Expert Meeting on Large Simple Trials (LST´s)

Clinical Trials Transformation Initiative

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

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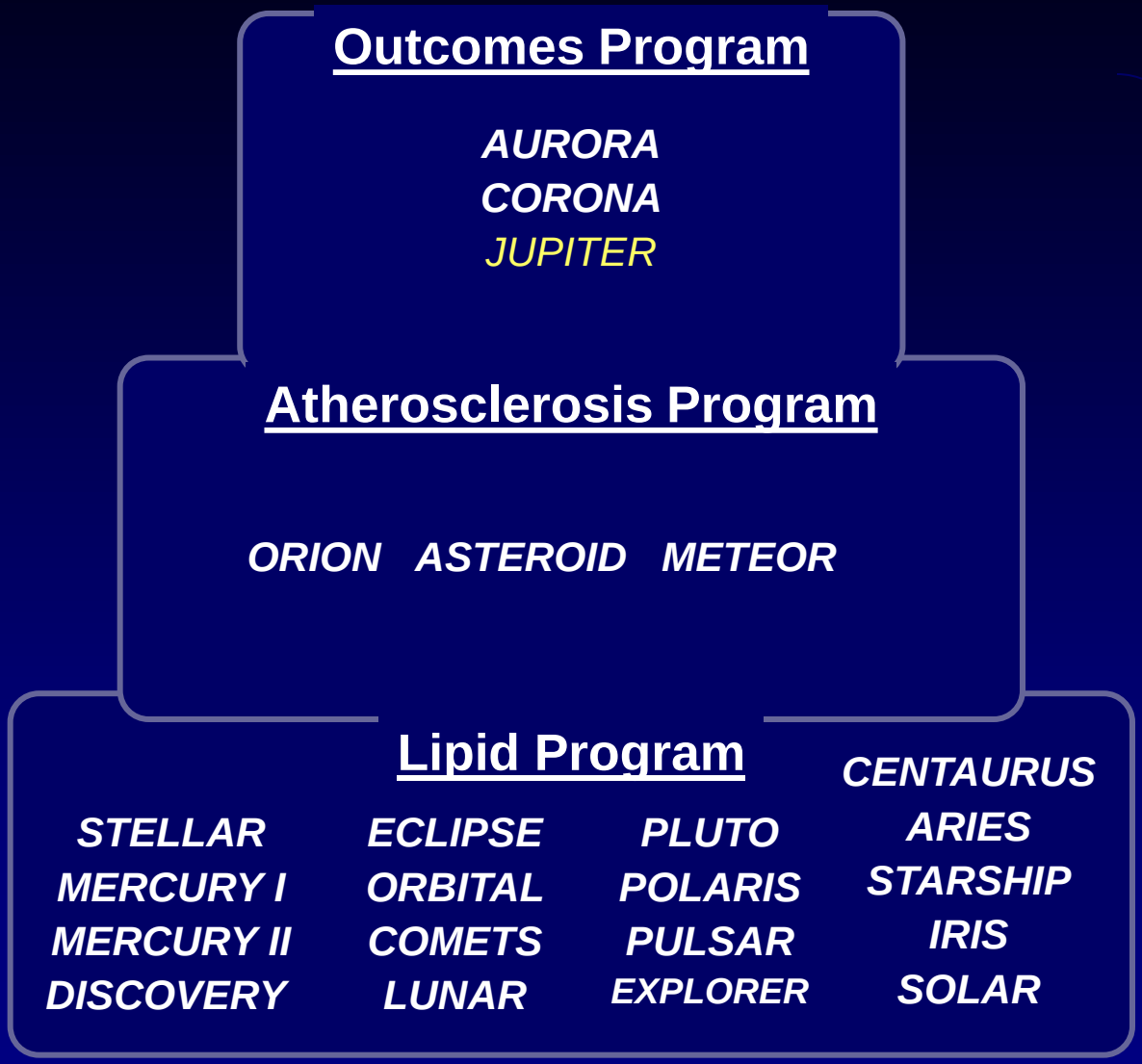
Definition of LST – was JUPITER an LST?

- **Inclusion/exclusion criteria are unambiguous and easily applied**
- **Primary endpoint is unambiguous and directly related to the patient´s health and well-being (not a surrogate)**
- **Dosing, mechanism, and potentially adverse effects of intervention are generally well understood**
- **Sample size and statistical power to detect a modest but still clinically meaningful treatment effect**
- **Streamlined data collection and monitoring**

GALAXY Program

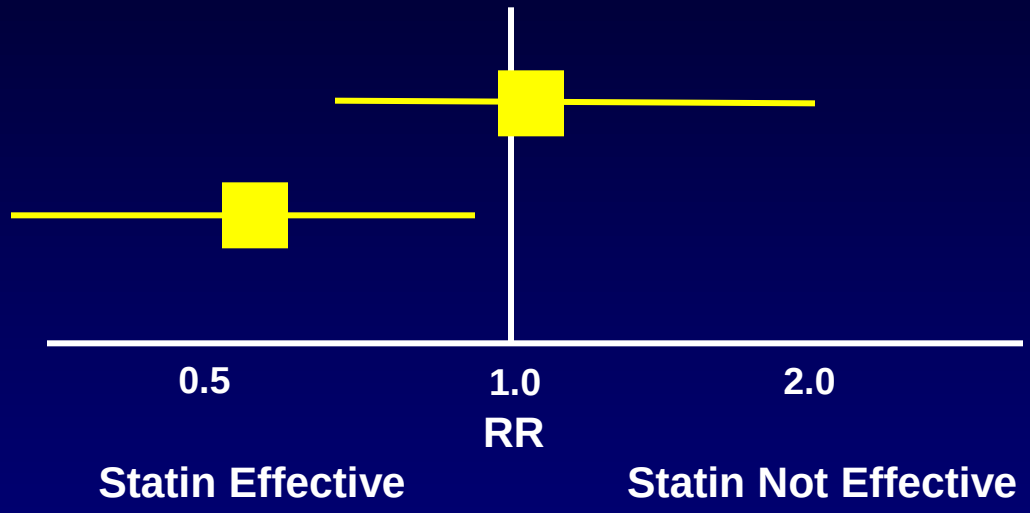


JUPITER: Why Consider Statins for Low LDL, High hsCRP Patients?

AFCAPS/TexCAPS Low LDL Subgroups

Low LDL, Low hsCRP

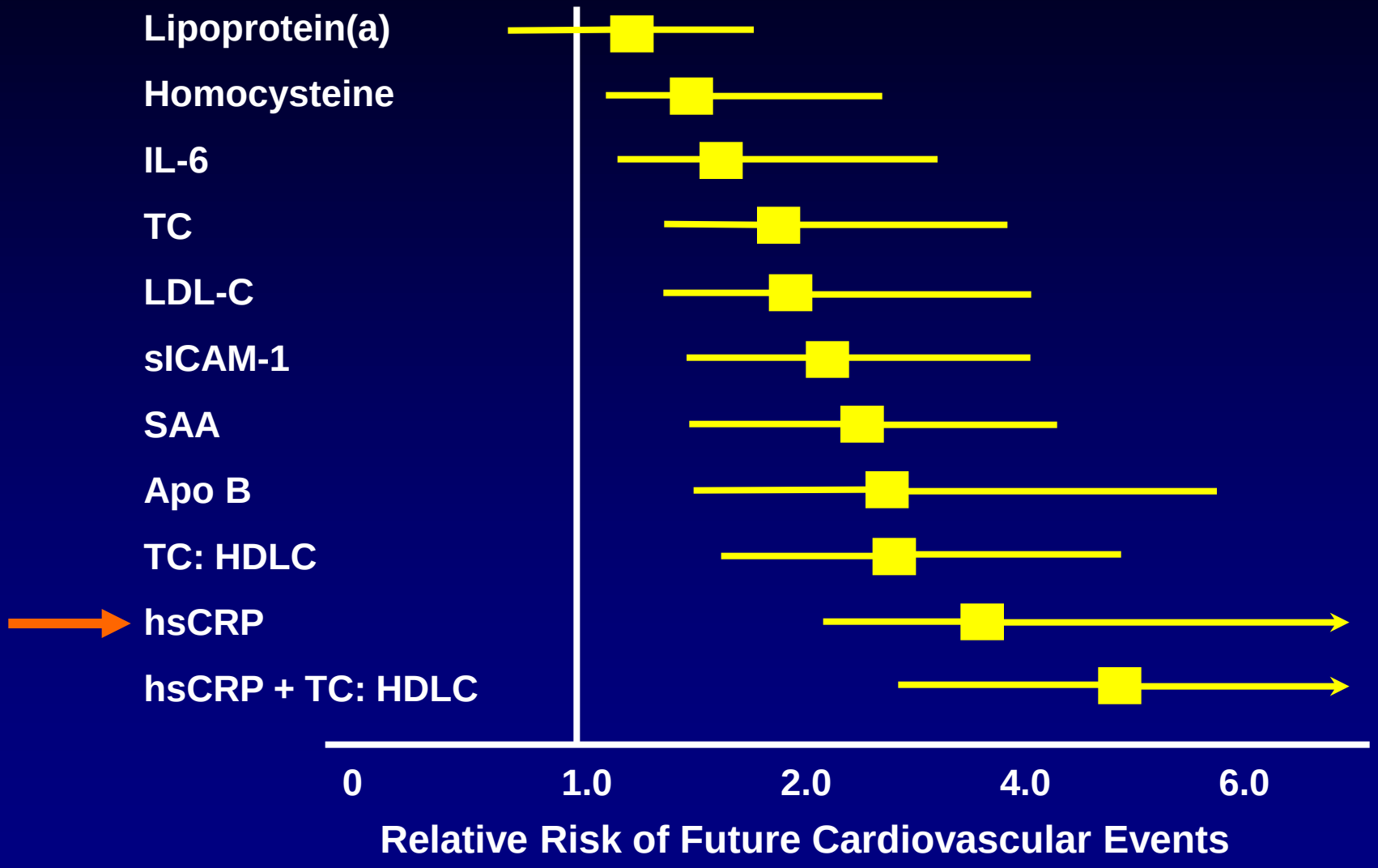
Low LDL, High hsCRP



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.

Risk Factors for Future Cardiovascular Events: WHS



Ridker et al, *N Engl J Med* 2000;342:836 43.

Inflammation, hsCRP, and Vascular Prevention

- **Is there evidence that individuals with elevated levels of the inflammatory biomarker hsCRP are at increased vascular risk?**
- **Is there evidence that individuals identified at increased risk due to inflammation benefit from a therapy they otherwise would not have received?**

Major inclusion criteria

- **Men aged ≥55 years; women aged ≥65 years**
- **Fasting LDL-C levels <3.4 mmol/L (130 mg/dL), CRP levels ≥2.0 mg/L and TG levels <5.7 mmol/L (500 mg/dL) on initial screening**

Ridker PM. *Circulation* 2003; 108: 2292–2297

Major exclusion criteria

- **Current use of statins or other lipid-lowering therapies**
- **Prior history of cardiovascular or cerebrovascular events, such as MI, unstable angina, prior arterial revascularisation or stroke, or CHD-risk equivalents**
- **Chronic inflammatory condition, such as severe arthritis, lupus or inflammatory bowel disease**

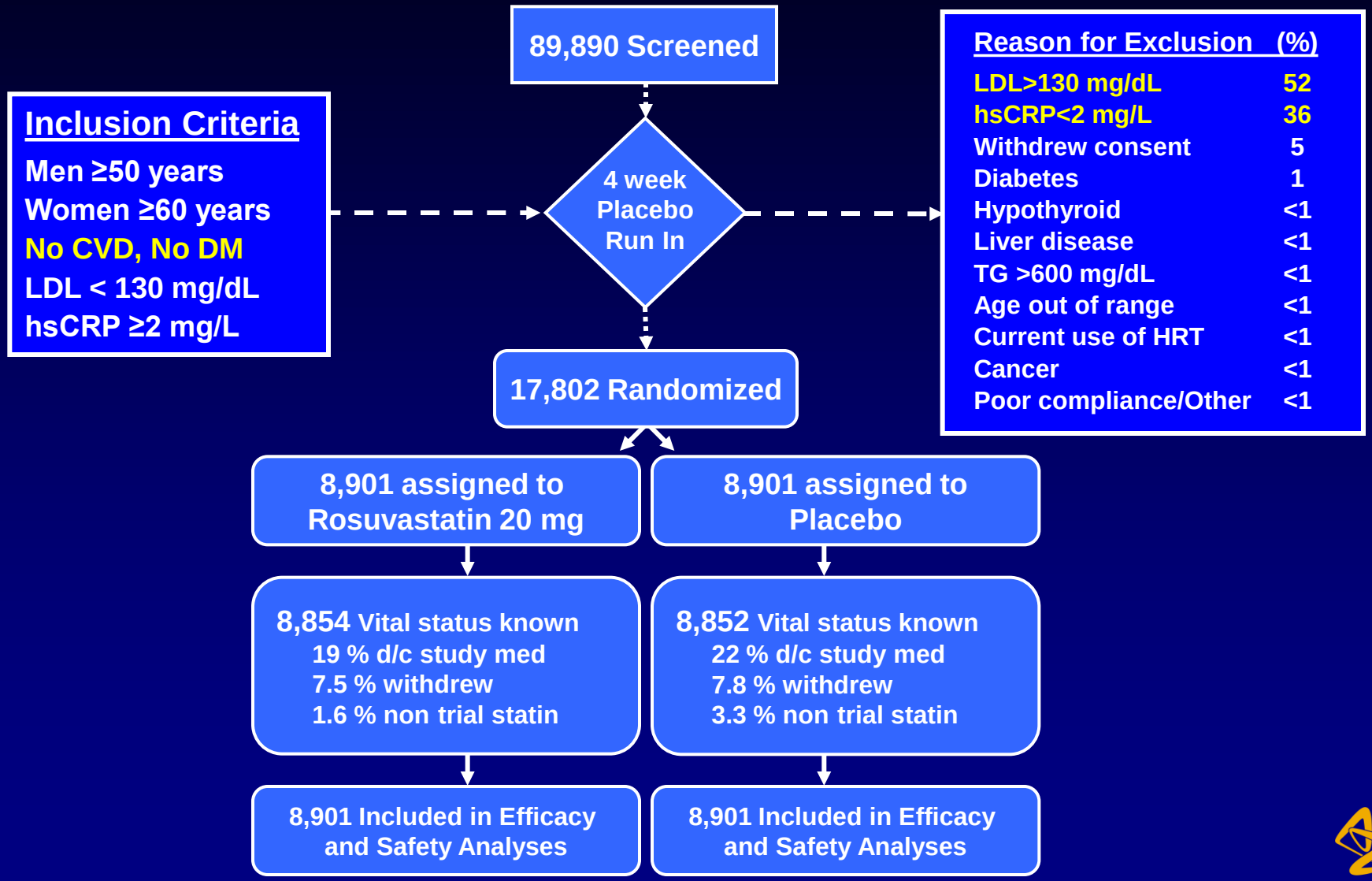
Ridker PM. *Circulation* 2003; 108: 2292–2297

JUPITER – study endpoints

- **Primary**
  - **time to the first occurrence of a major cardiovascular event (cardiovascular death, stroke, MI, unstable angina or arterial revascularisation)**
- **Secondary**
  - **Efficacy (incident diabetes mellitus, venous thromboembolic events, bone fractures)**
  - **Safety (total mortality noncardiovascular mortality, adverse events)**

Ridker PM. *Circulation* 2003; 108: 2

JUPITER: Inclusion and Exclusion Criteria, Study Flow



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)

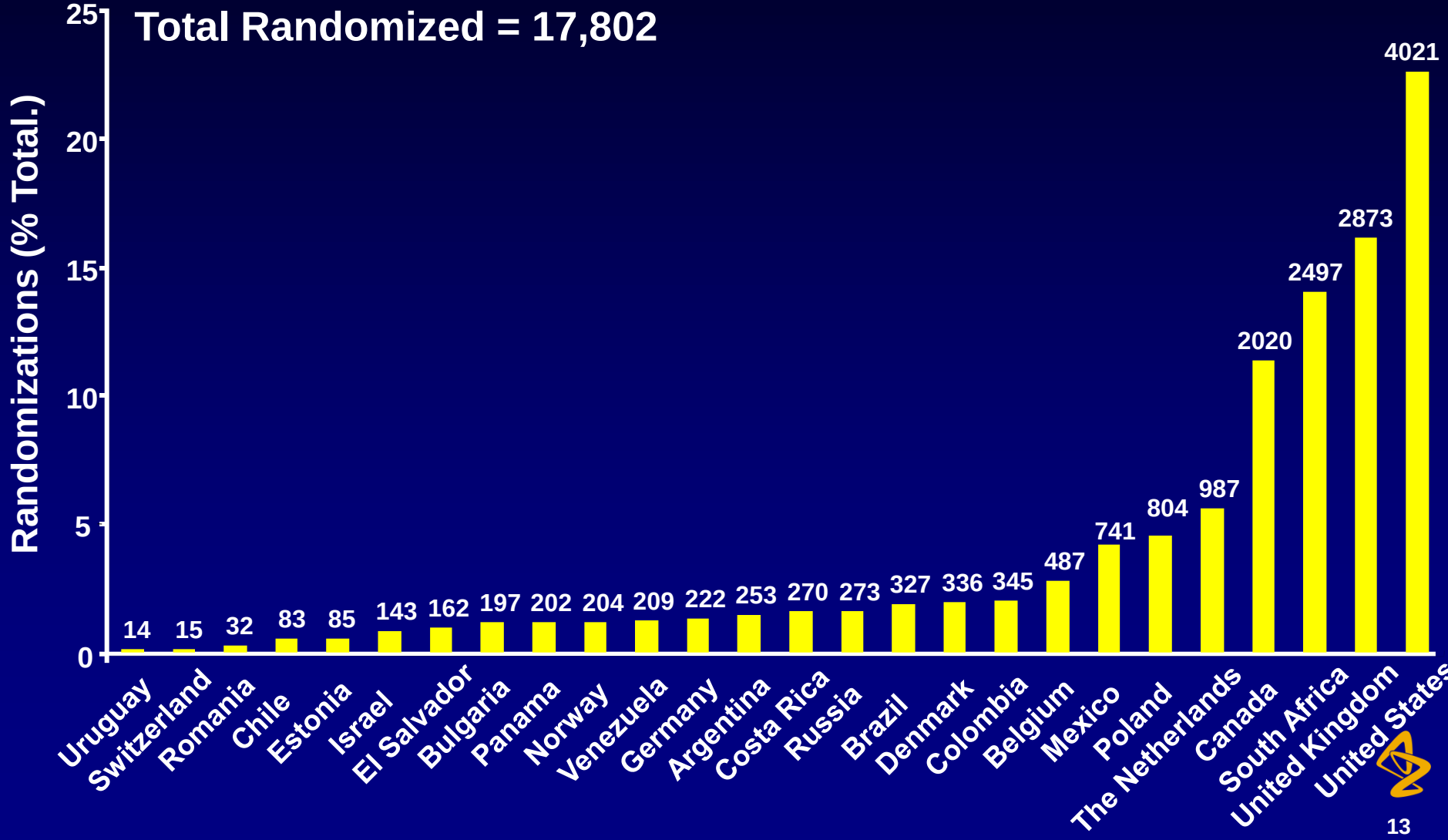
NEJM 2008; 359: 2195 2207

JUPITER: Trial Design

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:
17,802 Patients; 1,315 Sites; 26 Countries



JUPITER: Baseline Blood Levels (Median, Interquartile Range)

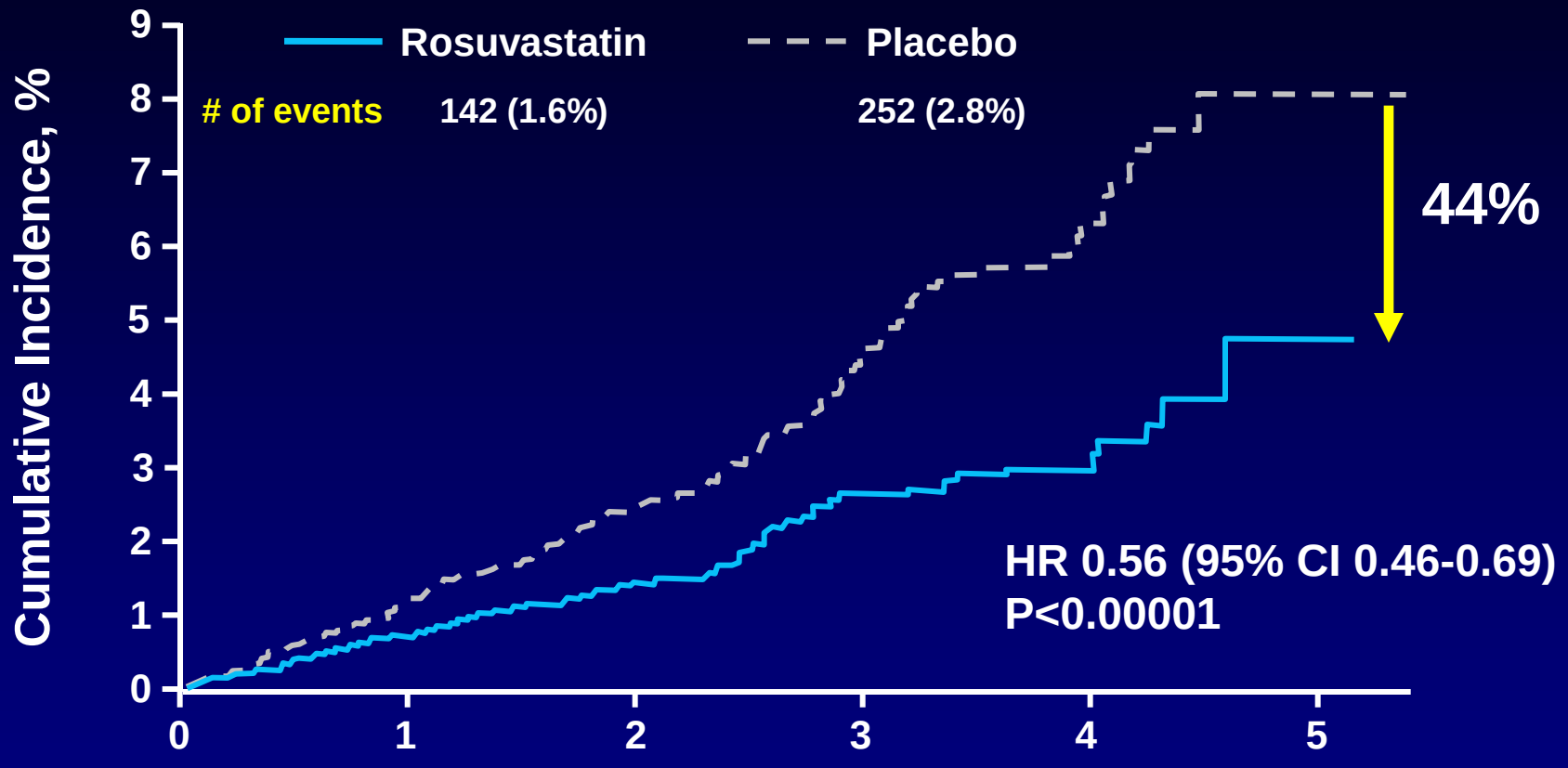
		Rosuvastatin (N=8901)	Placebo (N=8901)
hsCRP	mg/L	4.2 (2.8 – 7.1)	4.3 (2.8 – 7.2)
LDL	mg/dL	108 (94 – 119)	108 (94 – 119)
HDL	mg/dL	49 (40 – 60)	49 (40 – 60)
Triglycerides	mg/dL	118 (85 – 169)	118 (86 – 169)
Total Cholesterol	mg/dL	186 (168 – 200)	185 (169 – 199)
Glucose	mg/dL	94 (87 – 102)	94 (88 – 102)
Hb_{A1c}	%	5.7 (5.4 – 5.9)	5.7 (5.5 – 5.9)

All values are median (interquartile range)
[Mean LDL 104 mg/dL (2.69 mmol/L)]

JUPITER: Pre-specified Monitoring and Stopping Guidelines

- **JUPITER was an event-driven trial designed to continue until accrual of 520 confirmed primary endpoints to attain 90% power to detect a 25% reduction in the rate of the primary endpoint**
- **The monitoring plan specified interim efficacy analyses with O'Brien-Fleming stopping boundaries determined by the Lan-DeMets approach upon attainment of 37.5% and 75% of the targeted numbers of endpoints**
- **The IDMB charter specified that an early stopping recommendation required proof beyond reasonable doubt that for all, or some specific types of patients, prolonged use of rosuvastatin is clearly indicated or clearly contraindicated based on the interim analyses or other sources which might reasonably be expected to influence clinicians' management decisions for subjects in the study. On March 29, 2008 the IDMB voted to recommend termination of the trial after a median follow-up of 1.9 years (maximum 5.0).**

JUPITER: Primary Endpoint



Number at risk

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

JUPITER: Individual Components of the Primary Endpoint

Endpoint	Rosuvastatin	Placebo	HR	95% CI	P
Primary Endpoint*	142	252	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	158	0.52	0.40-0.68	<0.00001
Adjudicated CV Death	35	44	0.80	0.51-1.24	0.32
Total Mortality	198	247	0.80	0.67-0.97	0.02

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

NEJM 2008;359:2195 2207.

JUPITER: Conclusions – Primary Endpoint

- **Among apparently healthy men and women with elevated hsCRP but low LDL-C, rosuvastatin reduced major cardiovascular events by 44%**
- **Benefits of rosuvastatin were consistent regardless of age, sex, region or ethnicity**
- **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**

JUPITER: Conclusions – Secondary Endpoints

- **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**
- **Rosuvastatin allocation was associated with a 27 percent increase in investigator-reported diabetes**
- **With regard to venous thromboembolism, rosuvastatin allocation was associated with a 43 percent reduction in deep vein thrombosis and/or pulmonary embolism**
- **With regard to bone fracture, rosuvastatin allocation was not associated with an increase or decrease in events**

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