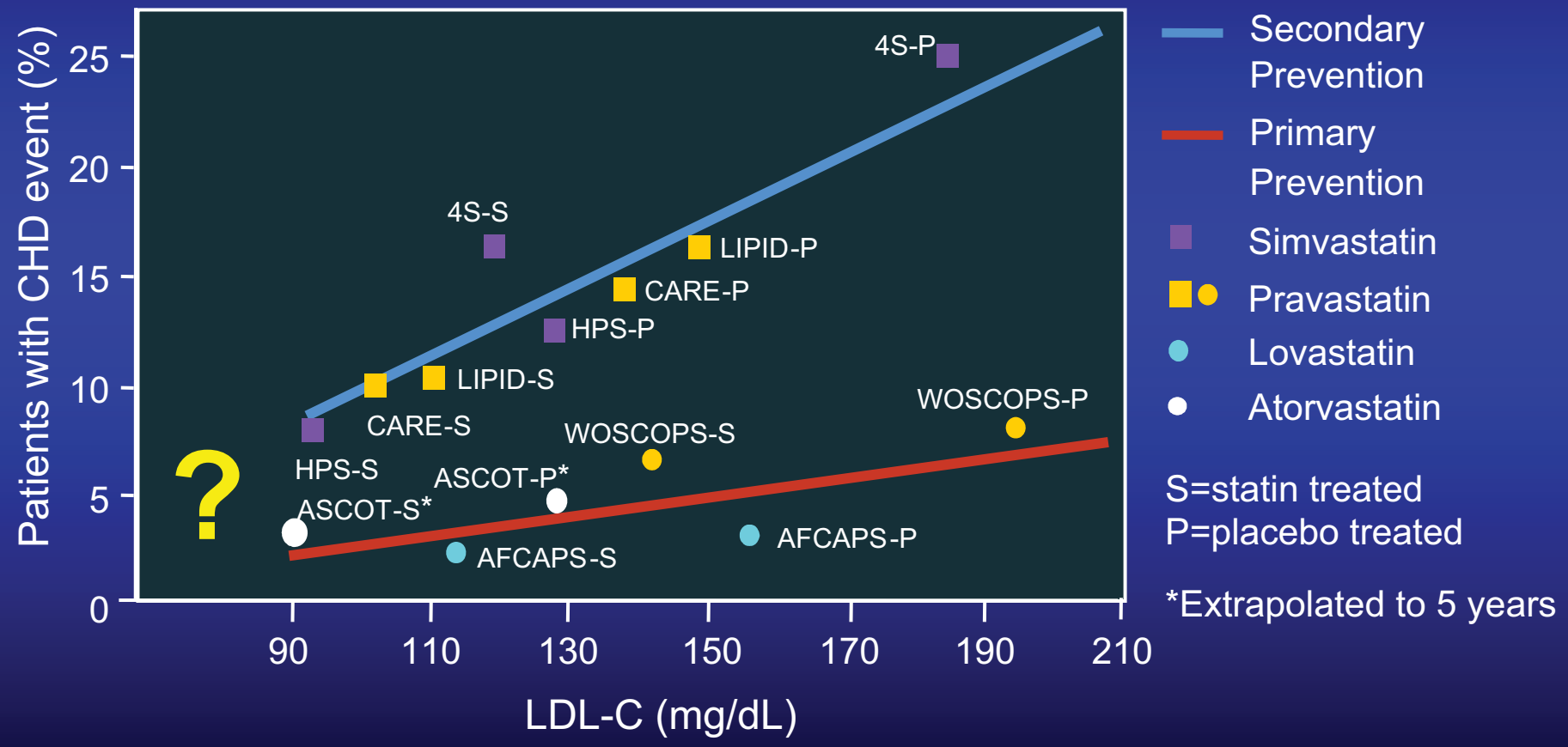
Background

- statins reduce the incidence of death, MI and stroke in patients with chronic CHD, ACS, or those without CHD
- demonstrated in placebo-controlled trials

Effects of statin therapy on CHD events in placebo-controlled trials



Modified from Kastelein JJP. *Atherosclerosis.* 1999;143(Suppl 1): S17-S21.

Mechanism of benefit from statin is uncertain

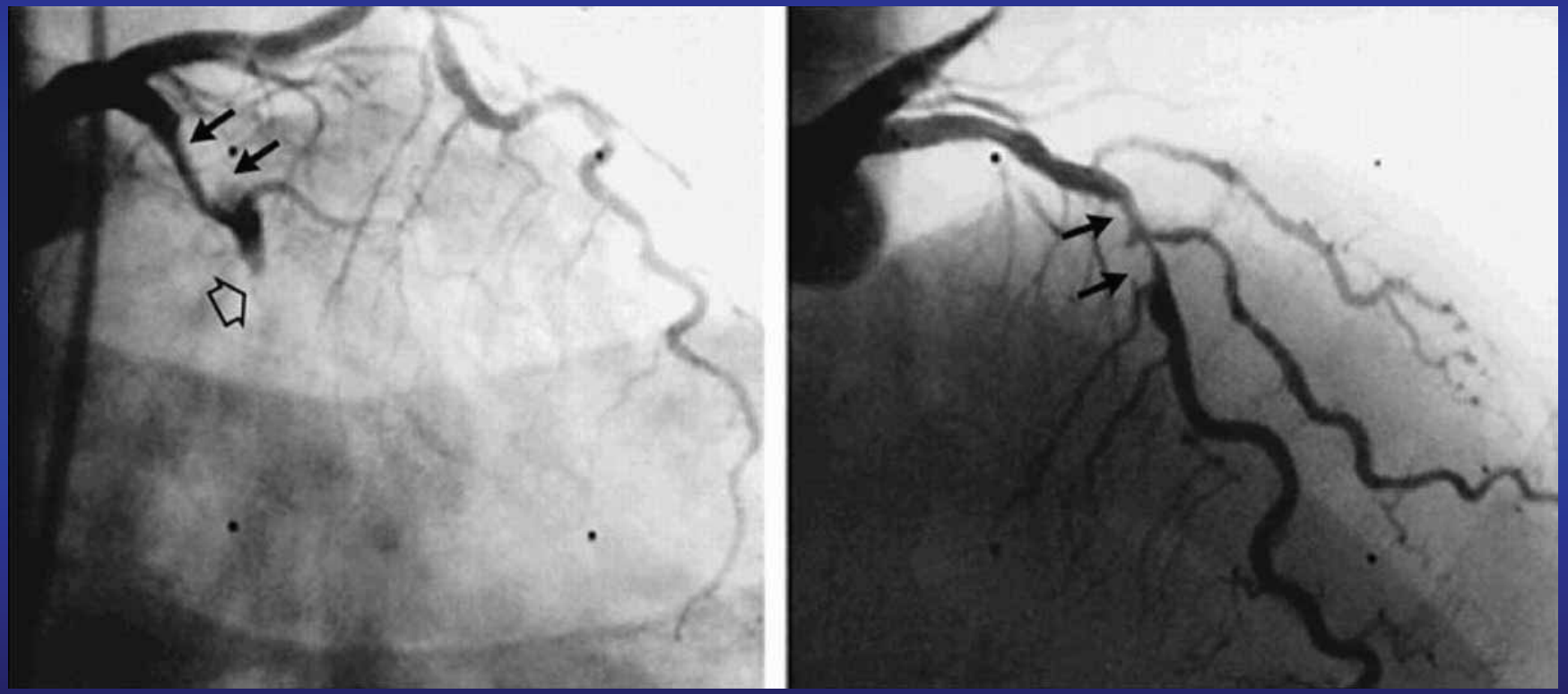
- LDL cholesterol reduction is important
- there are other effects of statins [anti-inflammatory effects etc]
- UK Heart Protection Study (with simvastatin) showed benefit at high or low initial LDL cholesterol

New and important questions have emerged

- how low to go with LDL cholesterol?
- is aggressive LDL cholesterol reduction better than moderate LDL reduction?

Atorvastatin 80mg/day and Pravastatin 40mg/day have now been directly compared in 2 recently published trials and this has led to remarkable insight into lesion progression and clinical outcomes

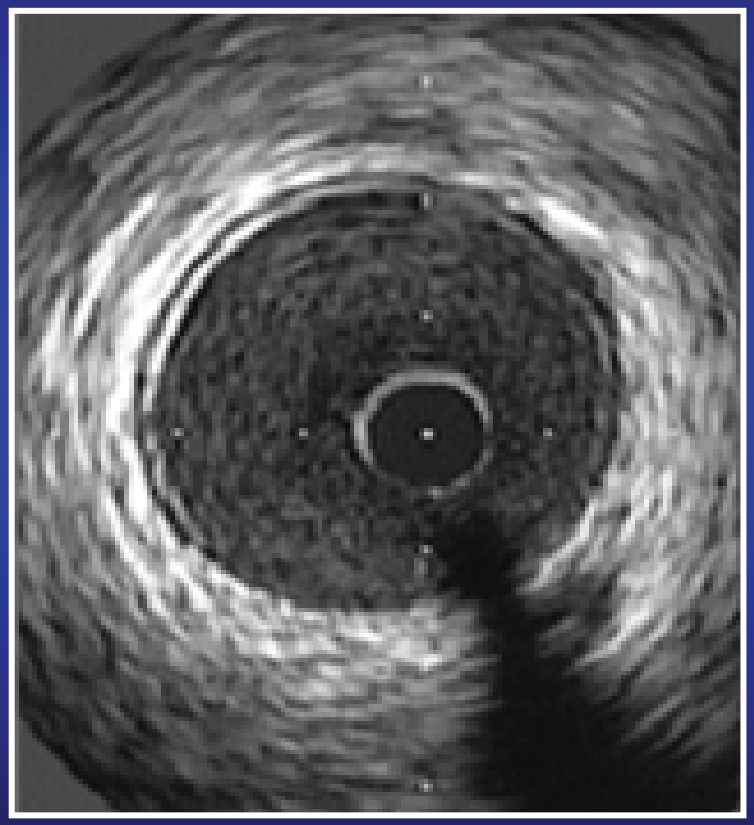
- **REVERSAL trial – an imaging study using IVUS** [Nissen SE et al. JAMA 2004;291:1071-80]
- **PROVE-IT – a clinical outcomes study** [Cannon CP et al. N Engl J Med 2004;350:1495-504]



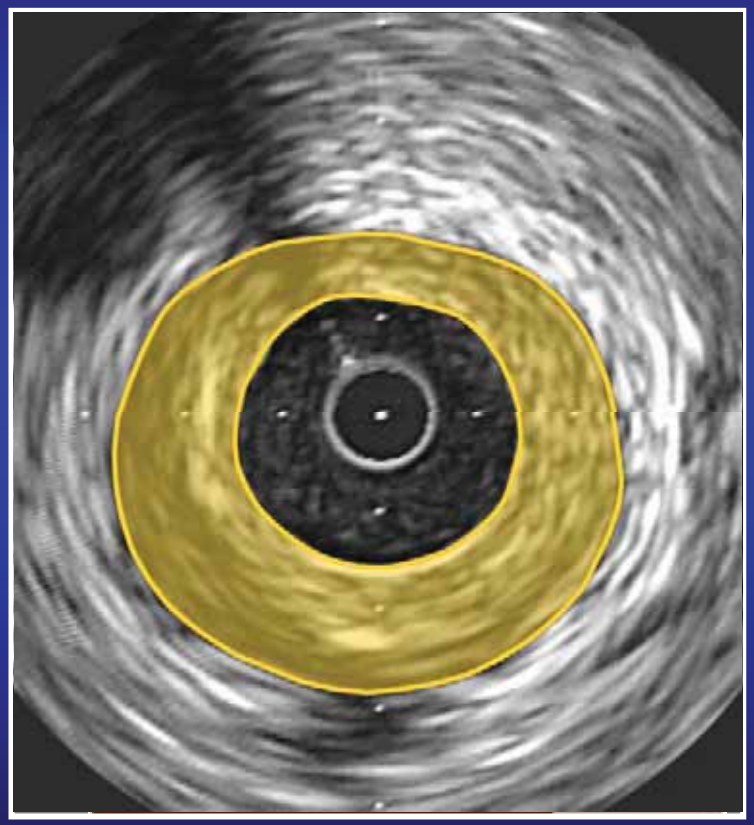
Rationale for selecting IVUS for REVERSAL

- Angiography is often insufficient to detect early- to mid-stage atherosclerotic disease
- Early atherosclerotic plaque confers risk of clinical events even in the absence of significant stenosis
- IVUS provides a more sensitive method for assessing the impact of lipid-lowering therapy on progression of atherosclerosis

IVUS: Normal and diseased anatomy

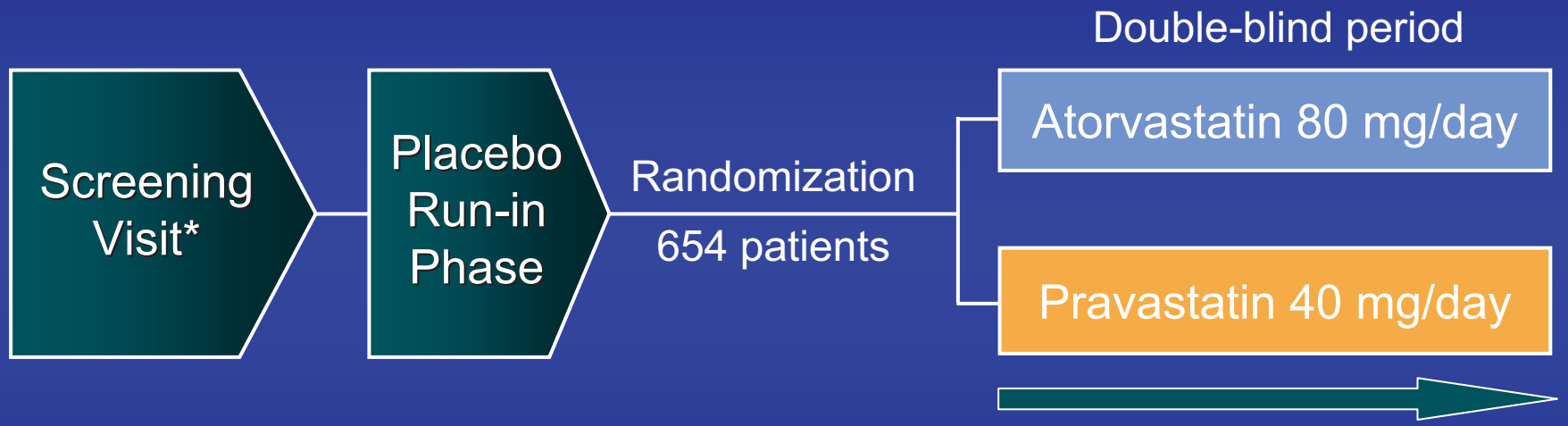


Normal Anatomy



Concentric Disease

REVERSAL: Study design



*Includes baseline intravascular ultrasound (IVUS)

18-month follow-up with IVUS

Design – Prospective, randomized, double-blind, multicenter trial

Setting – 34 community and tertiary care hospitals in the United States

REVERSAL: Patient population

- Inclusion criteria:
  - Patients requiring diagnostic coronary angiography for a clinical indication
  - Aged 30-75 years
  - LDL-cholesterol 125-210 mg/dL (3.2-5.4 mmol/L)
  - TG <600 mg/dL (6.8 mmol/L)
- Angiographic inclusion criteria:
  - Angiographic evidence of CHD defined as ≥1 lesion with ≥20% reduction in lumen diameter in any coronary artery
  - ≤50% reduction in lumen diameter of the left main coronary artery
  - The vessel undergoing IVUS evaluation (the 'target' vessel) should have ≤50% stenosis throughout a segment of minimum length 30 mm

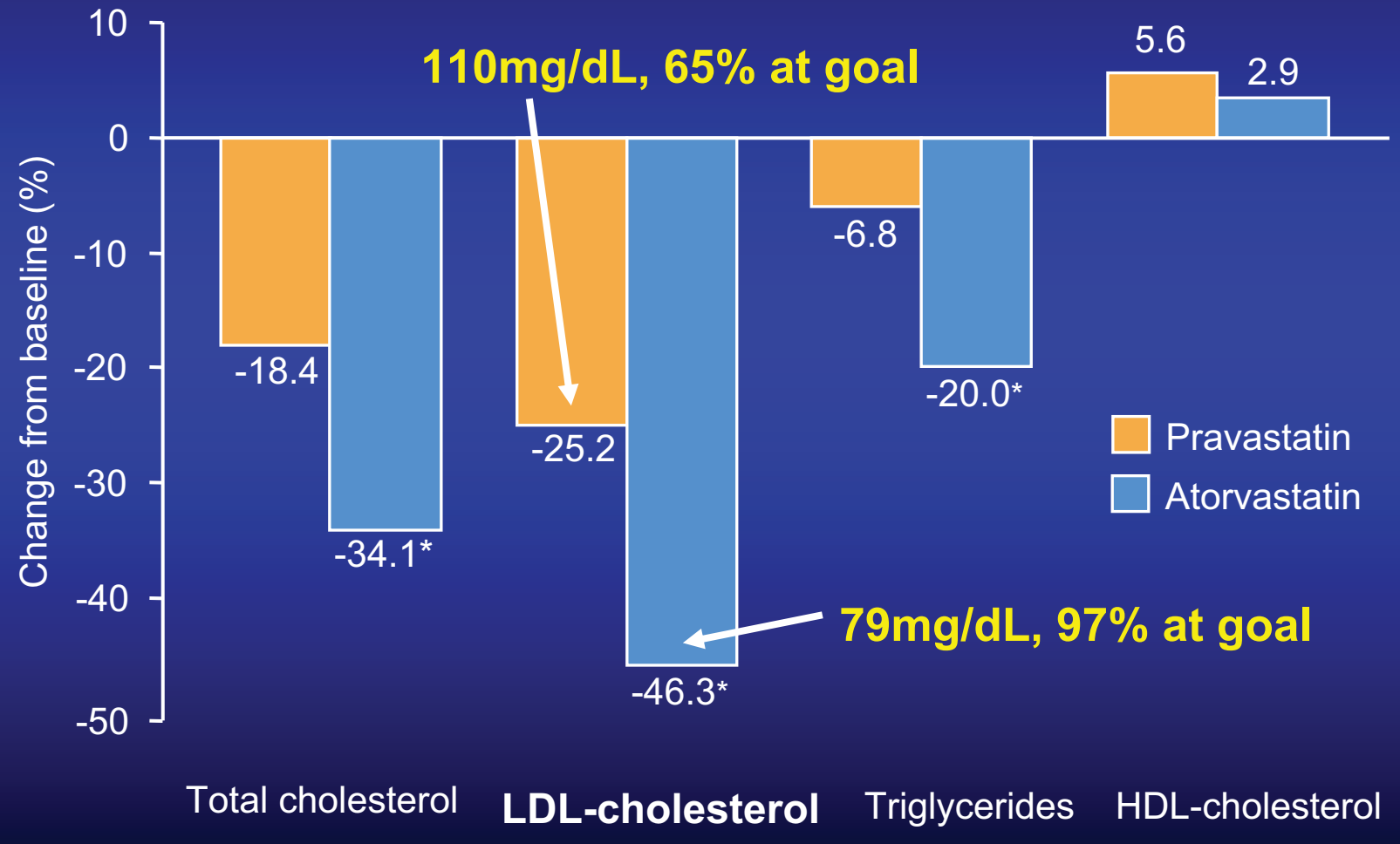
REVERSAL: Baseline characteristics

Characteristic	Atorvastatin 80 mg (n=253)	Pravastatin 40 mg (n=249)
Age* (years)	56	57
Male (%)	71	73
Body mass index (kg/m^2)	30.5	30.5
Current smoker (%)	26	27
Diabetes (%)	20	18
Hypertension (%)	68	70
TC* (mg/dL[mmol/L])	232 [6.0]	233 [6.0]
LDL-C* (mg/dL[mmol/L])	150 [3.9]	150 [3.9]

NCEP ATP III LDL-C Treatment Goals

Risk Category	LDL-C Goal (mg/dl)
CHD or CHD Risk Equivalents (10-year risk >20%)	<100
2+ Risk Factors (10-year risk ≤20%)	<130
0–1 Risk Factor	<160

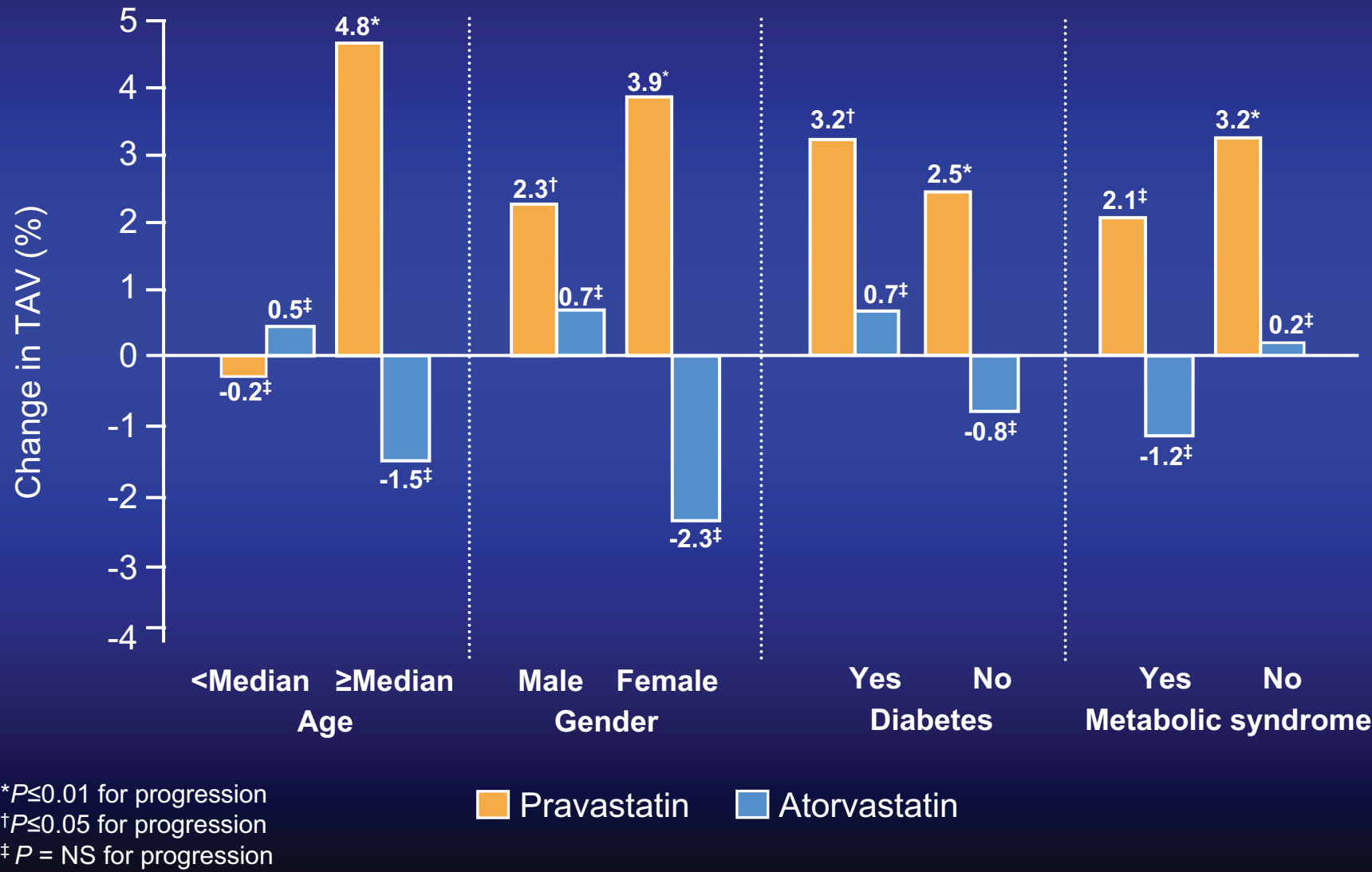
Change from baseline in lipid parameters



*P<0.001 vs pravastatin

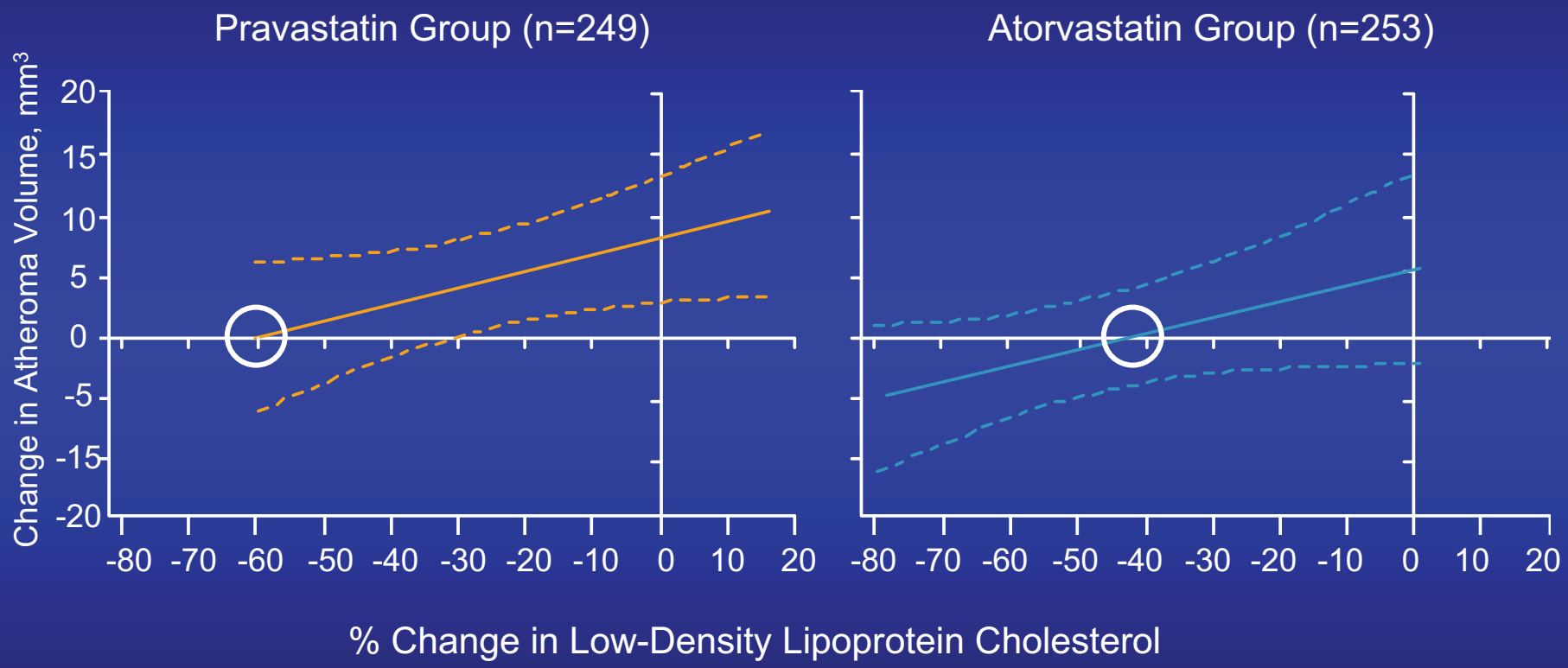
Data are mean percent change from baseline to 18-month follow-up.

Selected prespecified subgroup analyses



*$P \leq 0.01$ for progression
†$P \leq 0.05$ for progression
‡ P = NS for progression

LDL-C reduction and change in atheroma volume



Patients receiving pravastatin who experienced LDL-C reductions >50% continued to show disease progression.

The progression rate at any level of LDL-C reduction was lower with atorvastatin than with pravastatin.

The dashed lines indicate upper and lower 95% CIs for the mean values

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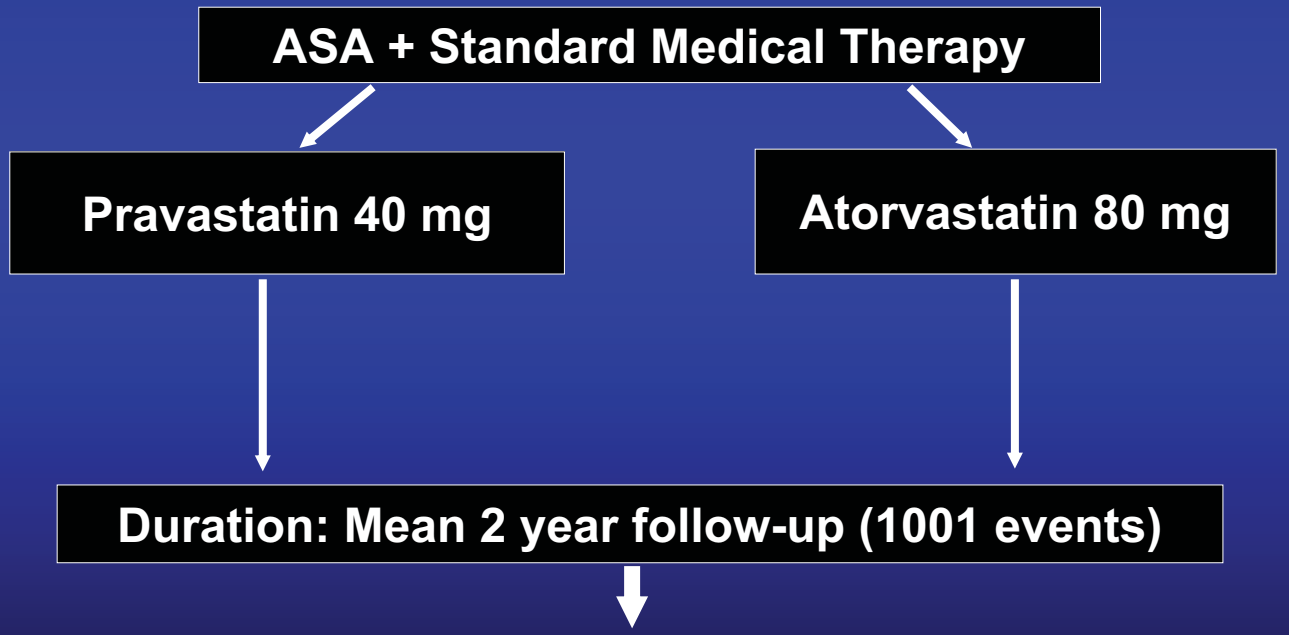
PROVE-IT: study design

Double-blind, randomized trial in 4,162 patients with Acute Coronary Syndrome <10 days and Total Cholesterol ≤ 6.2 mmol/L



Primary Endpoint: Death, MI, Documented UA requiring hospitalization, revascularization (> 30 days after randomization), or Stroke

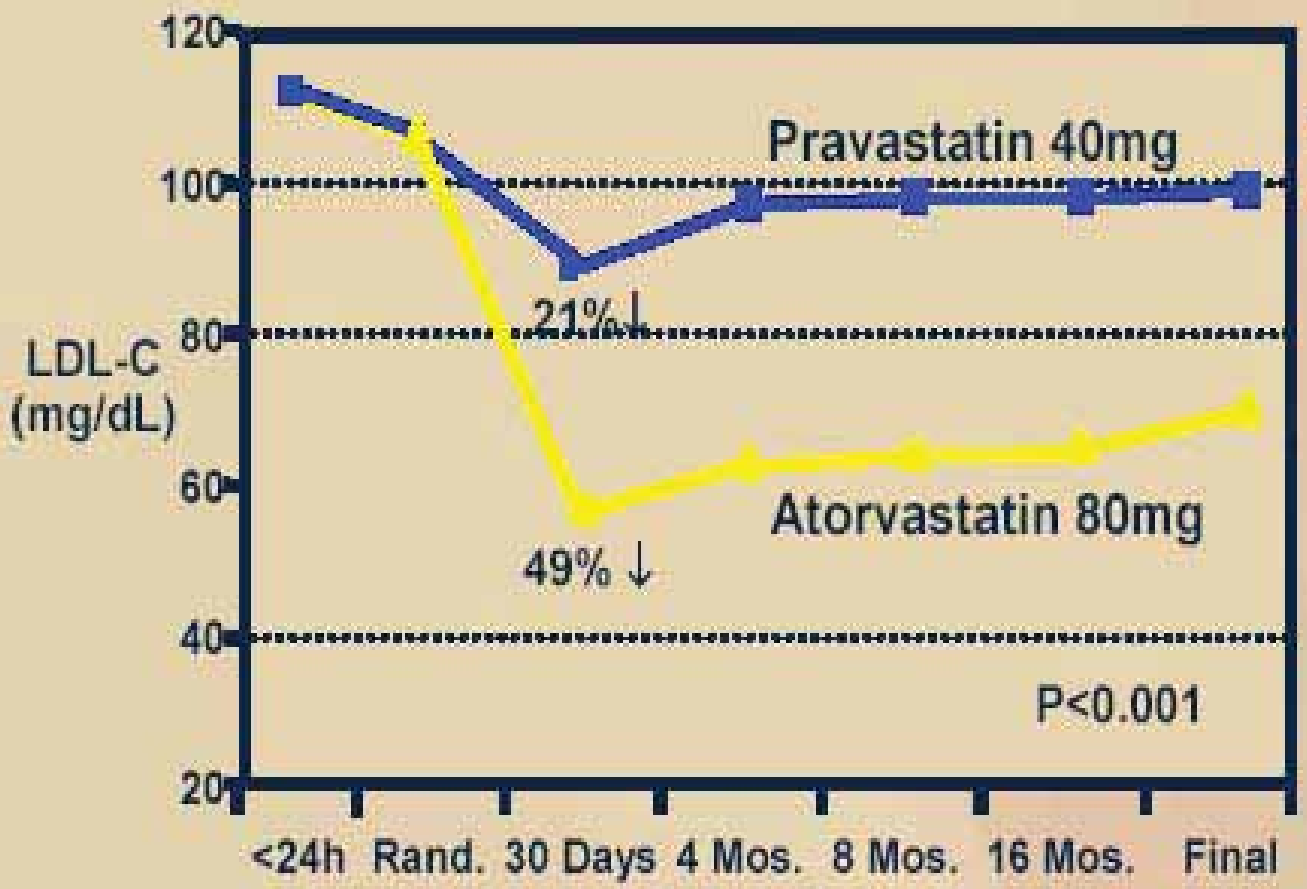
Concomitant therapies

PCI for initial ACS	69%
Aspirin	93%
Warfarin	8%
Clopidogrel (initial) (at F/U)	72% 20%
β-blockers	85%
ACE	69%
ARB	14%

PROVE-IT: baseline characteristics

	Atorvastatin 80mg (2099)	Pravastatin 40mg (2063)
Mean Age (years)	58	58
Male (%)	78	78
History of Hypertension (%)	51	49
Current Smoker (%)	36	37
History of Diabetes (%)	19	18
History of CHD (%)	37	39
UA/NSTEMI/STEMI (%)	30 / 37 / 33	29 / 36 / 36
Prior Statin Use (%)	26	25

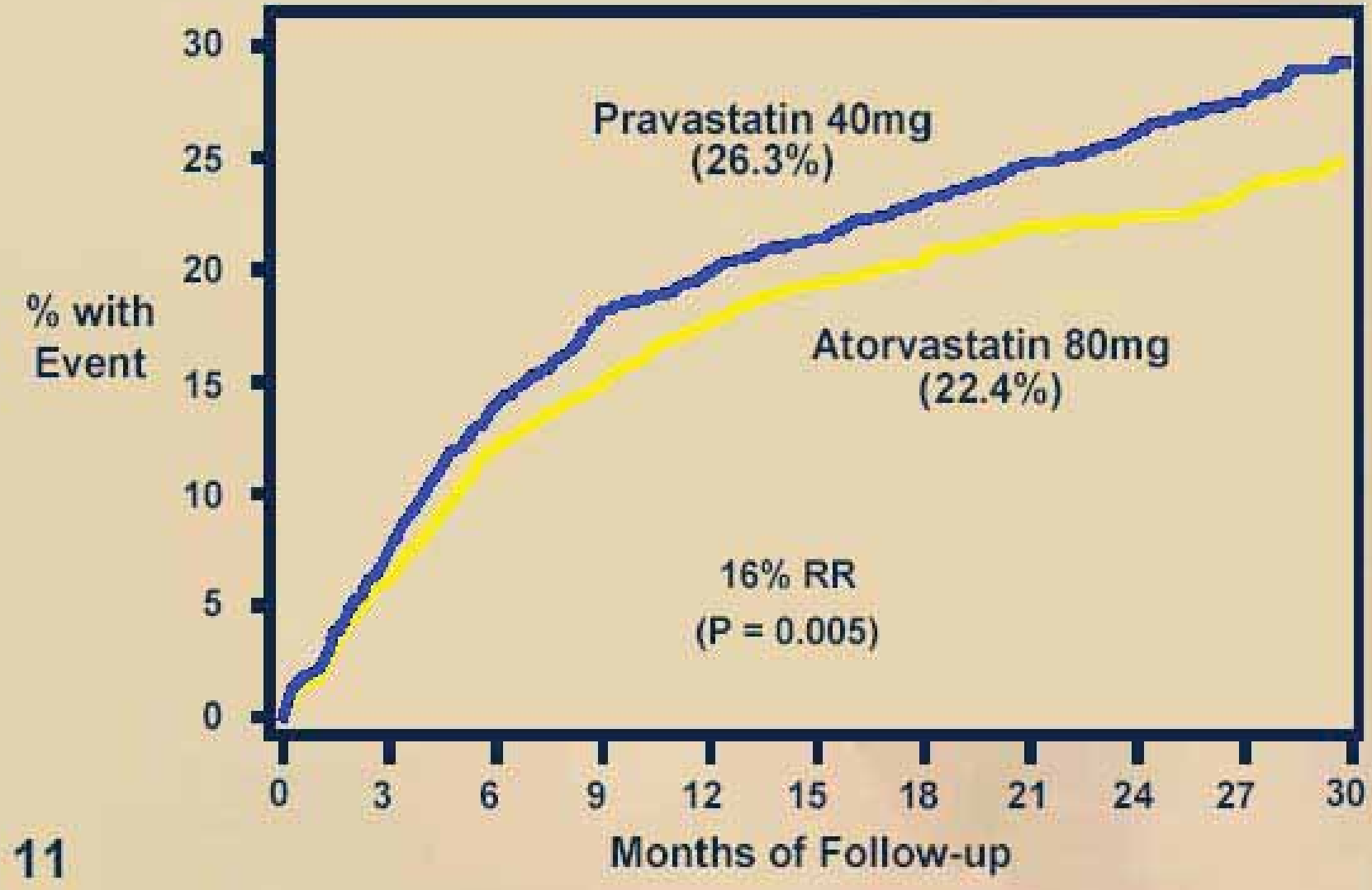
Changes from (Post-ACS) Baseline in Median LDL-C



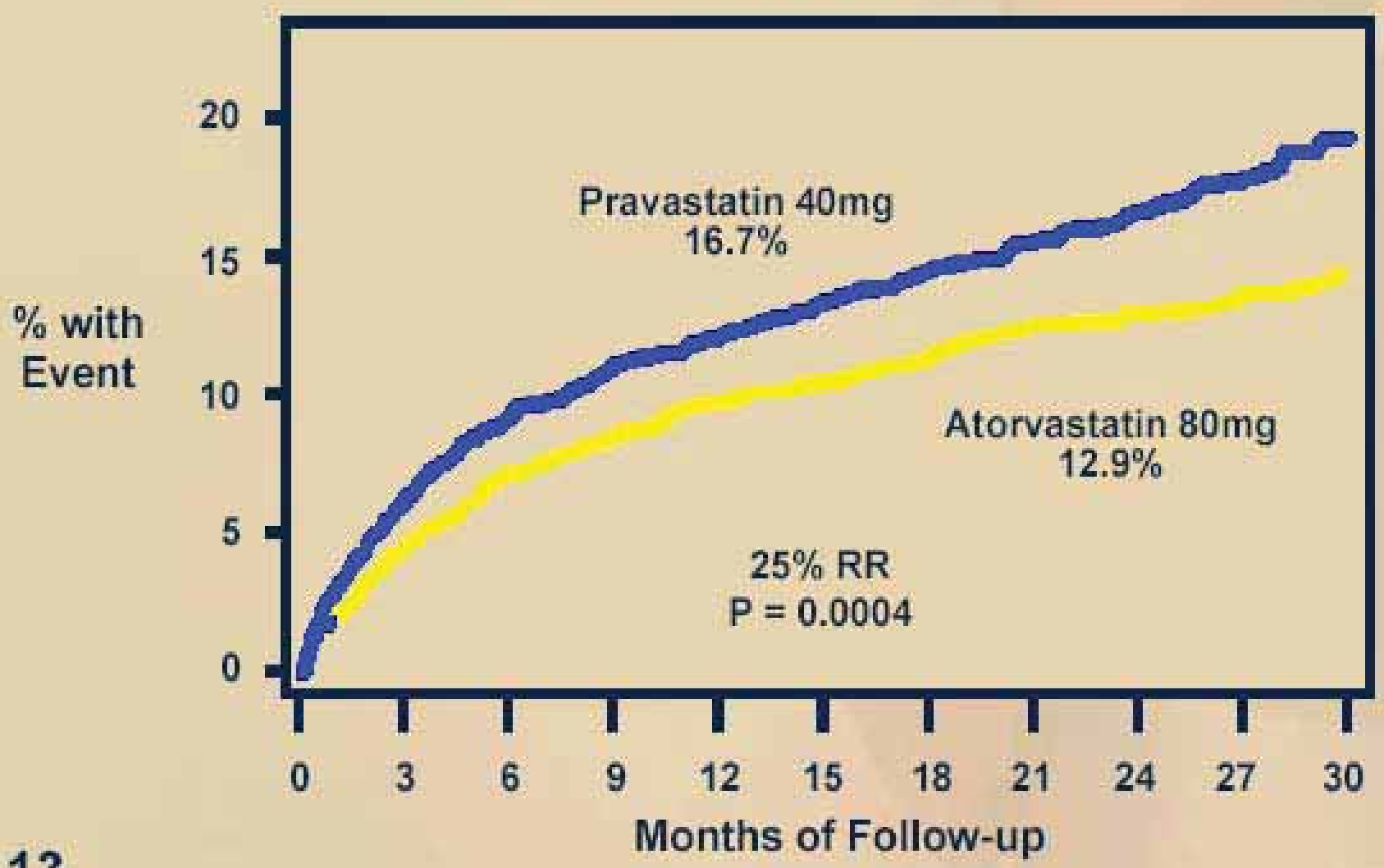
Median LDL-C (Q1, Q3)
95 (79, 113)
82 (60, 79)

Cannon CP et al. N Engl J Med 2004;350:1495-504

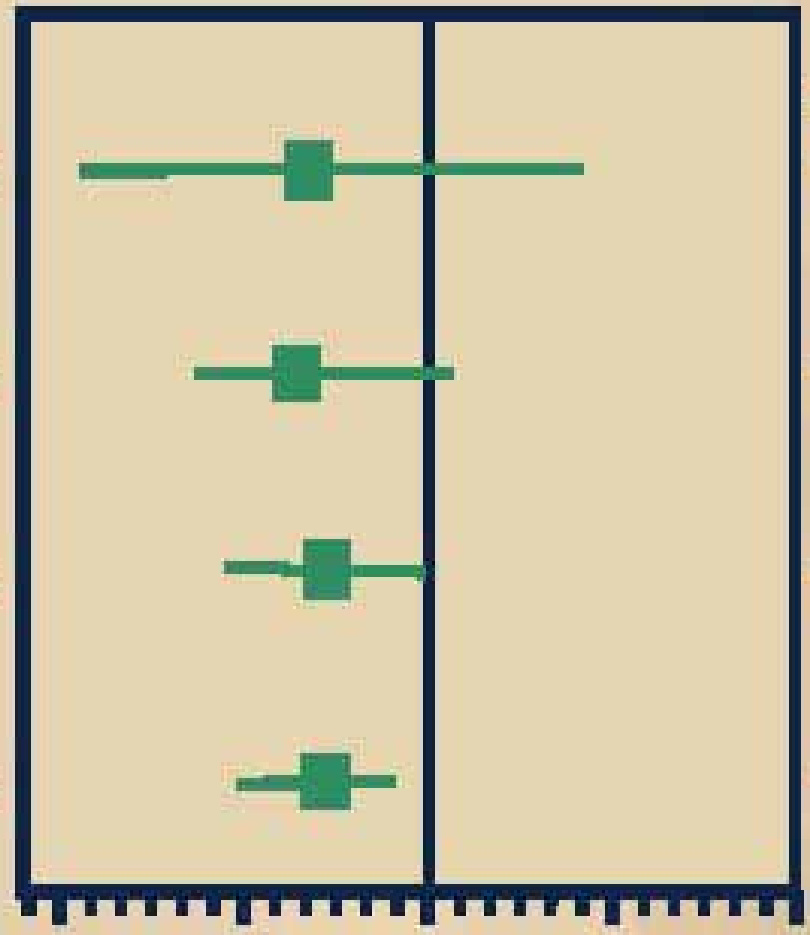
All-Cause Death or Major CV Events in All Randomized Subjects



All-Cause Death, Non-Fatal MI, or Urgent Revascularization



Primary Endpoint Over Time



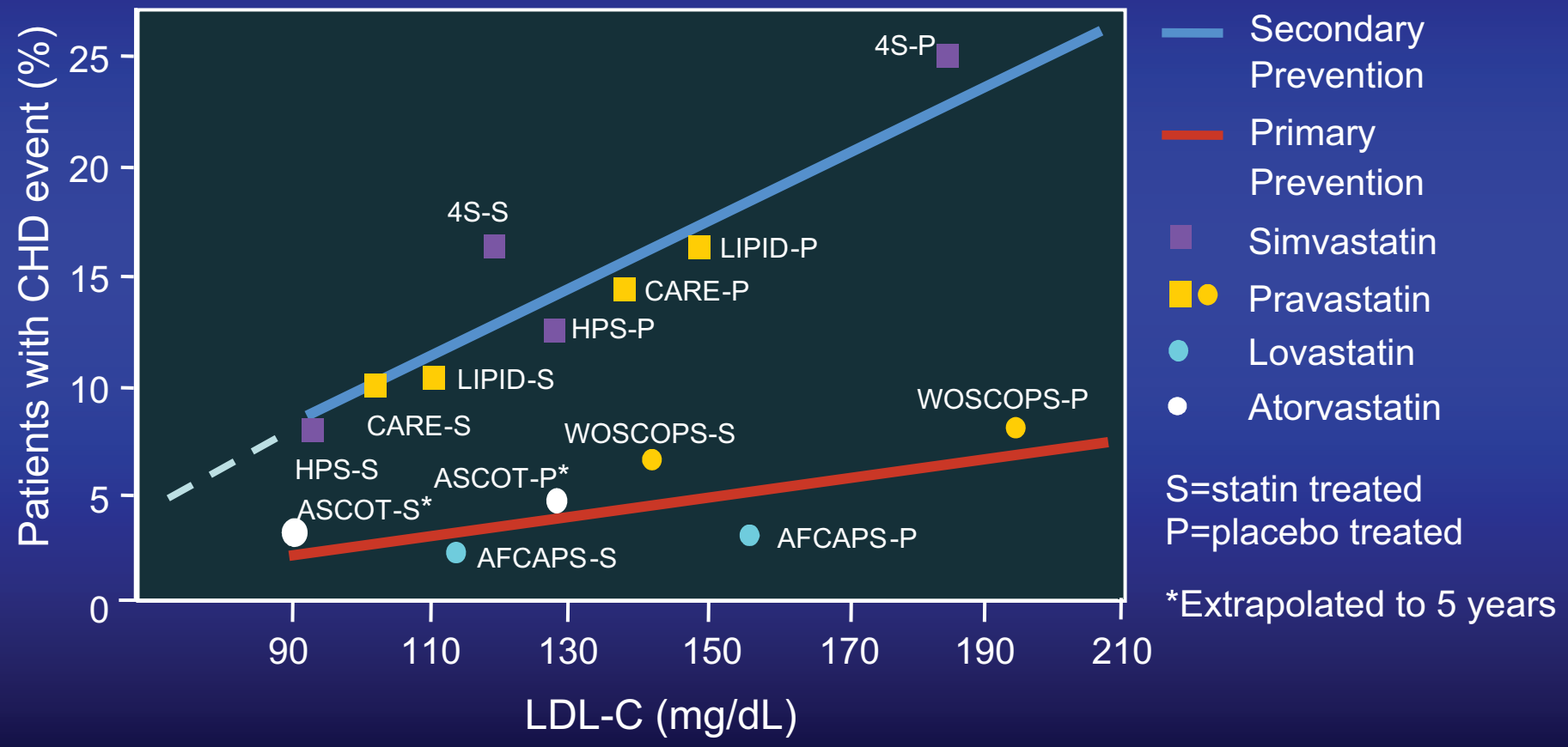
	Events Rates		
	RR	Atorva 80	Prava 40
30 Days	17%	1.9%	2.2%
90 Days	18%	6.3%	7.7%
180 Days	14%	12.2%	14.1%
End of Follow-up	16%	22.4%*	26.3%*

*2-year event rates

Liver and Muscle Effects

	Atorvastatin 80mg	Pravastatin 40mg	P-value
ALT ≥ 3 ULN	3.3%	1.1%	<0.001
CK ≥ 3 ULN	1.5%	1.1%	0.24
D/C for Myalgia/CK elevations	3.3%	2.7%	0.23

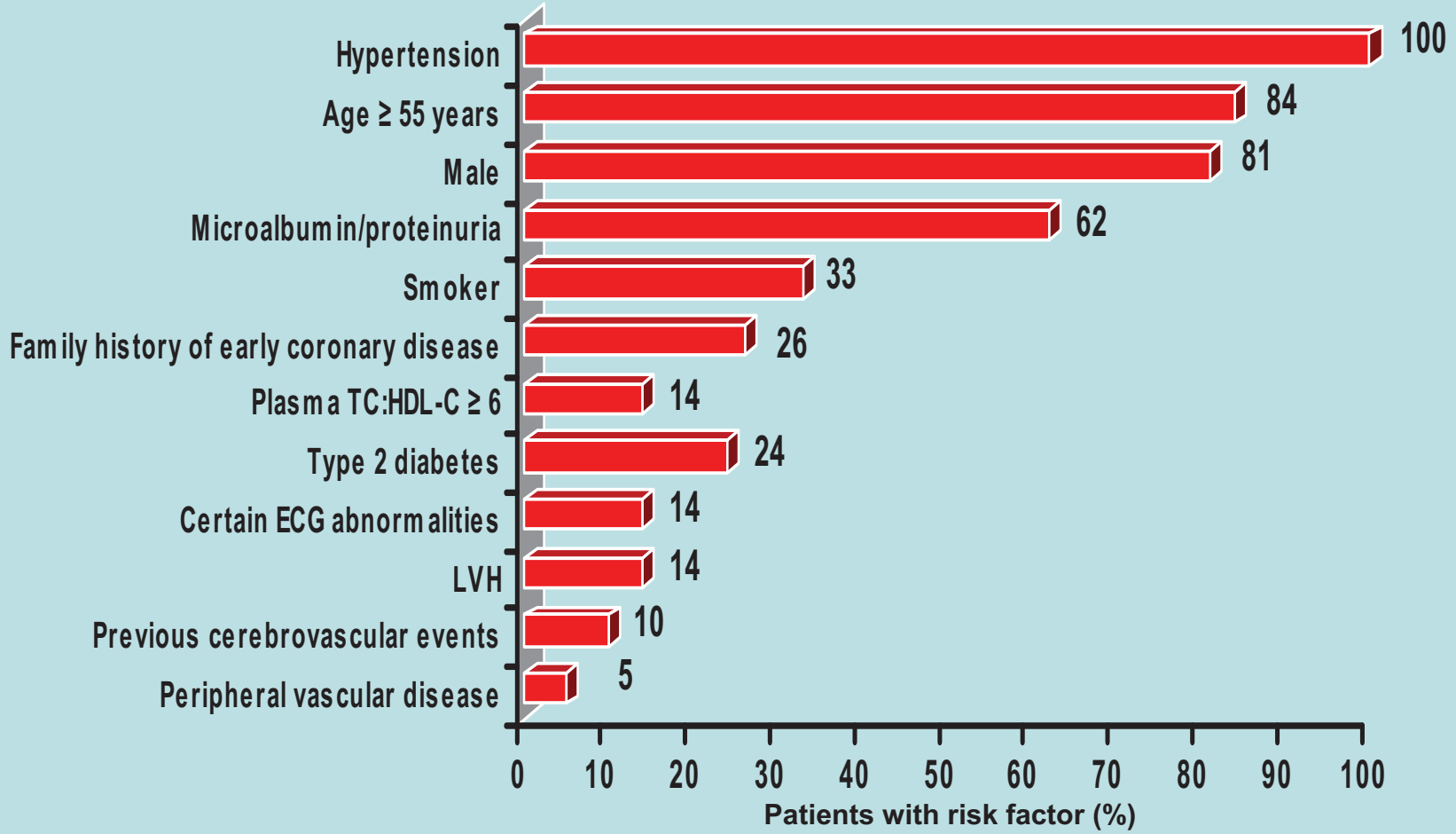
Effects of statin therapy on CHD events in placebo-controlled trials



Modified from Kastelein JJP. *Atherosclerosis.* 1999;143(Suppl 1): S17-S21.

ASCOT LLA: Risk Factor Profile

All patients in ASCOT have hypertension plus ≥3 risk factors for CHD



Sever PS, Dahlöf B, Poulter N, Wedel H, et al, for the ASCOT Investigators. Lancet. 2003;361:1149-58

Conclusions from REVERSAL and PROVE-IT

In patients with demonstrated CAD

- intensive therapy with atorvastatin reduces progression of atherosclerosis compared to moderate therapy using pravastatin
- patients treated with atorvastatin 80mg had no change in atherosclerosis burden, those treated with pravastatin 40mg had progression of coronary atherosclerosis

Conclusions from REVERSAL and PROVE-IT

In patients with ACS

- the differential effect of atorvastatin versus pravastatin seen with IVUS appears to translate into greater protection against death or a major CV event
- this effect emerges within 30 days and is maintained over several years
- there may be a need to re-define LDL treatment targets in patients with CHD

Conclusions from REVERSAL and PROVE-IT (and other studies)

- these and other studies justify aggressive lipid therapy in all patients without diagnosed CAD but who may be at increased coronary risk by virtue of the presence of multiple risk factors

- the different statins may not be equivalent in this role