Endocrinologic and Metabolic Drugs Advisory Committee Meeting
Gaithersburg, Maryland
December 15, 2009

CRESTOR (Rosuvastatin calcium)
NDA 21-366
JUPITER

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Outline

- Background
- NCEP treatment guidelines
- JUPITER trial
  - Design
  - Disposition/Demographics
  - Efficacy
  - Safety

CRESTOR: Background

- CRESTOR (rosuvastatin calcium) is a HMG-CoA reductase inhibitor
- United States approval 12 August 2003
- Available in 5, 10, 20, and 40 mg tablets

CRESTOR: Current indications

- Patients with primary hyperlipidemia and mixed dyslipidemia as an adjunct to diet
- Patients with hypertriglyceridemia as an adjunct to diet
- Patients with primary dysbetalipoproteinemia as an adjunct to diet
- Patients with homozygous familial hypercholesterolemia to reduce LDL-C, total-C, and Apo-B
- Slowing the progression of atherosclerosis as part of a treatment strategy to lower total-C and LDL-C as an adjunct to diet
- Pediatric patients 10 to 17 years of age with heterozygous familial hypercholesterolemia to reduce elevated total-C, LDL-C, and Apo B after failing diet therapy

Indication sought based on JUPITER

- *For prevention of cardiovascular disease in adult patients with an increased risk of cardiovascular disease based on the presence of cardiovascular disease risk markers such as an elevated hsCRP level, age, hypertension, low HDL-C, smoking or a family history of premature coronary heart disease, CRESTOR is indicated to:*

Indication sought based on JUPITER

<u>Reduce the risk of:</u>

- *total mortality*
- *cardiovascular death*
- *stroke*
- *myocardial infarction*
- *arterial revascularization*
- *unstable angina*

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NCEP: ATP-III 2001 guidelines

- Major risk factors (exclusive of LDL-C)
  - Cigarette smoking
  - Hypertension (BP ≥ 140/90 mmHg or on antihypertensive medication)
  - Low HDL-C (<40 mg/dL)*
  - Family history of premature coronary heart disease (CHD)
    - CHD in male first degree relative <55 years
    - CHD in female first degree relative <65 years
  - Age (men ≥45 years; women ≥55 years)

* HDL-C ≥60 mg/dL counts as a "negative" risk factor; its presence removes one risk factor from the total count.

Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP-III). JAMA 2001

LDL-C goals and cutpoints for therapy according to risk

Risk Category	LDL Goal	LDL Level at Which to Initiate Therapeutic Lifestyle Changes (TLC)	LDL Level at Which to Consider Drug Therapy
CHD or CHD Risk Equivalents (10-year risk >20%)	<100 mg/dL	≥100 mg/dL	≥130 mg/dL (100-129 mg/dL: drug optional)*
2+ Risk Factors (10-year risk ≤20%)	<130 mg/dL	≥130 mg/dL	10-year risk 10-20%: ≥130 mg/dL 10-year risk <10%: ≥160 mg/dL
0-1 Risk Factor†	<160 mg/dL	≥160 mg/dL	≥190 mg/dL (160-189 mg/dL: LDL-lowering drug optional)

* *Some authorities recommend use of LDL-lowering drugs in this category if an LDL cholesterol <100 mg/dL cannot be achieved by therapeutic lifestyle changes. Others prefer use of drugs that primarily modify triglycerides and HDL, e.g., nicotinic acid or fibrate. Clinical judgment also may call for deferring drug therapy in this subcategory.*

† *Almost all people with 0-1 risk factor have a 10-year risk <10%, thus 10-year risk assessment in people with 0-1 risk factor is not necessary.*

Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP-III). JAMA 2001

NCEP 2004 Report

- Reviewed the results of 5 major clinical trials using statin therapy and clinical endpoints
  - Heart Protection Study (HPS)
  - Prospective Study of Pravastatin in the Elderly at Risk (PROSPER)
  - Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial-Lipid Lowering Trial (ALLHAT-LLT)
  - Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA)
  - Pravastatin or Atorvastatin Evaluation and Infection-Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI)

Grundy et al. Implications of recent clinical trials for the national cholesterol education program adult treatment panel III guidelines. JACC 2004;44:720-32

ATP-III Goals and Cutpoints Modified

Risk category	LDL-C Goal	Initiate TLC	Consider Drug Therapy
High risk: CHD or CHD risk equivalents (10-year risk >20%)	<100 mg/dL (optional goal: <70 mg/dL)	≥100 mg/dL	≥100 mg/dL (<100 mg/dL: consider drug options)
Moderately high risk: 2+ risk factors (10-year risk 10-20%)	<130 mg/dL (optional goal: <100 mg/dL)	≥ 130 mg/dL	≥130 mg/dL (100-129 mg/dL: consider drug options)
Moderate risk: 2+ risk factors (10-year risk <10%)	<130 mg/dL	≥ 130 mg/dL	≥ 160 mg/dL
Lower risk: 0-1 risk factors	<160 mg/dL	≥ 160 mg/dL	≥ 190 mg/dL (160-189 mg/dL: LDL-lowering drug optional)

Grundy et al. Implications of recent clinical trials for the national cholesterol education program adult treatment panel III guidelines. JACC 2004;44:720-32

ATP-III Goals and Cutpoints Modified

- According to NCEP ATP-III 2001 guidelines all individuals eligible for enrollment in the JUPITER trial would not be candidates for statin therapy

- Applying the NCEP 2004 proposed modifications, approximately 22% of JUPITER subjects could be considered for statin therapy based on age and the presence of additional risk factors, a 10-year risk of 10-20%, and LDL of 100-129 mg/dL at baseline

- The first patients enrolled in JUPITER occurred before the 2004 NCEP report

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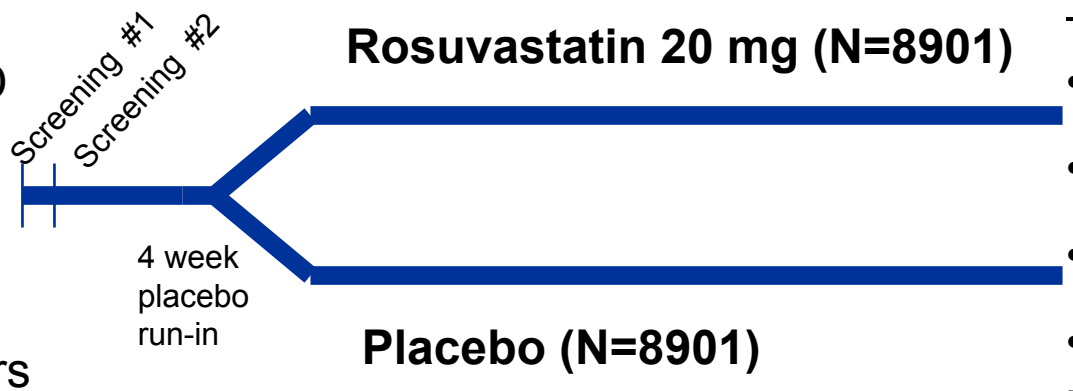
JUPITER: trial design

Eligibility criteria

- No CVD or CHD risk equivalent
- No diabetes
- Men ≥50 years, Women ≥60 years
- LDL <130 mg/dL
- hsCRP ≥2 mg/L



Time to first event:

- CV death
- MI
- Stroke
- Hospitalization for unstable angina
- Revascularization

Study procedures

- Initial screening for study eligibility could not occur within 2 weeks of a major viral or bacterial illness
- CRP and lipid levels drawn at the initial screening visit determined eligibility for a second screening visit
- A second CRP level was drawn 2 weeks after the initial screening visit at Screening Visit #2
- Baseline CRP was considered the average of these 2 CRP values

Study procedures (cont.)

- With the occurrence of a subject's first cardiovascular event
  - Blinded study medication was discontinued
  - Subject continued scheduled follow-up assessments
  - Treatment was left to investigator's discretion
- For subjects who discontinued study medication
  - Reason for medication discontinuation assessed
  - Subject could continue scheduled follow-up assessments (office visit or telephone contact) for adverse events and clinical endpoints
- Assessment of vital status was to be done on all randomized JUPITER subjects

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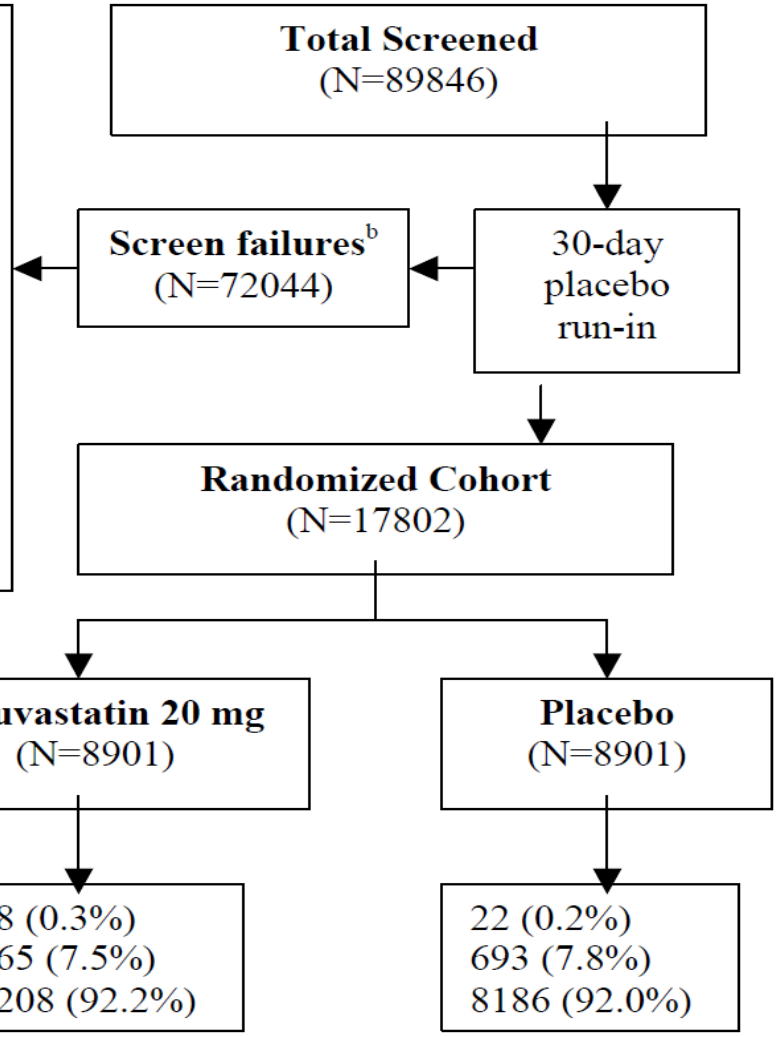
Disposition of study subjects

Reason for exclusion	%
Investigator's discretion	<1
Did not meet incl/excl criteria	92
Approx 52% excluded for LDL-C[a]	
Approx 36% excluded for hsCRP[a]	
No information	<1
Lost to follow-up	<1
Adverse event	<1
Protocol non-compliance	<1
Informed consent withdrawn	5
Other reason	<1



Disposition of study subjects

- Median duration of follow-up was 2 years
- Discontinuation of study medication occurred in 19.2% and 21.6% of rosuvastatin and placebo groups respectively
- Study withdrawal or lost-to-follow up status occurred in 7.8% and 8% of rosuvastatin and placebo groups respectively

JUPITER: BASELINE CHARACTERISTICS	Rosuvastatin 20 mg N=8901	Placebo N=8901
Males, n (%)	5475 (61.5)	5526 (62.1)
Age (years)	66.0 (7.64)	66.0 (7.79)
Caucasian, n (%) Black Hispanic Asian	6358 (71.4) 1100 (12.4) 1121 (12.6) 147 (1.7)	6325 (71.1) 1124 (12.6) 1140 (12.8) 136 (1.5)
Body mass index, kg/m^2	29.1 (6.69)	29.0 (5.67)
BMI >25 kg/m^2, n (%)	6826 (76.7)	6839 (76.8)
Systolic BP, mmHg	135.6 (16.75)	135.6 (16.79)
Diastolic BP, mmHg	80.7 (9.09)	80.7 (8.96)
Fasting serum glucose ≥ 100 mg/dL, n (%)	2755 (31.0)	2817 (31.6)
Metabolic syndrome, n (%)	3652 (41.0)	3725 (41.8)

Baseline Characteristics

JUPITER: BASELINE CHARACTERISTICS	Rosuvastatin 20 mg N=8901	Placebo N=8901
Framingham risk score Mean (SD)	11.6 (7.0)	11.6 (6.9)
Framingham risk category		
Low, n (%)	3615 (40.6)	3602 (40.5)
Intermediate, n (%)	4485 (50.4)	4516 (50.7)
High, n (%)	786 (8.8)	772 (8.7)

Major ATP-III risk factors present at baseline

Major risk factor	Rosuvastatin 20 mg n (%)	Placebo n (%)
Smoking (last month)	1400 (15.7)	1420 (16.0)
Hypertension (BP≥140/90 or on antihypertensives	5079 (57.1)	5129 (57.6)
Low HDL (<40 mg/dL)	1980 (22.2)	2023 (22.7)
Family history of premature CHD	997 (11.2)	1048 (11.8)
Age (men≥45y, women≥55 y)	8901 (100.0)	8901 (100.0)

HDL ≥60 mg/dL at baseline was present in 25% of rosuvastatin and placebo treated subjects

Number of ATP-III risk factors present at baseline

Total number of risk factors	Rosuvastatin 20 mg n (%)	Placebo n (%)
1 risk factor (age only)	2199 (24.7)	2080 (23.4)
2 risk factors	4373 (49.1)	4423 (49.7)
3 risk factors	1931 (21.7)	2017 (22.7)
4 risk factors	371 (4.2)	361 (4.1)
5 risk factors	27 (0.3)	20 (0.2)

Baseline lipoprotein/hsCRP

	Rosuvastatin 20 mg Mean (SD)	Placebo Mean (SD)
LDL (mg/dL)	104 (18.9)	105 (18.5)
hsCRP (mg/L) **Mean (SD)** **Median**	 6.6 (8.6) 4.2	 6.9 (9.2) 4.3
HDL (mg/dL)	51 (15.3)	51 (15.2)
Total cholesterol (mg/dL)	183 (24.7)	183 (24.2)
Triglycerides (mg/dL)	138 (73.4)	138 (73.5)
Apolipoprotein B (mg/dL)	109 (21.7)	109 (21.0)

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Primary efficacy endpoint

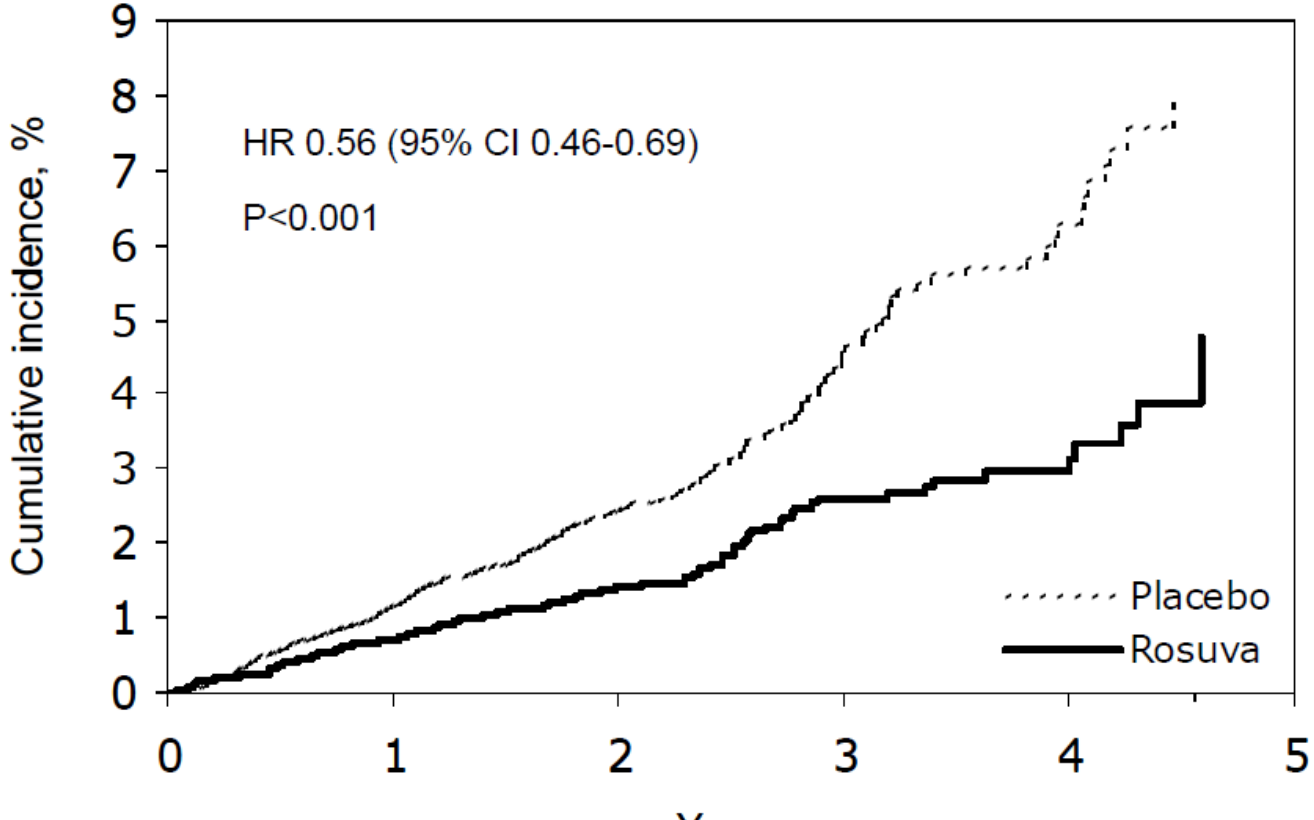
- Time to first event of the cardiovascular composite of:
  - Cardiovascular death
  - Non-fatal myocardial infarction
  - Non-fatal stroke
  - Hospitalization for unstable angina
  - Arterial revascularization

Number of Subjects with any Event		Event rate/1000 patient years		Hazard ratio (95% CI) p-value	Relative risk reduction	Absolute risk reduction	Number needed to treat
Rosuvastatin N=8901 n (%)	Placebo N=8901 n (%)	Rosuvastatin	Placebo				
142 (1.6)	252 (2.8)	7.6	13.6	0.56 (0.46, 0.69) <0.001	44%	1.2%	83

FDA analysis of NNT using Kaplan-Meier estimates

	Rosuvastatin Survival probablities	**Placebo** Survival probabilities	**NNT (95%CI)**
Year 1	0.993	0.998	200 (128, 460)
Year 2	0.986	0.975	91 (65, 153)
Year 3	0.974	0.954	50 (33, 100)
Year 4	0.968	0.937	32 (22, 60)

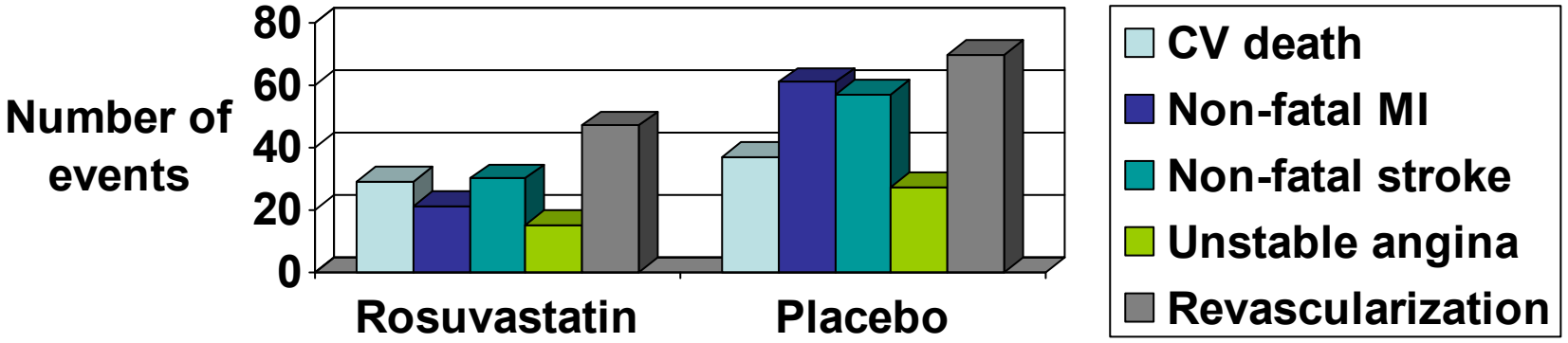
Kaplan-Meier curve of time to primary composite endpoint



Number at risk

RSV	8901	8412	3892	1352	543	156
Placebo	8901	8353	3872	1333	534	173

First MCE distribution of composite



First MCE of the composite	142	252
• Cardiovascular death	29	37
• Non-fatal MI	21	61
• Non-fatal stroke	30	57
• Hospitalized unstable angina	15	27
• Arterial revascularization	47	70

Individual components of primary endpoint

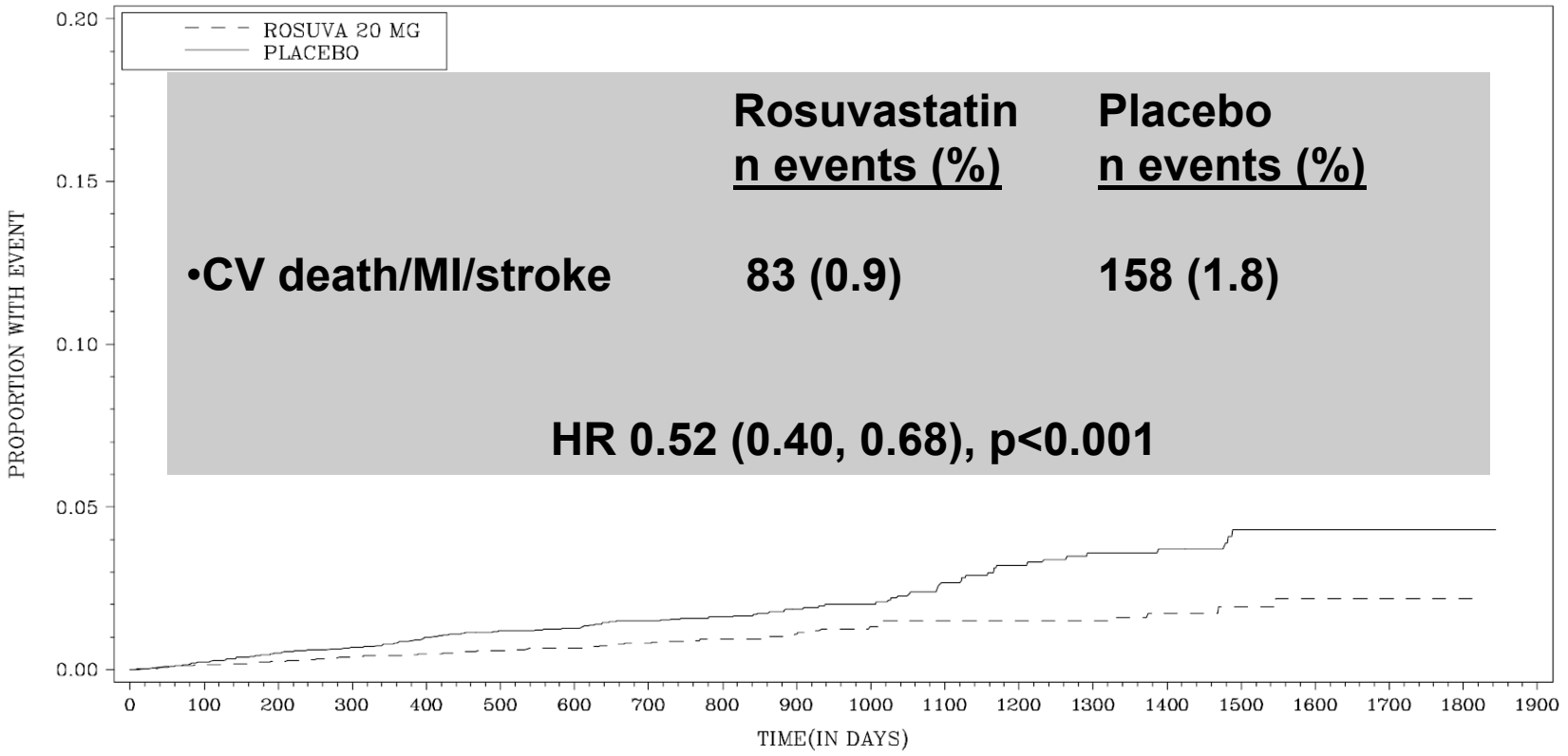
Endpoint	Rosuva n (%)	Placebo n (%)	HR	95% CI	p-value
Cardiovascular death	35 (0.4)	44 (0.5)	0.80	0.51, 1.24	0.315
Non-fatal stroke	30 (0.3)	58 (0.7)	0.52	0.33, 0.80	0.003
Non-fatal MI	22 (0.2)	62 (0.7)	0.35	0.22, 0.58	<0.001
Hospitalization unstable angina	16 (0.2)	27 (0.3)	0.59	0.32, 1.10	0.093
Arterial revascularization	71 (0.8)	131 (1.5)	0.54	0.41, 0.72	<0.001
Coronary	50 (0.6)	101 (1.1)	0.50	0.35, 0.69	<0.001
Peripheral	17 (0.2)	28 (0.3)	0.61	0.33, 1.12	0.105
Carotid	6 (0.1)	4 (<0.1)	1.52	0.43, 5.37	0.515

Breakdown of total cardiovascular deaths

	Rosuvastatin	Placebo
Total cardiovascular deaths	**35**	**44**
Fatal MI	9	7
Fatal stroke	5	9
Sudden death	9	18
Other	12	10

Other category includes cases where the investigator recorded the cause of death as “unstable angina”, “procedure related, including revascularization”, or “other cardiovascular death of unknown etiology”.

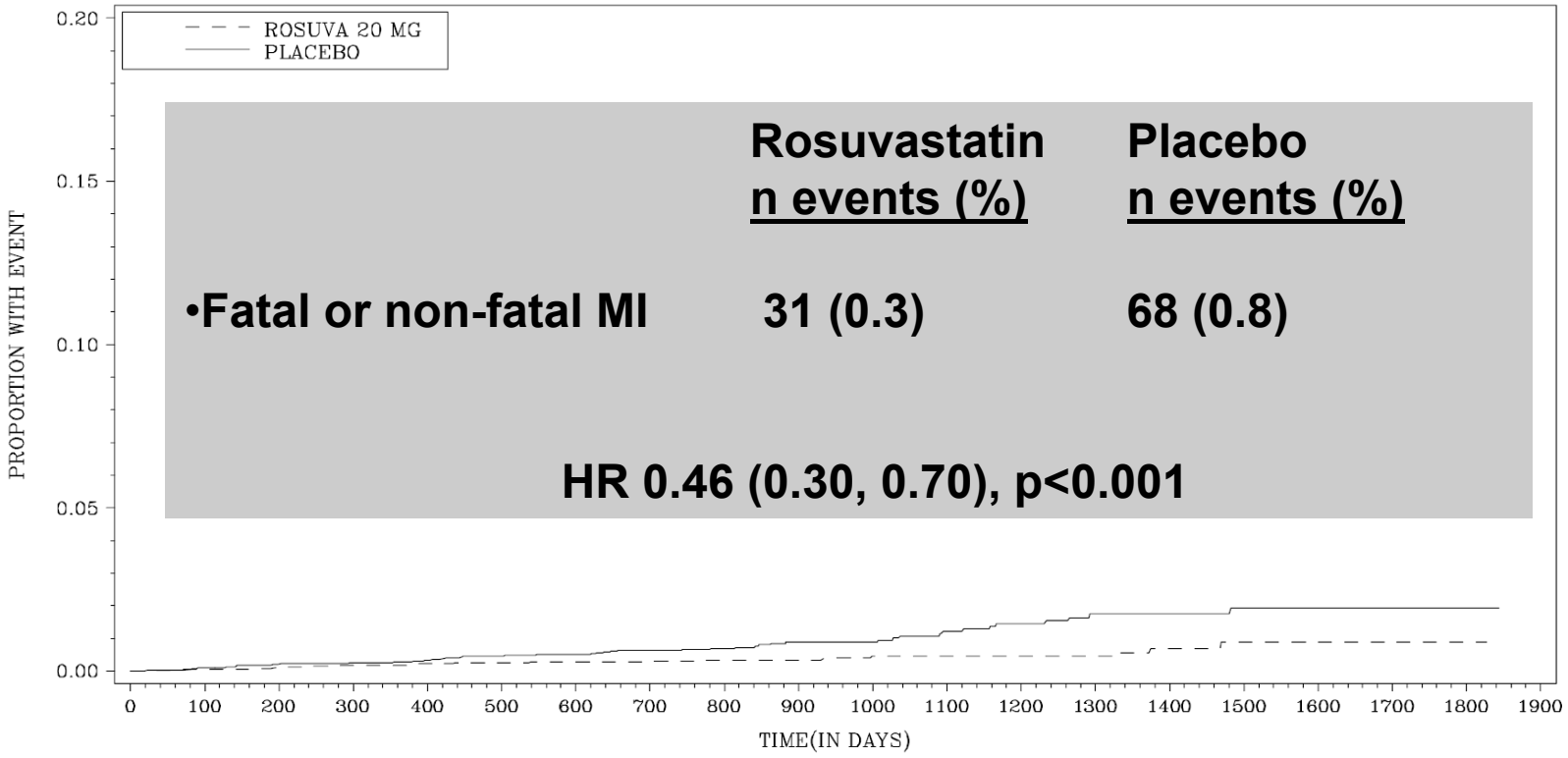
CV death/MI/stroke composite



	Rosuvastatin n events (%)	Placebo n events (%)
•CV death/MI/stroke	83 (0.9)	158 (1.8)

HR 0.52 (0.40, 0.68), p<0.001

Fatal or non-fatal MI composite

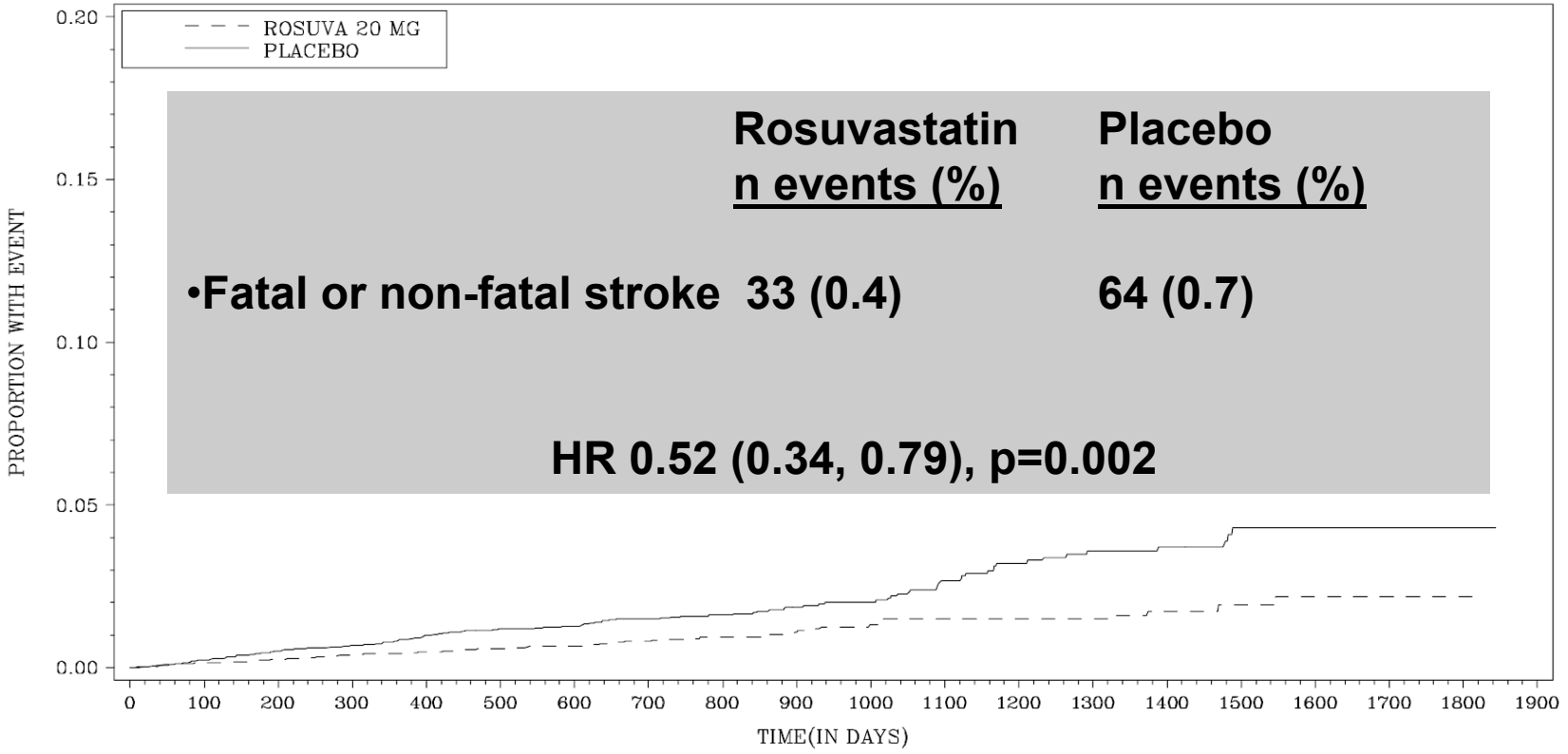


	Rosuvastatin n events (%)	Placebo n events (%)
•Fatal or non-fatal MI	31 (0.3)	68 (0.8)

HR 0.46 (0.30, 0.70), p<0.001

9 fatal MI in the rosuvastatin group and 6 fatal MI in the placebo group

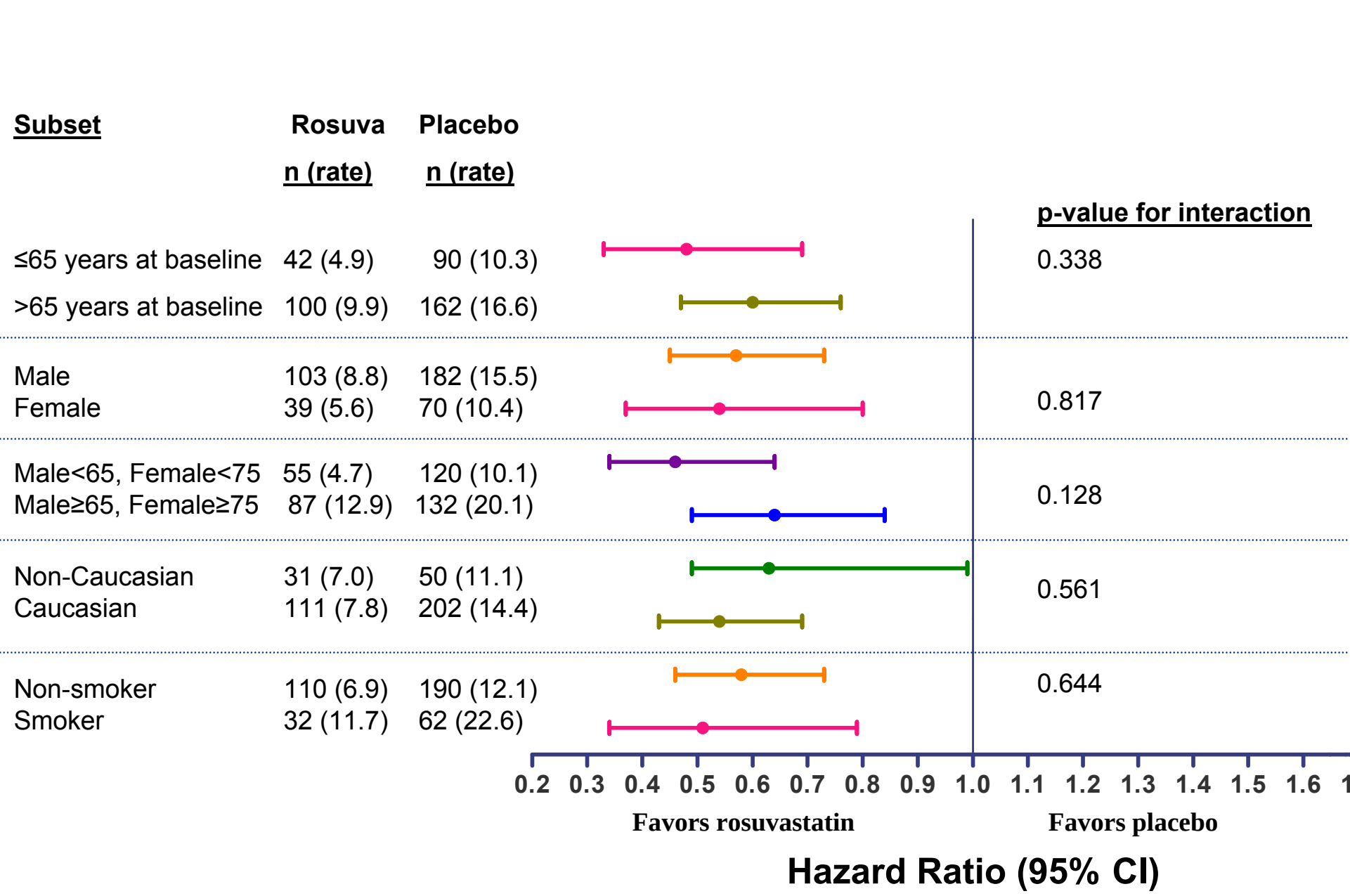
Fatal or non-fatal stroke composite



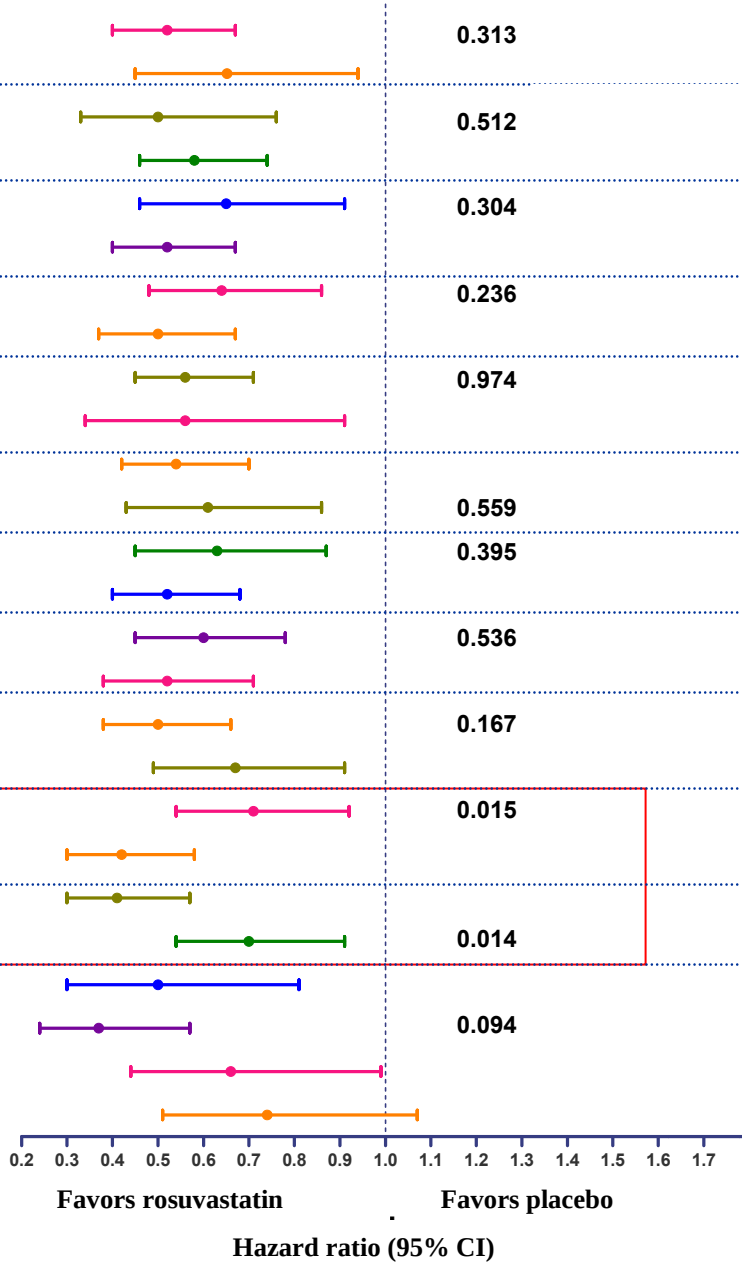
	Rosuvastatin n events (%)	Placebo n events (%)
•Fatal or non-fatal stroke	33 (0.4)	64 (0.7)

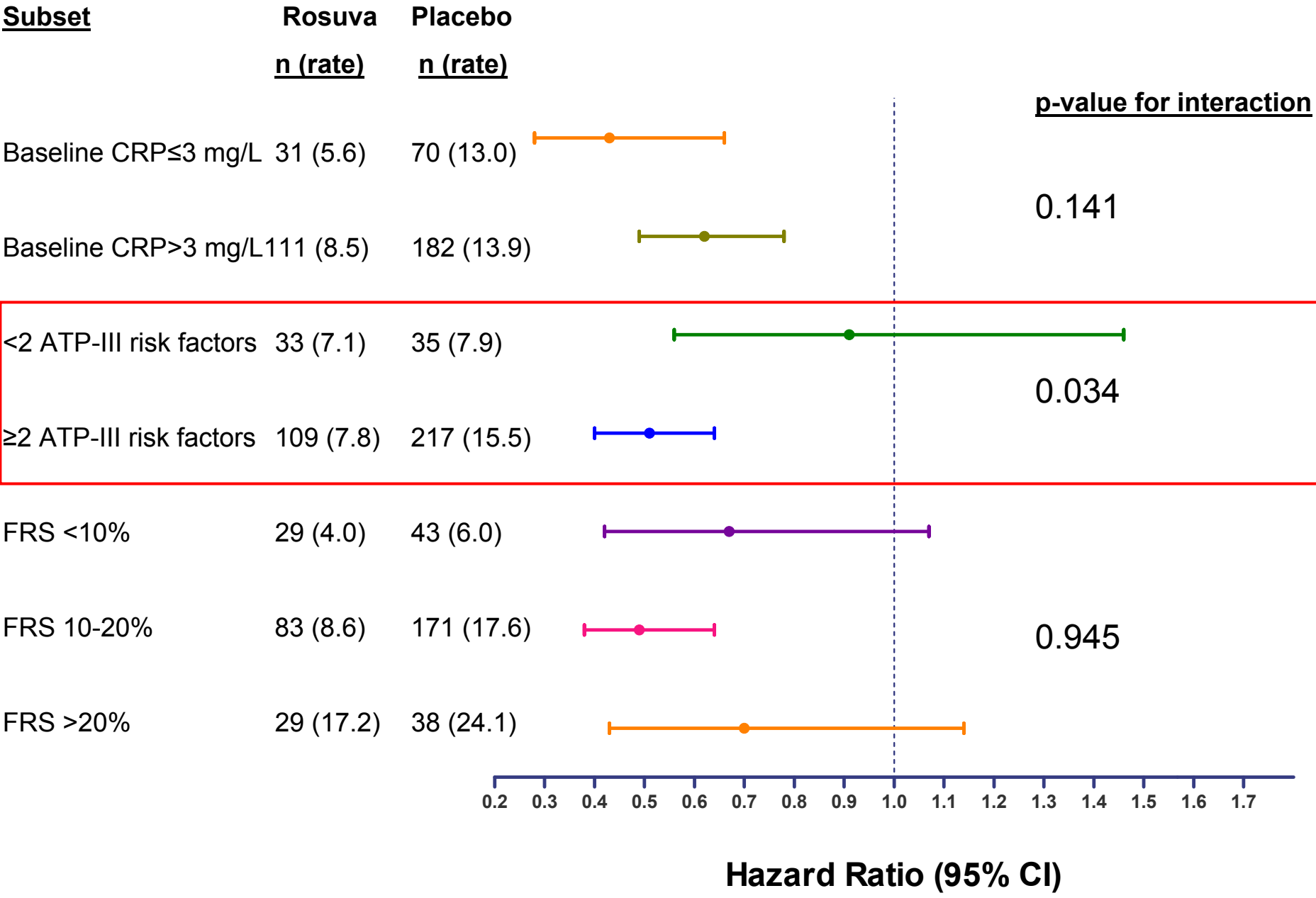
HR 0.52 (0.34, 0.79), p=0.002

3 fatal strokes in the rosuvastatin group and 6 in the placebo group


Subset
Rosuva
n (rate)
Placebo
n (rate)
p-value for interaction
≤65 years at baseline 42 (4.9) 90 (10.3) 0.338
>65 years at baseline 100 (9.9) 162 (16.6)
Male 103 (8.8) 182 (15.5)
Female 39 (5.6) 70 (10.4) 0.817
Male<65, Female<75 55 (4.7) 120 (10.1)
Male≥65, Female≥75 87 (12.9) 132 (20.1) 0.128
Non-Caucasian 31 (7.0) 50 (11.1)
Caucasian 111 (7.8) 202 (14.4) 0.561
Non-smoker 110 (6.9) 190 (12.1)
Smoker 32 (11.7) 62 (22.6) 0.644
0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0 1.1 1.2 1.3 1.4 1.5 1.6
Favors rosuvastatin
Favors placebo
Hazard Ratio (95% CI)

Subset	Rosuva n (rate)	Placebo n (rate)	interaction
BMI ≤30	94 (8.2)	179 (15.9)	0.313
BMI>30	47 (6.6)	73 (10.2)	
HDL <40 mg/dL	32 (7.6)	65 (15.3)	0.512
HDL ≥ 40 mg/dL	110 (7.7)	187 (13.1)	
LDL ≤100 mg/dL	55 (8.7)	86 (13.5)	0.304
LDL >100 mg/dL	87 (7.1)	166 (13.7)	
Below median LDL	74 (8.3)	114 (13.1)	0.236
Above median LDL	68 (7.0)	138 (14.1)	
Triglycerides <200 mg/dL	117 (7.6)	208 (13.6)	0.974
Triglycerides ≥200 mg/dL	25 (7.7)	44 (13.7)	
HTN	89 (8.5)	166 (15.8)	
No HTN	53 (6.6)	86 (10.8)	0.559
US	58 (10.7)	94 (16.9)	0.395
Countries other than US	84 (6.4)	158 (12.2)	
US or Canada	81 (9.7)	137 (16.3)	0.536
Countries other than US/Canada	61 (6.0)	115 (11.4)	
Metabolic syndrome NO	75 (6.9)	149 (14.0)	0.167
Metabolic syndrome YES	67 (8.7)	102 (13.1)	
Above median CRP	89 (9.7)	128 (13.7)	0.015
Below median CRP	53 (5.6)	124 (13.5)	
CRP ≤4 mg/L	50 (5.6)	119 (13.8)	
CRP >4 mg/L	92 (9.5)	133 (13.5)	0.014
Below median LDL and CRP	24 (5.6)	47 (11.3)	
Above median LDL and below median CRP	29 (5.7)	77 (15.3)	0.094
Above median LDL and CRP	39 (8.5)	61 (12.8)	
Below median LDL and above median CRP	50 (10.9)	67 (14.7)	

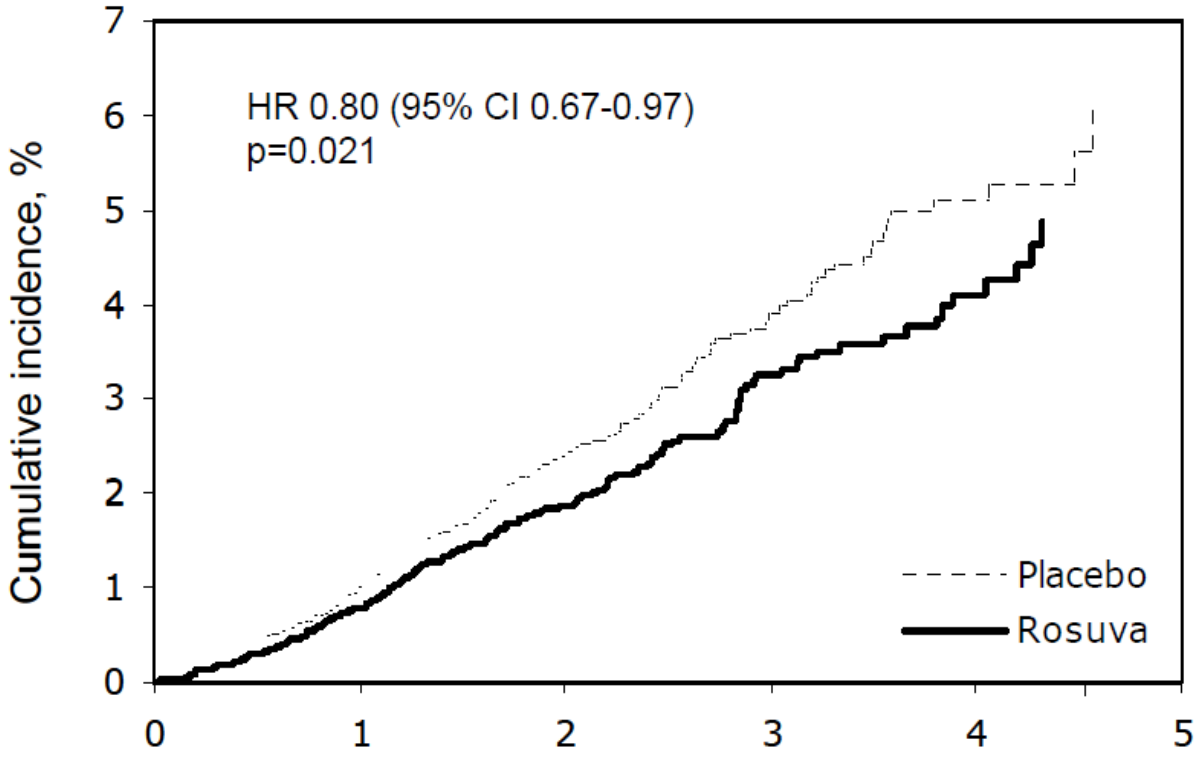



Subset
Rosuva
n (rate)
Placebo
n (rate)
p-value for interaction
Baseline CRP≤3 mg/L 31 (5.6) 70 (13.0)
0.141
Baseline CRP>3 mg/L 111 (8.5) 182 (13.9)
<2 ATP-III risk factors 33 (7.1) 35 (7.9)
0.034
≥2 ATP-III risk factors 109 (7.8) 217 (15.5)
FRS <10% 29 (4.0) 43 (6.0)
FRS 10-20% 83 (8.6) 171 (17.6)
0.945
FRS >20% 29 (17.2) 38 (24.1)
0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0 1.1 1.2 1.3 1.4 1.5 1.6 1.7
Hazard Ratio (95% CI)

Secondary endpoints

- Total mortality
- Non-cardiovascular mortality
- Incident diabetes mellitus
- Venous thromboembolic events
- Bone fractures

Kaplan-Meier curve of time to death (total mortality) including external vital status data



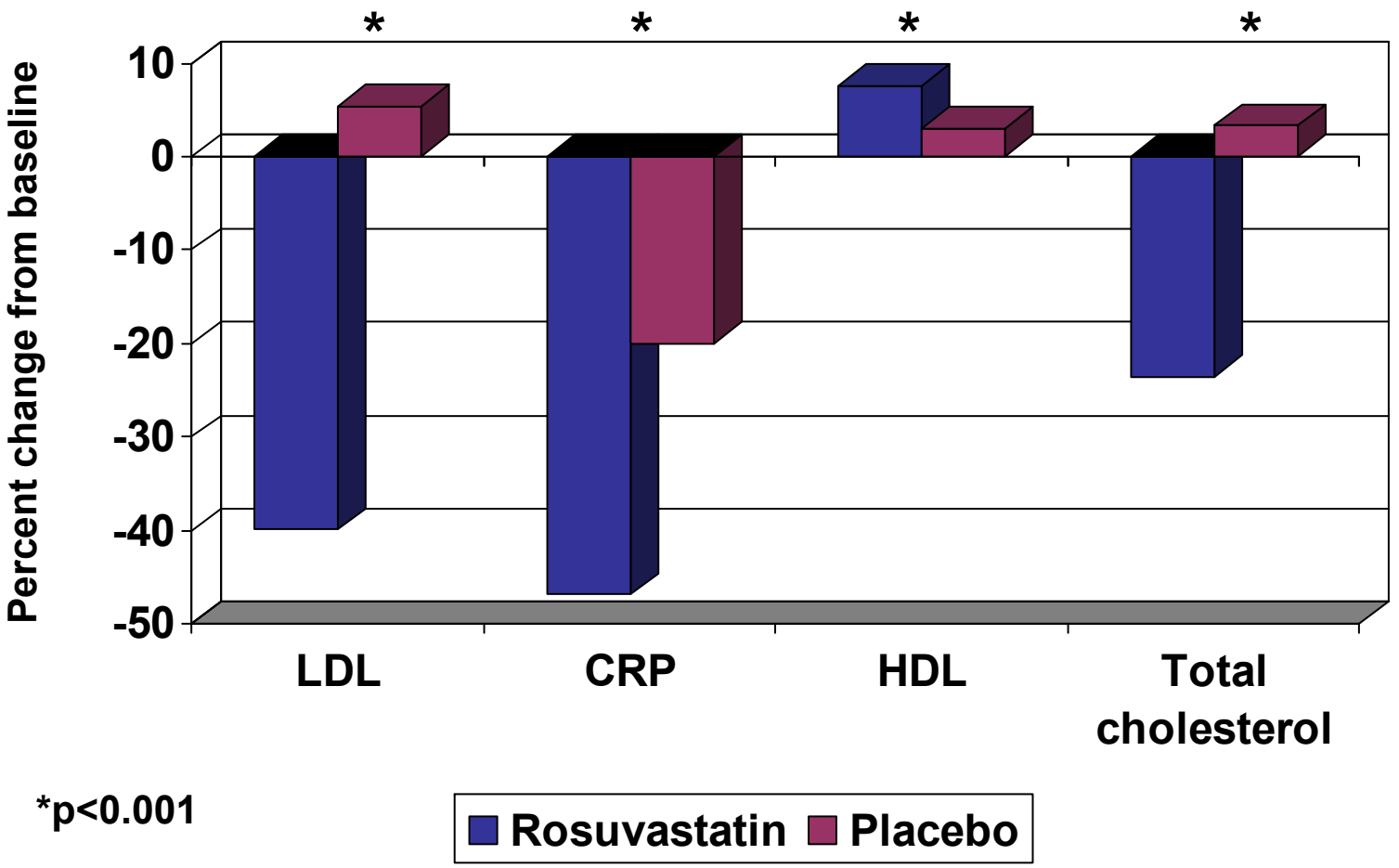
Number at risk

RSV	8901	8787	4313	1601	682	226
Placebo	8901	8782	4323	1613	683	245

Other secondary endpoints

	Rosuvastatin N=8901	Placebo N=8901	HR (95% CI)	p-value
Venous thromboembolic events	26 (0.3)	46 (0.5)	0.57 (0.35, 0.91)	0.018
Non-cardiovascular death	105 (1.2)	126 (1.4)	0.84 (0.64, 1.08)	0.172
New bone fractures	226 (2.5)	214 (2.4)	1.06 (0.88, 1.28)	0.548

Lipoproteins (mean) and hsCRP (median) percent change from baseline at Year 1



*p<0.001

JUPITER efficacy conclusions

- Rosuvastatin 20 mg daily resulted in a 44% reduction in relative risk and 1.2% reduction in absolute risk of major cardiovascular events in subjects with LDL <130 mg/dL, hsCRP ≥2 mg/L, and at least one major ATP-III risk factor relative to placebo

JUPITER efficacy conclusions

- The three pre-specified secondary outcomes
  - Cardiovascular death/MI/stroke,
  - Fatal or non-fatal MI,
  - Fatal or non-fatal stroke

  which controlled for Type I error, demonstrated a significant reduction in events in the rosuvastatin-treated group compared to the placebo-treated group

JUPITER efficacy conclusions

- The individual components of cardiovascular death and hospitalization for unstable angina did not reach statistical significance, although the numbers trended in favor of rosuvastatin

- In subjects with no ATP-III risk factors except age a significant treatment benefit was not observed

- The analysis for the secondary outcome variable total mortality, which did not control for Type 1 error, achieved a nominal p-value of 0.02

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- JUPITER study rationale
- JUPITER trial
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JUPITER rosuvastatin exposure

- Overall, mean exposure 1.9 years for both rosuvastatin and placebo treatment groups
- In U.S. mean exposure was 2.4 years in rosuvastatin group and 2.3 years in placebo group

Adverse Events

Event category	Rosuvastatin 20 mg N=8901 n (%)	Placebo N=8901 n (%)
Any adverse event (AE)	6968 (78.3)	6907 (77.6)
AE leading to death	141 (1.6)	179 (2.0)
Serious AE	1341 (15.1)	1372 (15.4)
Withdrawal due to AE	143 (1.6)	158 (1.8)

- Musculoskeletal disorders (myalgia) most common reason for study withdrawal

Adverse events of interest

- Hepatic
- Musculoskeletal
- Renal
- Neoplastic

	Rosuvastatin 20 mg N=8901 n (%)	Placebo N=8901 n (%)
Any hepatic-related adverse event	**216 (2.4)**	**186 (2.1)**
AST >3x ULN and/or ALT>3x ULN	124 (1.4)	88 (1.0)
ALT>3x ULN on 2 consecutive occasions	23 (0.3)	17 (0.2)
ALT increased	127 (1.4)	93 (1.0)
Hepatic cirrhosis	3 (0.03)	4 (0.04)
Hepatitis	3 (0.03)	2 (0.02)
Chronic hepatic failure	2 (0.02)	0
Hepatic failure	0	2 (0.02)

- HPS (10269 subjects 40 mg simvastatin) ALT 2-4x ULN occurred in 1.35%
- In a report funded by the company in controlled trials with rosuvastatin, 0.2% of over 10,000 subjects exposed to rosuvastatin 5-40 mg experienced a clinically significant ALT elevation
- AFCAPS/TexCAPS 0.6% of subjects with clinically significant ALT or AST elevation
- No Hy's law cases reported

	Rosuvastatin 20 mg N=8901 n (%)	Placebo N=8901 n (%)
Any muscle-related adverse event	**1421 (16.0)**	**1375 (15.4)**
Myalgia	714 (8.0)	639 (7.2)
Myositis	9 (0.1)	8 (0.1)
Myopathy	0	1 (0.01)
Rhabdomyolysis	1 (<0.1)	0
Blood creatine phosphokinase increased	61 (0.7)	34 (0.4)
CK >10x ULN	2 (0.02)	1 (0.01)

- 0.1% simvastatin-treated subjects in HPS and 0.7% lovastatin-treated subjects in AFCAPS/TexCAPS experienced CK >10x ULN
- No cases of myopathy in the rosuvastatin group (muscle symptoms and CK>10x ULN)
- One case of rhabdomyolysis reported CK of 13,000, baseline creatinine 1.3 to 1.5 mg/dL, concomitant influenza and immobility

	Rosuvastatin 20 mg N=8901 n (%)	Placebo N=8901 n (%)
Any renal-related AE	**535 (6.0)**	**480 (5.4)**
Hematuria	241 (2.7)	203 (2.3)
Proteinuria	149 (1.7)	127 (1.4)
Renal failure	25 (0.3)	23 (0.3)
Renal failure chronic	23 (0.3)	28 (0.3)
Renal failure acute	19 (0.2)	16 (0.2)
Creatinine >100% above baseline	16 (0.2)	10 (0.1)

	Rosuvastatin 20 mg (N=8901)		Placebo (N=8901)	
	N	n (%)	N	n (%)
Urine protein				
Increase at any time	8031	290 (3.6)	8065	236 (2.9)
Persistent[a]	7803	19 (0.2)	7816	17 (0.2)
Urine blood				
Increase at any time	8150	415 (5.1)	8149	339 (4.2)
Persistent[a]	7921	38 (0.5)	7890	28 (0.4)

[a] Persistent is defined as subjectw with a change from none or trace at baseline to ++ or greater at the last 2 post-baseline visits.

- Conflicting reports of statin use associated with increased versus a null/decreased effect on cancer incidence

	Rosuvastatin 20 mg N=8901 n (%)	Placebo N=8901 n (%)
Cancer deaths	40 (0.4)	65 (0.7)
Non-fatal neoplastic SAE	258 (2.9)	261 (2.9)
Any neoplastic AE	608 (6.8)	676 (7.6)
Neoplastic SAE in subjects with LDL <50 mg/dL	104/4154 (2.5%)	9/232 (3.9%)

Shepherd et al. Lancet 2002;360:1623-30
Sacks et al NEJM 1996; 335:1001-09
Poynter et al. NEJM 2005; 352:2184-92
Cholesterol Treatment Trialists (CTT) Collaborators. Lancet 2005;366:1267-78
Dale et al. JAMA 2006; 295;74-80

Neurocognitive adverse events

- Memory loss listed in CRESTOR's postmarketing adverse event section
- FDA has received MedWatch reports of memory loss and compelling anecdotal reports with statin use

Neurocognitive adverse events

Preferred term	Rosuvastatin 20mg N=8901 n (%)	Placebo N=8901 n (%)
Nervous system disorders (selected)	**69 (0.8)**	**76 (0.9)**
Amnesia	30 (0.3)	33 (0.4)
Memory impairment	18 (0.2)	16 (0.2)
Dementia	12 (0.1)	9 (0.1)
Dementia Alzheimer's type	7 (0.1)	7 (0.1)
Disturbance in attention	3 (<0.1)	1 (<0.1)
Amnestic disorder	2 (<0.1)	1 (<0.1)
Global amnesia	2 (<0.1)	1 (<0.1)
Senile dementia	1 (<0.1)	2 (<0.1)
Cognitive disorder	0	6 (0.1)
Vascular dementia	0	1 (<0.1)

Preferred term	Rosuvastatin 20mg N=8901 n (%)	Placebo N=8901 n (%)
Psychiatric disorders (selected)	**515 (5.8)**	**533 (6.0)**
Insomnia	226 (2.5)	208 (2.3)
Depression	184 (2.1)	214 (2.4)
Anxiety	128 (1.4)	157 (1.8)
Confusional state	18 (0.2)	4 (<0.1)
Depressed mood	12 (0.1)	12 (0.1)
Nervousness	8 (0.1)	7 (0.1)
Generalized anxiety disorder	2 (<0.1)	1 (<0.1)
Major depression	2 (<0.1)	0
Suicidal ideation	2 (<0.1)	0
Completed suicide	1 (<0.1)	1 (<0.1)
Suicide attempt	1 (<0.1)	0
Depression suicidal	0	1 (<0.1)
Depressive symptom	0	1 (<0.1)
Initial insomnia	0	1 (<0.1)
Personality change	0	1 (<0.1)

"Confusional state"

- 18 rosuvastatin-treated versus 4 placebo-treated subjects reported a confusional state
- Overall the narratives for these cases are uninformative with respect to assessing drug causality
- JUPITER not designed to measure neurocognitive function
  - No systematic, active assessment
- Clinical significance of the imbalance is unclear, but given prior statin data, may represent a signal worthy of more rigorous evaluation
  - This would apply to all statins

Gastrointestinal disorders

Gastrointestinal AE leading to death

- There were 13 deaths in the rosuvastatin-treated group compared to 1 in the placebo-treated group
  - Two deaths were miscoded in rosuvastatin group
- Of the remaining 11 deaths in the rosuvastatin group
  - 10 men, 1 woman
  - Four deaths occurred in the U.S.
  - Age range 57 to 87 years old
  - Mean time on study 308 days (range 72-1052)

Gastrointestinal AE leading to death

Preferred term MISCODED	Rosuvastatin N=8901 n (%)	Placebo N=8901 n (%)
Any GI adverse event leading to death	13 (0.1)	1 (0.0)
Gastrointestinal hemorrhage	2 (0.0)	0
Pancreatitis acute	2 (0.0)	0
Peritonitis	2 (0.0)	1 (0.0)
Abdominal pain	1 (0.0)	0
Duodenal ulcer	1 (0.0)	0
Gastroesophageal reflux disease	1 (0.0)	0
Inguinal hernia	1 (0.0)	0
Intestinal obstruction	1 (0.0)	0
Intra-abdominal hemorrhage	1 (0.0)	0
Esophageal hemorrhage	1 (0.0)	0
Esophageal rupture	1 (0.0)	0

POST-OPERATIVE COMPLICATION

Preferred term	Rosuvastatin N=8901 n (%)	Placebo N=8901 n (%)
Any GI adverse event leading to death	11 (0.1)	1 (0.0)
Gastrointestinal hemorrhage	2 (0.0)	0
Pancreatitis acute	2 (0.0)	0
Peritonitis	2 (0.0)	1 (0.0)
Abdominal pain	1 (0.0)	0
Inguinal hernia	1 (0.0)	0
Intestinal obstruction	1 (0.0)	0
Intra-abdominal hemorrhage	1 (0.0)	0
Esophageal hemorrhage	1 (0.0)	0
Esophageal rupture	1 (0.0)	0

Preferred term	Rosuvastatin N=8901 n (%)	Comments
Gastrointestinal hemorrhage	2 (0.0)	•57 M, coffee ground emesis, hiatal hernia, esophagitis •59 M, off RSV 66 days. On Cox-2 inhibitor, acenocoumarin
Pancreatitis acute	2 (0.0)	•62 M, hospitalized with N/V, elevated lipase, abd pain, arrested during central line placement •83 M, hospitalized with abd pain, elevated amylase, new afib, met acidosis
Peritonitis	2 (0.0)	•62 M, hospitalized with N/V, elevated lipase, abd pain, arrested during central line placement •61 F, HTN arthritis
Abdominal pain	1 (0.0)	•69 M, diagnosed with liver cancer
Intestinal obstruction	1 (0.0)	•57 M, diagnosed with gastric cancer
Esophageal hemorrhage	1 (0.0)	•59 M, alcoholic cirrhosis, recurrent esophageal bleed
Esophageal rupture	1 (0.0)	•68 M, longstanding GERD, died at home, autopsy report esophageal rupture

Gastrointestinal AE leading to death

- In the two-year, placebo-controlled study of rosuvastatin, METEOR, there were no deaths attributed to gastrointestinal disorders in either the rosuvastatin group or the placebo group.
- In the five-year, placebo-controlled trial, CORONA, five (0.2%) deaths and 22 (0.9%) deaths in the rosuvastatin and placebo treatment groups, respectively were attributed to a gastrointestinal cause.
- AURORA, a placebo-controlled trial in subjects with ESRD, an equal number of deaths, 29 (2.1%) occurred in both rosuvastatin (10 mg) and placebo groups.

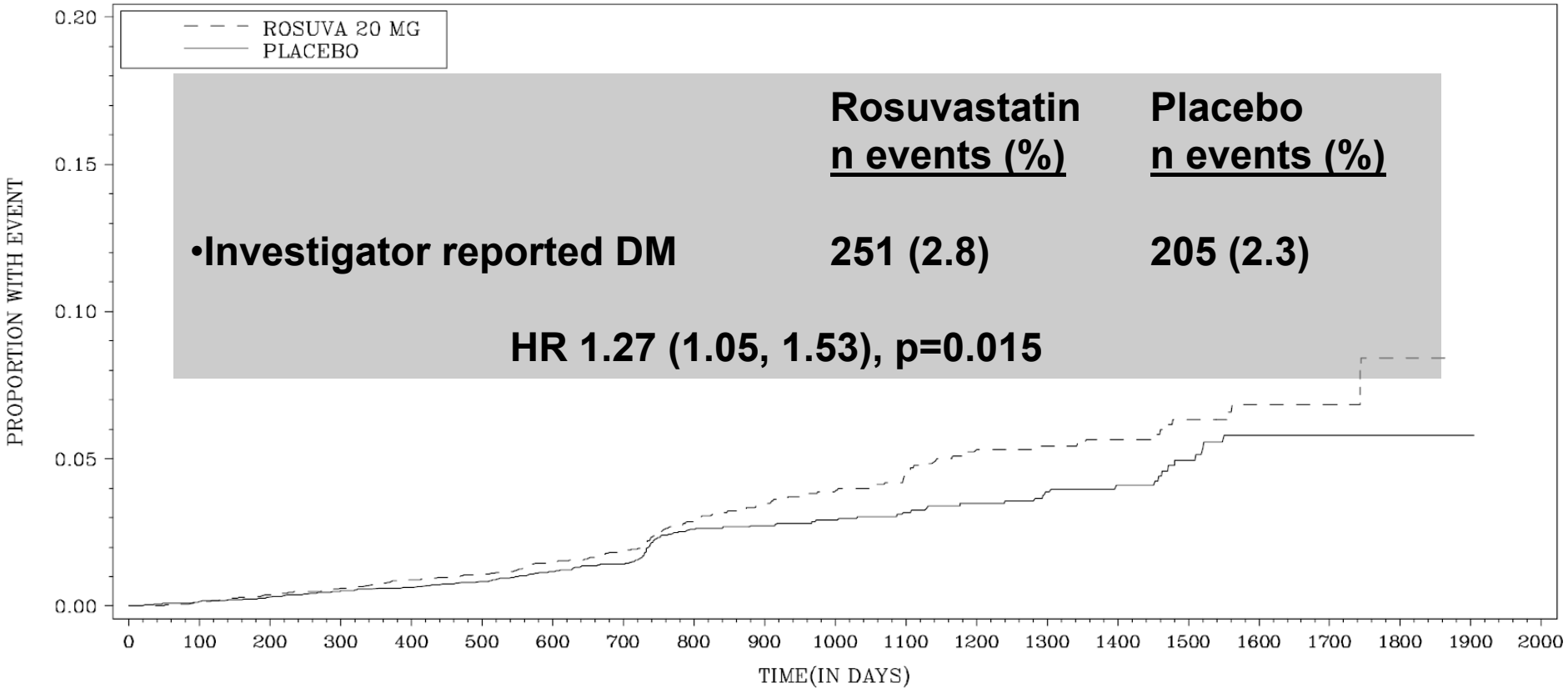
Investigator-reported diabetes mellitus

- Pre-specified but not adjudicated endpoint
- WOSCOPS trial a 30% reduction in incident diabetes (pravastatin)
- ASCOT-LLA development of diabetes mellitus (HR 1.15, 0.91-1.44, p-value 0.2493)

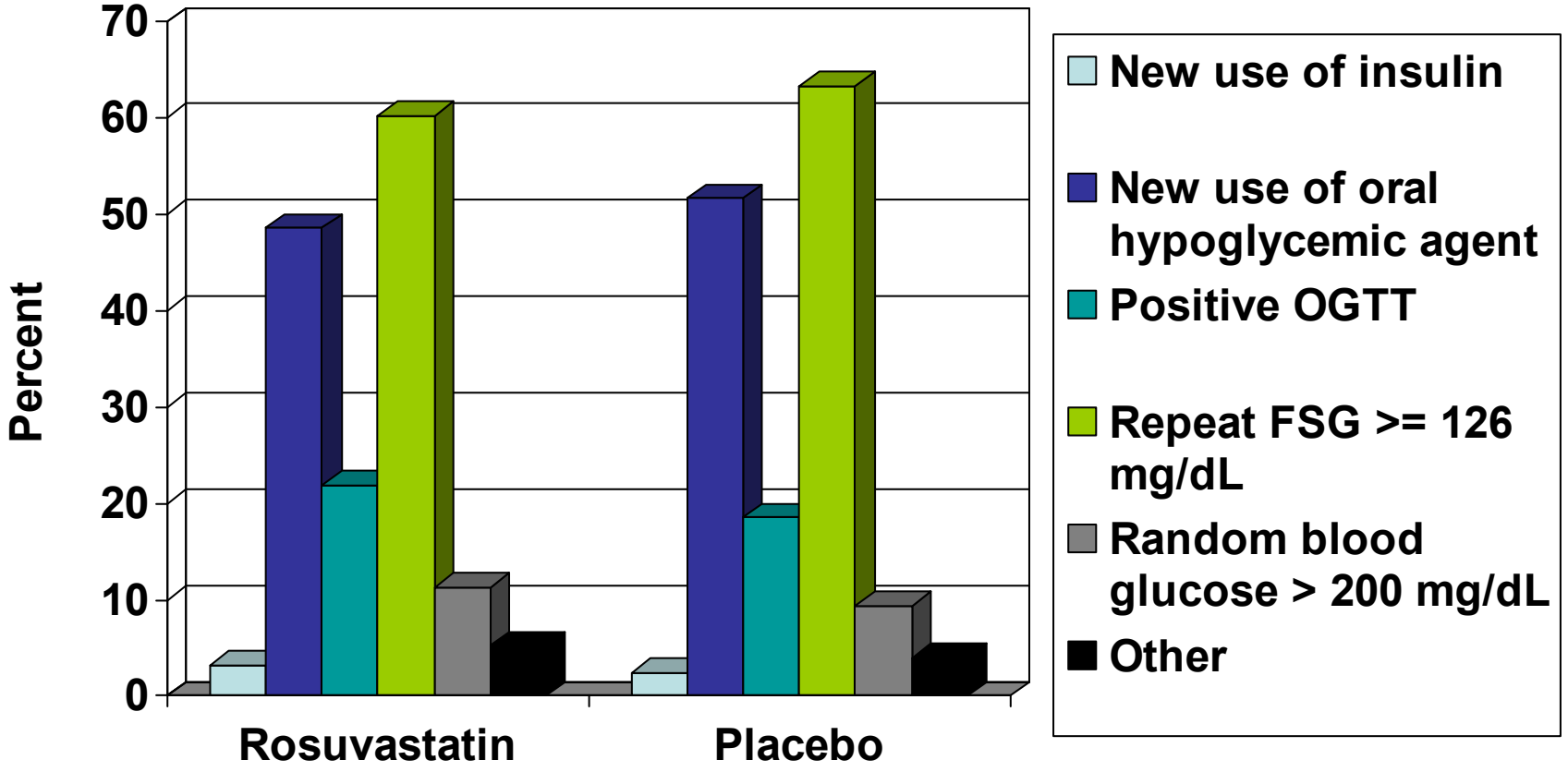
Pre-specified secondary efficacy endpoint

	Rosuvastatin n events (%)	Placebo n events (%)
•Investigator reported DM	251 (2.8)	205 (2.3)

HR 1.27 (1.05, 1.53), p=0.015



Criteria for investigator-reported DM
(unadjudicated)

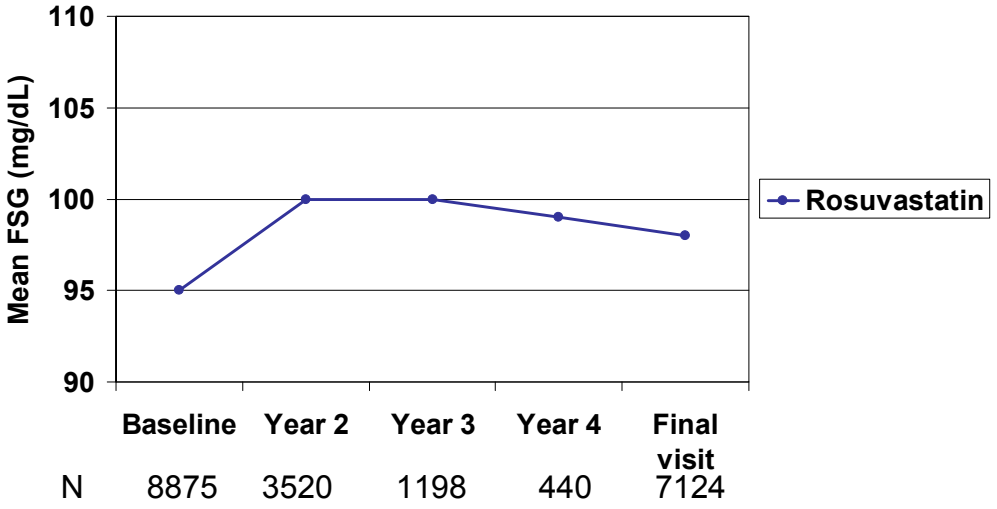


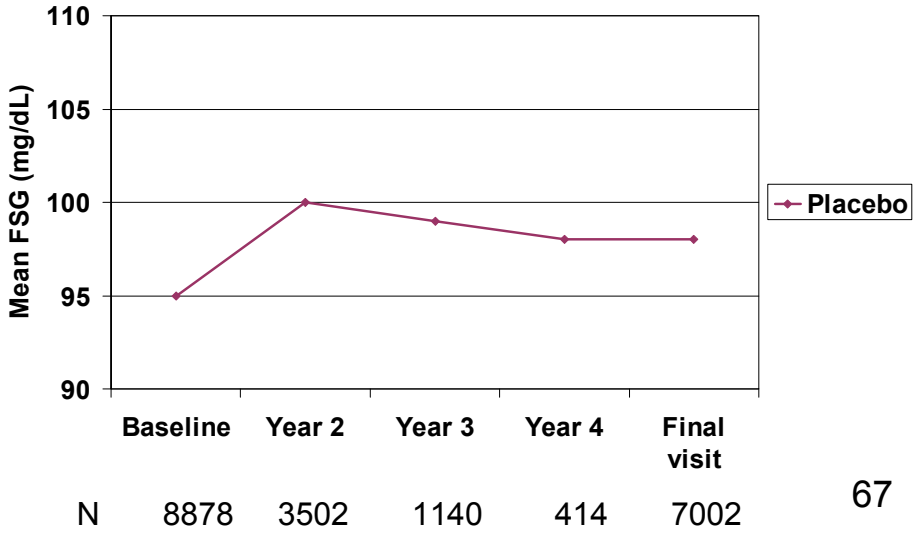
Characteristics of subjects who did or did not develop diabetes

Baseline characteristics	Diabetes		No diabetes	
	Rosuvastatin	Placebo	Rosuvastatin	Placebo
N	251	205	8650	8696
FSG≥100 mg/dl, %	76.5	76.1	29.6	30.6
BMI ≥ 25 kg/m^2, %	92.4	91.7	76.3	76.6
Triglycerides ≥ 150 mg/dL, %	57.0	51.7	31.9	32.5
Metabolic syndrome, %	77.7	79.0	40.0	41.0

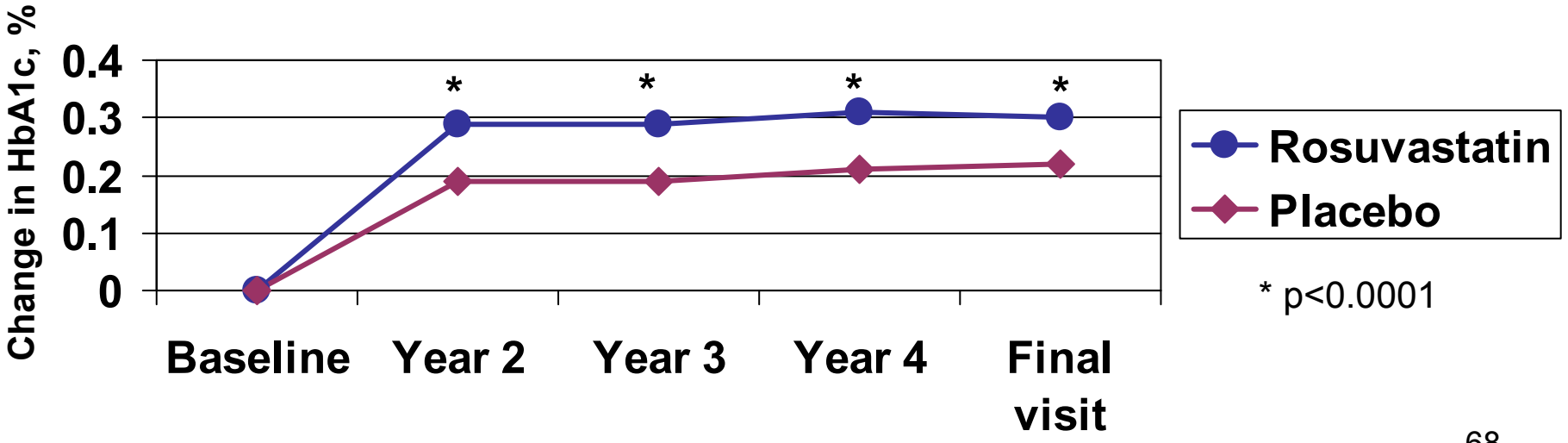
- Both the rosuvastatin- and placebo-treated subjects who developed diabetes had less weight gain compared to baseline than subjects who did not develop diabetes.
  - Diabetes: Rosuva 0.10 kg, Placebo -0.96 kg
  - No diabetes: Rosuva 0.45 kg, Placebo 0.18 kg

- No significant differences in fasting glucose throughout study between treatment groups
- Increase of 3% mean change from baseline in both groups



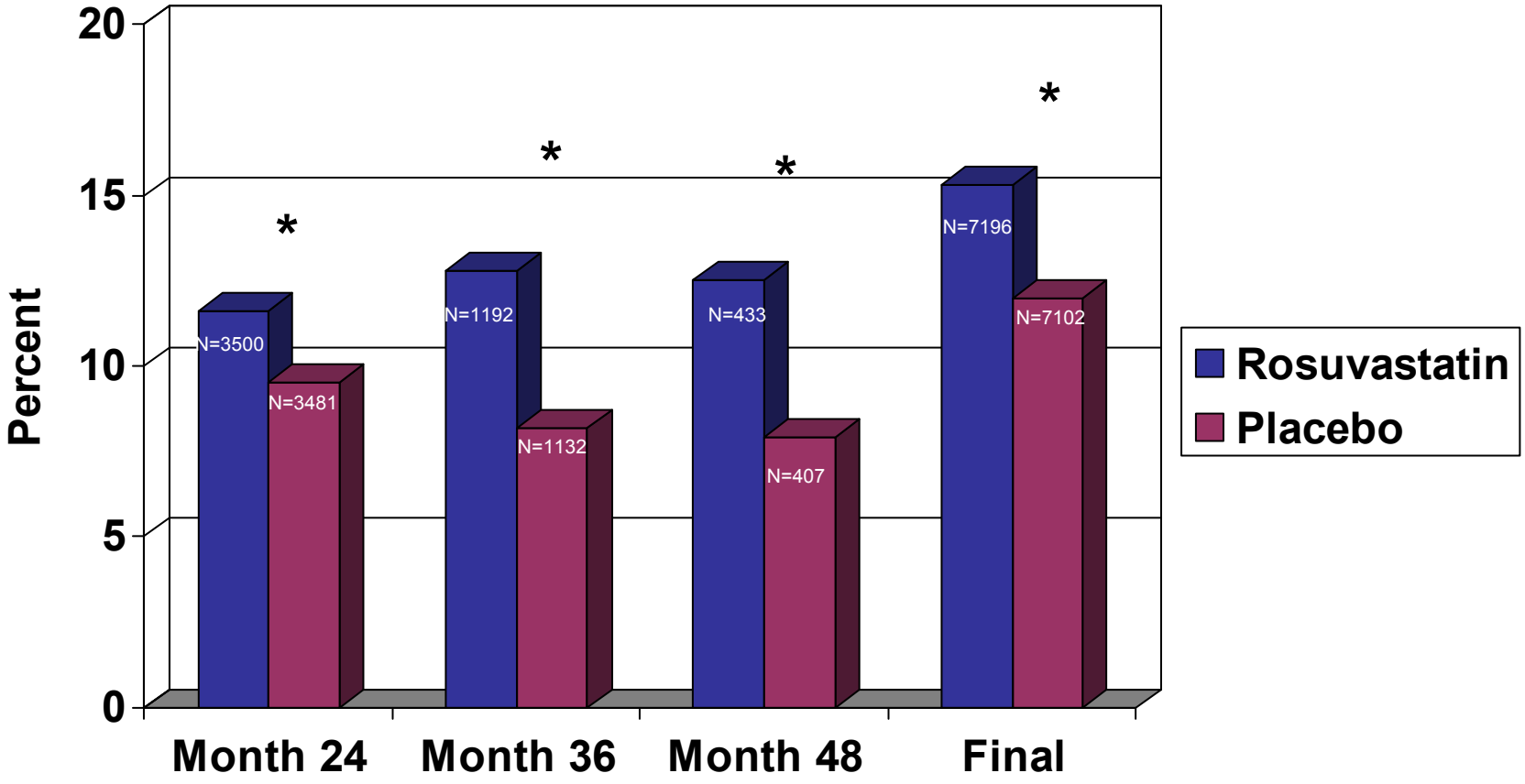


- HbA1c levels rose in both groups
- At final visit there was a significantly different change from baseline of 0.08% points between the two treatment groups

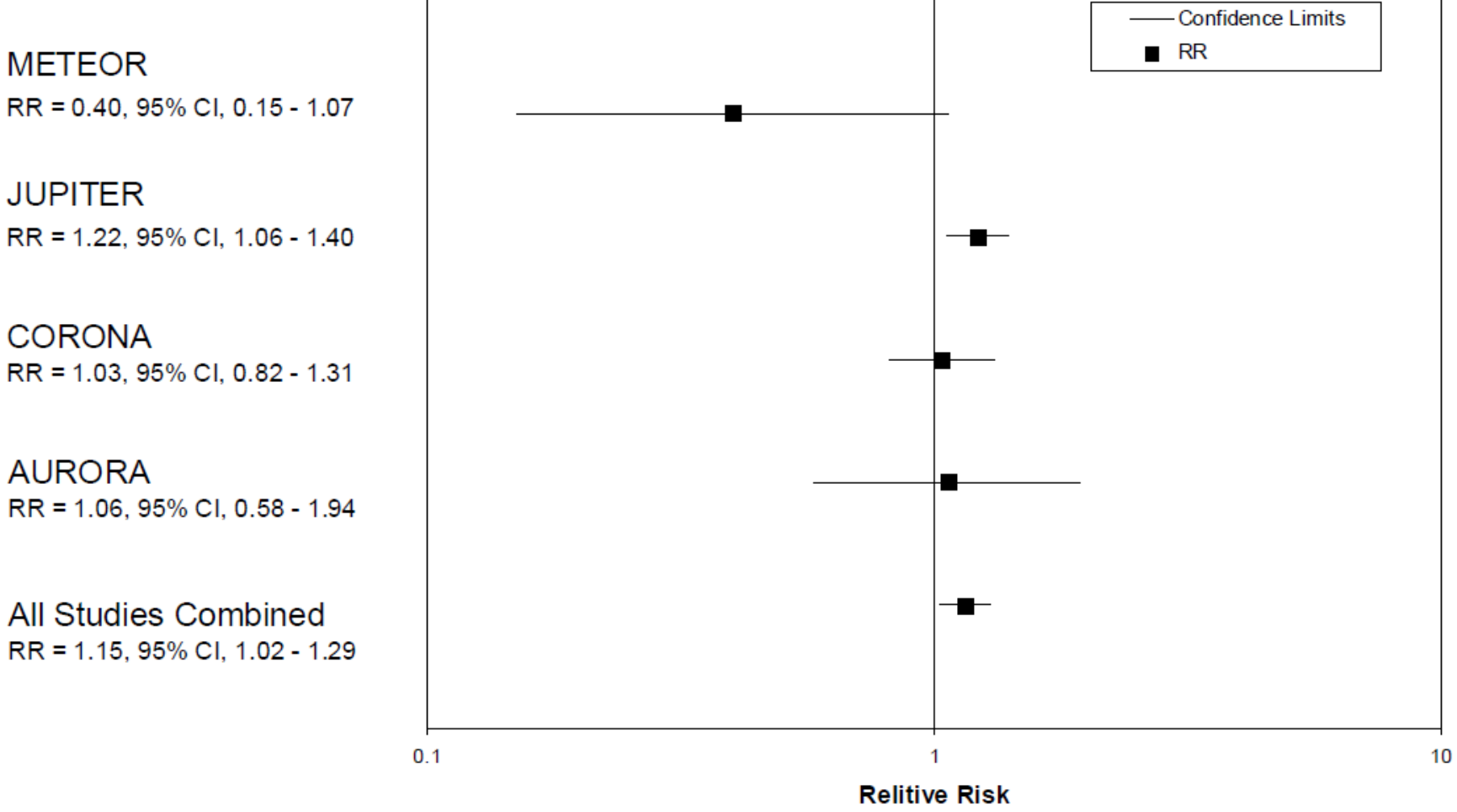


Rosuva, N	3506	1191	438	7115
Placebo, N	3480	1131	406	7013

Subjects developing diabetes using HbA1c >6.5% or FSG ≥126 mg/dL



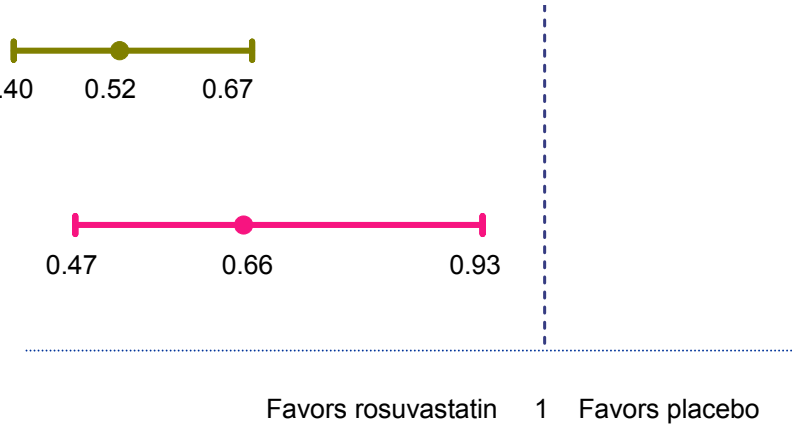
* p value <0.0001



- Suggested a 15% increase risk in diabetes-related AEs in rosuvastatin-exposed subjects

- Of subjects with impaired fasting glucose at baseline there was a 34% reduction in major cardiovascular events

	Rosuva	Placebo	HR (95% CI)
FSG <100	**87 (6.9)**	**167 (13.3)**	0.40 0.52 0.67
FSG≥100	**55 (9.4)**	**84 (14.2)**	0.47 0.66 0.93



JUPITER Safety Conclusions

- Overall hepatic, musculoskeletal, and renal-related AEs occurred with similar frequencies between treatment groups
- Hepatic, musculoskeletal, and renal-related AEs were consistent with the known safety profile of rosuvastatin
- There was no overall difference in cancer deaths and subjects who achieved an LDL less than 50 mg/dL did not have a higher rate of neoplastic SAEs

JUPITER Safety Conclusions

- Of the selected neuropsychiatric-related AEs, an imbalance in confusional state was observed (18 rosuvastatin vs 4 placebo)
- An imbalance was also noted in the number of deaths (13 rosuvastatin, 1 placebo) recorded as due to gastrointestinal disorders
- There was a 27% increase in investigator-reported diabetes in the rosuvastatin-treated subjects compared to placebo-treated subjects

Study Limitations

- Limitations to consider
  - Short mean duration of follow-up: 2 years
  - Generalizability
    - 80% of subjects screened did not qualify
    - However, estimated 6.5 million U.S. adults would be eligible for statin therapy based on JUPITER inclusion/exclusion criteria
  - JUPITER not designed to answer how change in hsCRP affects treatment benefit
  - No group with hsCRP <2 mg/L to determine presence of treatment benefit

Risk-Benefit

- Benefits
- 44% reduction in relative risk of MCE
- Similar reduction in relative risk of
  - CV death/MI/stroke
  - Non-fatal and fatal MI
  - Non-fatal and fatal stroke

- Risks
- Neurocognitive concerns
- Increase in incident diabetes

Charge to committee

- In the JUPITER trial, there were 18 patients who reported a confusional state in the treatment arm versus 4 in the placebo arm.
  - Please comment on the significance of this imbalance.

- In the JUPITER trial, there were 13 deaths due to Gastrointestinal Disorders in the treatment arm versus 1 in the placebo arm.
  - Please comment on the significance of this imbalance.

Charge to committee

- In the JUPITER trial, there was a statistically significant increase in investigator-reported diabetes mellitus in the treatment arm versus the placebo arm, 2.8% vs. 2.3%, respectively with a hazard ratio of 1.27 (95% CI 1.05, 1.53; p=0.015).
  - Please comment on the significance of this imbalance.

Charge to committee

- Please discuss whether the JUPITER trial has identified an appropriate new target population, defined by LDL<130 mg/dL, hsCRP≥ 2 mg/L, plus at least one additional cardiovascular risk factor, for treatment with rosuvastatin for the primary prevention of major cardiovascular adverse events.

Charge to committee

- Has the sponsor established sufficient benefit to offset the observed risks to support the use of rosuvastatin in individuals meeting the following criteria?
  - Men ≥ 50 years, Women ≥ 60 years
  - Fasting LDL< 130 mg/dL; hsCRP ≥ 2.0 mg/L; Triglycerides <500 mg/dL;
  - No prior history of cardiovascular or cerebrovascular events or CHD risk equivalent as defined by NCEP ATP-III guidelines.

- Please elaborate on the rationale for your vote.