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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

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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.*

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Trial Design

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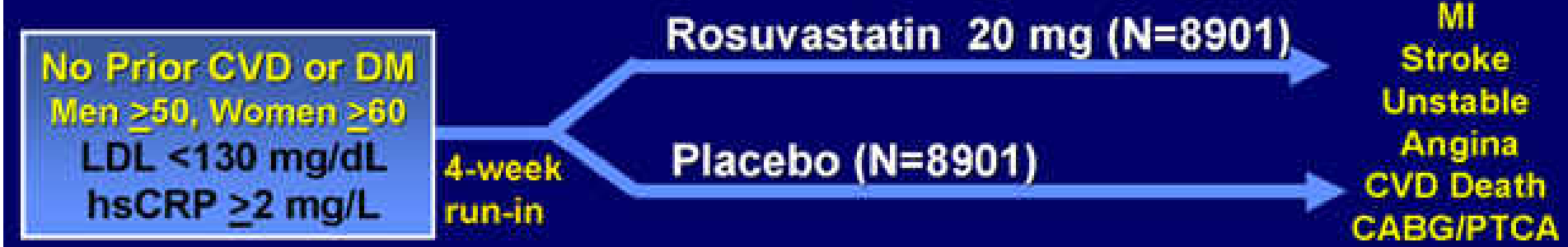
Multi-National Randomized Double Blind Placebo Controlled Trial of Rosuvastatin in the Prevention of Cardiovascular Events Among Individuals With Low LDL and Elevated hsCRP



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.

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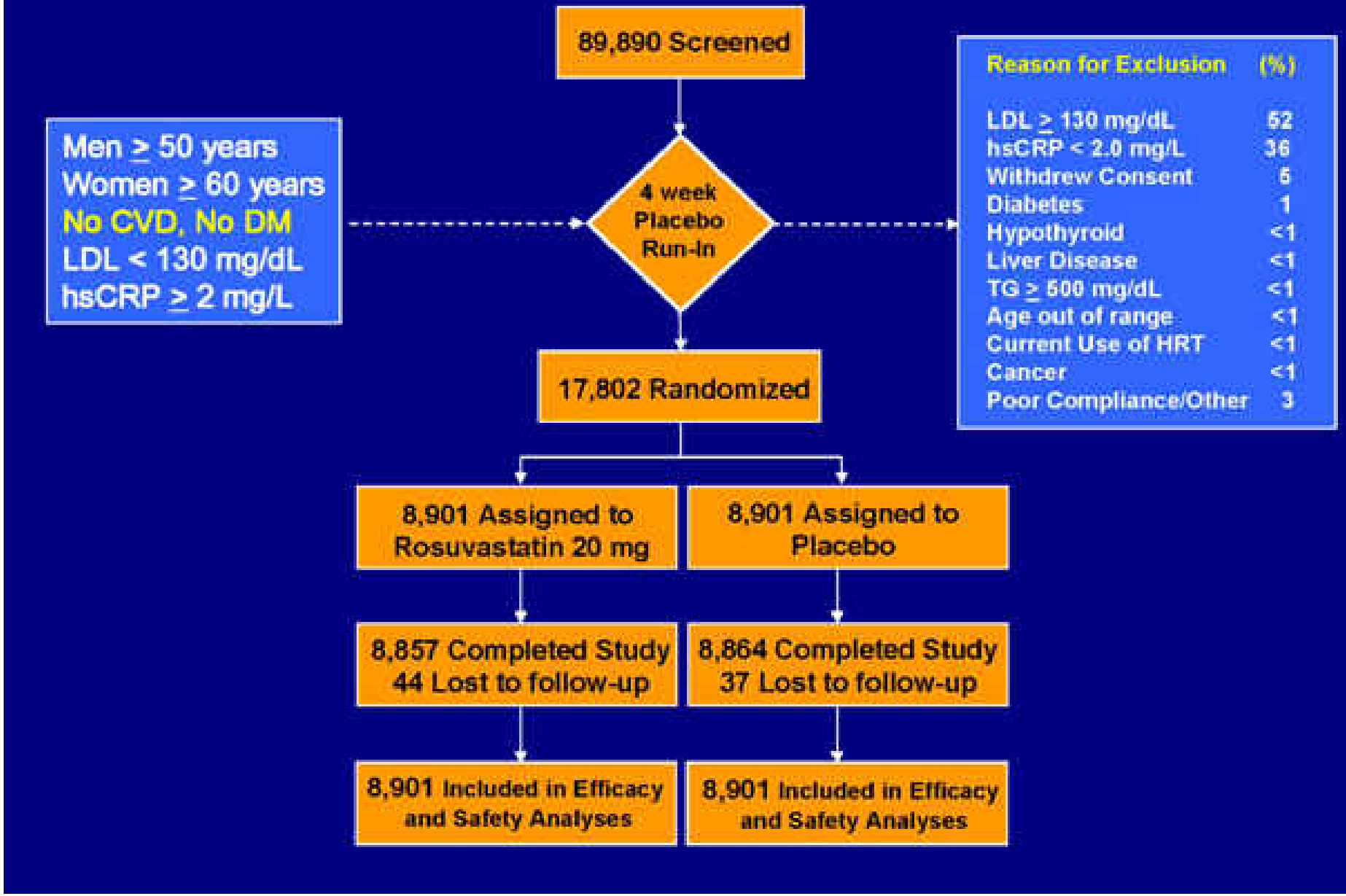
Inclusion and Exclusion Criteria, Study Flow

Ridker et al NEJM 2008



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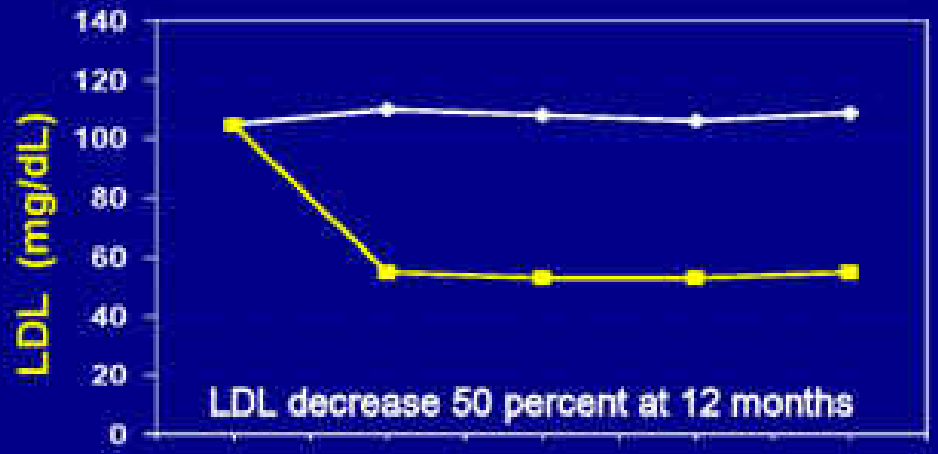
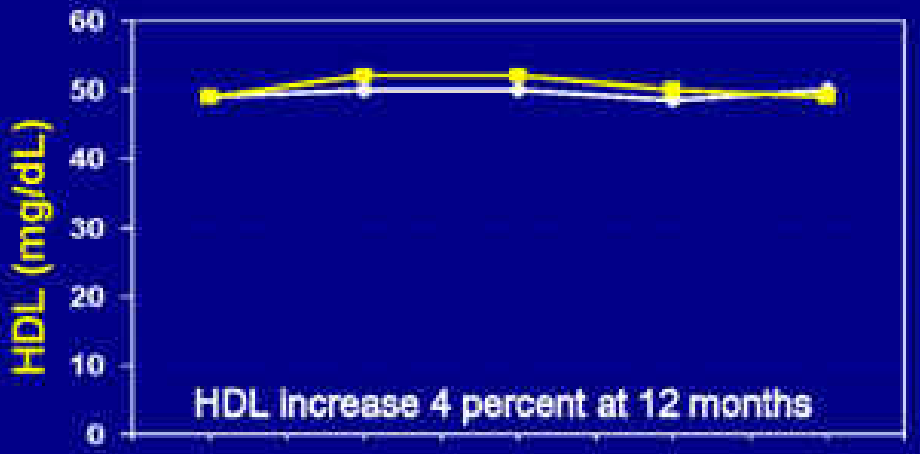
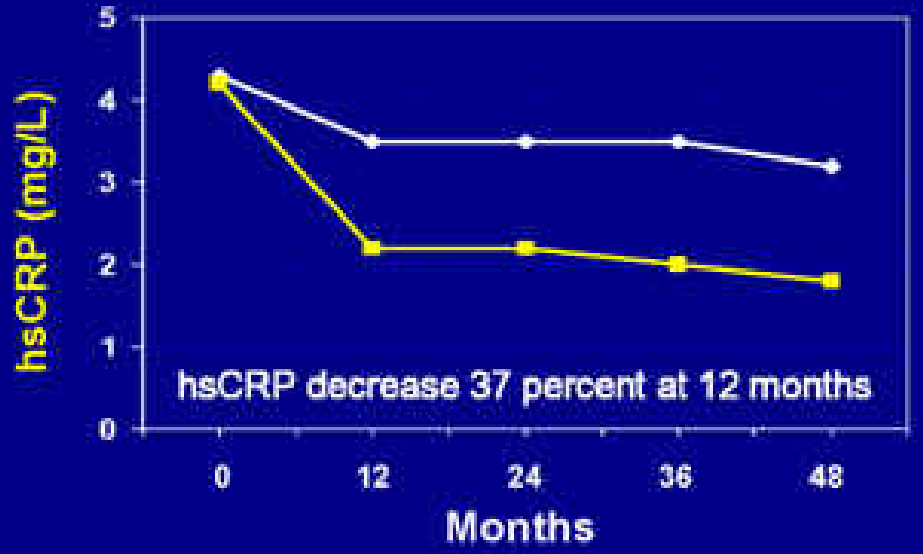
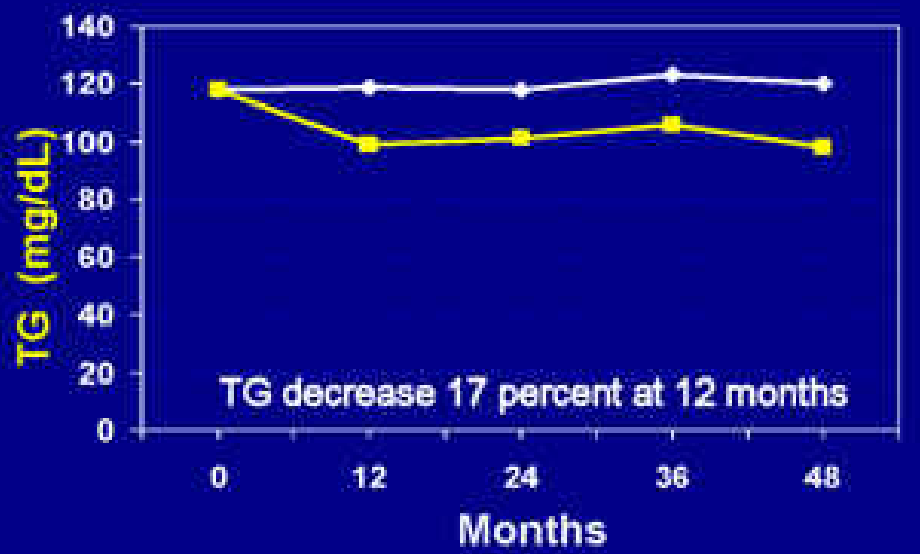
Ridker et al NEJM 2008

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









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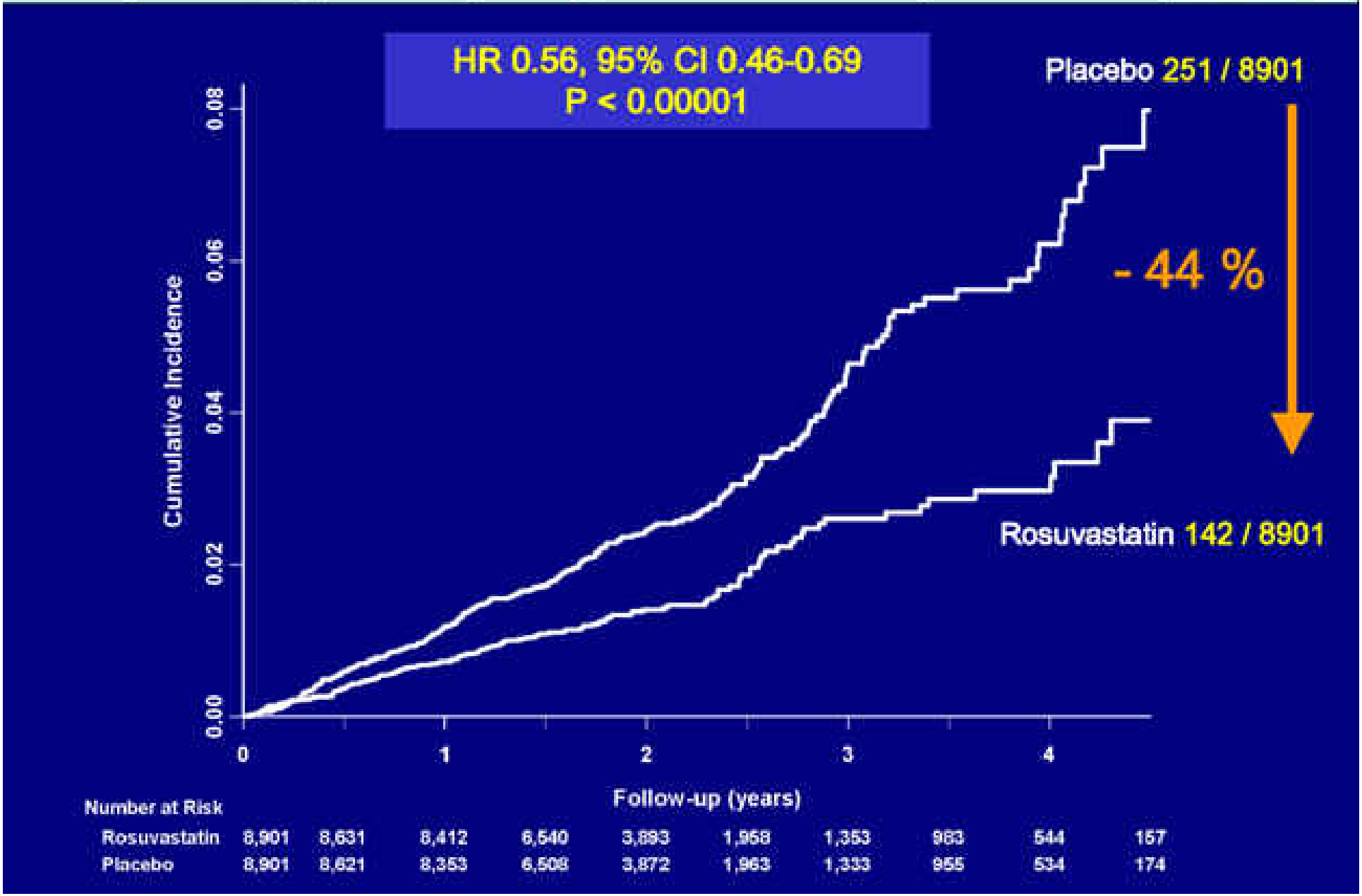
Primary Trial Endpoint : MI, Stroke, UA/Revascularization, CV Death



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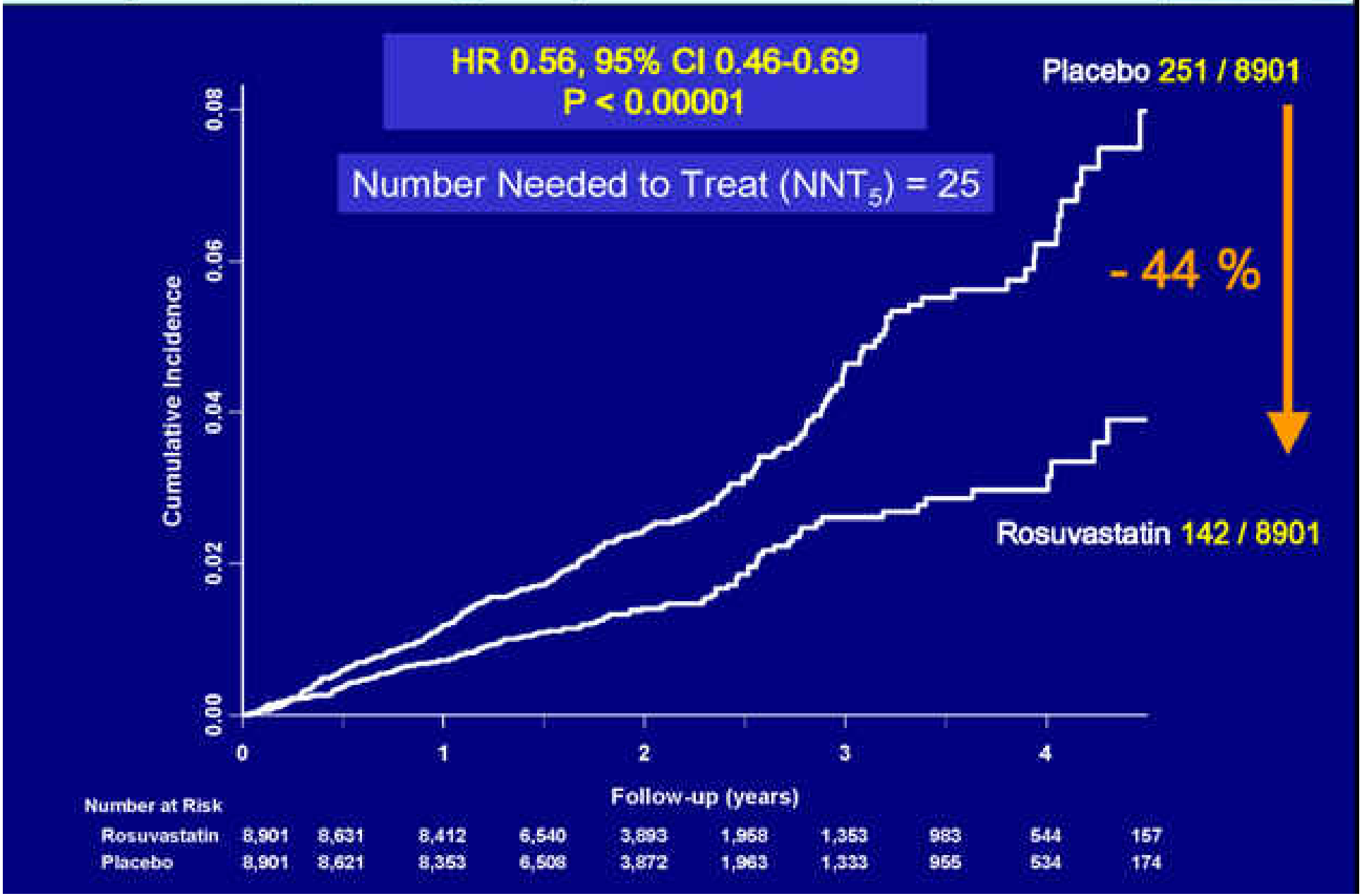
Primary Trial Endpoint : MI, Stroke, UA/Revascularization, CV Death



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Grouped Components of the Primary Endpoint

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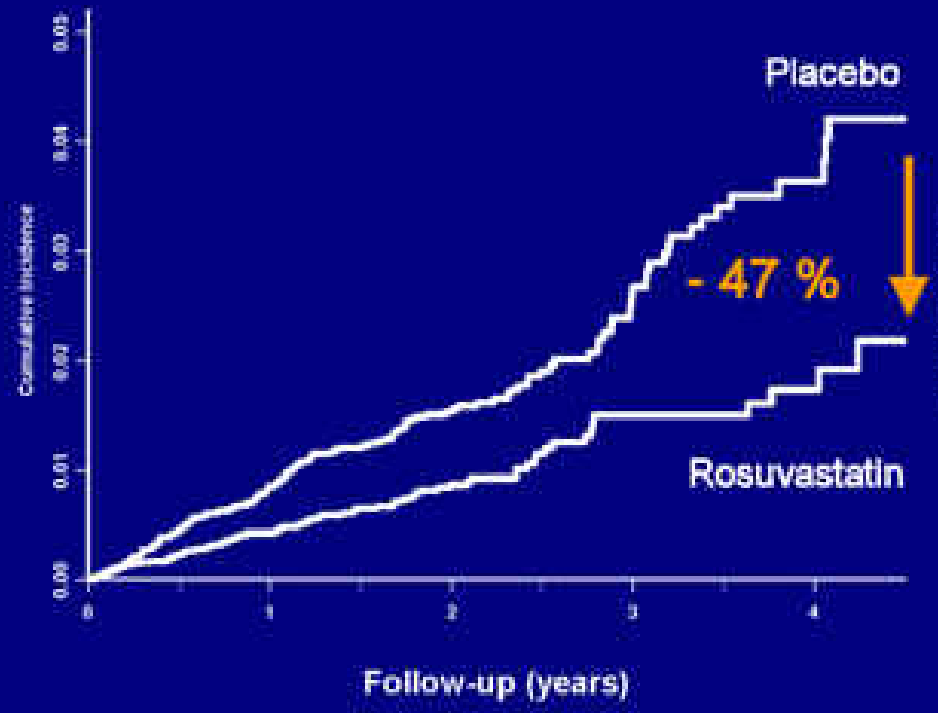
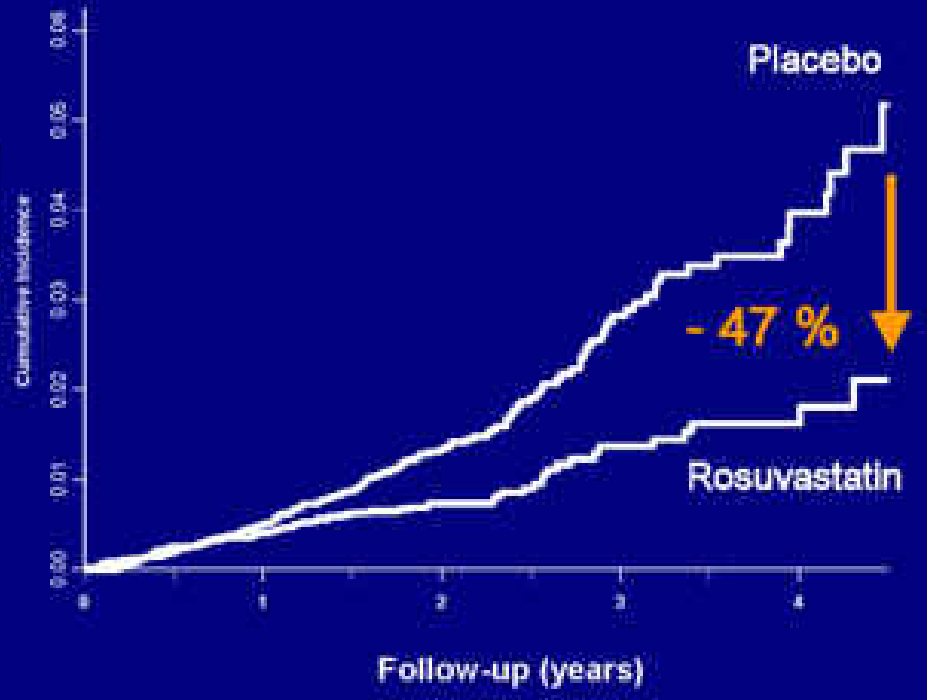
Myocardial Infarction, Stroke, or Cardiovascular Death

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



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Individual Components of the Primary Endpoint

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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

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Primary Endpoint – Subgroup Analysis I

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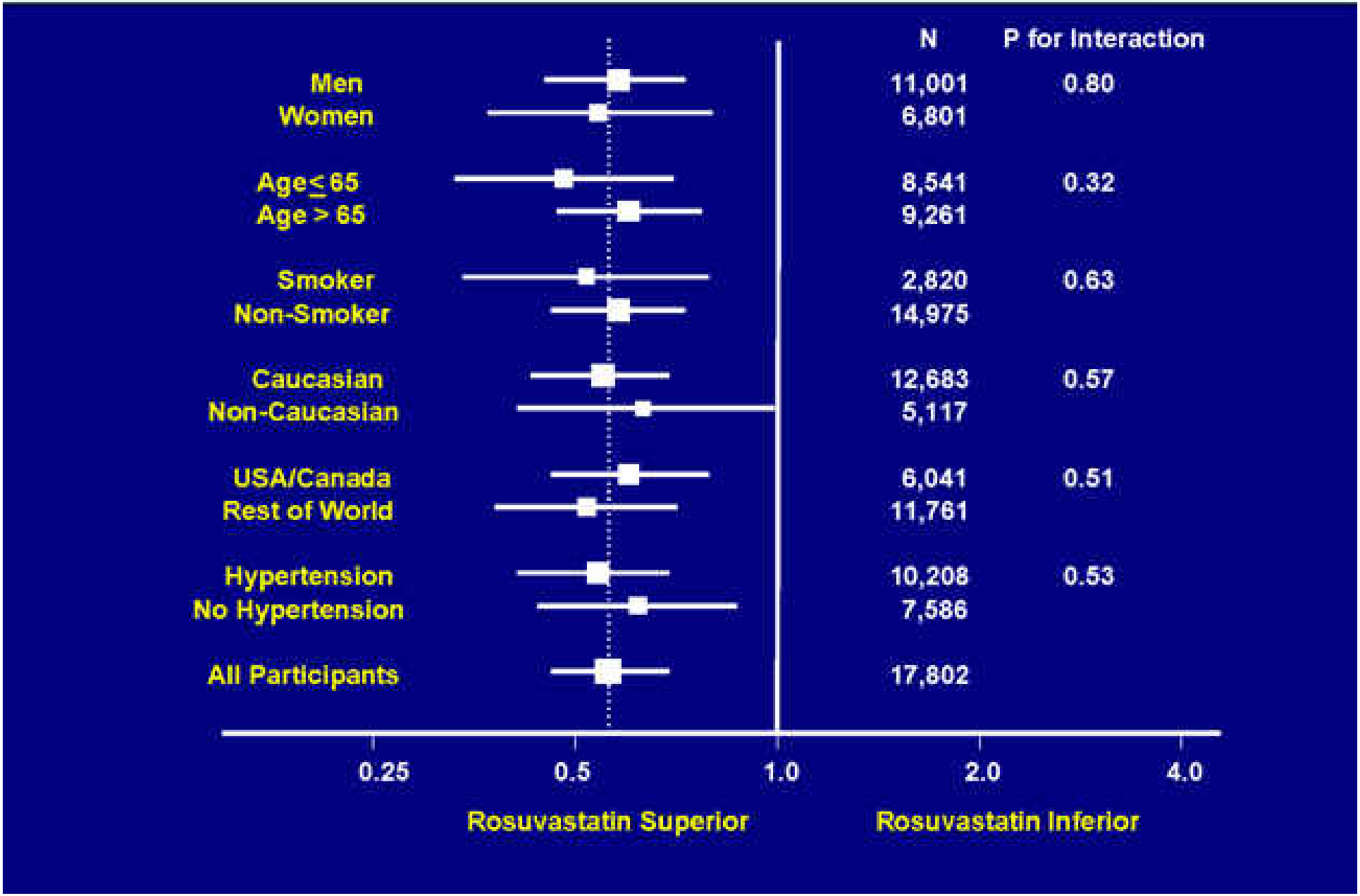

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Primary Endpoint – Subgroup Analysis II

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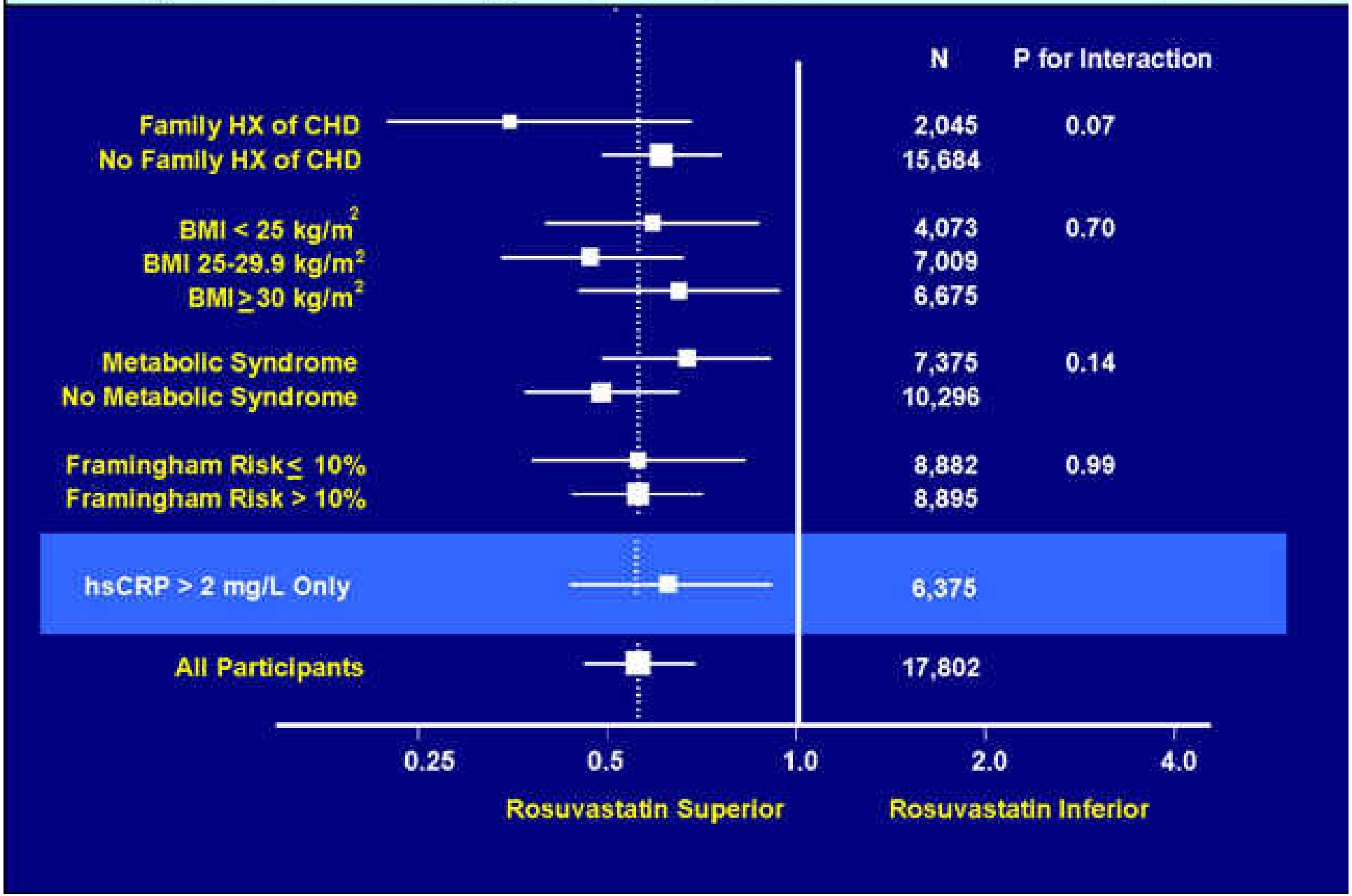

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Adverse Events and Measured Safety Parameters

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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 (%)

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Secondary Endpoint – All Cause Mortality

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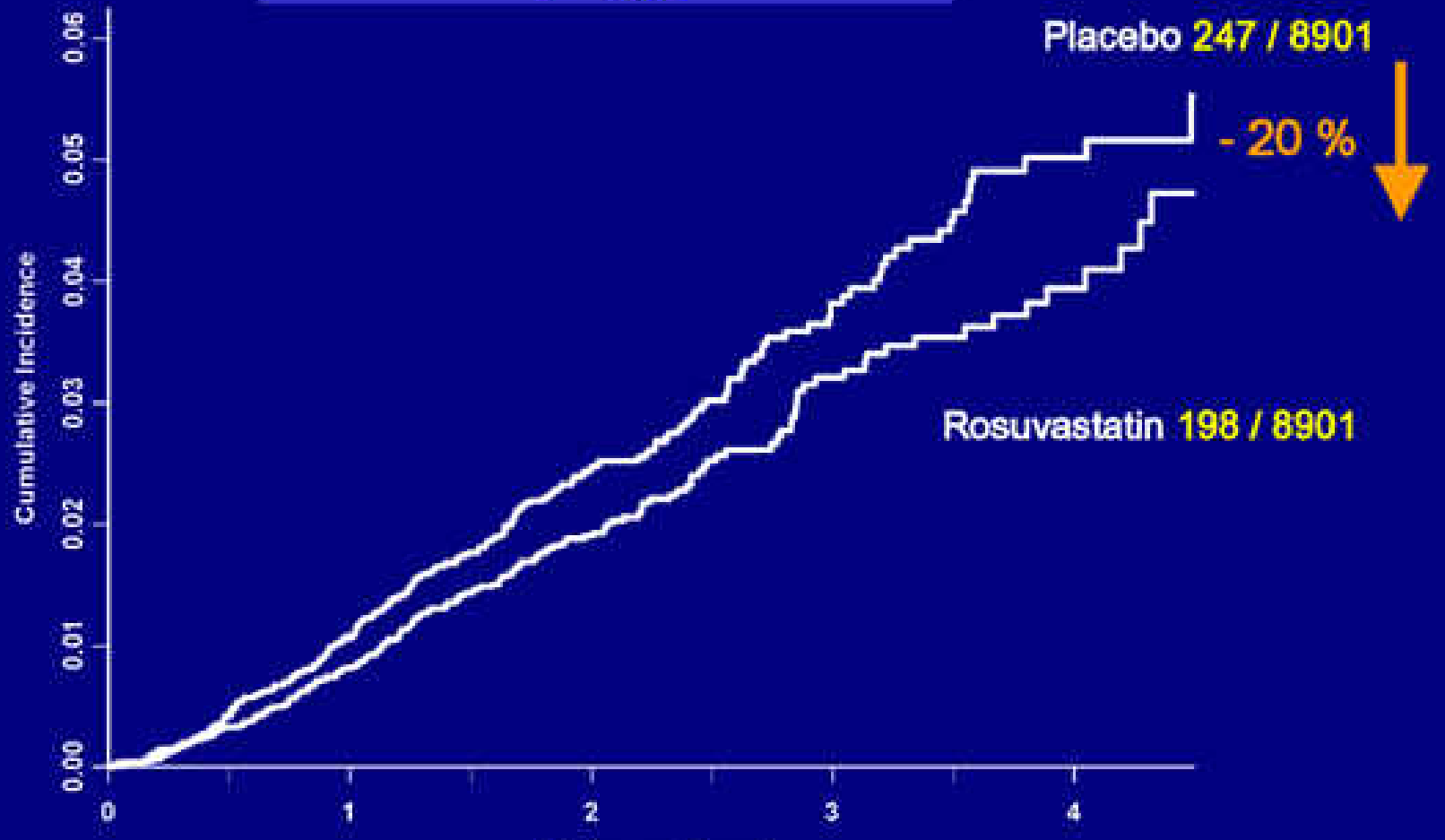
HR 0.80, 95%CI 0.67-0.97
P= 0.02



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

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Conclusions – Efficacy I

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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.

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Conclusions – Efficacy II

Ridker et al NEJM 2008

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.

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Conclusions - Safety

Ridker et al NEJM 2008

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

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Implications for Primary Prevention

Ridker et al NEJM 2008

A simple evidence based approach to statin therapy for primary prevention.

Among men and women age 50 or over :

If diabetic, treat
If LDLC > 160 mg/dL, treat
If hsCRP > 2 mg/L, treat

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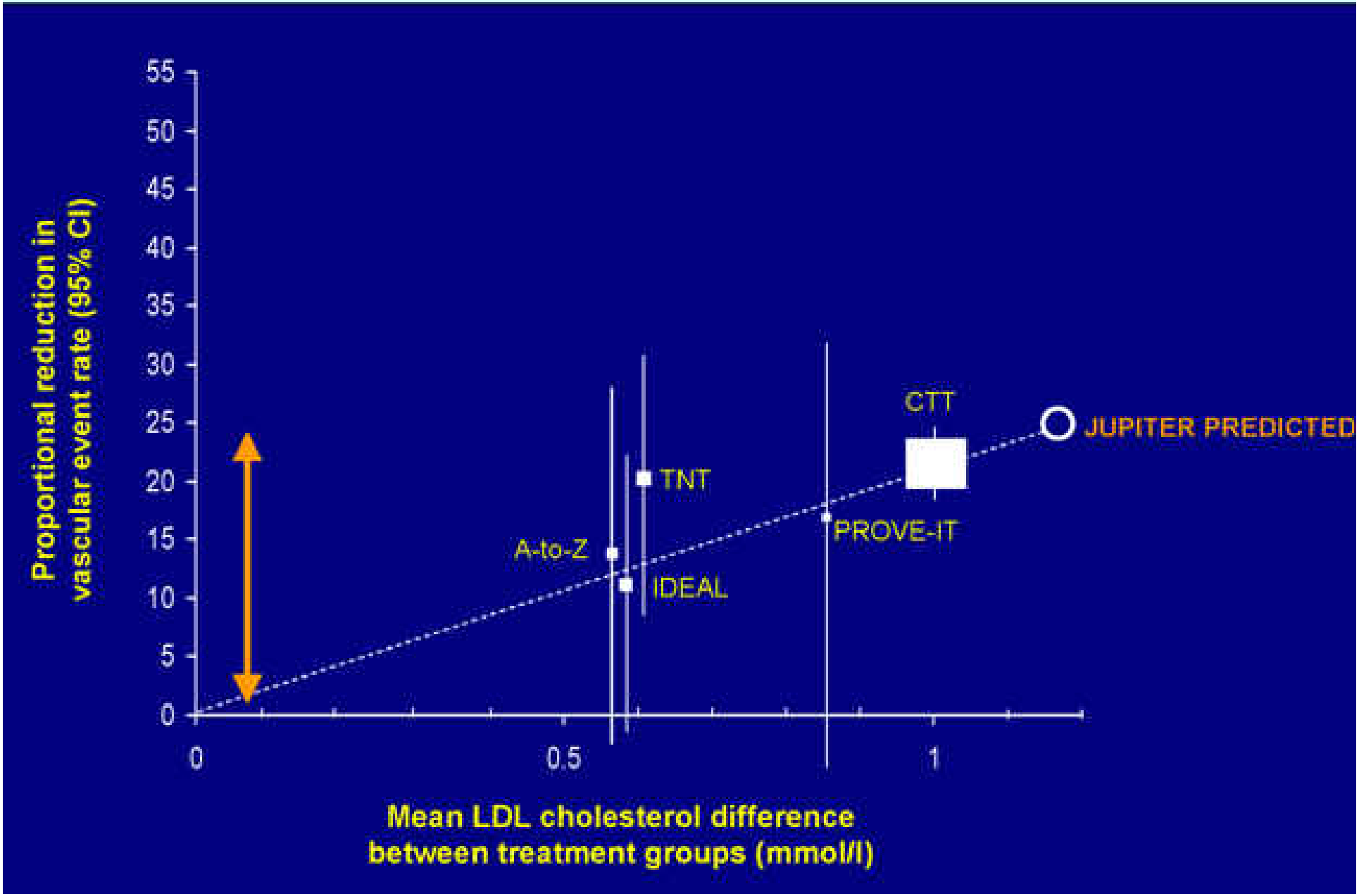
Predicted Benefit Based on LDL Reduction vs Observed Benefit



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Predicted Benefit Based on LDL Reduction vs Observed Benefit