



Randomized Evidence on Rosuvastatin for Primary Prevention in Individuals 70 Years of Age or Older: The JUPITER Trial

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on behalf of the JUPITER Trial Study Group

An Investigator Initiated Trial Funded by AstraZeneca, USA

** The 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.*



Background

Statins are underutilized in high risk older individuals with clear indications*

Use of statins for primary prevention in older people remains controversial

Relative hazards associated with elevated cholesterol decline markedly with advancing age†, and risk scores such as Framingham reflect this interaction with decreased points associated with elevated cholesterol in older people

Yet older age is the dominant risk factor for CVD and absolute risk is critical for treatment decisions

*S DeWilde et al. Heart 2003; †S Lewington et al. Lancet 2007



Ample subgroup data in secondary prevention trials and in diabetics show strong benefits of statins in older people

In PROSPER* (age range 70-82 year), 40 mg/day pravastatin reduced the incidence of vascular events by 15% ($p=0.01$), but among the 56% of participants without prior vascular disease there was a non-significant 6% reduction

Mean ages at randomization in prior primary prevention trials were 55, 58, and 58 years in WOSCOPS, AFCAPS/TEXCAPS, and MEGA, respectively, compared with 66 years in JUPITER

Thus, prior randomized evidence on statins for primary prevention in non-diabetic older people is limited

*J Shepherd et al. *Lancet* 2002



Main goal: To examine absolute and relative treatment effects on the primary cardiovascular endpoint among participants in the JUPITER trial aged 70 years and older, and compare these with observed effects in younger participants.

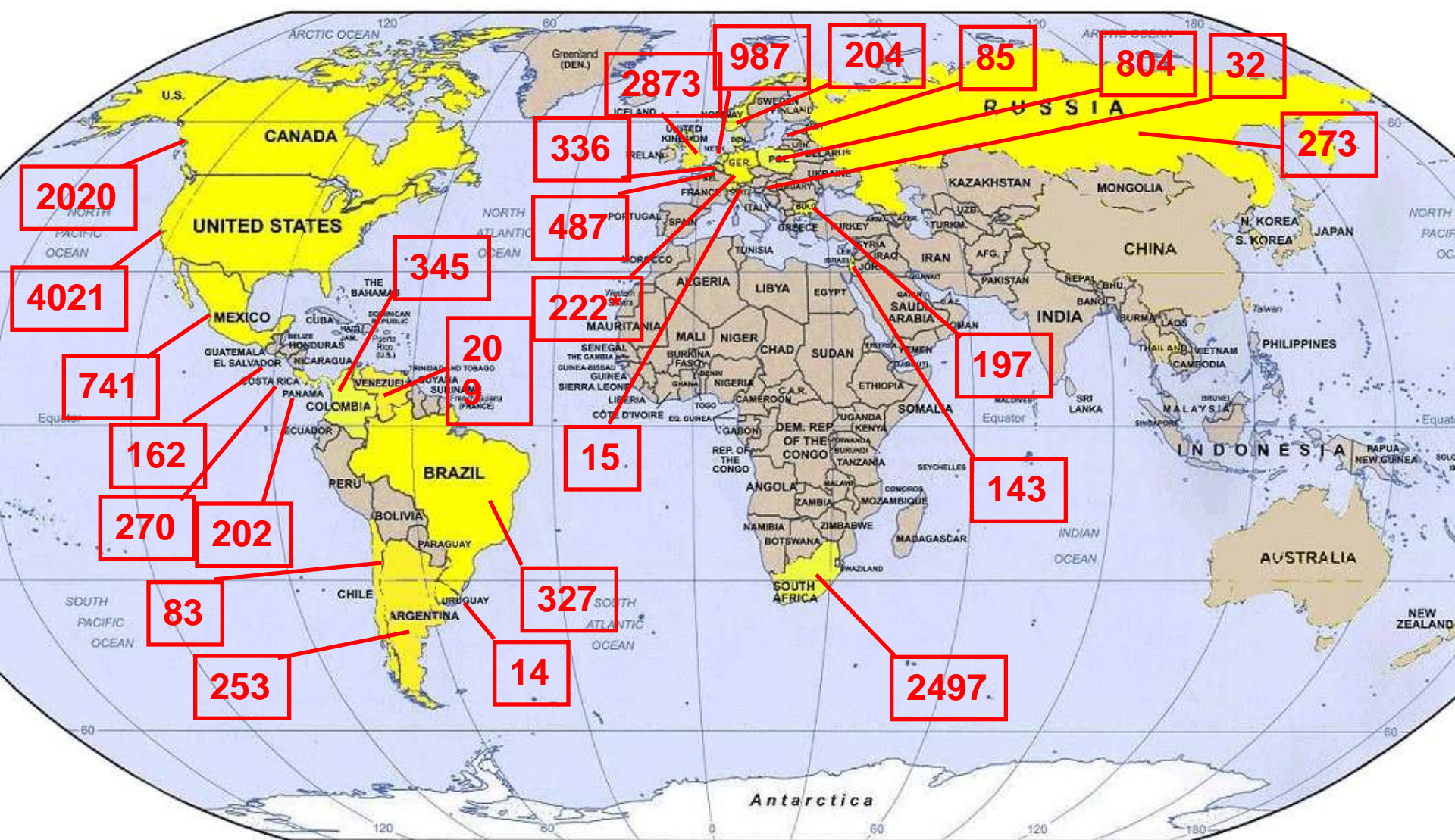
Secondary goals: To compare rates of pre-specified secondary endpoints, including total mortality, venous thromboembolism and diabetes, by age and treatment group. And to evaluate rates of serious adverse events by age and treatment group.



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 \geq 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.

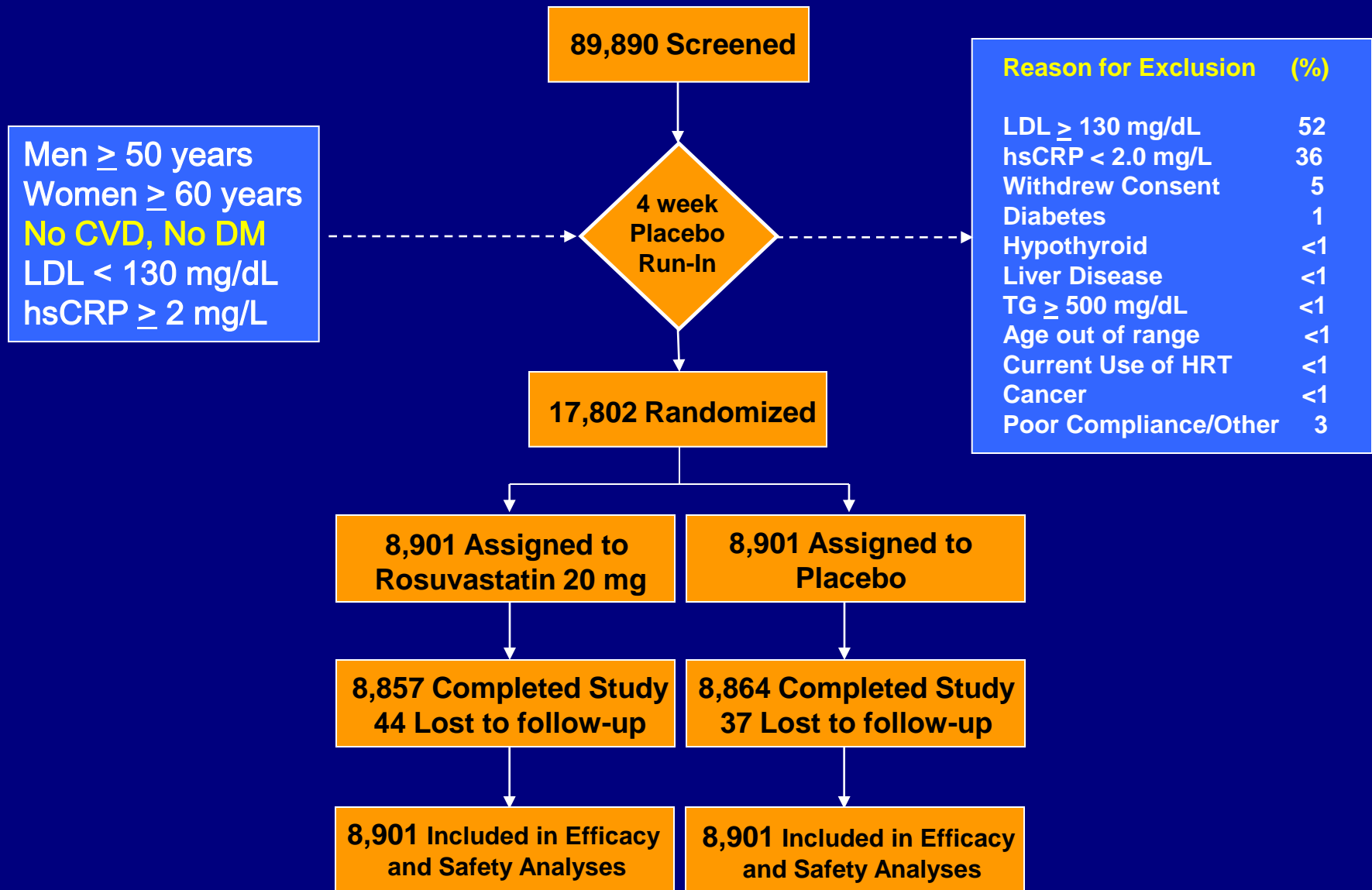


JUPITER Enrollment – 17,802 Patients

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 UK USA Uruguay Venezuela



Inclusion and Exclusion Criteria, Study Flow





Primary efficacy analyses counted all events diagnosed by March 30, 2008 according to the intention to treat principle

Possible heterogeneity in the relative treatment effect by age evaluated through interaction terms in a proportional hazards model. Heterogeneity in absolute treatment effects by age evaluated through comparison of age-specific rate differences

Estimates of net clinical benefits compared the number needed to treat (NNT) in older vs younger participants for the primary endpoint as well as composite endpoints including total mortality and venous thromboembolism.



	Age 70-97 years (N = 5,695)	Age 50-69 years (N = 12,107)
Age, years (IQR)	74 (72-78)	63 (58-66)
Female, N (%)	2,931 (51)	3,870 (32)
Ethnicity, N (%)		
<i>Caucasian</i>	3,983 (70)	8,700 (72)
<i>Black</i>	752 (13)	1,470 (12)
<i>Hispanic</i>	803 (14)	1,458 (12)
Body mass index ≥ 30 kg/m², N (%)	1,822 (32)	4,852 (40)
Hypertension, N (%)	3,732 (66)	6,476 (53)
Smoker, N (%)	477 (8)	2,343 (19)
Metabolic Syndrome, N (%)	2,257 (41)	5,118 (42)
hsCRP≥ 5 mg/L, N (%)	2,415 (42)	4,929 (41)
LDL>2.6 mmol/L, N (%)	3,725 (65)	7,806 (64)
HDL<1.03 mmol/L (men), <1.29 (women), N (%)	1,709 (30)	3,980 (33)
Framingham risk score > 10, N (%)	3,932 (69)	4,963 (41)

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



Biomarker	Age	12 months		36 months	
		Active	Placebo	Active	Placebo
hsCRP (mg/L)	≥70	2.3 (1.3-4.7)	3.6 (2.0-6.5)	2.0 (1.1-4.2)	3.3 (1.8-6.1)
	<70	2.2 (1.2-4.3)	3.5 (2.0-6.1)	2.0 (1.2-3.7)	3.6 (1.9-5.9)
LDL (mmol/L)	≥70	1.4 (1.1-1.8)	2.8 (2.4-3.2)	1.4 (1.1-1.8)	2.7 (2.3-3.1)
	<70	1.4 (1.1-1.9)	2.8 (2.4-3.3)	1.4 (1.1-1.8)	2.8 (2.4-3.1)
HDL (mmol/L)	≥70	1.4 (1.2-1.7)	1.3 (1.1-1.6)	1.4 (1.1-1.7)	1.4 (1.1-1.7)
	<70	1.3 (1.1-1.6)	1.3 (1.0-1.5)	1.3 (1.0-1.5)	1.2 (1.0-1.5)
Triglycerides (mmol/L)	≥70	1.1 (0.8-1.4)	1.3 (1.0-1.7)	1.1 (0.9-1.5)	1.3 (1.0-1.8)
	<70	1.2 (0.9-1.6)	1.4 (1.0-2.0)	1.3 (0.9-1.7)	1.5 (1.1-2.1)

Shown are medians with interquartile ranges

JUPITER

Summary of overall trial results

Ridker et al. NEJM 2008;
Glynn et al. NEJM 2009



Endpoint	Rosuvastatin	Placebo	HR	95%CI	P
Primary Endpoint*	142	251	0.56	0.46-0.69	<0.001
Any MI	31	68	0.46	0.30-0.70	<0.001
Any Stroke	33	64	0.52	0.34-0.79	0.002
MI, Stroke, CV Death	83	157	0.53	0.40-0.69	<0.001
Any Death	198	247	0.80	0.67-0.97	0.02
VTE	34	60	0.57	0.37-0.86	0.007
Primary Endpoint or Death or VTE	320	483	0.66	0.57-0.76	<0.001

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

Endpoint	Age	Events	Placebo rate†	HR	95%CI	P
Primary Endpoint*	≥70	194	1.99	0.61	0.46-0.82	<0.001
	<70	199	1.06	0.51	0.38-0.69	<0.001
Any MI	≥70	47	0.50	0.55	0.31-1.00	0.046
	<70	52	0.30	0.37	0.21-0.69	<0.001
Any Stroke	≥70	61	0.64	0.55	0.33-0.93	0.023
	<70	36	0.20	0.45	0.22-0.91	0.020
Revascularization or Unstable Angina	≥70	87	0.95	0.51	0.33-0.80	0.003
	<70	132	0.69	0.54	0.38-0.77	<0.001
MI/Stroke/CV Death	≥70	133	1.36	0.61	0.43-0.86	0.004
	<70	107	0.60	0.43	0.29-0.65	<0.001

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

†Incidence rates are per 100 person-years



Endpoint	Age	Events	Placebo rate†	HR	95%CI	P
Any death	≥70	241	2.04	0.80	0.62-1.04	0.090
	<70	204	0.86	0.80	0.60-1.05	0.10
VTE	≥70	40	0.41	0.59	0.31-1.11	0.096
	<70	54	0.28	0.55	0.31-0.96	0.031
Primary endpoint* or any death	≥70	371	3.63	0.69	0.56-0.85	<0.001
	<70	365	1.79	0.63	0.51-0.78	<0.001
Primary endpoint*, death or VTE	≥70	398	3.91	0.69	0.56-0.84	<0.001
	<70	405	2.00	0.62	0.51-0.76	<0.001

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

†Incidence rates are per 100 person-years



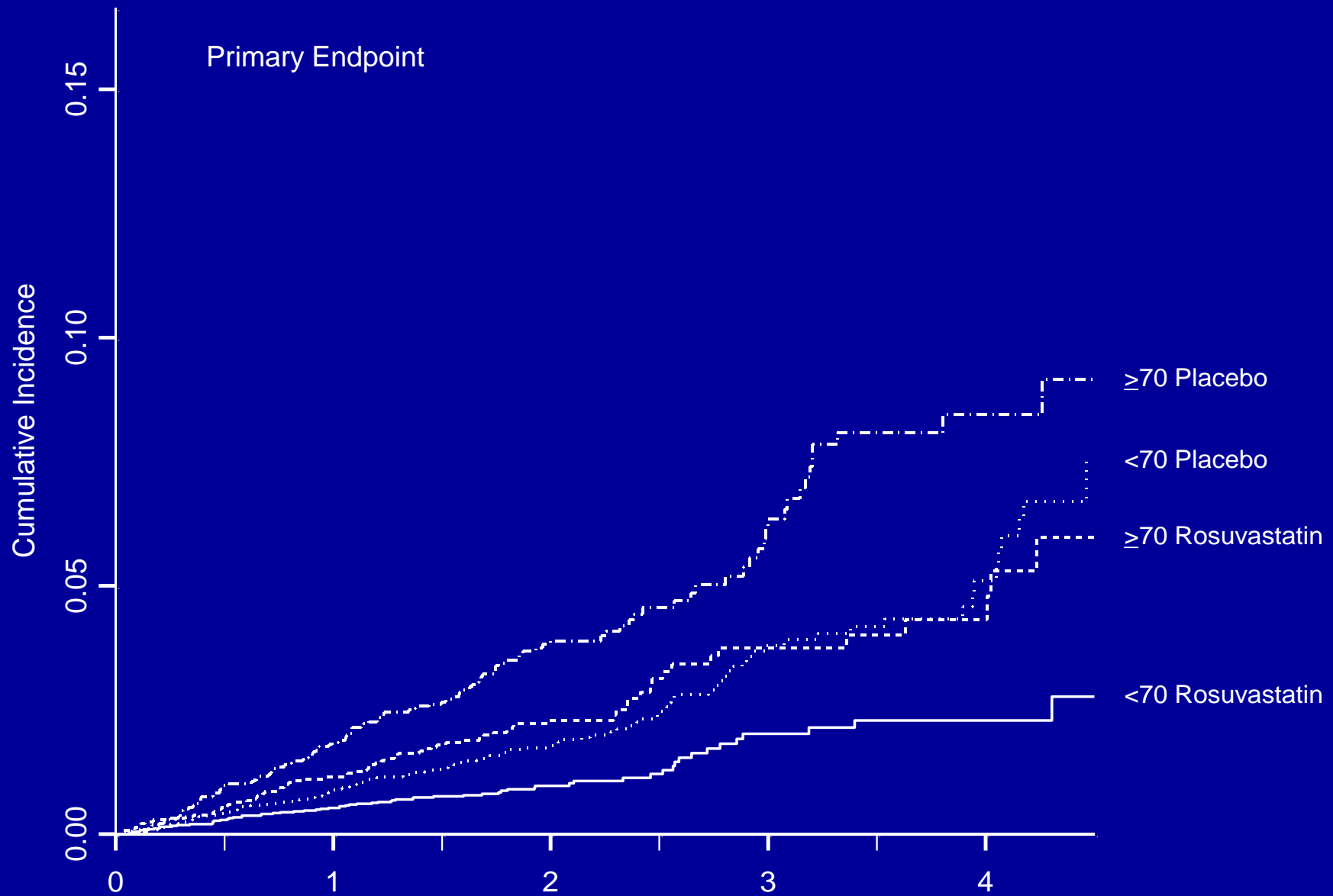
Endpoint	Age	Events	Placebo rate	RD‡	95%CI	NNT*
Primary endpoint†	≥70	194	1.99	0.77	0.32-1.22	19
	<70	199	1.06	0.52	0.29-0.74	29
MI, Stroke or CV death	≥70	133	1.36	0.54	0.17-0.91	29
	<70	107	0.60	0.34	0.18-0.50	55
Primary endpoint† or any death	≥70	371	3.63	1.13	0.51-1.75	15
	<70	365	1.79	0.66	0.35-0.96	23
Primary endpoint†, death or VTE	≥70	398	3.91	1.23	0.58-1.88	14
	<70	405	2.00	0.75	0.44-1.07	21

*NNT is the number needed to treat for 5 years to prevent 1 endpoint
 †Nonfatal MI, nonfatal stroke, revascularization, unstable angina, CV death
 ‡RD is the difference in event rates (placebo-rosuvastatin) per 100 person-years



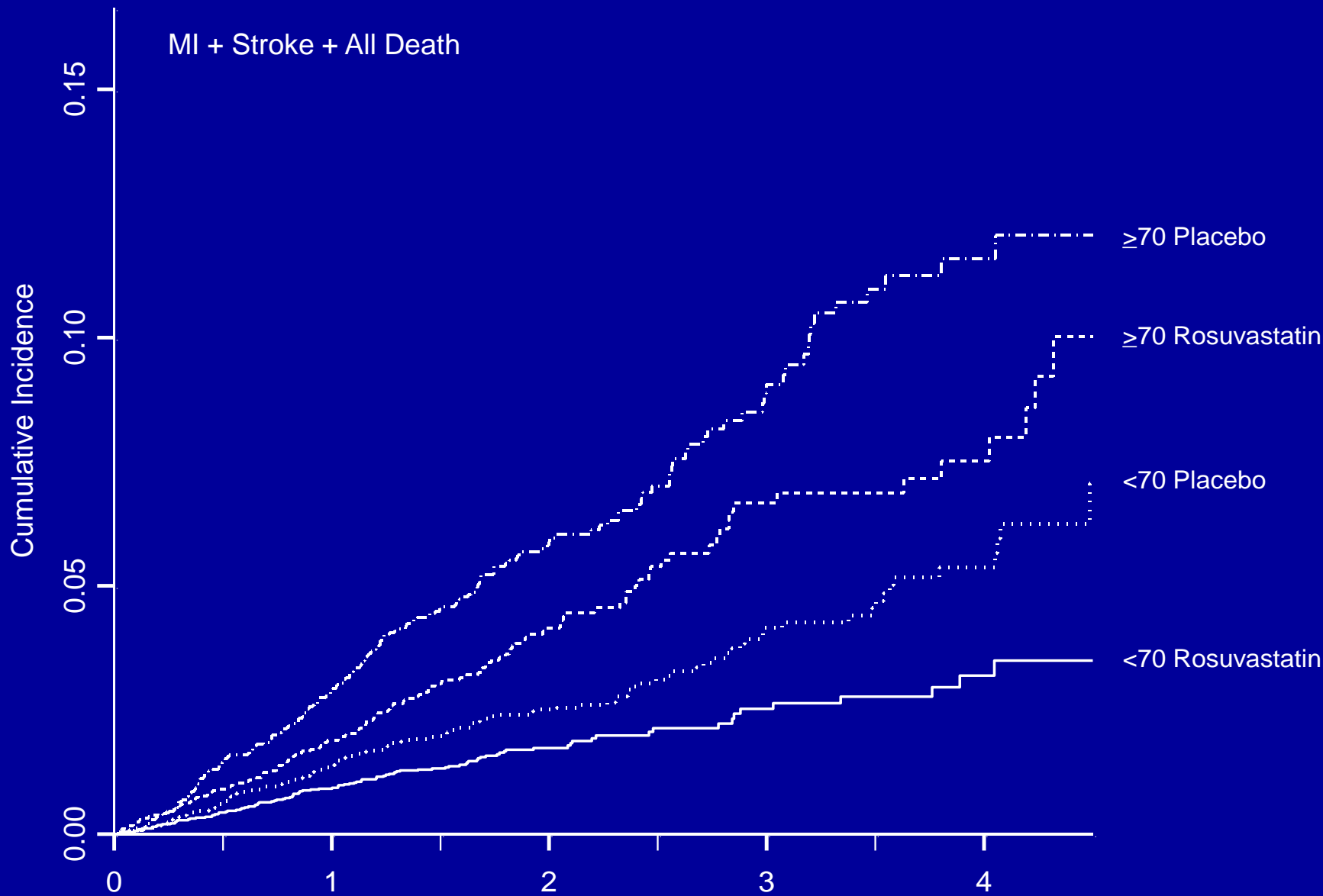
Endpoint	Age	Events	Placebo rate*	HR	95%CI	P
Any SAE	≥70	1,206	10.45	1.05	0.93-1.17	0.44
	<70	1,523	6.51	0.93	0.84-1.03	0.17
Muscle weakness, stiffness or pain	≥70	961	8.50	1.04	0.92-1.19	0.50
	<70	1,835	7.85	1.04	0.94-1.13	0.46
Renal disorder	≥70	413	3.17	1.14	0.94-1.39	0.18
	<70	602	2.28	1.10	0.94-1.29	0.24
Hepatic disorder	≥70	120	0.95	1.01	0.71-1.45	0.95
	<70	282	0.99	1.24	0.98-1.57	0.07
Incident diabetes	≥70	146	1.03	1.25	0.90-1.74	0.18
	<70	300	1.18	1.26	1.02-1.56	0.03

*Incidence rates are per 100 person-years

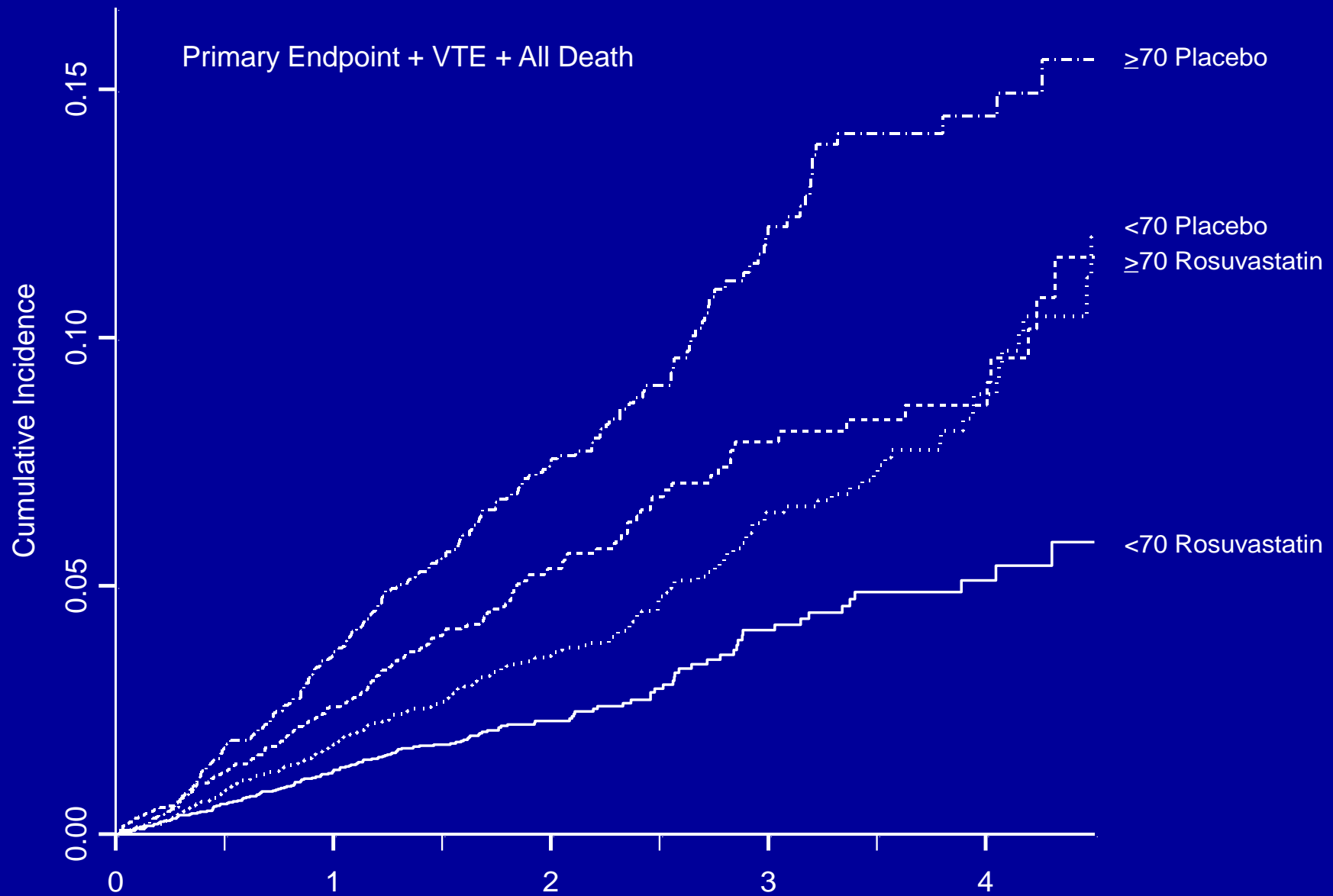


No. at Risk	Follow-up (years)									
	0	0.5	1	1.5	2	2.5	3	3.5	4	4.5
≥70 Rosuvastatin	2,878	2,779	2,694	2,187	1,413	695	474	351	198	59
Placebo	2,817	2,692	2,588	2,113	1,342	705	476	332	196	67
<70 Rosuvastatin	6,023	5,852	5,718	4,353	2,480	1,263	879	632	340	98
Placebo	6,084	5,929	5,765	4,395	2,530	1,258	857	623	335	107

MI + Stroke + All Death



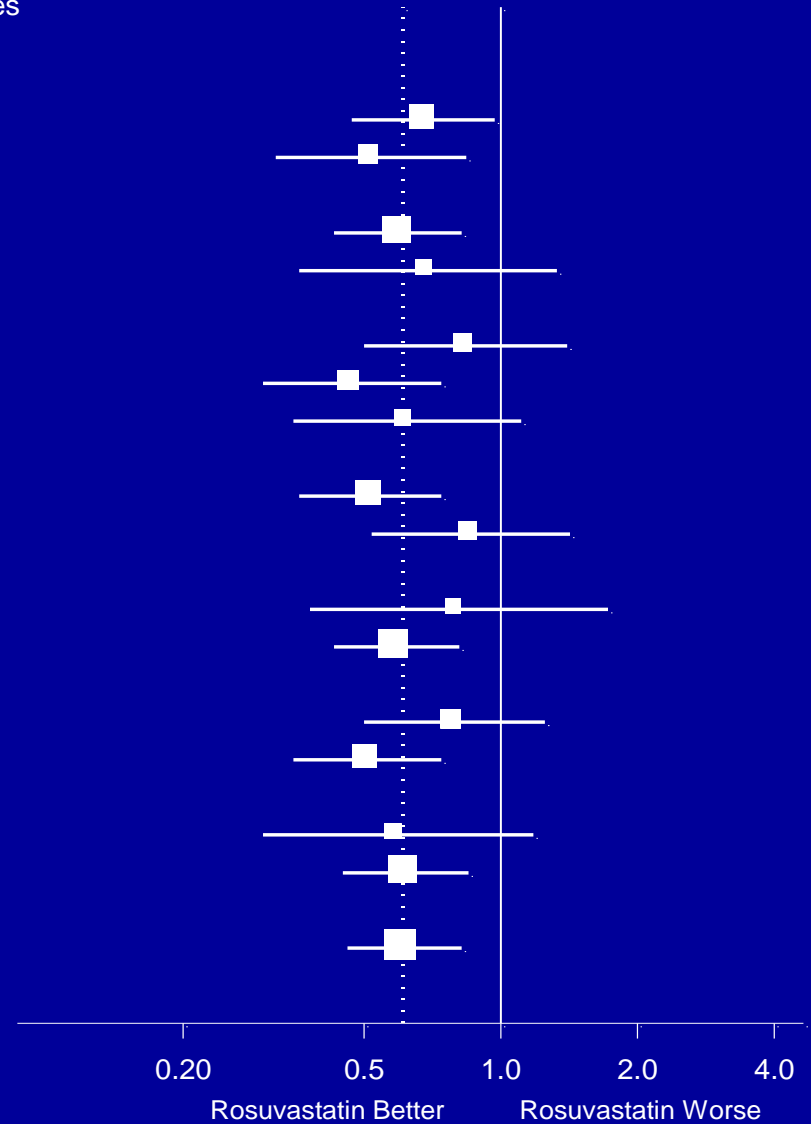
No. at Risk		Follow-up (years)								
	0	0.5	1	1.5	2	2.5	3	3.5	4	4.5
≥70 Rosuvastatin	2,878	2,783	2,704	2,201	1,426	706	480	358	201	60
Placebo	2,817	2,697	2,602	2,128	1,363	715	488	340	201	68
<70 Rosuvastatin	6,023	5,860	5,733	4,370	2,495	1,273	890	640	344	99
Placebo	6,084	5,936	5,779	4,414	2,555	1,277	877	639	346	113



No. at Risk	Follow-up (years)									
	0	0.5	1	1.5	2	2.5	3	3.5	4	4.5
≥70 Rosuvastatin	2,878	2,774	2,686	2,179	1,404	693	474	351	198	59
Placebo	2,817	2,690	2,583	2,106	1,337	698	468	327	193	65
<70 Rosuvastatin	6,023	5,850	5,714	4,346	2,476	1,258	874	628	338	98
Placebo	6,084	5,922	5,755	4,380	2,517	1,251	852	618	332	105

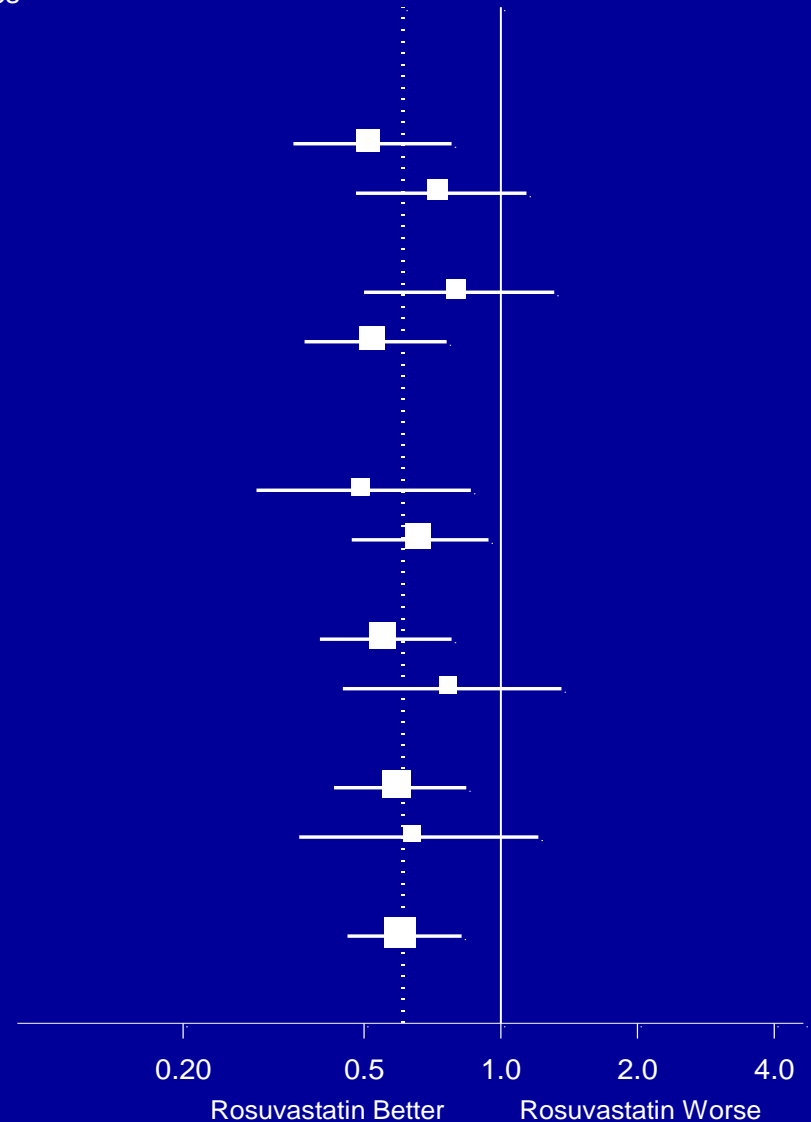
Age ≥ 70 Subgroup Analysis

	N	# of Events	Incidence Rates (Placebo)
Men	2,764	122	2.46
Women	2,931	72	1.54
Caucasian	3,983	156	2.16
Black, Hispanic, Other	1,711	38	1.51
BMI <25.0 kg/m ²	1,500	59	2.04
BMI 25.0-29.9 kg/m ²	2,359	86	2.32
BMI ≥ 30.0 kg/m ²	1,822	48	1.52
Hypertension	3,732	132	2.24
No Hypertension	1,960	62	1.55
Smoker	477	27	3.08
Non-smoker	5,215	167	1.89
Metabolic Syndrome	2,257	74	1.73
No Metabolic Syndrome	3,397	119	2.17
Framingham Risk $\leq 10\%$	1,753	35	1.15
Framingham Risk $>10\%$	3,932	159	2.39
All Participants	5,695	194	1.99



Age ≥ 70 Subgroup Analysis

	N	# of Events	Incidence Rates (Placebo)
hsCRP <5 mg/L	3,280	108	2.01
hsCRP ≥ 5 mg/L	2,415	86	1.97
LDLC <100 mg/dL	1,969	68	1.85
LDLC >100 mg/dL	3,725	126	2.07
HDL Cholesterol(mg/dL)			
Men <40/Women <50	1,709	57	2.15
Men ≥ 40 /Women ≥ 50	3,985	137	1.93
Triglycerides <150 mg/dL	4,074	143	2.14
Triglycerides ≥ 150 mg/dL	1,620	51	1.62
Time of Event ≤ 24 Months	5,695	151	1.94
Time of Event >24 Months	2,755	43	2.20
All Participants	5,695	194	1.99





JUPITER provides convincing evidence for a benefit of statin therapy in older individuals in the context of primary prevention

Relative treatment effects and the safety profile were comparable in those 70 years of age or older compared with younger participants

Absolute treatment benefits were somewhat larger in older individuals giving rise to lower estimated numbers needed to treat in this age group, particularly for more serious events