met Syn, (%)	41.5	38.3	42.2	43.5	37.8
hsCRP, mg/L	4.2	4.2	4.2	5.4	3.2
LDLC, mg/dL	108	112	106	108	109
HDLC, mg/dL	49	50	49	49	49
TG, mg/dL	118	115	119	120	116
ApoB:ApoA	0.7	0.7	0.7	0.7	0.7
HbA1c	5.7	5.7	5.7	5.7	5.7

JUPITER
LDL reduction, hsCRP reduction, or both?

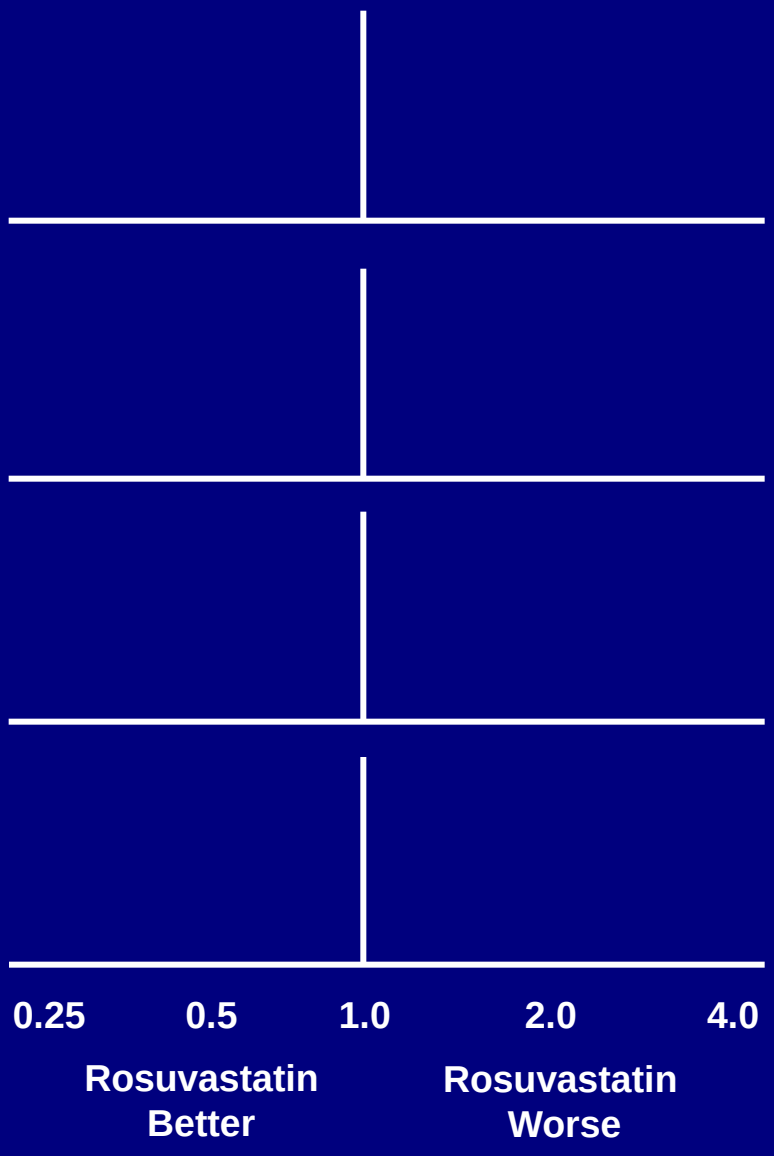
Minimal Correlation between change in LDL and change in hsCRP

	r value
Achieved LDLC, Achieved hsCRP	0.10
Percent change in LDLC, Percent change in hsCRP	0.15

Less than 2 percent of the variance in achieved hsCRP was explained by the variance in achieved LDLC

JUPITER

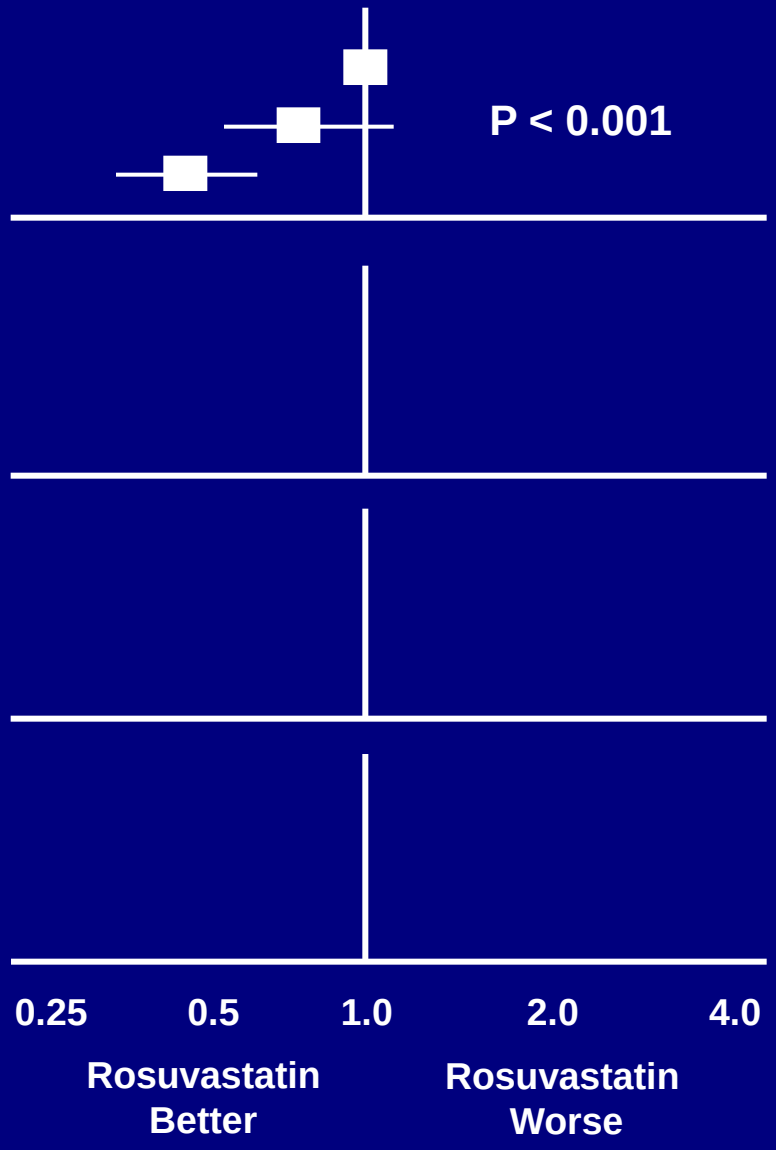
LDL reduction, hsCRP reduction, or both?



JUPITER

LDL reduction, hsCRP reduction, or both?

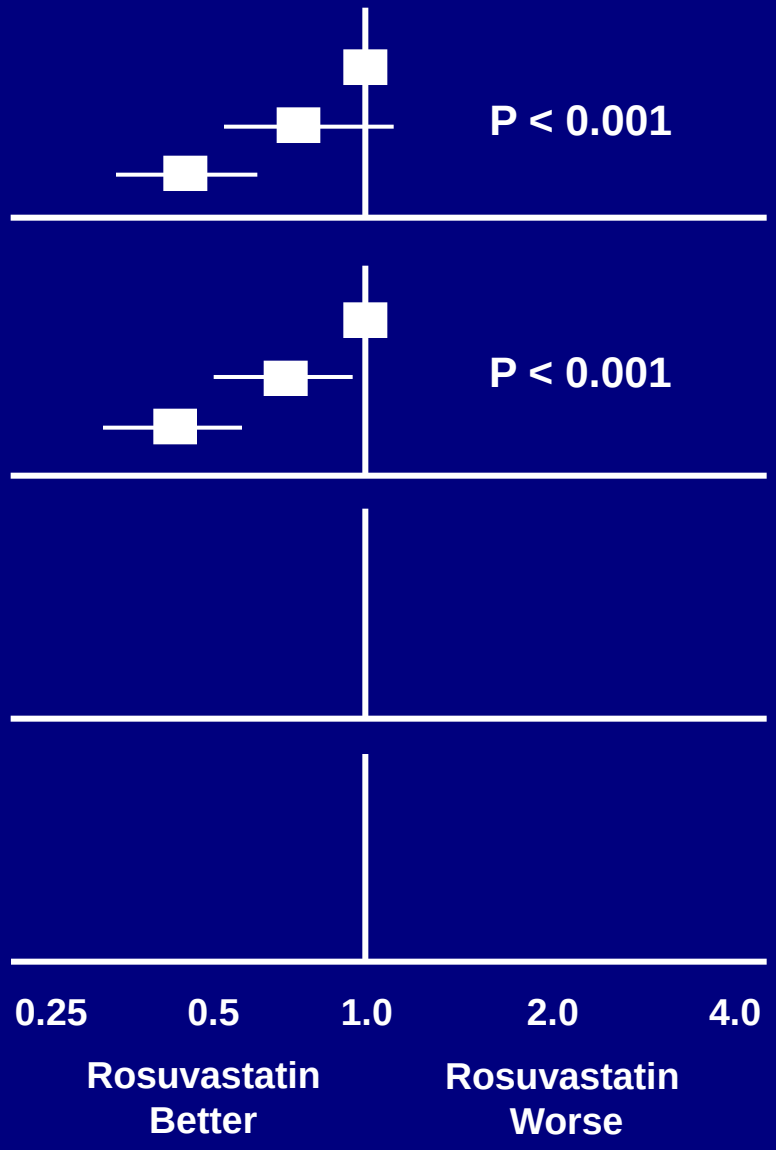
	N	Rate
Placebo	7832	1.11
LDL Achieved ≥ 70 mg/dL	2110	0.91
LDL Achieved < 70 mg/dL	5606	0.51
Placebo		
LDL Reduction < 50 %		
LDL Reduction ≥ 50 %		
Placebo		
hsCRP Achieved ≥ 2 mg/L		
hsCRP Achieved < 2 mg/L		
Placebo		
hsCRP Reduction < 50 %		
hsCRP Reduction ≥ 50 %		



JUPITER

LDL reduction, hsCRP reduction, or both?

	N	Rate
Placebo	7832	1.11
LDL Achieved ≥ 70 mg/dL	2110	0.91
LDL Achieved < 70 mg/dL	5606	0.51
Placebo	7832	1.11
LDL Reduction < 50 %	4181	0.74
LDL Reduction ≥ 50 %	3535	0.47
Placebo		
hsCRP Achieved ≥ 2 mg/L		
hsCRP Achieved < 2 mg/L		
Placebo		
hsCRP Reduction < 50 %		
hsCRP Reduction ≥ 50 %		



JUPITER

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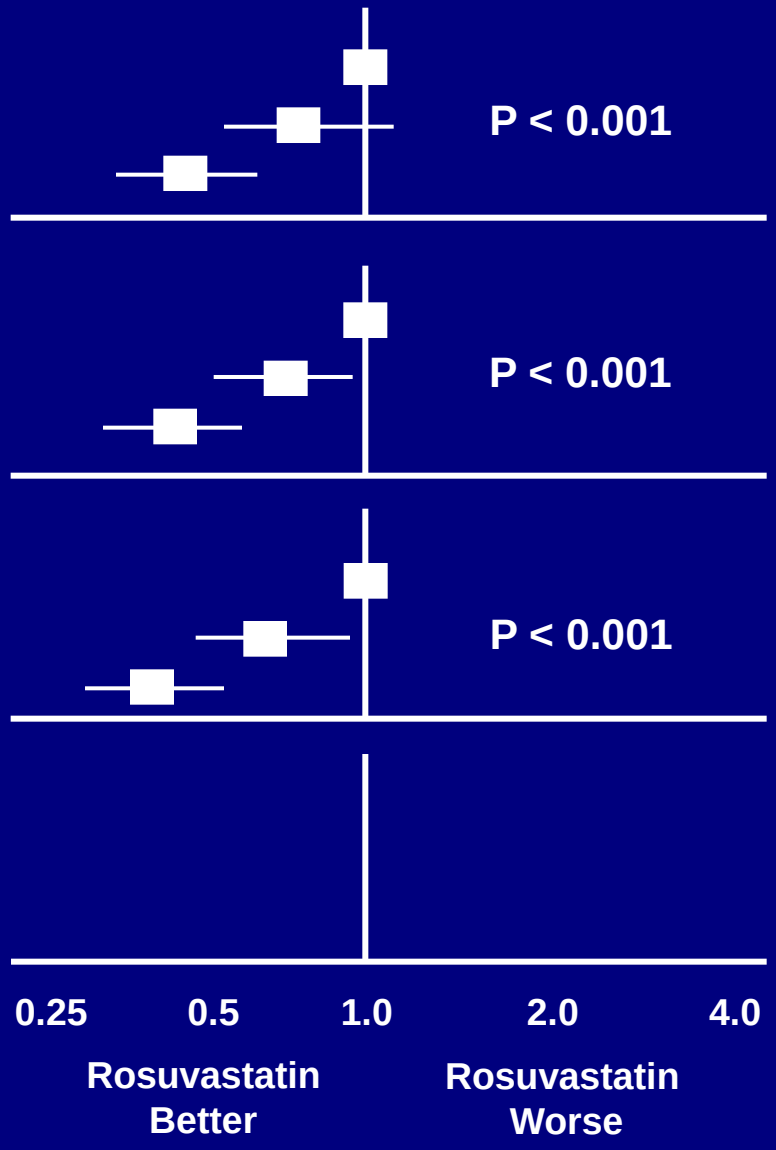
Placebo	7832	1.11
LDL Reduction < 50 %	4181	0.74
LDL Reduction ≥ 50 %	3535	0.47
Placebo	7832	1.11
hsCRP Achieved ≥ 2 mg/L	4305	0.77
hsCRP Achieved < 2 mg/L	3411	0.42
Placebo		
hsCRP Reduction < 50 %		
hsCRP Reduction ≥ 50 %		



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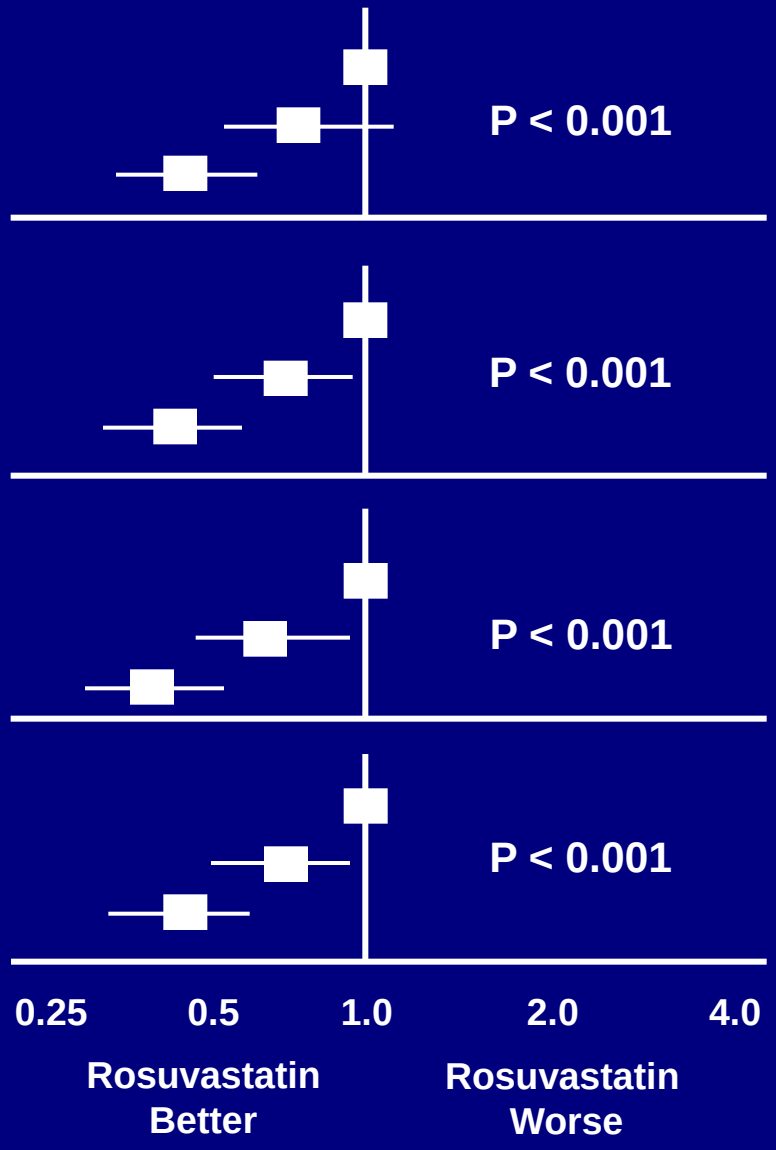
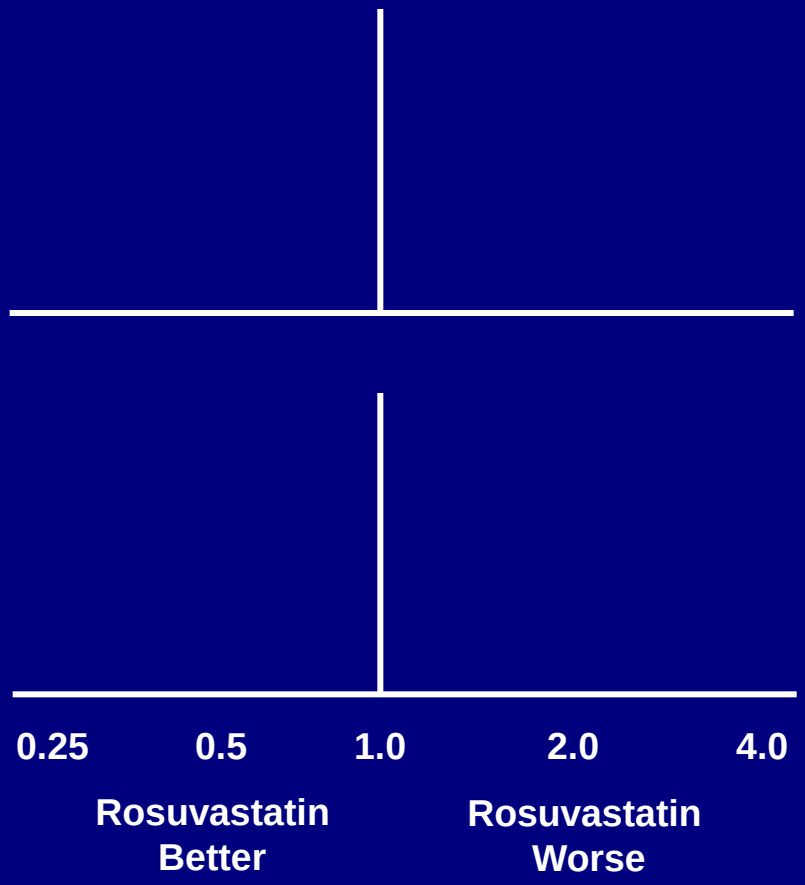
Placebo	7832	1.11
hsCRP Achieved ≥ 2 mg/L	4305	0.77
hsCRP Achieved < 2 mg/L	3411	0.42
Placebo	7832	1.11
hsCRP Reduction < 50 %	4143	0.70
hsCRP Reduction ≥ 50 %	3573	0.51



JUPITER

LDL reduction, hsCRP reduction, or both?

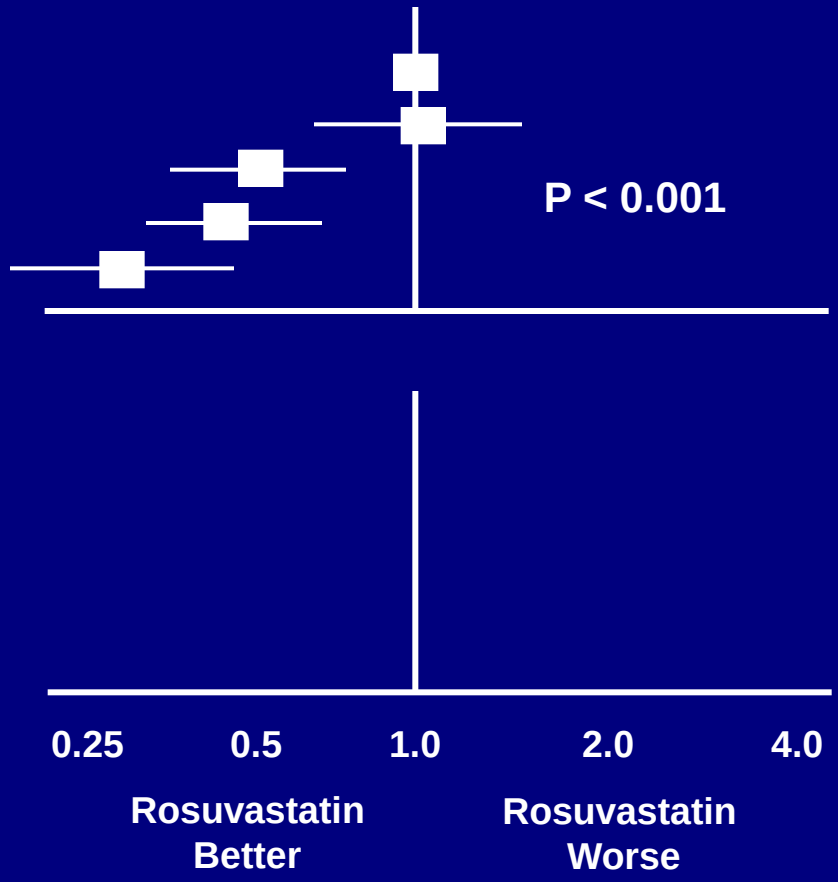
	N	Rate
Placebo		
LDL≥70mg/dL,hsCRP≥2 mg/L		
LDL<70mg/dL,hsCRP≥2 mg/L		
LDL≥70mg/dL,hsCRP<2 mg/L		
LDL<70mg/dL,hsCRP<2 mg/L		
Placebo		
LDL≥70mg/dL,hsCRP≥1 mg/L		
LDL<70mg/dL,hsCRP≥1 mg/L		
LDL≥70mg/dL,hsCRP<1 mg/L		
LDL<70mg/dL,hsCRP<1 mg/L		



JUPITER

LDL reduction, hsCRP reduction, or both?

	N	Rate
Placebo	7832	1.11
LDL≥70mg/dL,hsCRP≥2 mg/L	1384	1.11
LDL<70mg/dL,hsCRP≥2 mg/L	2921	0.62
LDL≥70mg/dL,hsCRP<2 mg/L	726	0.54
LDL<70mg/dL,hsCRP<2 mg/L	2685	0.38



Placebo
LDL≥70mg/dL,hsCRP≥1 mg/L
LDL<70mg/dL,hsCRP≥1 mg/L
LDL≥70mg/dL,hsCRP<1 mg/L
LDL<70mg/dL,hsCRP<1 mg/L

JUPITER

LDL reduction, hsCRP reduction, or both?

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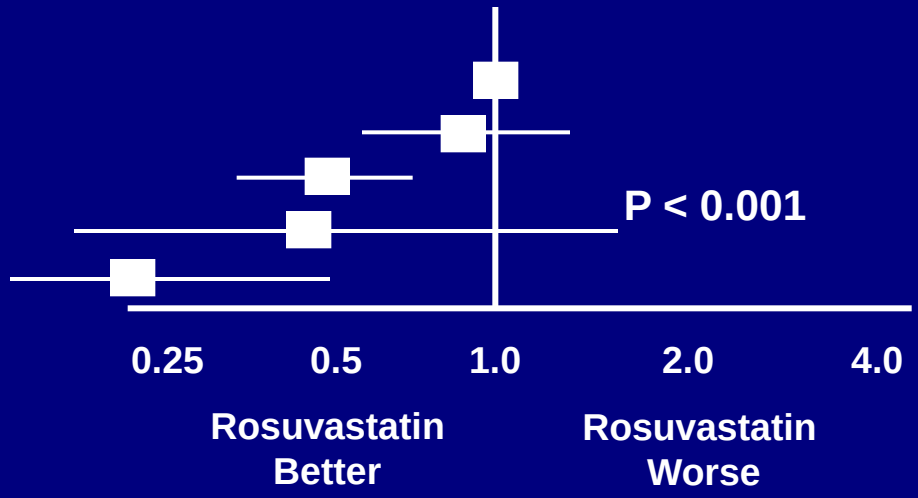
LDL≥70mg/dL,hsCRP<2 mg/L	726	0.54
LDL<70mg/dL,hsCRP<2 mg/L	2685	0.38

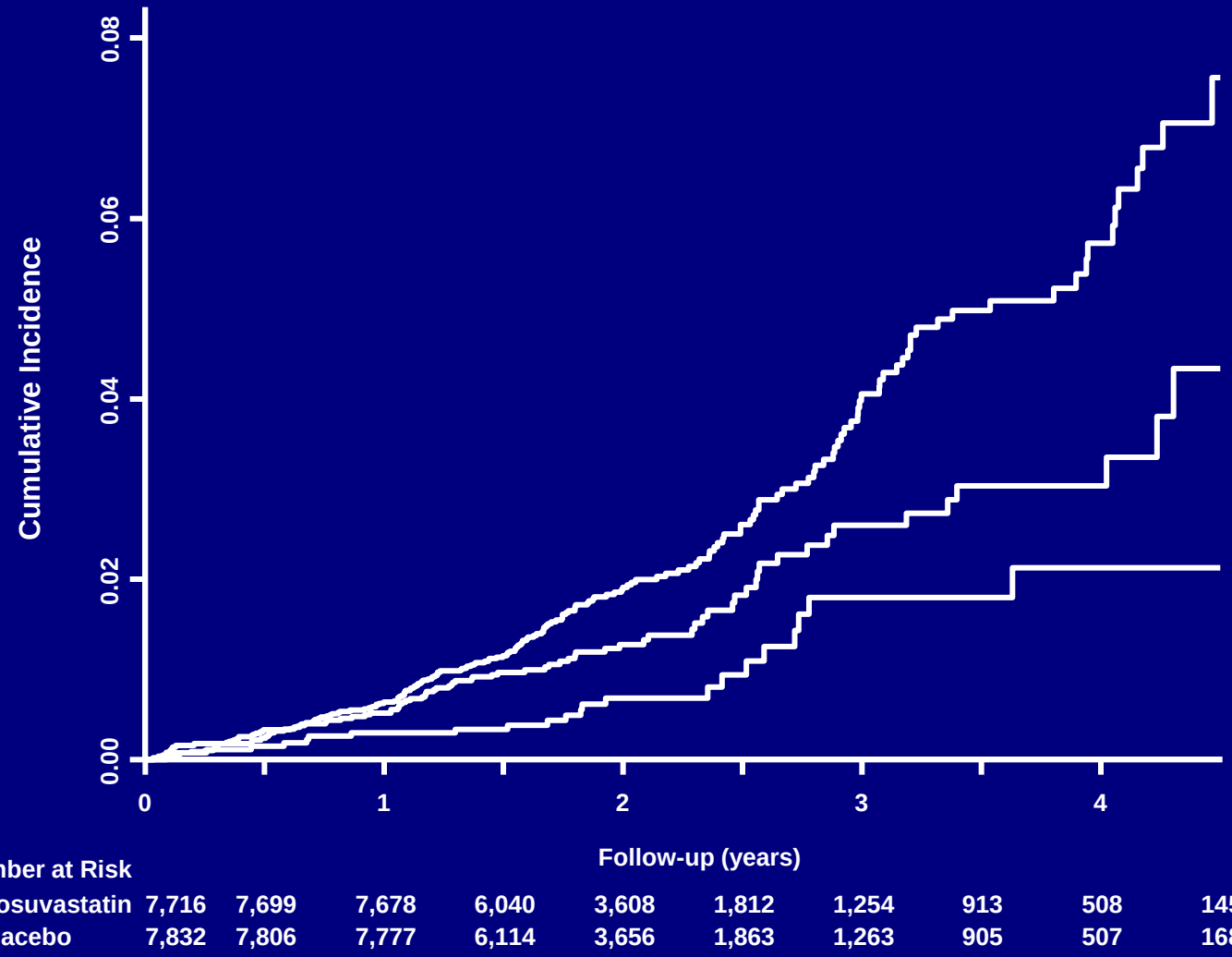
P < 0.001

Placebo	7832	1.11
LDL≥70mg/dL,hsCRP≥1 mg/L	1874	0.95
LDL<70mg/dL,hsCRP≥1 mg/L	4662	0.56
LDL≥70mg/dL,hsCRP<1 mg/L	236	0.64
LDL<70mg/dL,hsCRP<1 mg/L	944	0.24

P < 0.001



JUPITER
Dual Target Analysis: LDLC<70 mg/dL, hsCRP<2 mg/L



Placebo
HR 1.0 (referent)

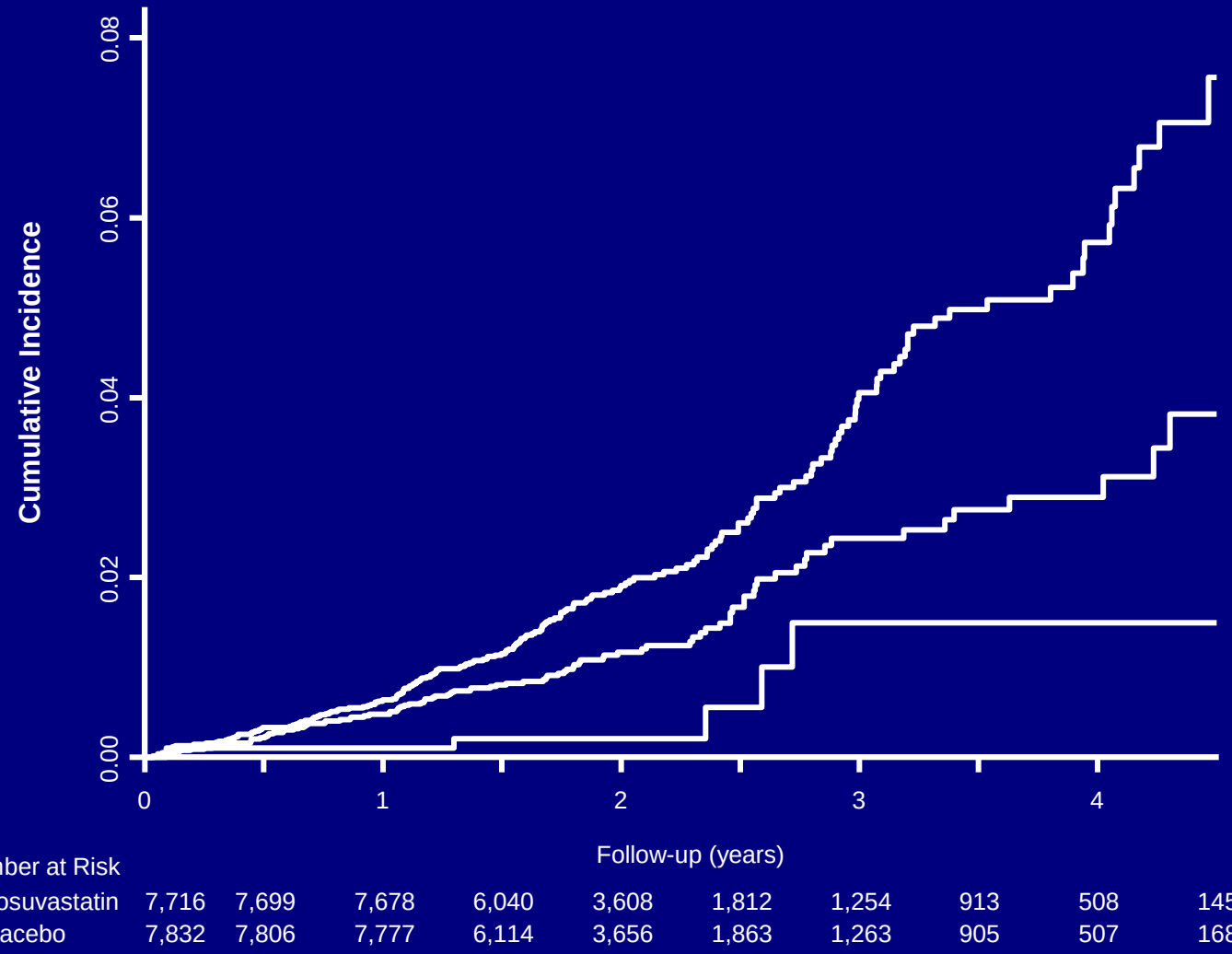
LDL > 70 mg/dL
and / or
hsCRP > 2 mg/L
HR 0.64 (0.49-0.84)

LDL < 70 mg/dL
and
hsCRP < 2 mg/L
HR 0.35 (0.23-0.54)

Number at Risk										
Rosuvastatin	7,716	7,699	7,678	6,040	3,608	1,812	1,254	913	508	145
Placebo	7,832	7,806	7,777	6,114	3,656	1,863	1,263	905	507	168

P < 0.0001

JUPITER
Dual Target Analysis: LDLC<70 mg/dL, hsCRP<1 mg/L



Number at Risk										
Rosuvastatin	7,716	7,699	7,678	6,040	3,608	1,812	1,254	913	508	145
Placebo	7,832	7,806	7,777	6,114	3,656	1,863	1,263	905	507	168

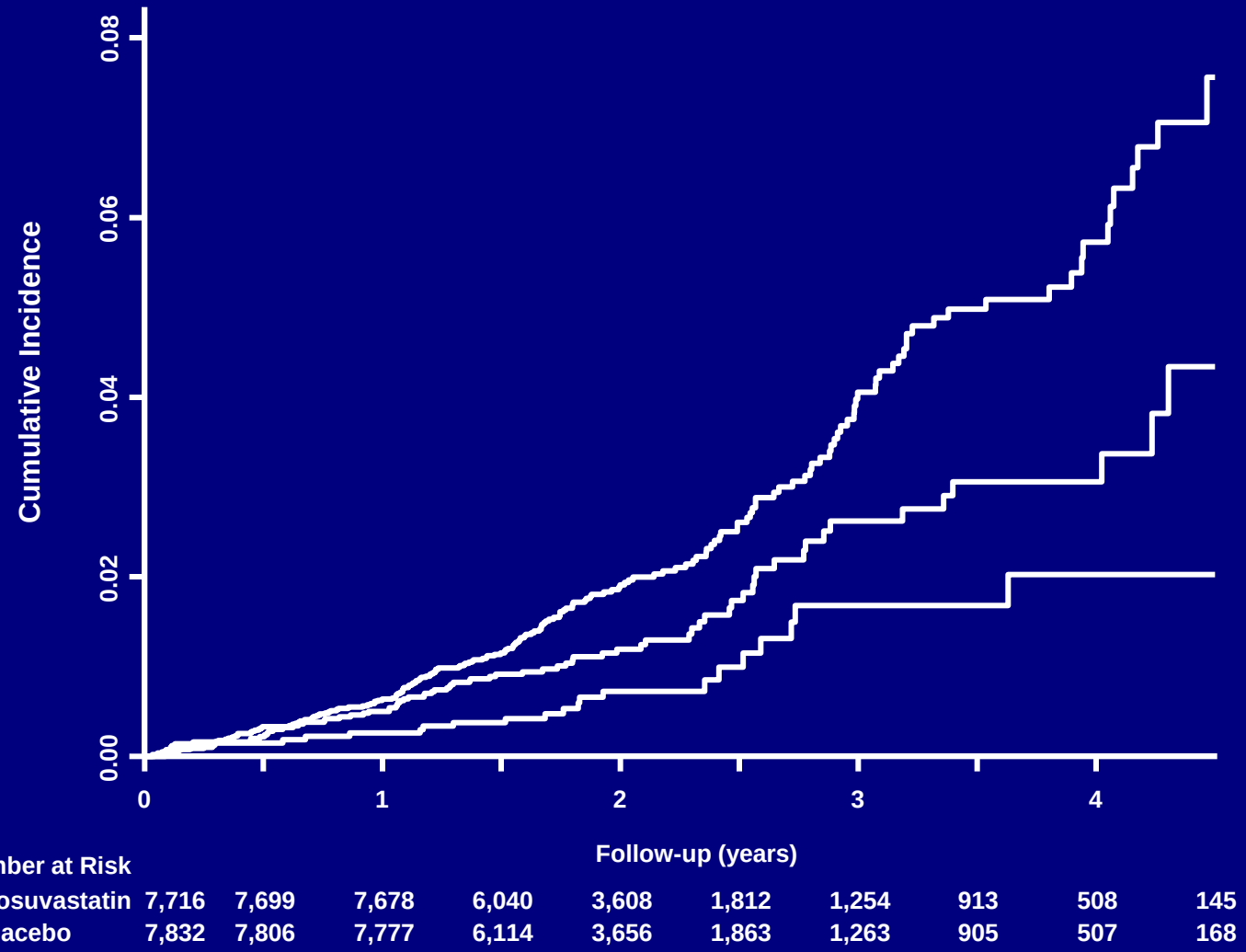
Placebo
HR 1.0 (referent)

LDL > 70 mg/dL
and / or
hsCRP > 1 mg/L
HR 0.59 (0.46-0.75)

LDL < 70 mg/dL
and
hsCRP < 1 mg/L
HR 0.21 (0.09-0.51)

P < 0.0001

JUPITER
Dual Target Analysis: ApoB<80 mg/dL, hsCRP<2 mg/L



Number at Risk										
Rosuvastatin	7,716	7,699	7,678	6,040	3,608	1,812	1,254	913	508	145
Placebo	7,832	7,806	7,777	6,114	3,656	1,863	1,263	905	507	168

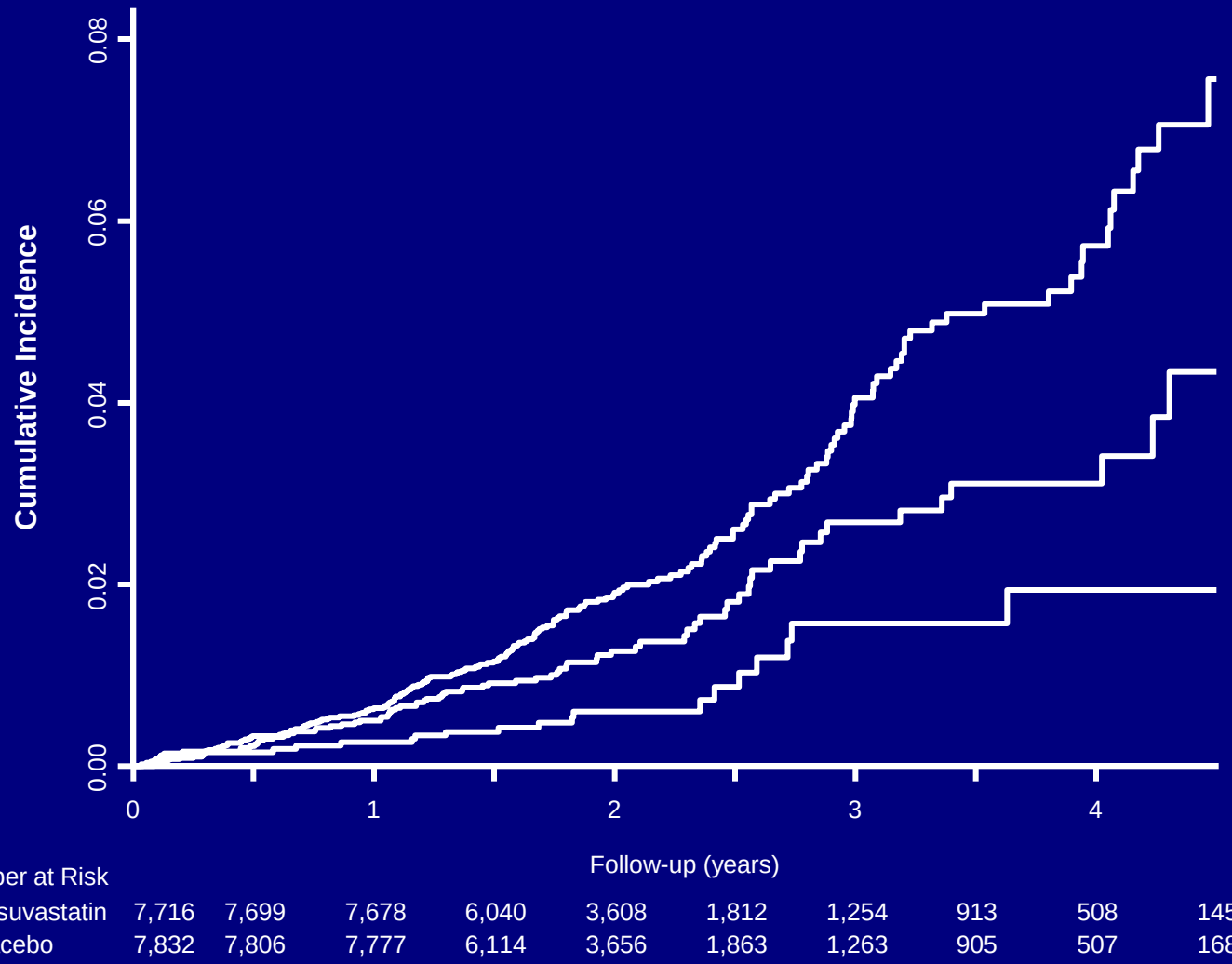
Placebo
HR 1.0 (referent)

ApoB > 80 mg/dL
and / or
hsCRP > 2 mg/L
HR 0.62 (0.50-0.85)

ApoB < 80 mg/dL
and
hsCRP < 2 mg/L
HR 0.36 (0.23-0.55)

P < 0.0001

JUPITER
Dual Target Analysis: ApoB:ApoA<0.5, hsCRP<2 mg/L



Placebo
HR 1.0 (referent)

ApoB:ApoA > 0.5
and / or
hsCRP > 2 mg/L
HR 0.62 (0.49-0.81)

ApoB:ApoA < 0.5
and
hsCRP < 2 mg/L
HR 0.34 (0.21-0.53)

P < 0.0001

Number at Risk										
Rosuvastatin	7,716	7,699	7,678	6,040	3,608	1,812	1,254	913	508	145
Placebo	7,832	7,806	7,777	6,114	3,656	1,863	1,263	905	507	168

JUPITER
Conclusions – Achieved LDLC and Achieved hsCRP

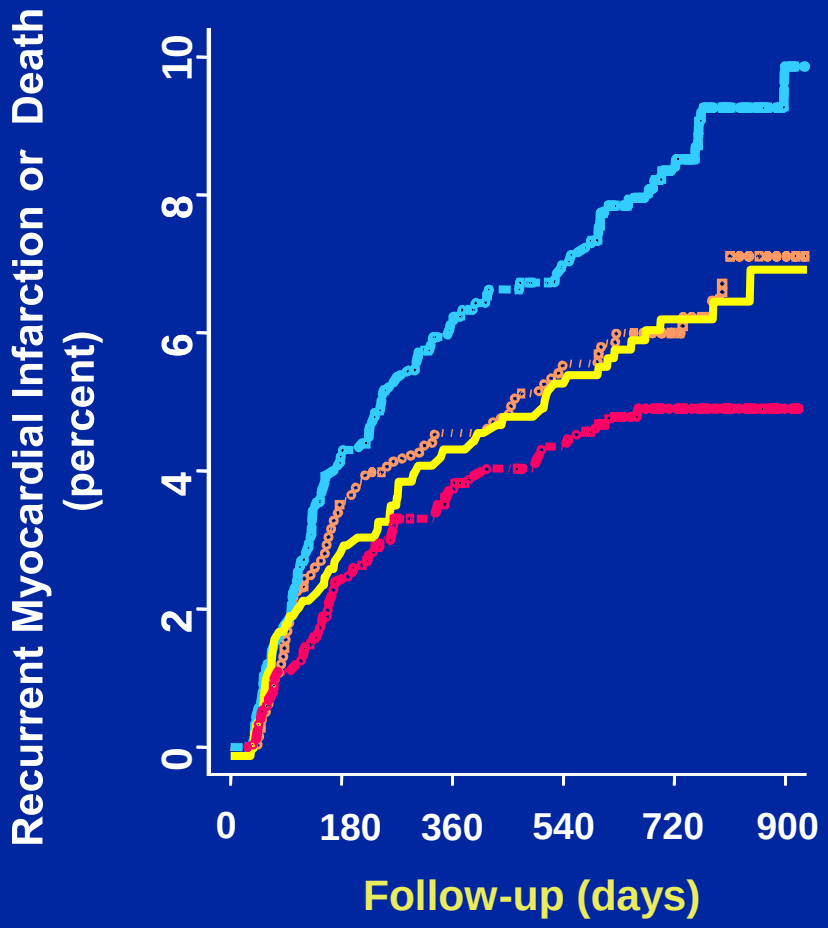
Among apparently healthy men and women initiating rosuvastatin therapy in the JUPITER trial, achieving low target levels of both LDLC *and* hsCRP was associated with significantly improved event-free survival compared with achieving neither target or with achieving a low LDLC alone.

Similar effects were observed after adjustment for all available baseline clinical characteristics including entry levels of LDLC and hsCRP, and in analyses based upon Apo B or the ApoB:ApoA ratio rather than upon LDLC.

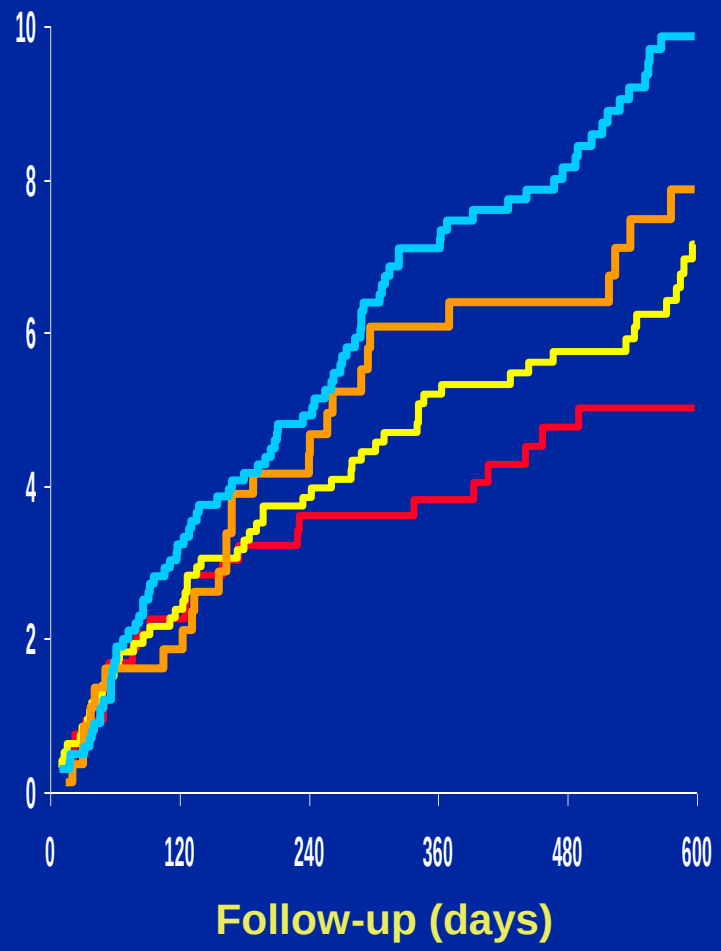
A 79 percent reduction in risk was observed among those who achieved LDLC < 70 mg/dL and the even more aggressive target of hsCRP < 1 mg/L.

Clinical Relevance of Achieving LDL-C < 70 mg/dL and hsCRP < 2 mg/L Following Initiation of Statin Therapy

LDL>70, hsCRP>2 LDL<70, hsCRP>2 LDL>70, hsCRP<2 LDL<70, hsCRP<2



PROVE IT – TIMI 22
NEJM 2005;352:20-28.



A to Z
Circulation 2006;114:281-8

CARE, AFCAPS, PROVE IT, A to Z, Reversal, JUPITER

Does Correct Use of Statin Therapy Require Evaluation for *both* LDLC and hsCRP?

1. LDL-C is a strong, independent predictor of future CV events

2. Statins Lower LDL-C

3. The level of LDL-C achieved after starting statin therapy predicts recurrent event rates (ie "lower is better")

1. hsCRP is a strong, independent predictor of future CV events

2. Statins Lower hsCRP

3. The level of hsCRP achieved after starting statin therapy predicts recurrent event rates (ie "lower is better")

Dual Goals for Statin Therapy :
LDL-C < 70 mg/dL and hsCRP < 2 mg/L

JUPITER
Public Health Implications

For patients with raised LDLC or raised hsCRP, initial interventions should include dietary restriction, exercise, and smoking cessation. However, as demonstrated in these prospective data, for those initiating drug therapy in primary prevention, reductions in both LDLC *and* hsCRP are indicators of the success of treatment with statin therapy.

We thank the 17,802 patients and the >1,000 investigators worldwide for their personal time, effort, and commitment to the JUPITER trial.

www.brighamandwomens.org/jupitertrial