JUPITER
AHA November 9, 2008

A Randomized Trial of Rosuvastatin in the Prevention of Cardiovascular Events Among 17,802 Apparently Healthy Men and Women With Elevated Levels of C-Reactive Protein (hsCRP): 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
Trial Structure

Independent Steering Committee : P Ridker (Chair), F Fonseca, J Genest, A Gotto, J Kastelein, W Koenig, P Libby, A Lorenzatti, B Nordestgaard, J Shepherd, J Willerson

Independent Academic Clinical Coordinating Center: P Ridker, E Danielson, R Glynn, J MacFadyen, S Mora (Boston)

Independent Academic Study Statistician: R Glynn (Boston)

Independent Data Monitoring Board: R Collins (Chair), K Bailey, B Gersh, G Lamas, S Smith, D Vaughan

Independent Academic Clinical Endpoint Committee: K Mahaffey (Chair), P Brown,D Montgomery, M Wilson, F Wood (Durham)

With thanks to the clinical development teams worldwide at AstraZeneca for their considerable efforts in data collection, site monitoring, and overall study coordination

JUPITER
Background and Prior Work

Current guidelines for the prevention of myocardial infarction stroke, and cardiovascular death endorse statin therapy among patients with established vascular disease, diabetes, and among those with hyperlidemia.

However, these screening and treatment strategies are insufficient as half of all heart attack and stroke events occur among apparently healthy men and women with average or even low levels of cholesterol.

JUPITER
Background and Prior Work

To improve detection of individuals at increased risk for cardiovascular disease, physicians often measure high sensitivity C-reactive protein (hsCRP), an inflammatory biomarker that reproducibly and independently predicts future vascular events and improves global risk classification, even when cholesterol levels are low.

Prior work has shown that statin therapy reduces hsCRP, and that among stable coronary disease patients as well as those with acute ischemia, the benefit associated with statin therapy relates not only to achieving low levels of LDL, but also to achieving low levels of hsCRP.

JUPITER

Why Consider Statins for Low LDL, high hsCRP Patients?

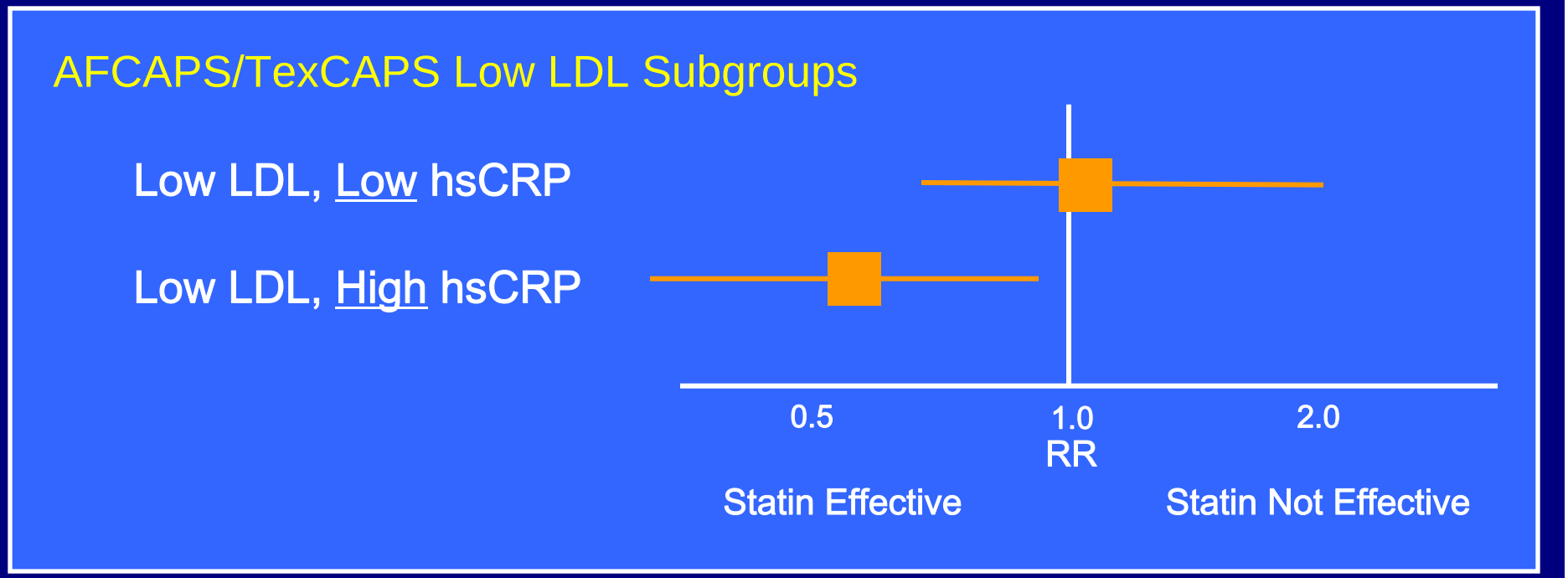
In 2001, in an hypothesis generating analysis of apparently healthy individuals in the AFCAPS / TexCAPS trial*, we observed that those with low levels of both LDL and hsCRP had extremely low vascular event rates and that statin therapy did not reduce events in this subgroup (N=1,448, HR 1.1, 95% CI 0.56-2.08). Thus, a trial of statin therapy in patients with low cholesterol and low hsCRP would not only be infeasible in terms of power and sample size, but would be highly unlikely to show clinical benefit.

In contrast, we also observed within AFCAPS/TexCAPS that among those with low LDL but high hsCRP, vascular event rates were just as high as rates among those with overt hyperlipidemia, and that statin therapy significantly reduced events in this subgroup (N=1,428, HR 0.6, 95% CI 0.34-0.98).

Ridker et al N Engl J Med 2001;344:1959-65

JUPITER

Why Consider Statins for Low LDL, high hsCRP Patients?



However, while intriguing and of potential public health importance, the observation in AFCAPS/TexCAPS that statin therapy might be effective among those with elevated hsCRP but low cholesterol was made on a *post hoc* basis. Thus, a large-scale randomized trial of statin therapy was needed to directly test this hypotheses.

Ridker et al, New Engl J Med 2001;344:1959-65

JUPITER
Primary Objectives

Justification for the Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin

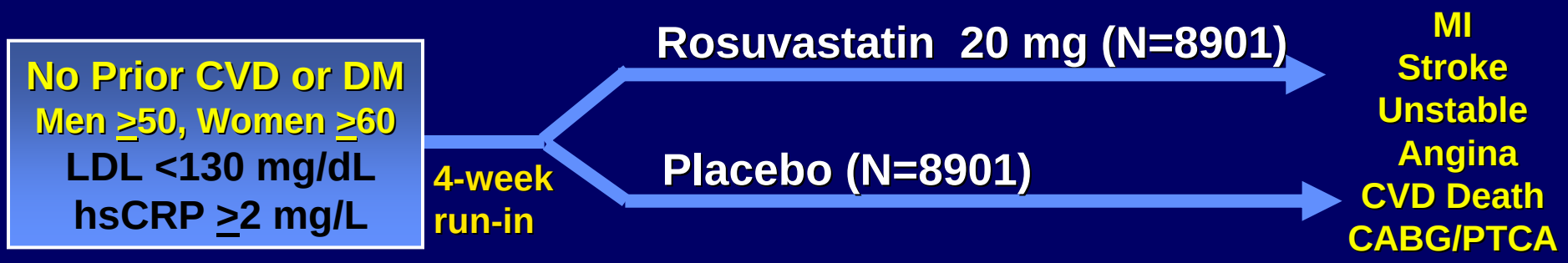
To investigate whether rosuvastatin 20 mg compared to placebo would decrease the rate of first major cardiovascular events among apparently healthy men and women with LDL < 130 mg/dL (3.36 mmol/L) who are nonetheless at increased vascular risk on the basis of an enhanced inflammatory response, as determined by hsCRP ≥ 2 mg/L.

To enroll large numbers of women and individuals of Black or Hispanic ethnicity, groups for whom little data on primary prevention with statin therapy exists.

JUPITER
Trial Design

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

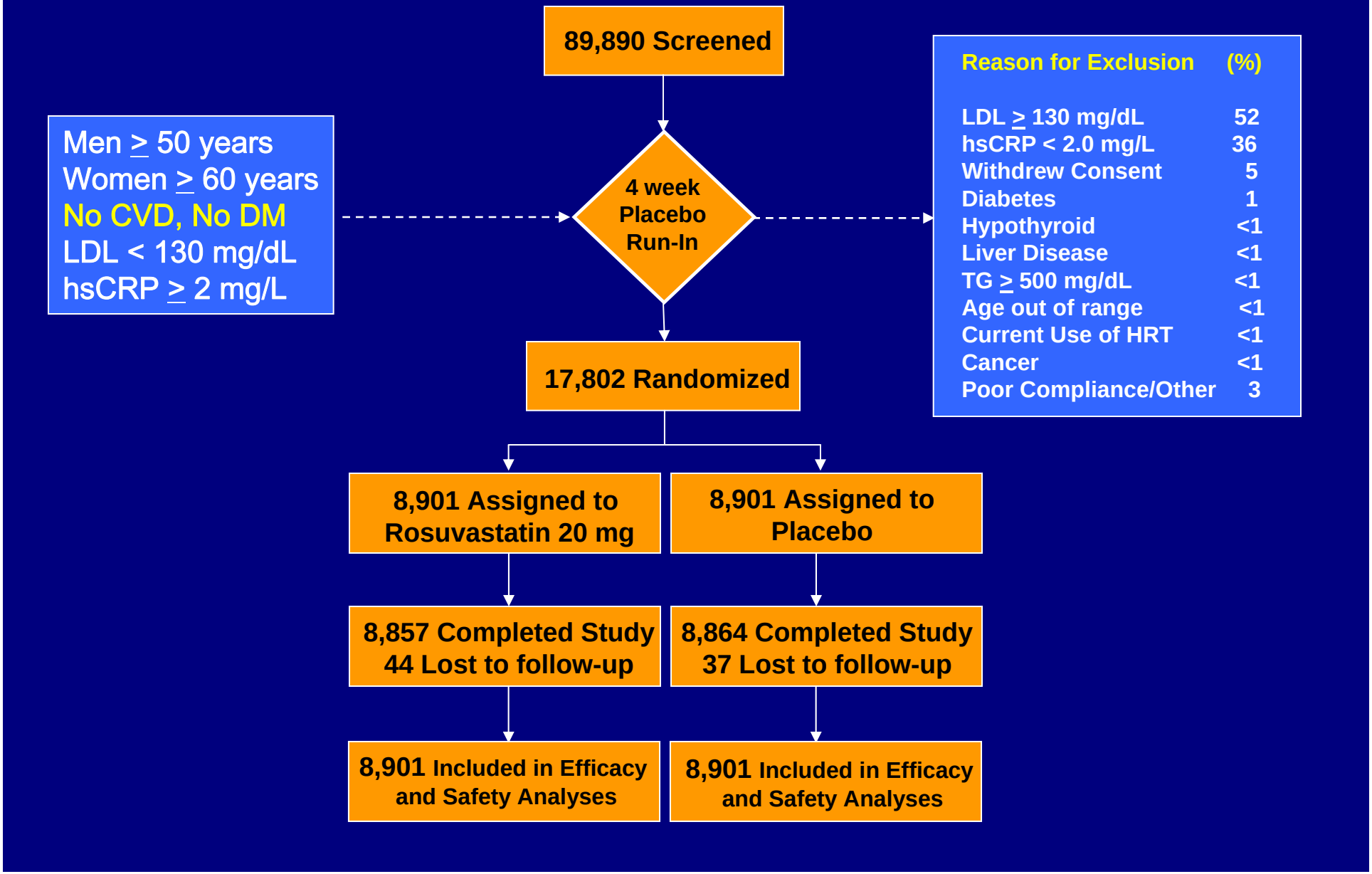


Argentina, Belgium, Brazil, Bulgaria, Canada, Chile, Colombia, Costa Rica, Denmark, El Salvador, Estonia, Germany, Israel, Mexico, Netherlands, Norway, Panama, Poland, Romania, Russia, South Africa, Switzerland, United Kingdom, Uruguay, United States, Venezuela

Ridker et al, Circulation 2003;108:2292-2297.

JUPITER

Inclusion and Exclusion Criteria, Study Flow



JUPITER
Baseline Clinical Characteristics

	Rosuvastatin (N = 8901)	Placebo (n = 8901)
Age, years (IQR)	66.0 (60.0-71.0)	66.0 (60.0-71.0)
Female, N (%)	3,426 (38.5)	3,375 (37.9)
Ethnicity, N (%)		
Caucasian	6,358 (71.4)	6,325 (71.1)
Black	1,100 (12.4)	1,124 (12.6)
Hispanic	1,121 (12.6)	1,140 (12.8)
Blood pressure, mm (IQR)		
Systolic	134 (124-145)	134 (124-145)
Diastolic	80 (75-87)	80 (75-87)
Smoker, N (%)	1,400 (15.7)	1,420 (16.0)
Family History, N (%)	997 (11.2)	1,048 (11.8)
Metabolic Syndrome, N (%)	3,652 (41.0)	3,723 (41.8)
Aspirin Use, N (%)	1,481 (16.6)	1,477 (16.6)

All values are median (interquartile range) or N (%)

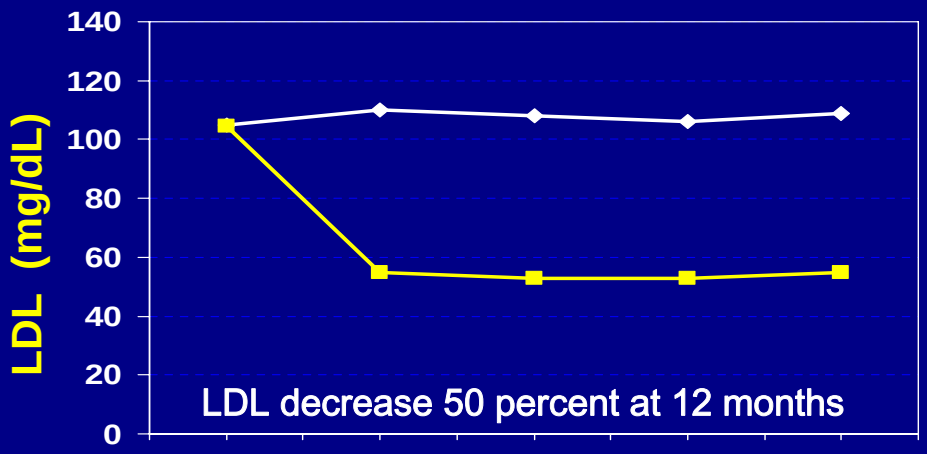
JUPITER
Baseline Blood Levels (median, interquartile range)

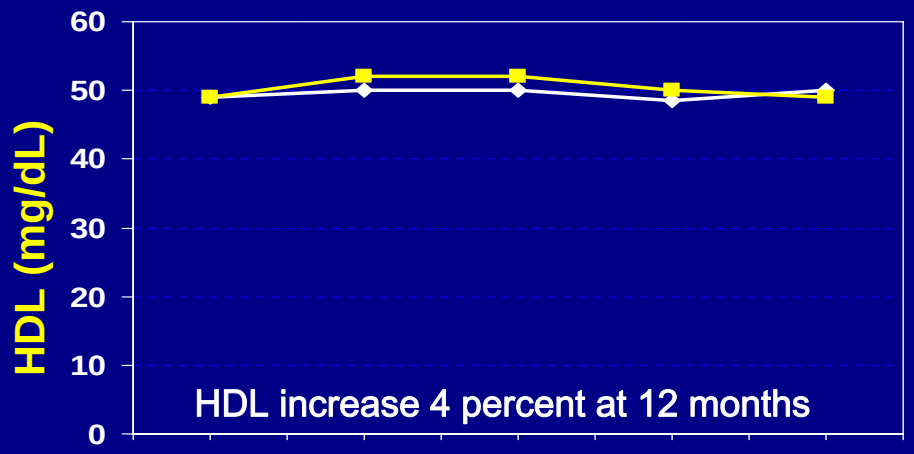
	Rosuvastatin (N = 8901)		Placebo (n = 8901)	
hsCRP, mg/L	4.2	(2.8 - 7.1)	4.3	(2.8 - 7.2)
LDL, mg/dL	108	(94 - 119)	108	(94 - 119)
HDL, mg/dL	49	(40 – 60)	49	(40 – 60)
Triglycerides, mg/L	118	(85 - 169)	118	(86 - 169)
Total Cholesterol, mg/dL	186	(168 - 200)	185	(169 - 199)
Glucose, mg/dL	94	(87 – 102)	94	(88 – 102)
HbA1c, %	5.7	(5.4 – 5.9)	5.7	(5.5 – 5.9)

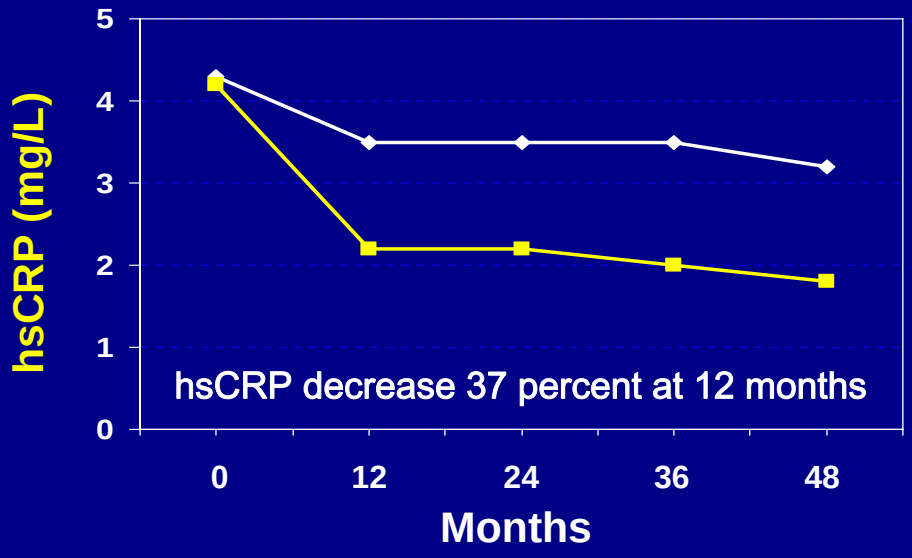
All values are median (interquartile range). [Mean LDL = 104 mg/dL]

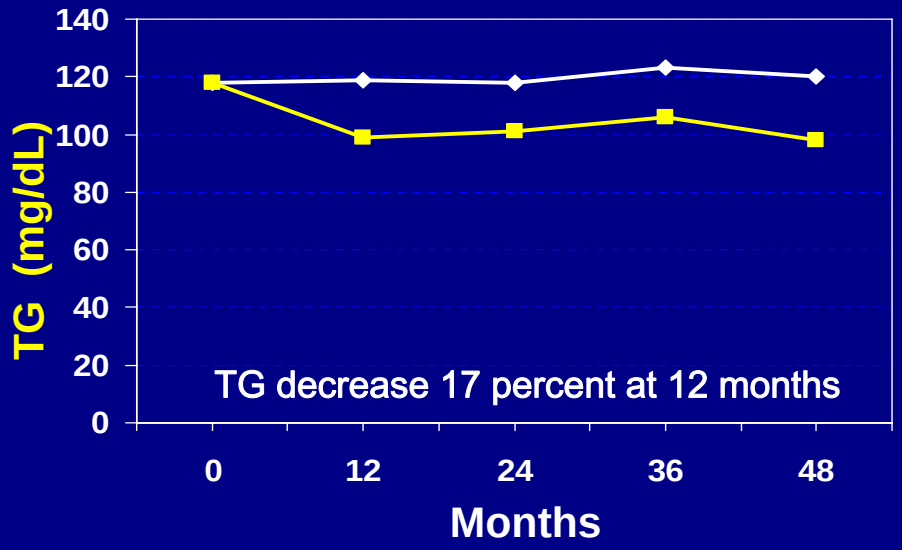
JUPITER

Effects of rosuvastatin 20 mg on LDL, HDL, TG, and hsCRP



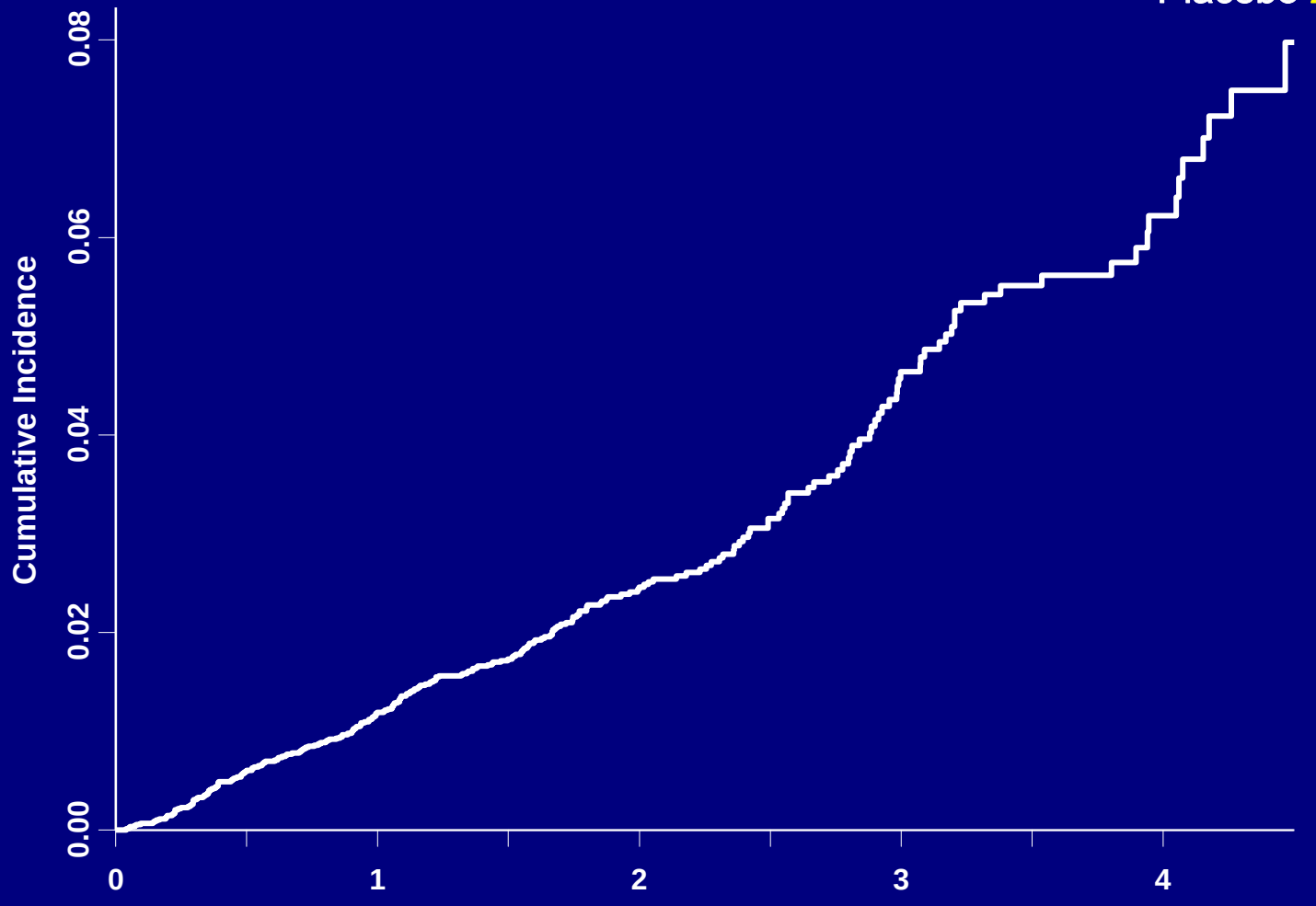






JUPITER

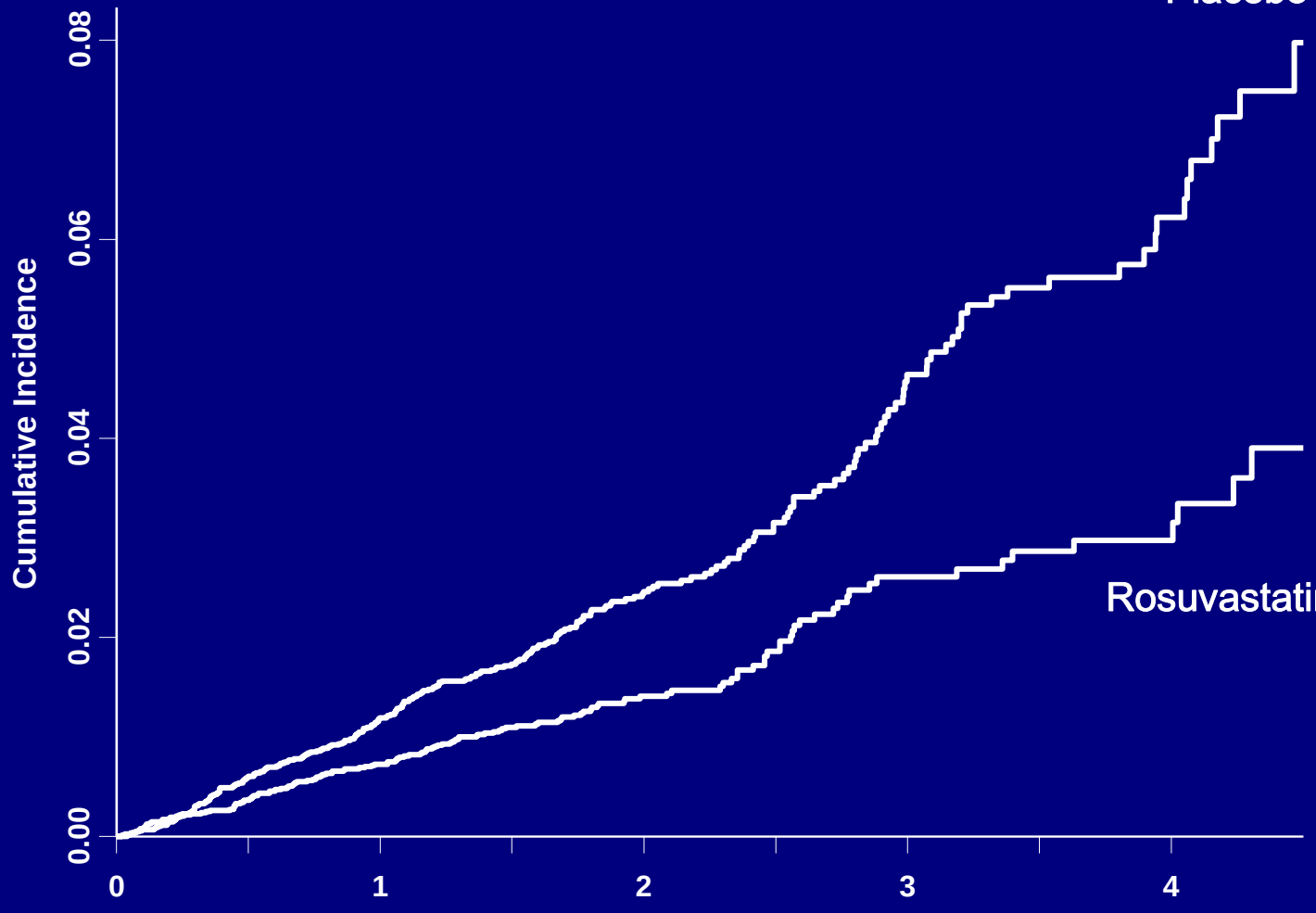
Primary Trial Endpoint：MI, Stroke, UA/Revascularization, CV Death



Number at Risk										
Rosuvastatin	8,901	8,631	8,412	6,540	3,893	1,958	1,353	983	544	157
Placebo	8,901	8,621	8,353	6,508	3,872	1,963	1,333	955	534	174

JUPITER

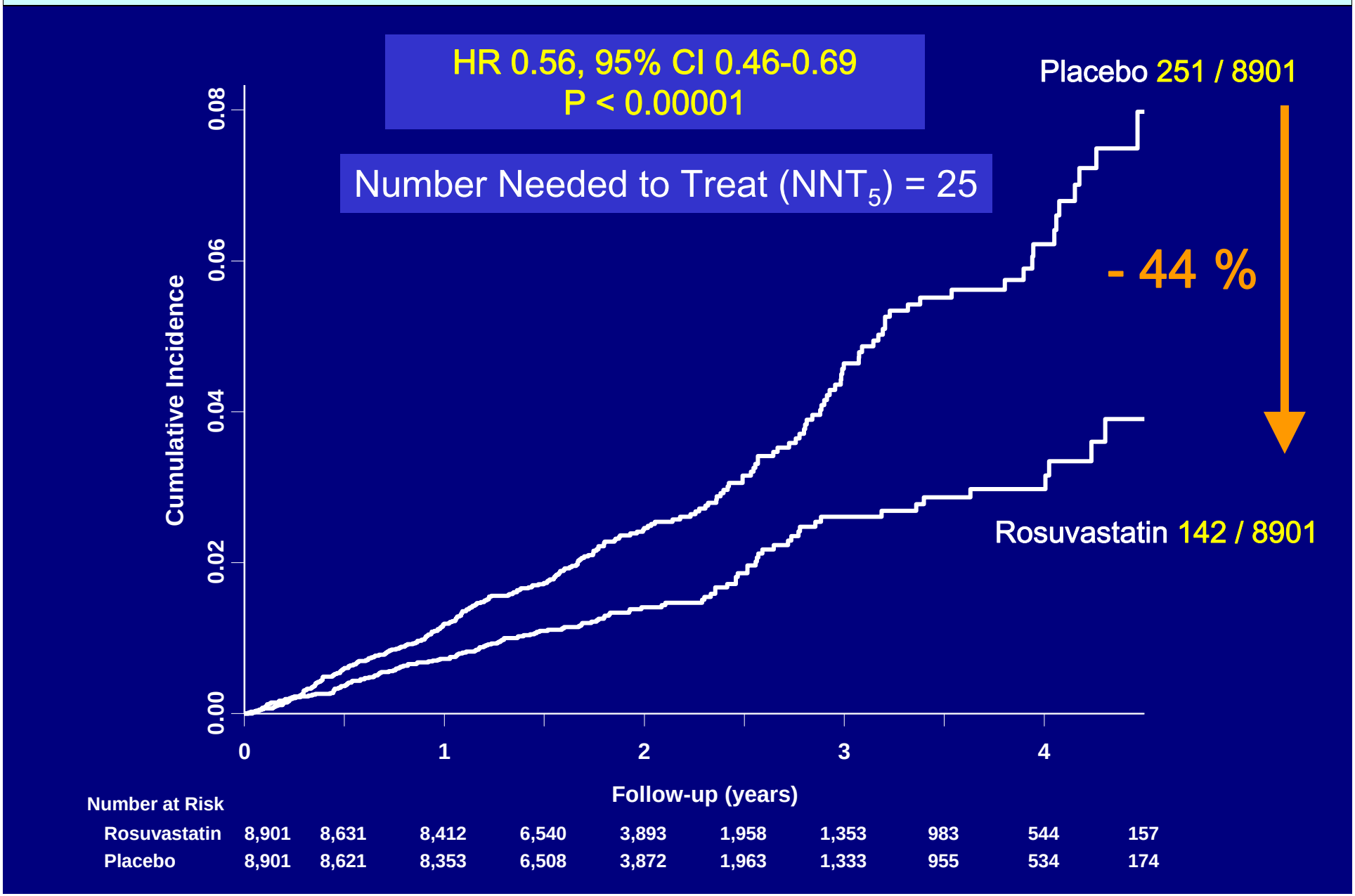
Primary Trial Endpoint：MI, Stroke, UA/Revascularization, CV Death



Number at Risk										
Rosuvastatin	8,901	8,631	8,412	6,540	3,893	1,958	1,353	983	544	157
Placebo	8,901	8,621	8,353	6,508	3,872	1,963	1,333	955	534	174

JUPITER

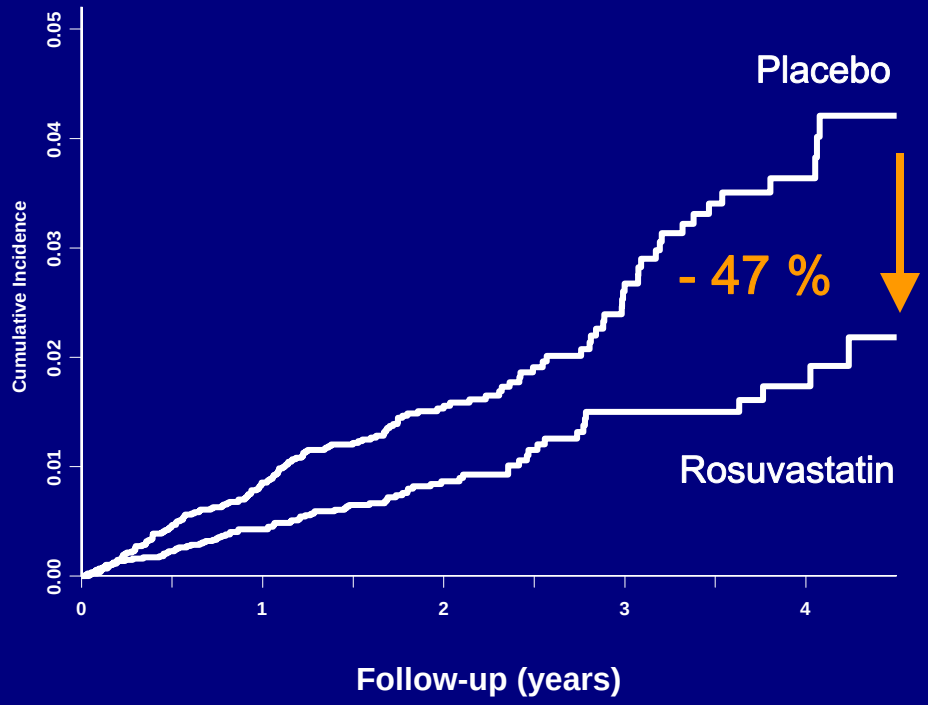
Primary Trial Endpoint：MI, Stroke, UA/Revascularization, CV Death



JUPITER
Grouped Components of the Primary Endpoint

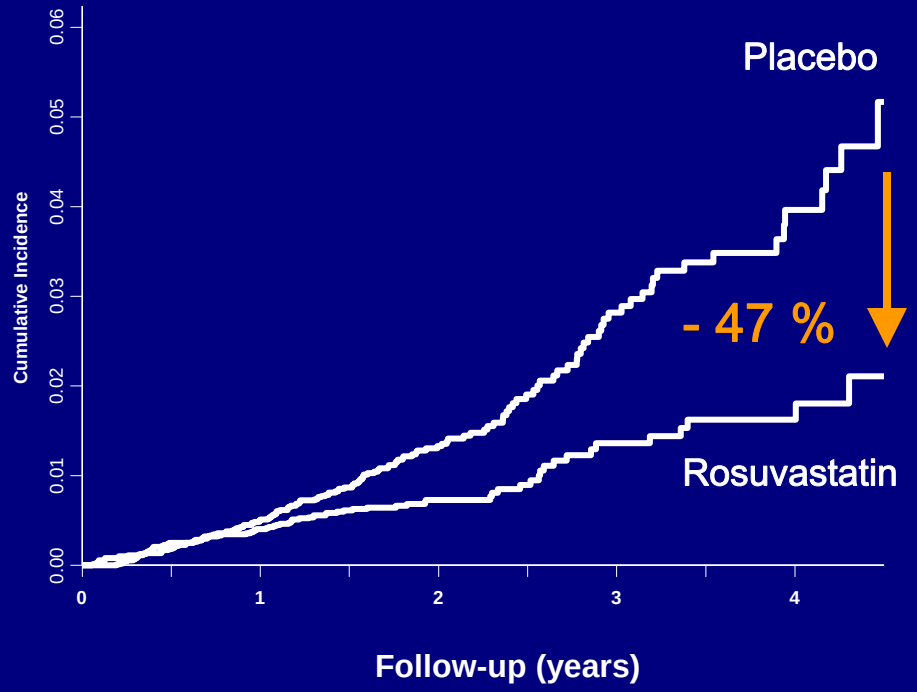
Myocardial Infarction, Stroke, or Cardiovascular Death

HR 0.53, CI 0.40-0.69
P < 0.00001



Arterial Revascularization or Hospitalization for Unstable Angina

HR 0.53, CI 0.40-0.70
P < 0.00001

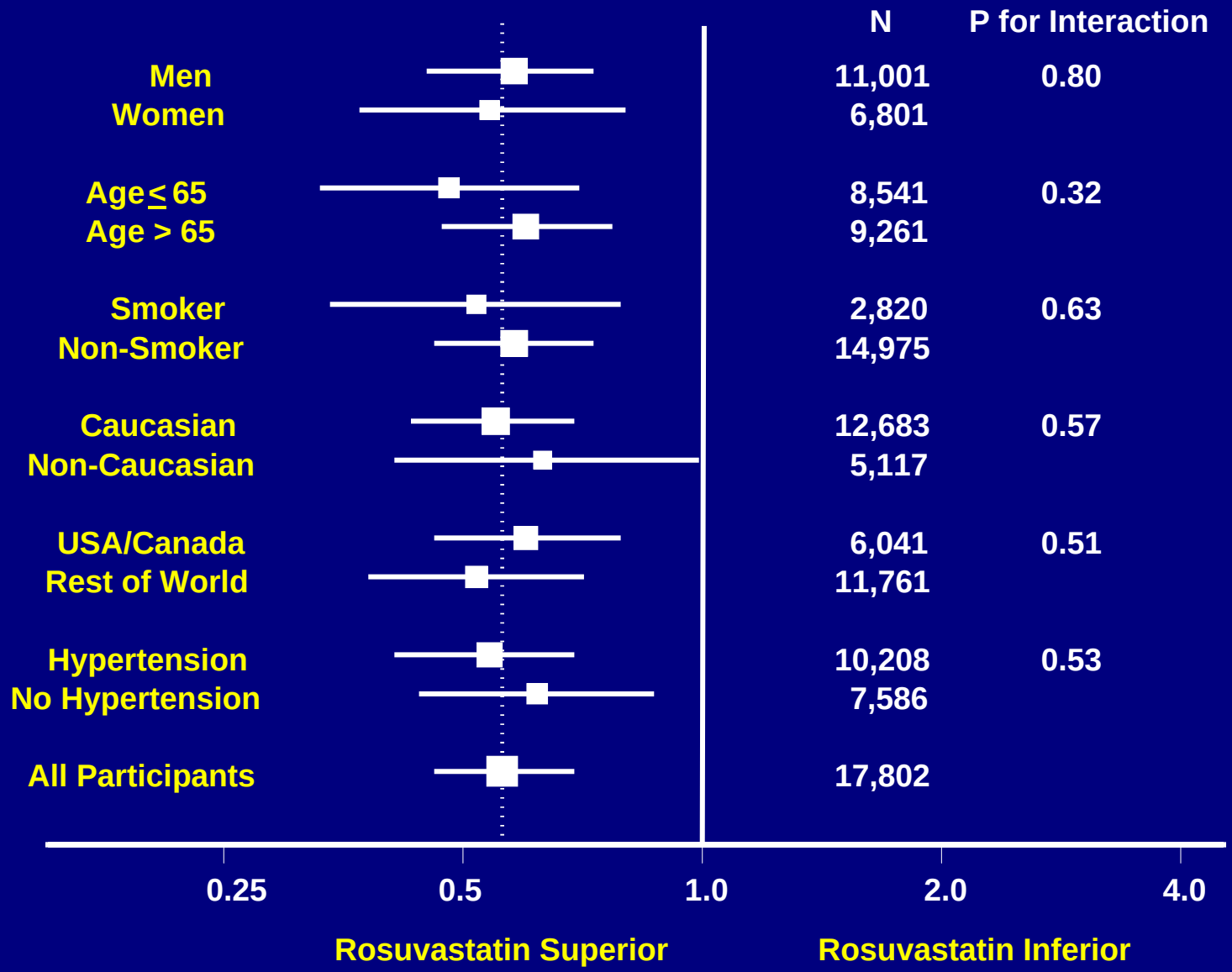


JUPITER
Individual Components of the Primary Endpoint

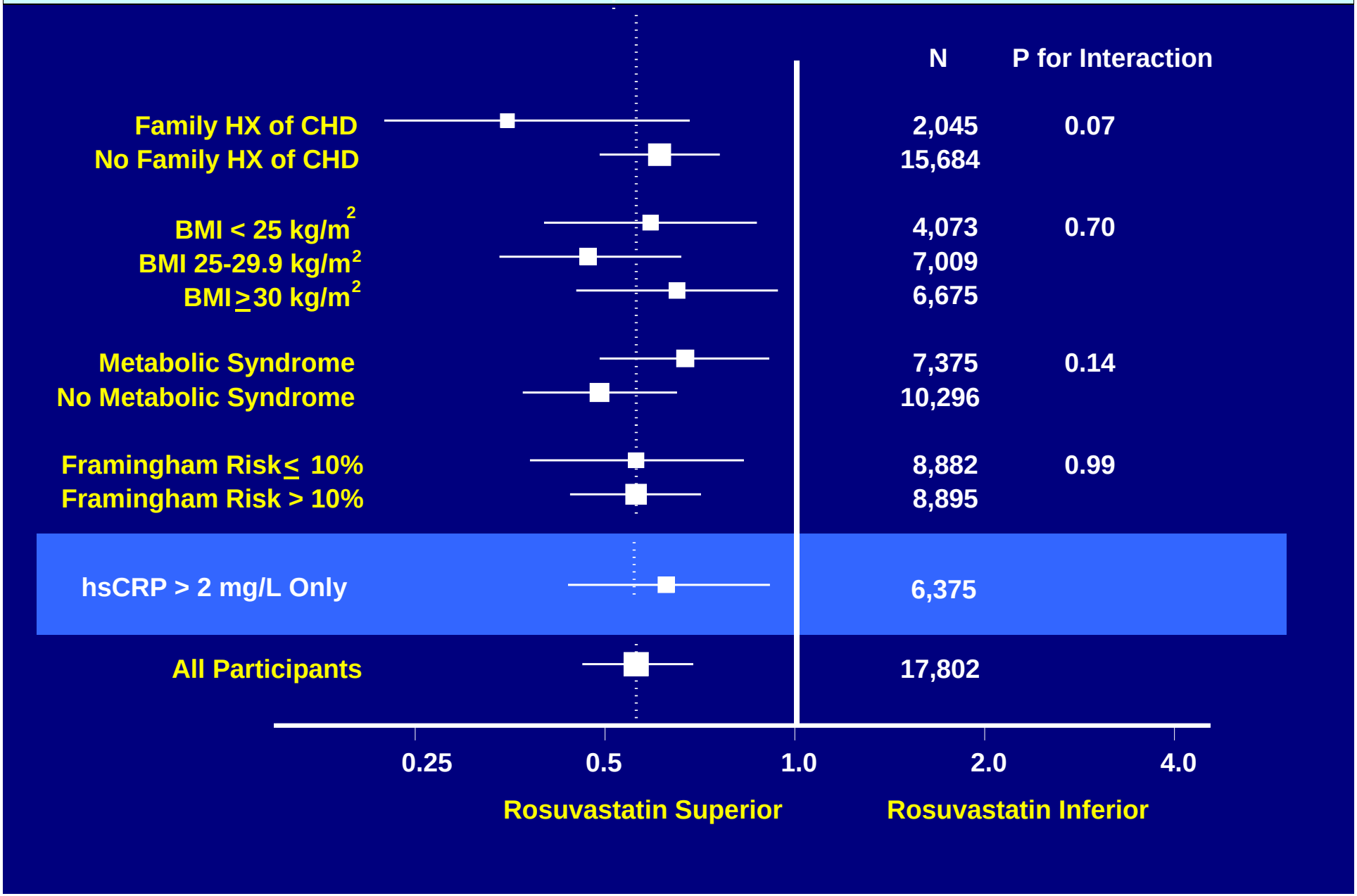
Endpoint	Rosuvastatin	Placebo	HR	95%CI	P
Primary Endpoint*	142	251	0.56	0.46-0.69	<0.00001
Non-fatal MI	22	62	0.35	0.22-0.58	<0.00001
Any MI	31	68	0.46	0.30-0.70	<0.0002
Non-fatal Stroke	30	58	0.52	0.33-0.80	0.003
Any Stroke	33	64	0.52	0.34-0.79	0.002
Revascularization or Unstable Angina	76	143	0.53	0.40-0.70	<0.00001
MI, Stroke, CV Death	83	157	0.53	0.40-0.69	<0.00001

*Nonfatal MI, nonfatal stroke, revascularization, unstable angina, CV death

JUPITER
Primary Endpoint – Subgroup Analysis I



JUPITER
Primary Endpoint – Subgroup Analysis II



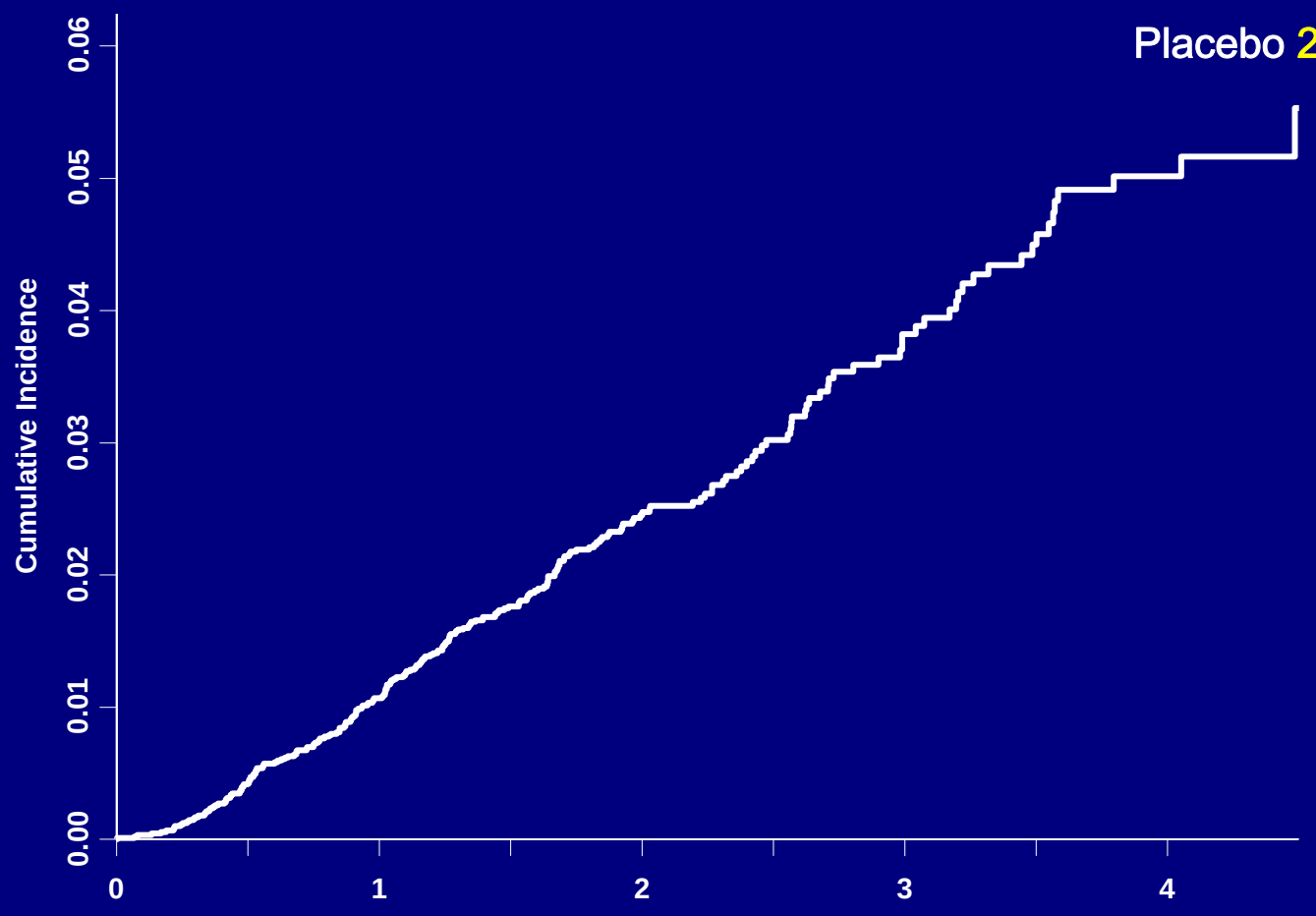
JUPITER
Adverse Events and Measured Safety Parameters

Event	Rosuvastatin	Placebo	P
Any SAE	1,352 (15.2)	1,337 (15.5)	0.60
Muscle weakness	1,421 (16.0)	1,375 (15.4)	0.34
Myopathy	10 (0.1)	9 (0.1)	0.82
Rhabdomyolysis	1 (0.01)*	0 (0.0)	--
Incident Cancer	298 (3.4)	314 (3.5)	0.51
Cancer Deaths	35 (0.4)	58 (0.7)	0.02
Hemorrhagic stroke	6 (0.1)	9 (0.1)	0.44
GFR (ml/min/1.73m^2 at 12 mth)	66.8 (59.1-76.5)	66.6 (58.8-76.2)	0.02
ALT > 3xULN	23 (0.3)	17 (0.2)	0.34
Fasting glucose (24 mth)	98 (91-107)	98 (90-106)	0.12
HbA1c (% at 24 mth)	5.9 (5.7-6.1)	5.8 (5.6-6.1)	0.01
Glucosuria (12 mth)	36 (0.5)	32 (0.4)	0.64
Incident Diabetes**	270 (3.0)	216 (2.4)	0.01

*Occurred after trial completion, trauma induced.
**Physician reported

All values are median (interquartile range) or N (%)

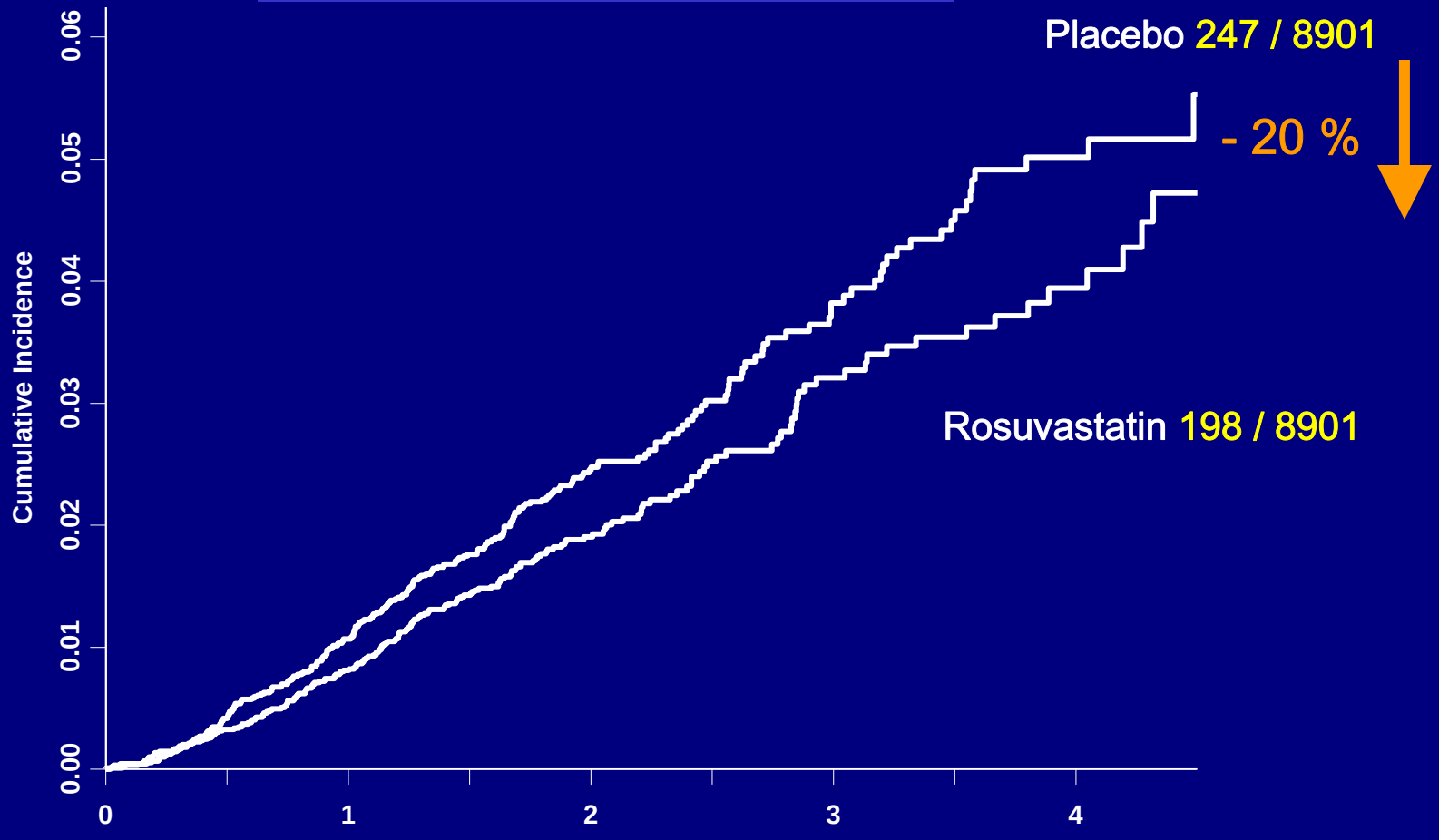
JUPITER
Secondary Endpoint – All Cause Mortality



Number at Risk										
Rosuvastatin	8,901	8,847	8,787	6,999	4,312	2,268	1,602	1,192	683	227
Placebo	8,901	8,852	8,775	6,987	4,319	2,295	1,614	1,196	684	246

JUPITER
Secondary Endpoint – All Cause Mortality

HR 0.80, 95%CI 0.67-0.97
P= 0.02



Number at Risk										
Rosuvastatin	8,901	8,847	8,787	6,999	4,312	2,268	1,602	1,192	683	227
Placebo	8,901	8,852	8,775	6,987	4,319	2,295	1,614	1,196	684	246

JUPITER
Conclusions – Efficacy I

Among apparently healthy men and women with elevated hsCRP but low LDL, rosuvastatin reduced by 47 percent incident myocardial infarction, stroke, and cardiovascular death.

Despite evaluating a population with lipid levels widely considered to be “optimal” in almost all current prevention algorithms, the relative benefit observed in JUPITER was greater than in almost all prior statin trials.

In this trial of low LDL/high hsCRP individuals who do not currently qualify for statin therapy, rosuvastatin significantly reduced all-cause mortality by 20 percent.

JUPITER
Conclusions – Efficacy II

Benefits of rosuvastatin were consistent in all sub-groups evaluated regardless of age, sex, ethnicity, or other baseline clinical characteristic, including those with elevated hsCRP and no other major risk factor.

Rates of hospitalization and revascularization were reduced by 47 percent within a two-year period suggesting that the screening and treatment strategy tested in JUPITER is likely to be cost-effective, benefiting both patients and payers.

The Number Needed to Treat in JUPITER was 25 for the primary endpoint, a value if anything smaller than that associated with treating hyperlipidemia in primary prevention.

JUPITER
Conclusions - Safety

With regard to safety , the JUPITER results

- show no increase in serious adverse events among those allocated to rosuvastatin 20 mg as compared to placebo in a setting where half of the treated patients achieved levels of LDL< 55 mg/dL (and 25 percent had LDL < 44 mg/dL).
- show no increase in myopathy, cancer, hepatic disorders, renal disorders, or hemorrhagic stroke with treatment duration of up to 5 years
- show no increase in systematically monitored glucose or glucosuria during follow-up, but small increases in HbA1c and physician reported diabetes similar to that seen in other major statin trials

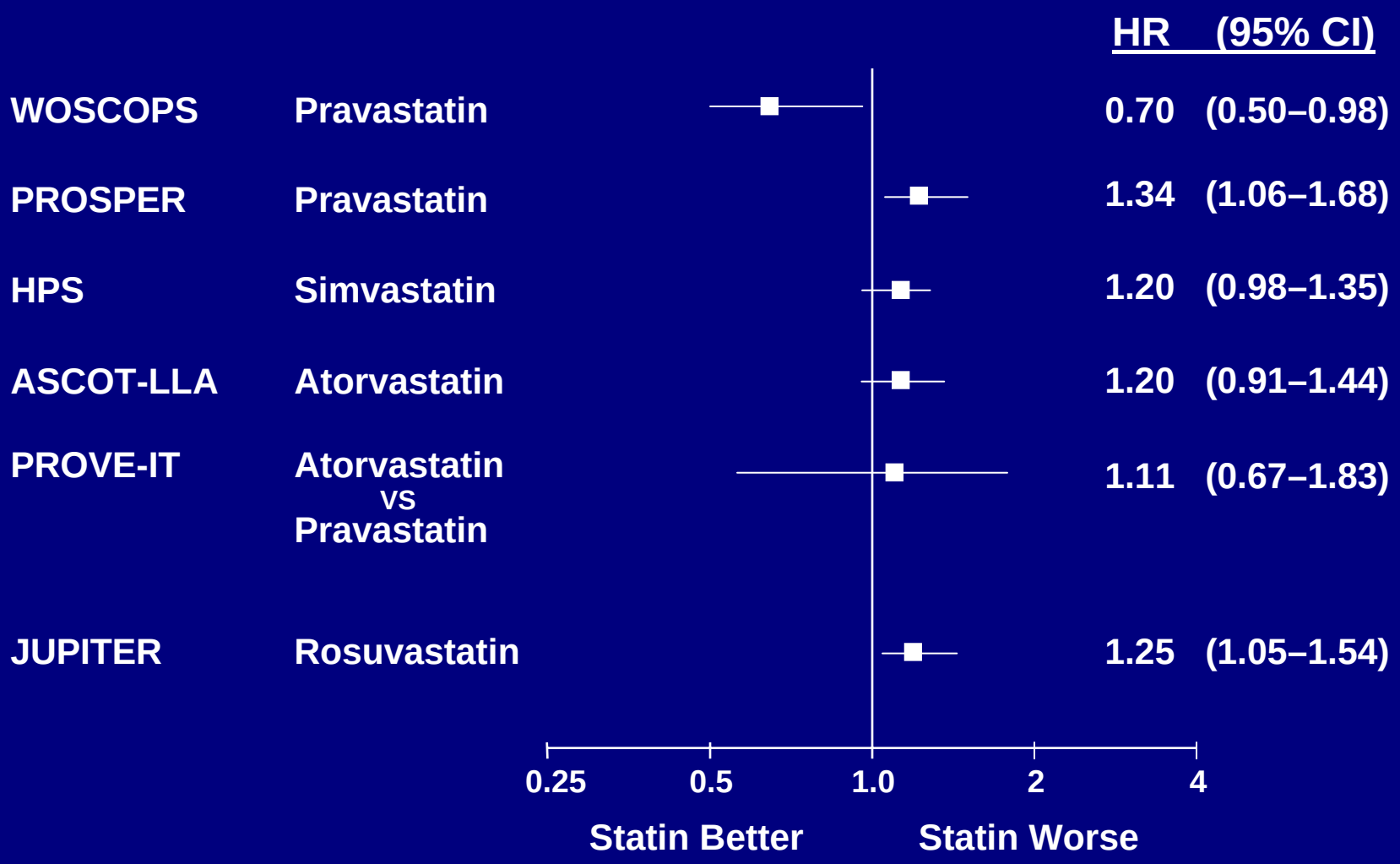
JUPITER
Public Health Implications

Application of the simple screening and treatment strategy tested in the JUPITER trial over a five-year period could conservatively prevent more than 250,000 heart attacks, strokes, revascularization procedures, and cardiovascular deaths in the United States alone.

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

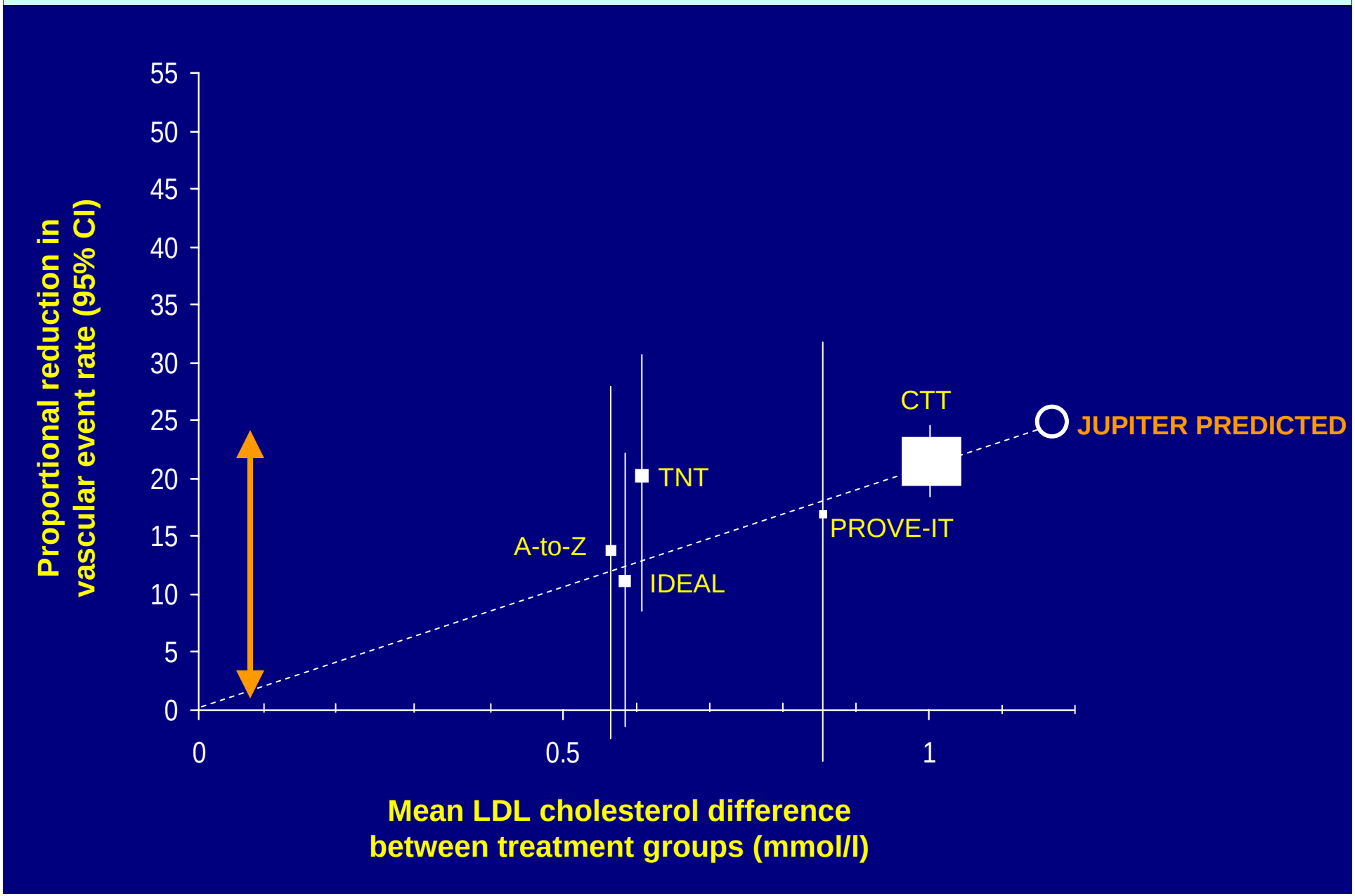
www.brighamandwomens.org/jupitertrial

JUPITER
Statins and the Development of Diabetes



JUPITER

Predicted Benefit Based on LDL Reduction vs Observed Benefit



JUPITER

Predicted Benefit Based on LDL Reduction vs Observed Benefit