Early use of Statins In Acute Coronary Syndromes

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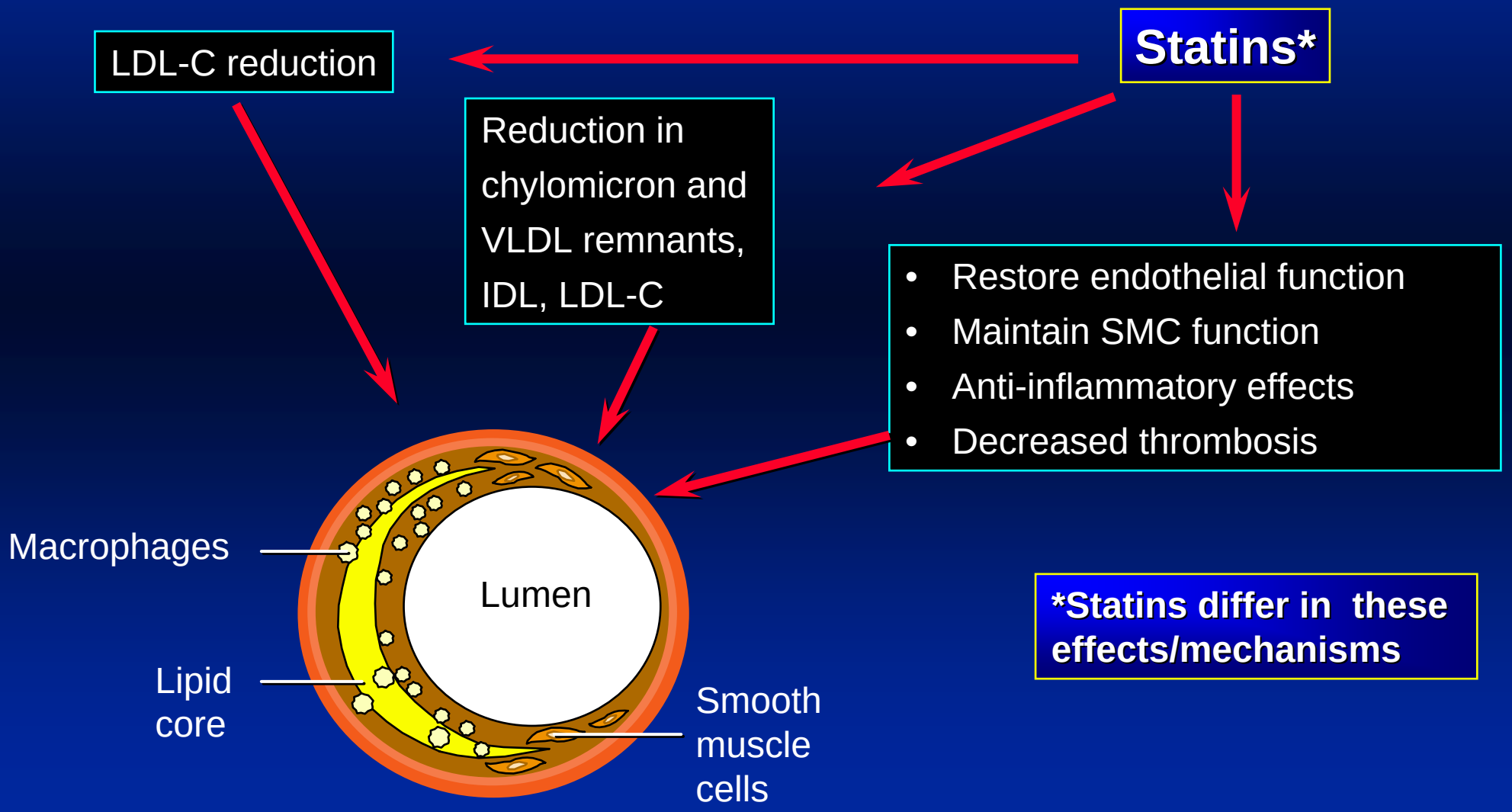
Early Statin Use and Outcomes
Background

- Secondary prevention benefit
- Non-lipid effects of statins
- Improved compliance
- Registries:
  - Supporting data for improved outcome
    - Pursuit
    - Registry of information and Knowledge
    - Prism Plus
    - Tactics
  - Non-supporting data for improved outcome
    - Symphony 1 & 2
- Randomized trials:
  - Miracl
  - PROVE-IT

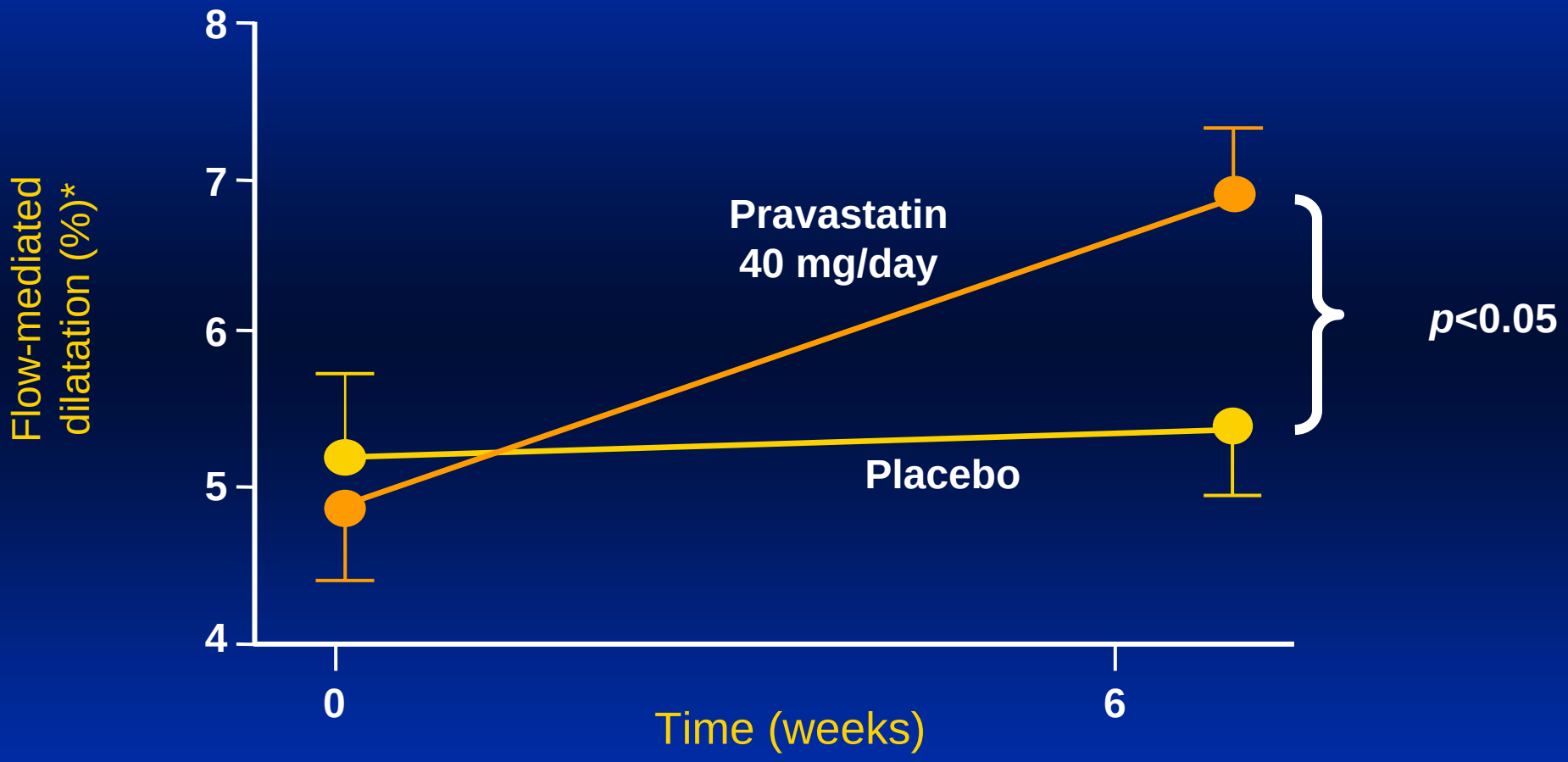
Rationale for early statin therapy

• Gives constant reduction in risk	most effective when absolute risk is highest and benefit begins sooner
• May stabilise plaque	maximum benefit when given early
• Other non-lipid-lowering effects	anti-inflammatory, anti-thrombotic etc
• Patients already in hospital	patients are more likely to comply with therapy
• Discharged on statin therapy	underscores the need for continued therapy and improves compliance

Potential mechanisms of benefit of statins in ACS



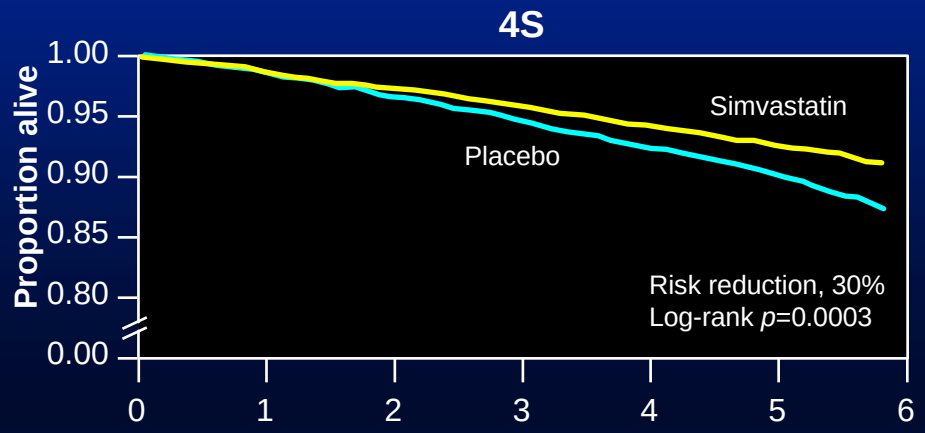
The RECIFE study: Pravastatin rapidly improves endothelial function after ACS

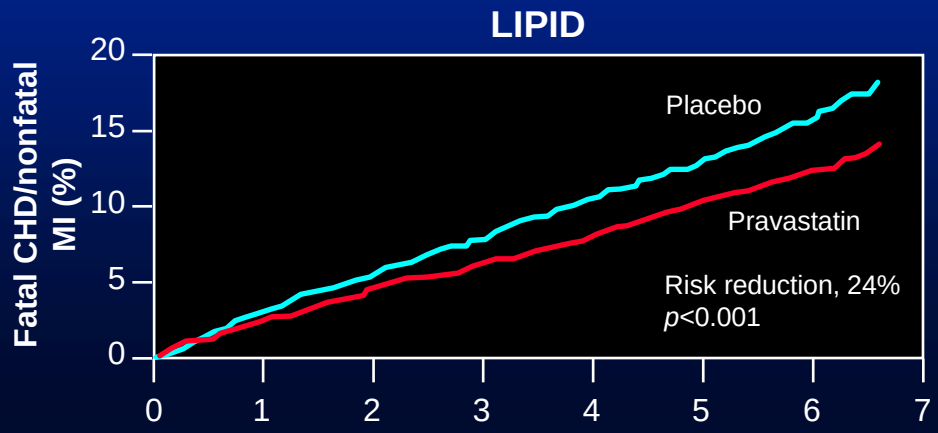


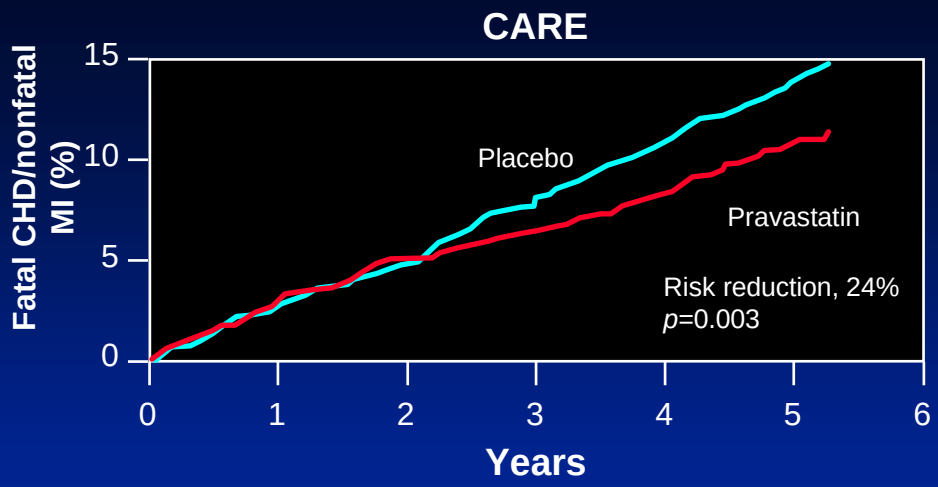
***60 patients admitted for acute MI or unstable angina, enrolled before hospital discharge**

Dupuis JACC 1998;31:380A

Early secondary prevention trials only focused on long-term event reductions in stable patients



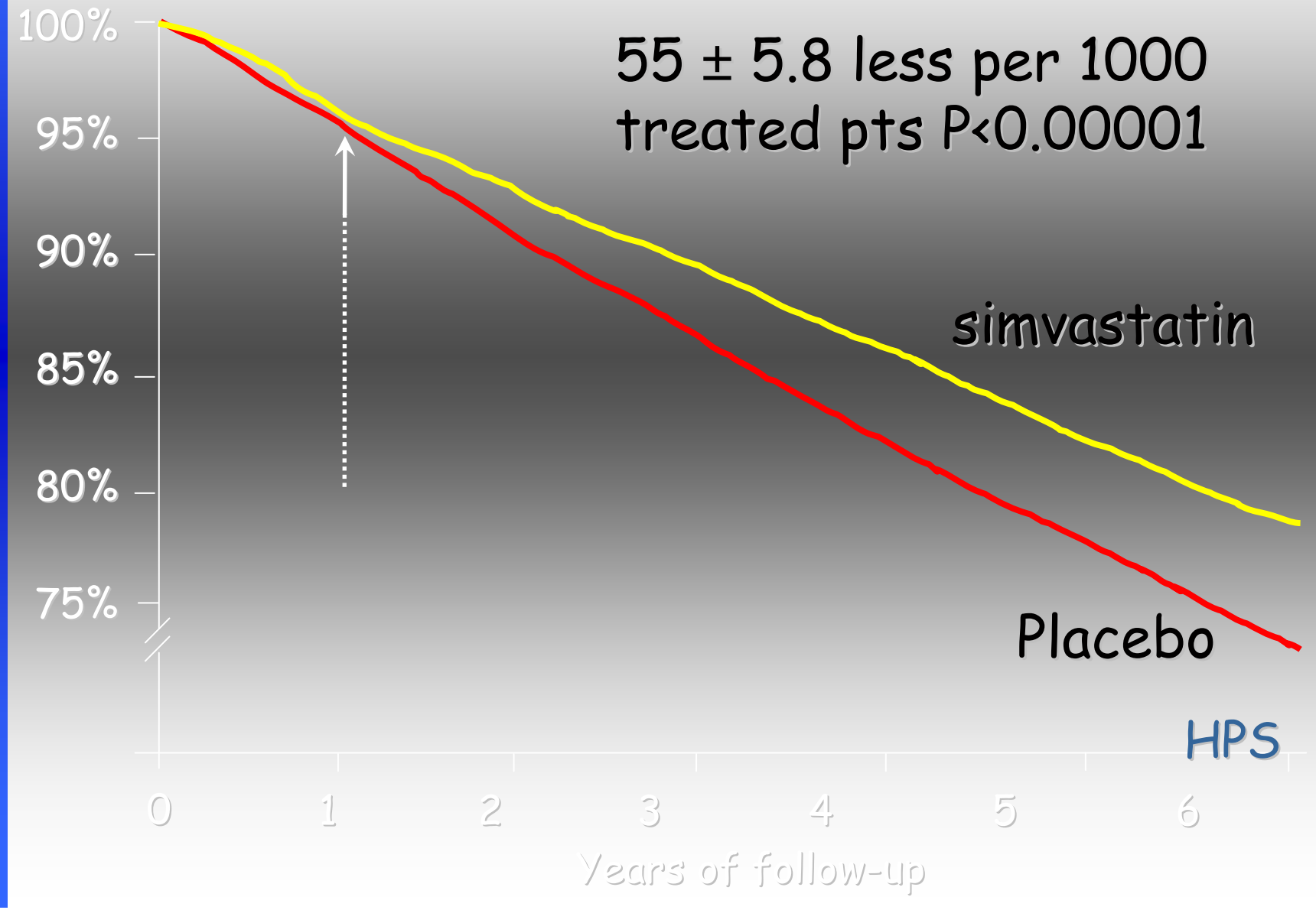


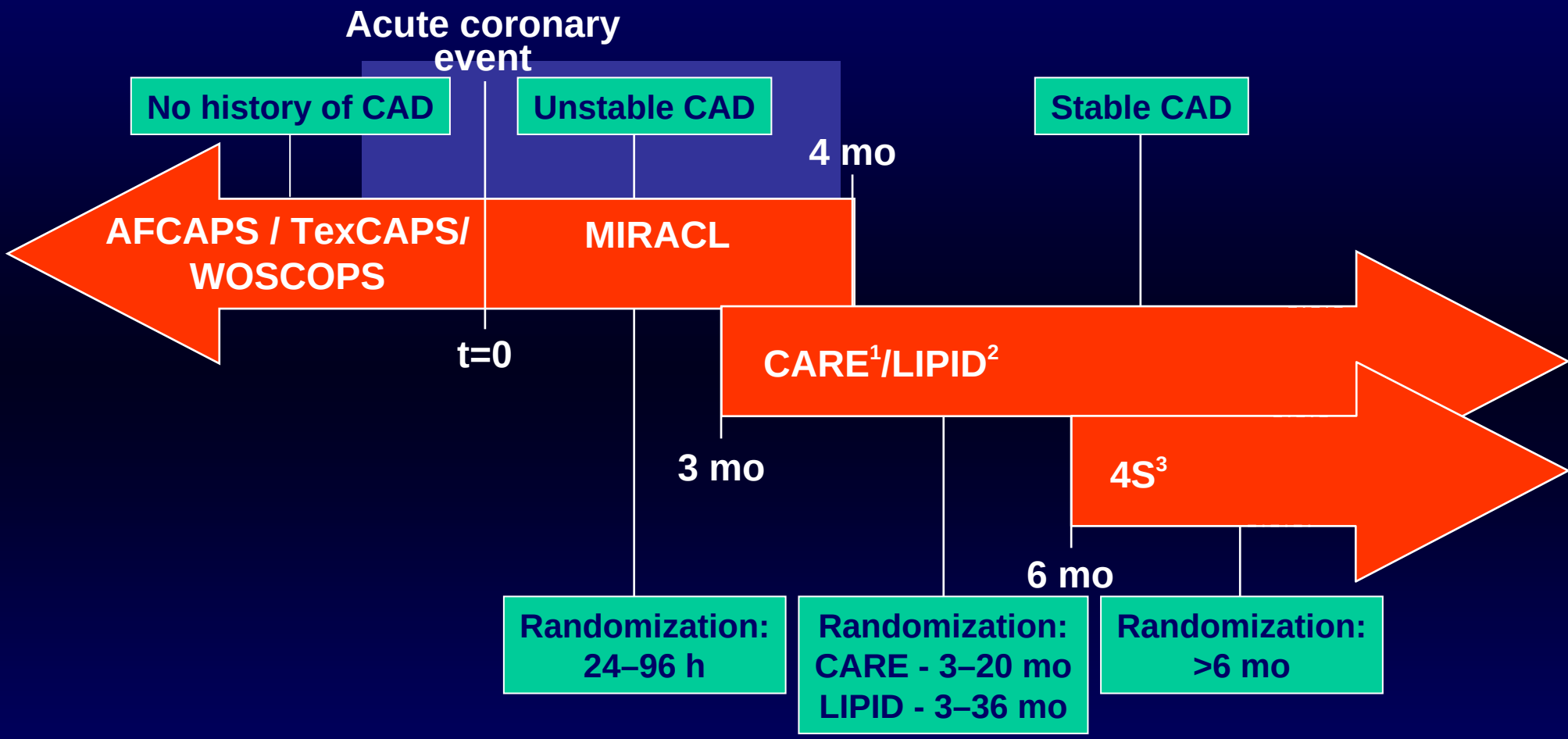


4S Study Group. *Lancet* 1994;**344**:1383–1389.
Sacks FM *et al*. *N Engl J Med* 1996;**335**:1001–1009.
LIPID study group. *N Engl J Med* 1998;**339**:1349–1357.

Vascular Events during Follow-up

Death, MI, stroke, or revascularization

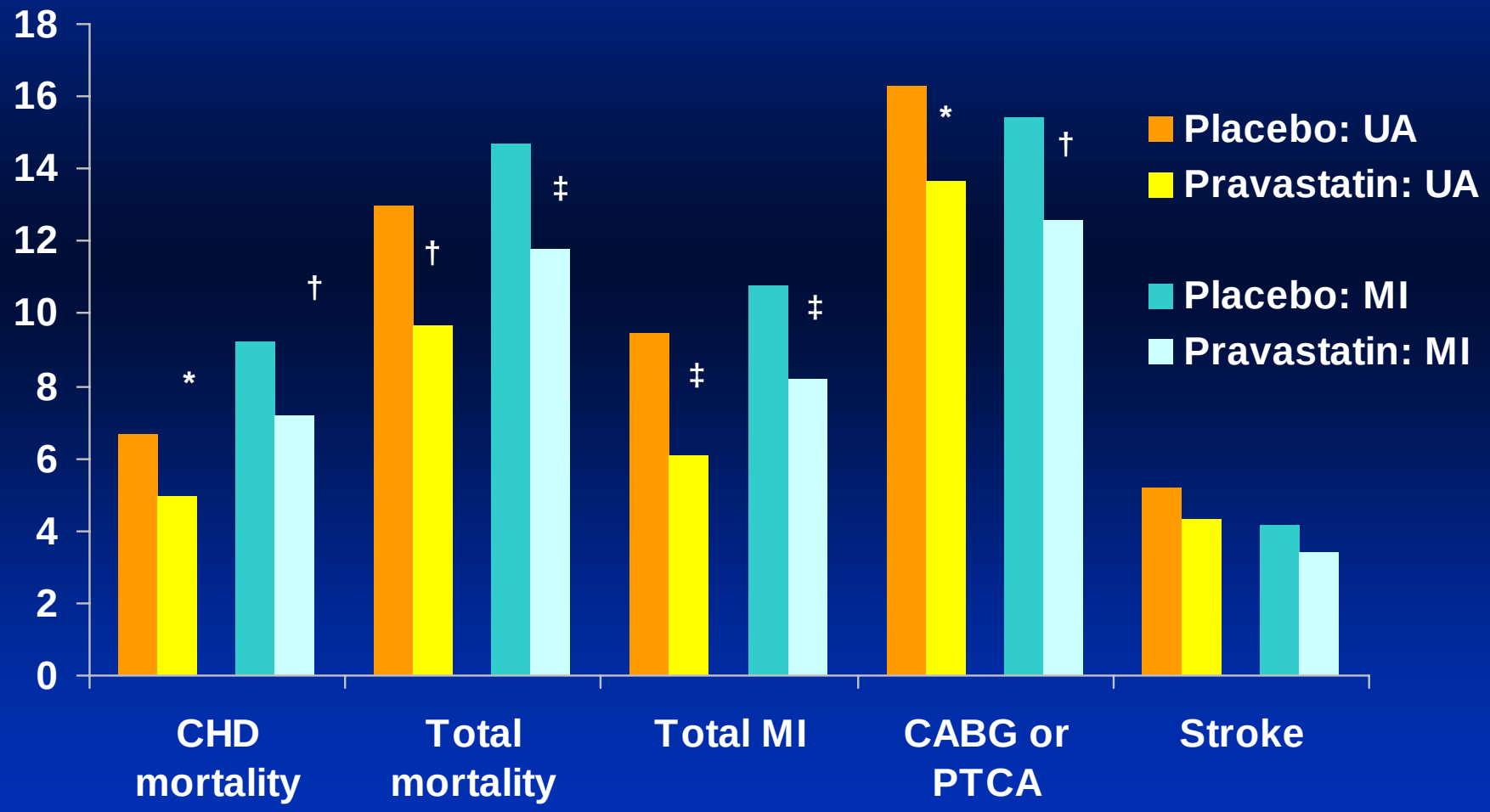




Duration of follow-up: [1]5.0 years; [2]6.1 years; [3]5.4 years.

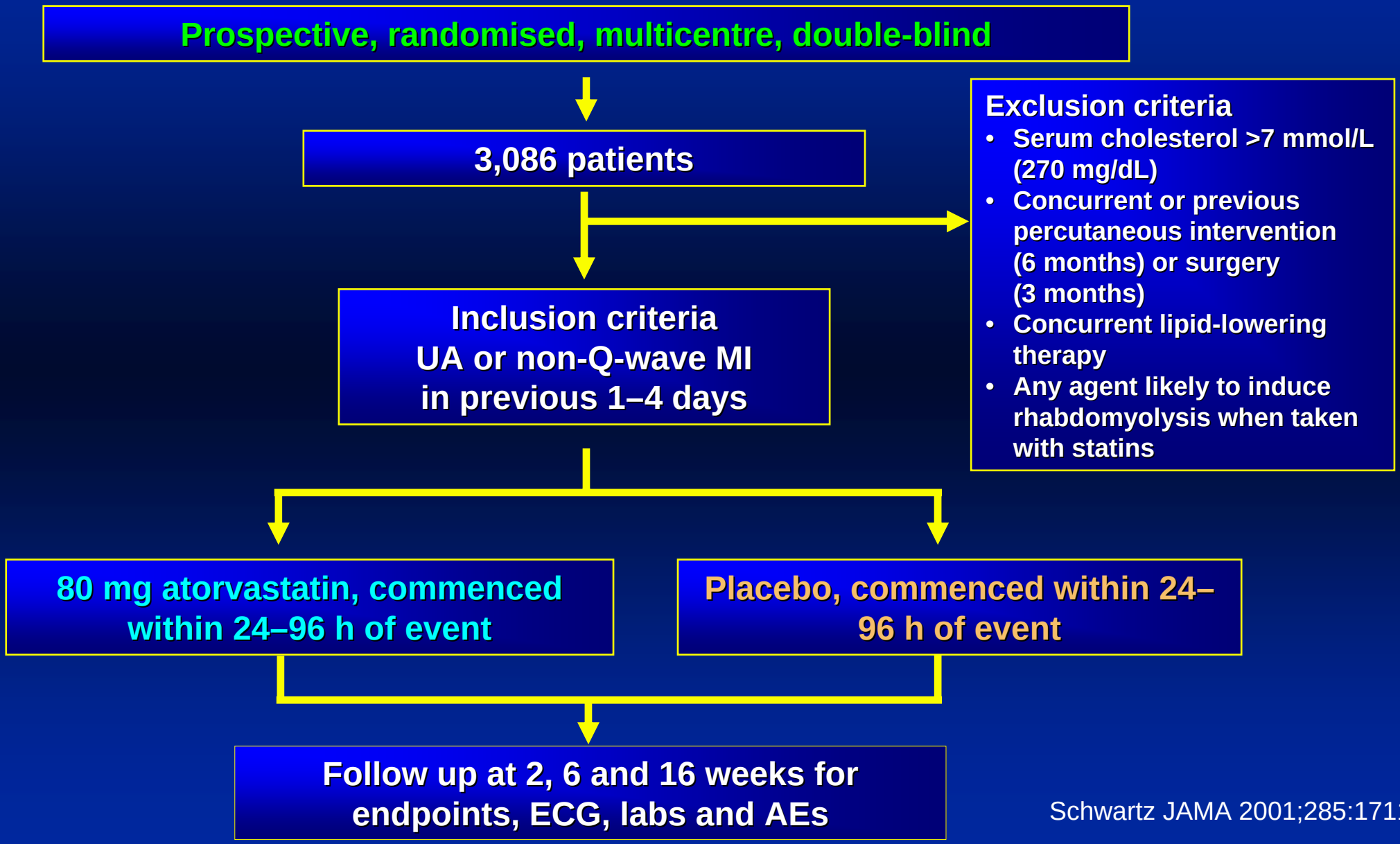
Schwartz GG *et al. Am J Cardiol* 1998;**81**:578–581.

Event rates in four groups



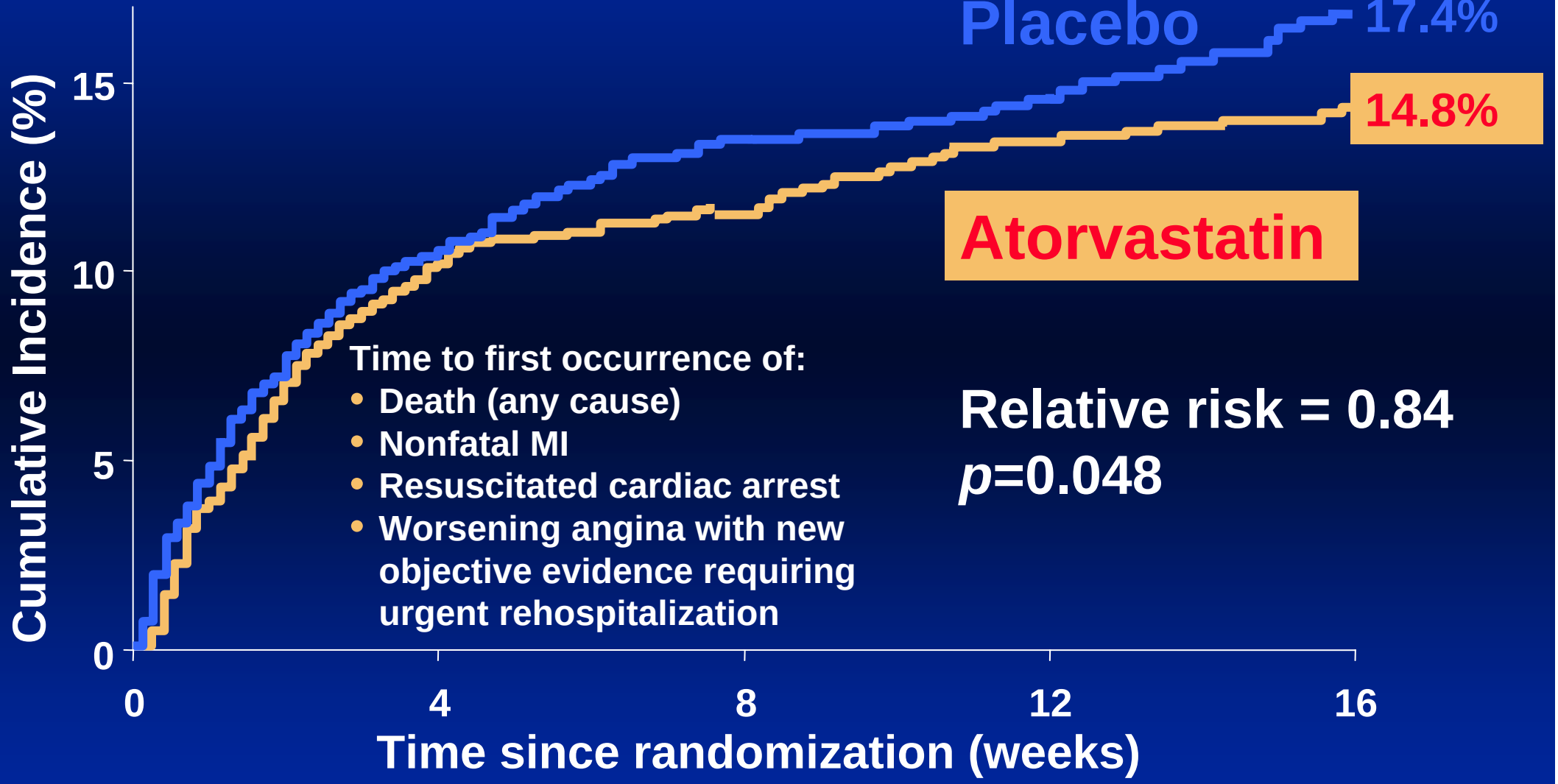
*P<0.05 †P<0.01 ‡P<0.001

MIRACL study design



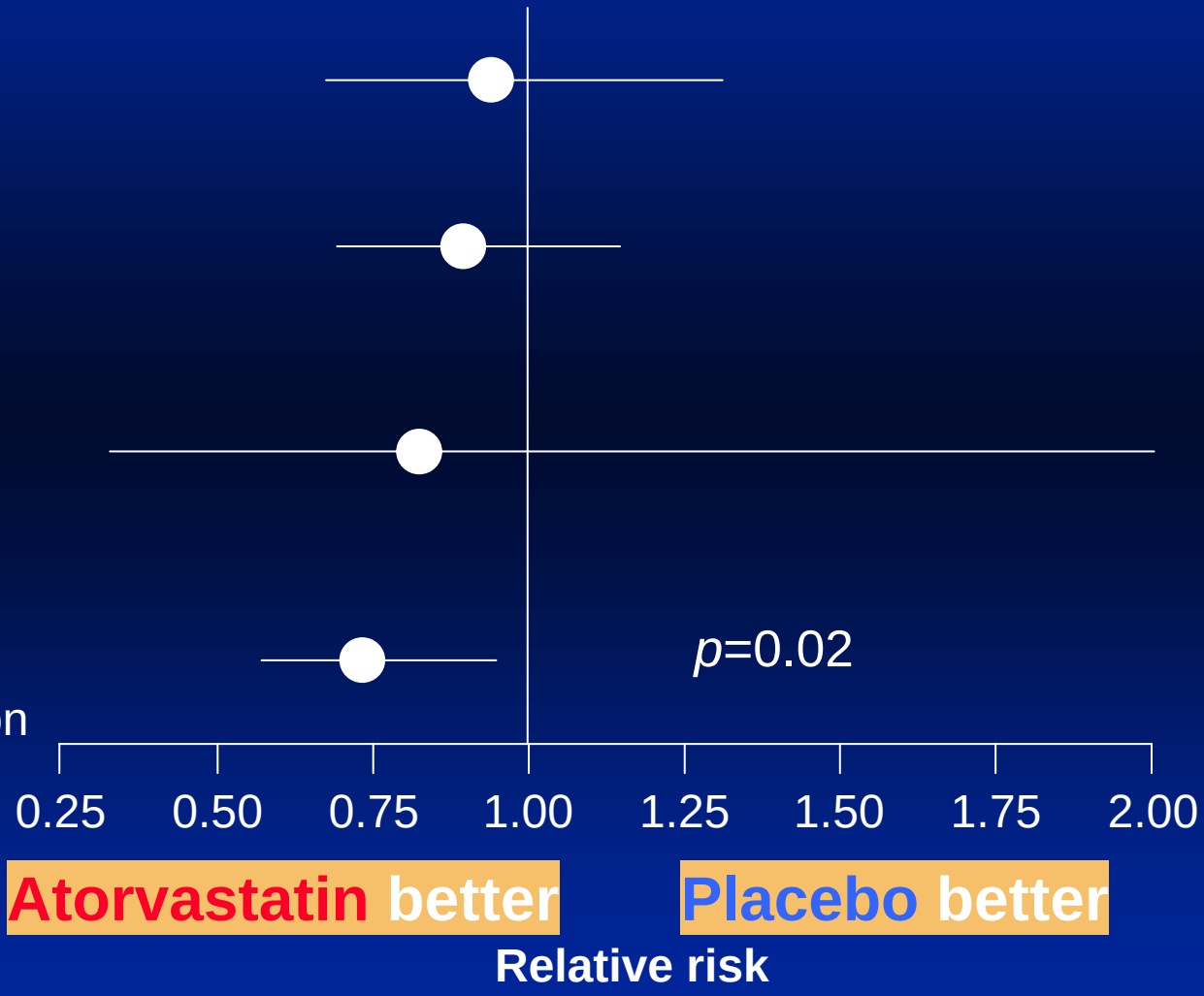
Schwartz JAMA 2001;285:1711

MIRACL: primary efficacy



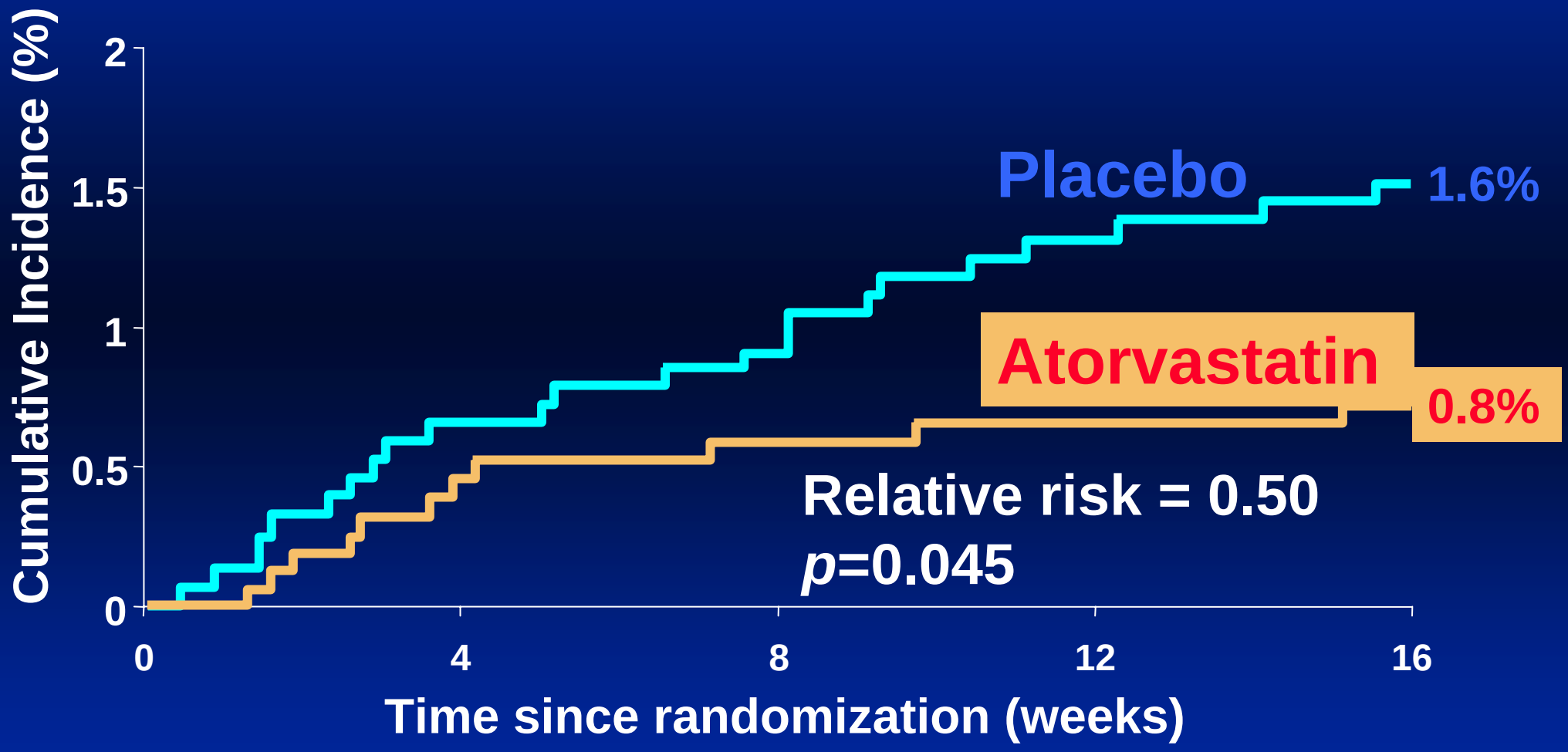
Schwartz JAMA 2001;285:1711

MIRACL: primary end point events



Schwartz JAMA 2001;285:1711

MIRACL: fatal or nonfatal stroke



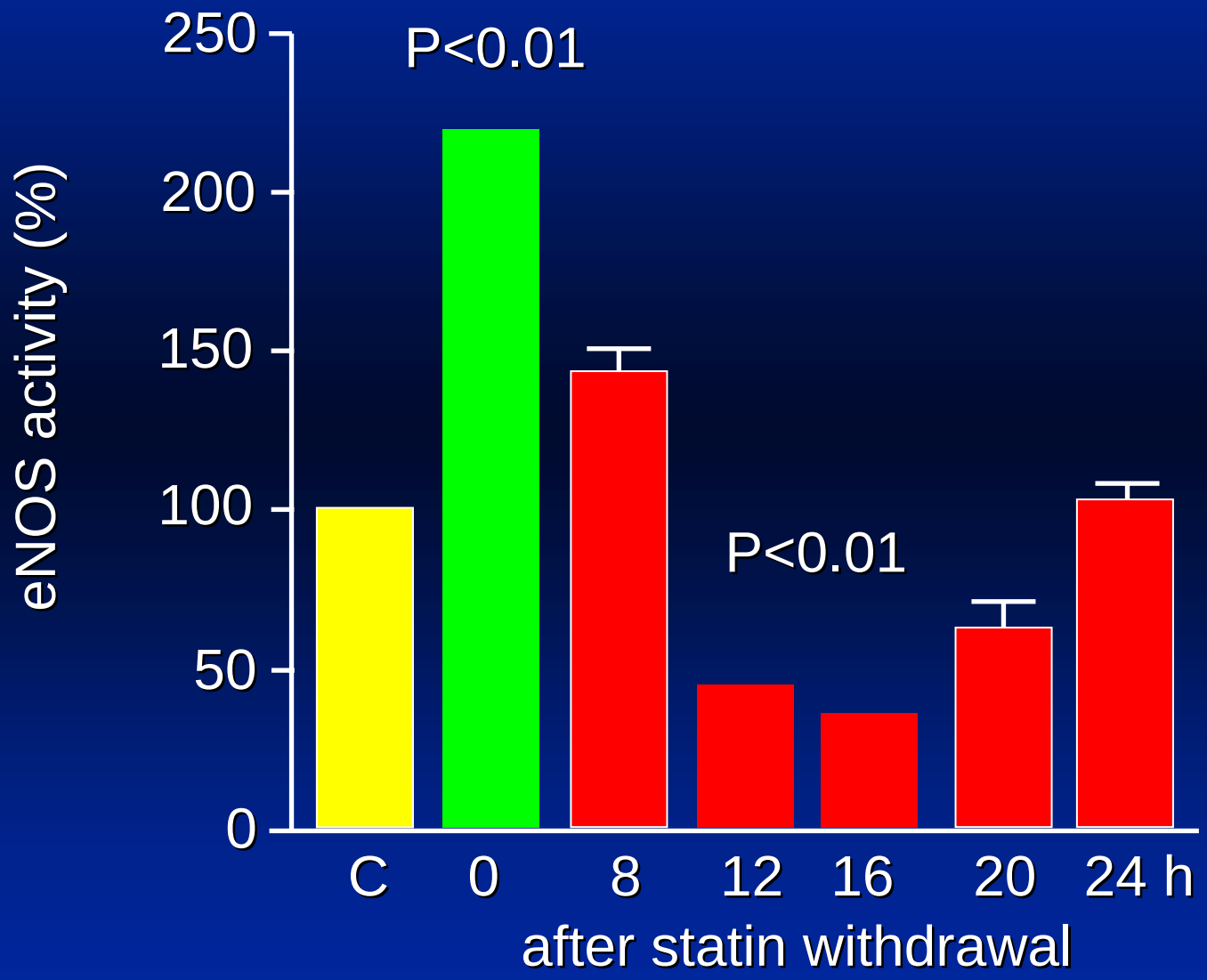
Schwartz JAMA 2001;285:1711

MIRACL Results

- Disappointing
- The primary endpoint was positive but the result was borderline; p=0.048 with two interim looks at the data
- The composite was driven by a difference in the rate of admissions for recurrent ischemia
- There was no significant difference in death or non-fatal myocardial infarction
- There was no difference in revascularization rates

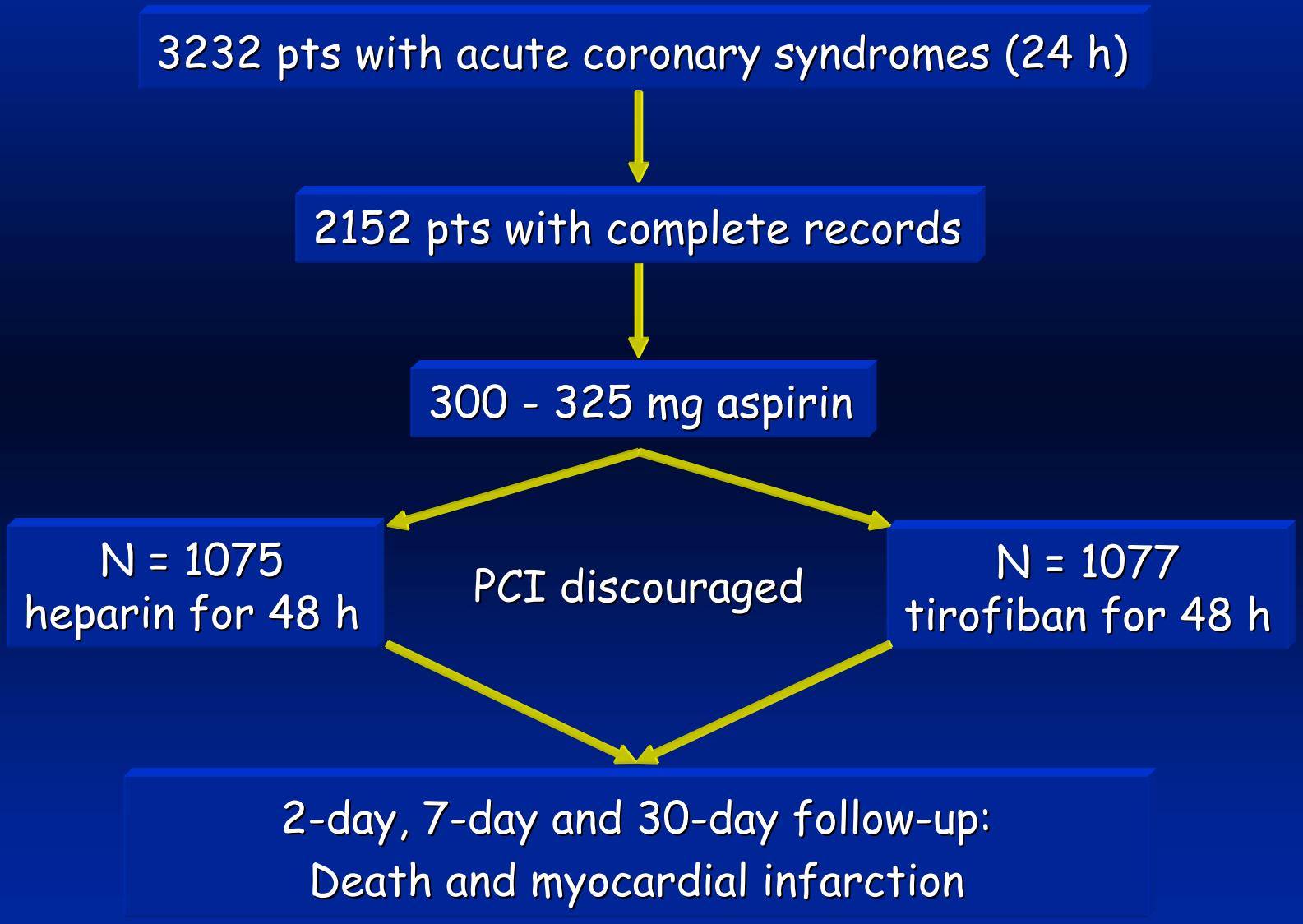
Schwartz JAMA 2001;285:1711

Withdrawal of Statins



Laufs U et al. Circulation 2000

PRISM: Study Design



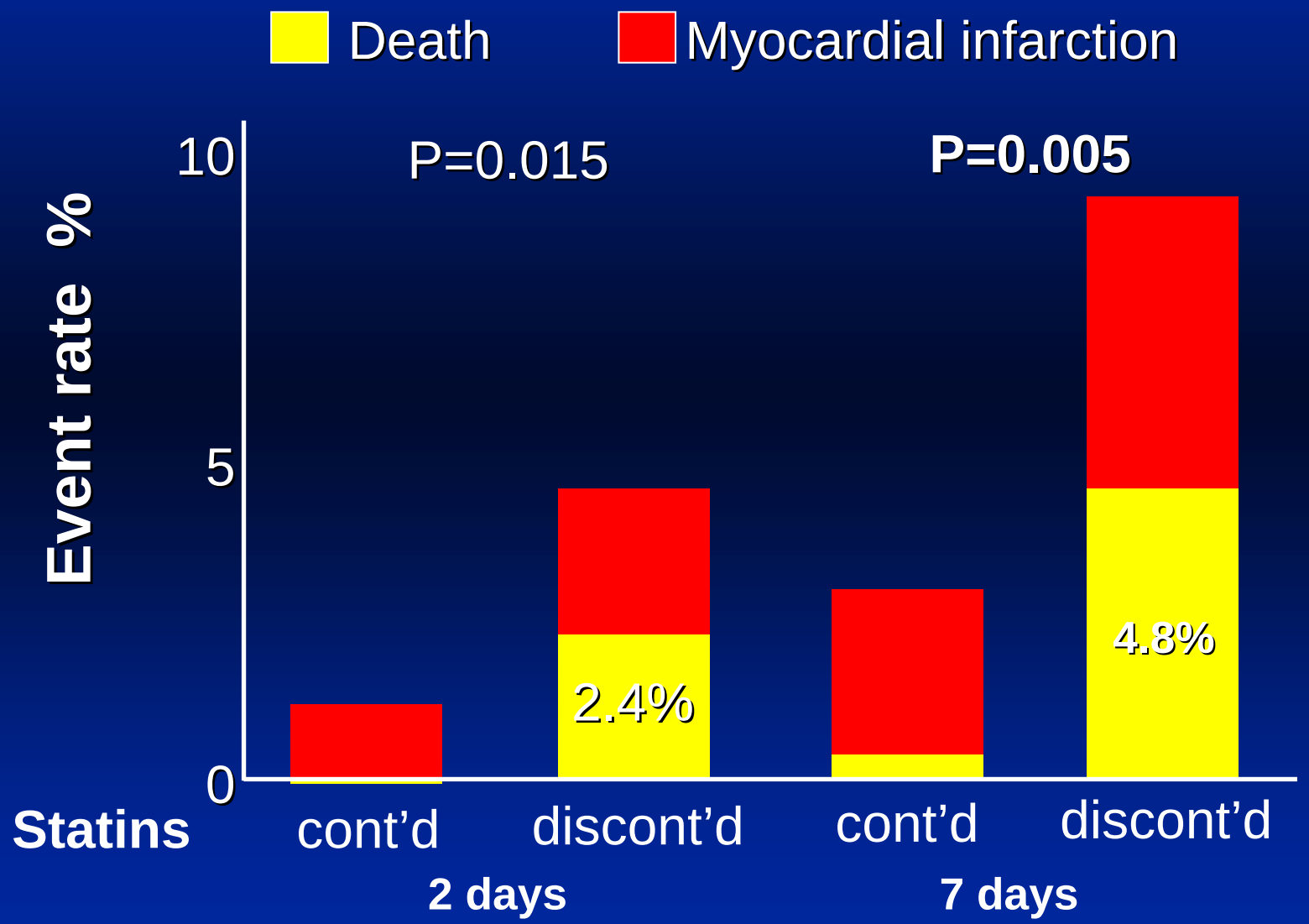
White, NEJM ,1998;338:1498

PRISM: Withdrawal of Statins
Definition of Subgroups

Statin pretreatment (n=302)	Pretreated for 6+ months Continued within 24 h
Statins withdrawn (n=86)	Pretreated for 6+ months No statin after hospitalization
No Statins (n=1249)	No statin past 6 months No statin during 30-day follow-up

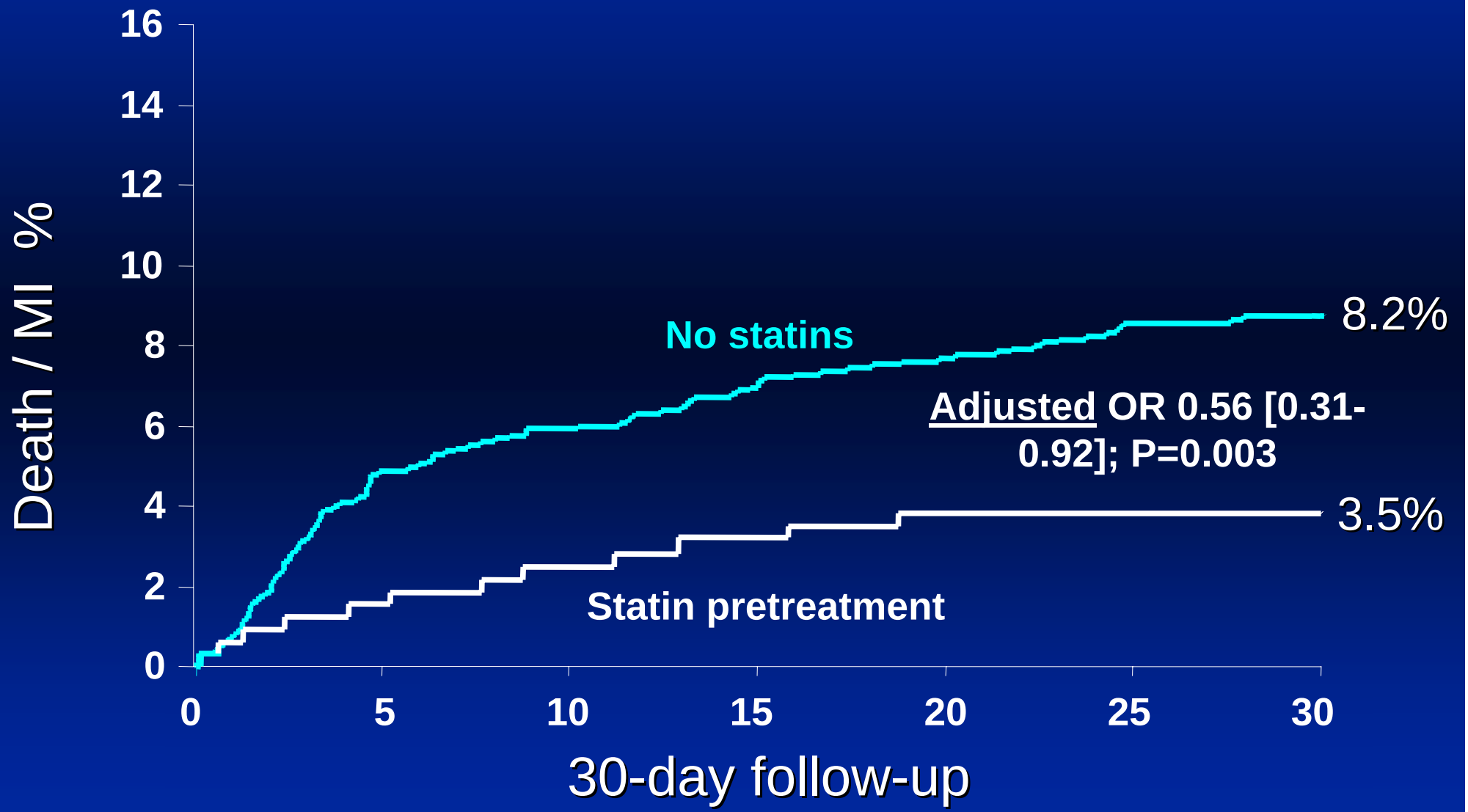
Heeschen CIRC 2002;105:1446

PRISM: Withdrawal of Statins



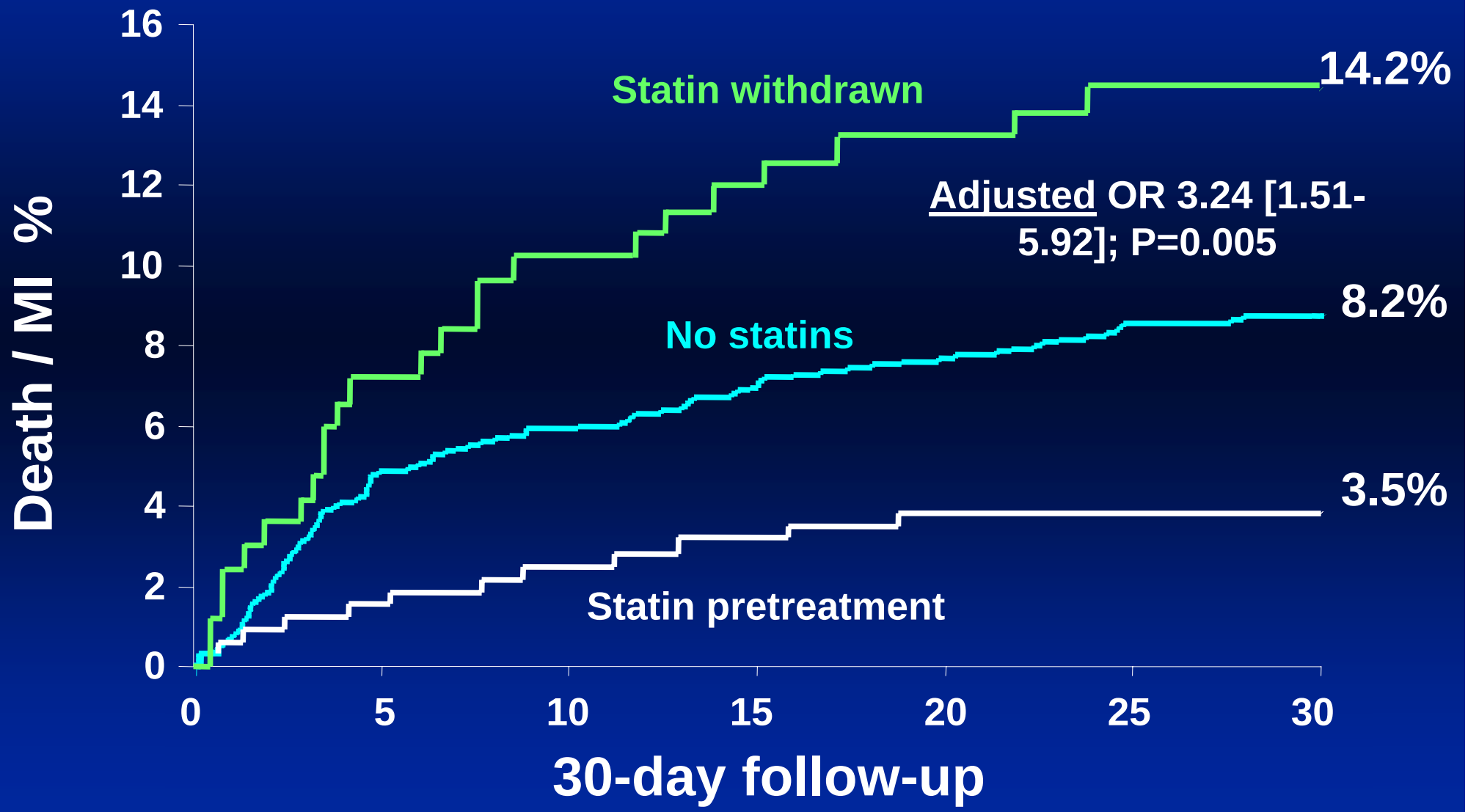
Heeschen CIRC 2002;105:1446

PRISM: Statin Pretreatment



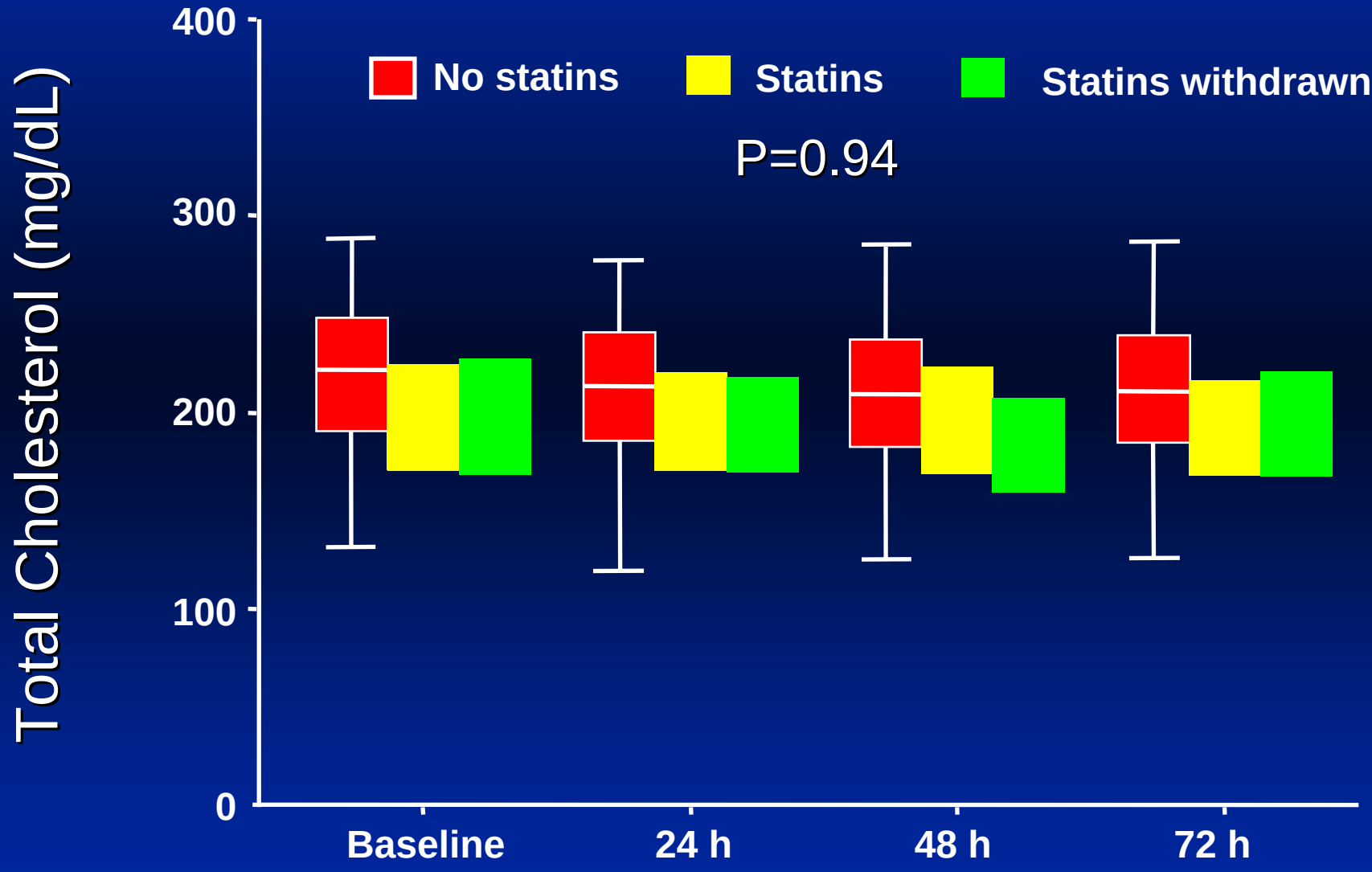
Heeschen CIRC 2002;105:1446

PRISM: Withdrawal of Statins



Heeschen CIRC 2002;105:1446

PRISM: Cholesterol Levels



Heeschen CIRC 2002;105:1446

PRISM: Withdrawal of Statins

Multivariate Analysis (30d FU)

Patients with statin pretreatment (n=455)

Variable	OR	95 % CI	P value
Gender	0.91	0.65 – 1.49	0.59
Age > 65 years	1.24	1.12 – 4.26	0.26
Diabetes mellitus	1.15	0.84 – 1.46	0.64
Hypercholerolemia	0.89	0.71 – 1.16	0.65
Hypertension	0.99	0.85 – 1.06	0.99
History of MI	0.89	0.72 – 1.25	0.66
History of PCI	0.73	0.58 – 1.13	0.53
History of CABG	1.16	0.91 – 1.24	0.65
ST changes	1.21	0.86 – 1.98	0.02
T-wave inversion	0.84	0.65 – 1.05	0.14
Troponin T elevation	2.68	1.54 - 5.89	0.005
Tirofiban	0.82	0.45 – 1.08	0.15
Statins discontinued	3.24	1.64 – 6.27	0.008

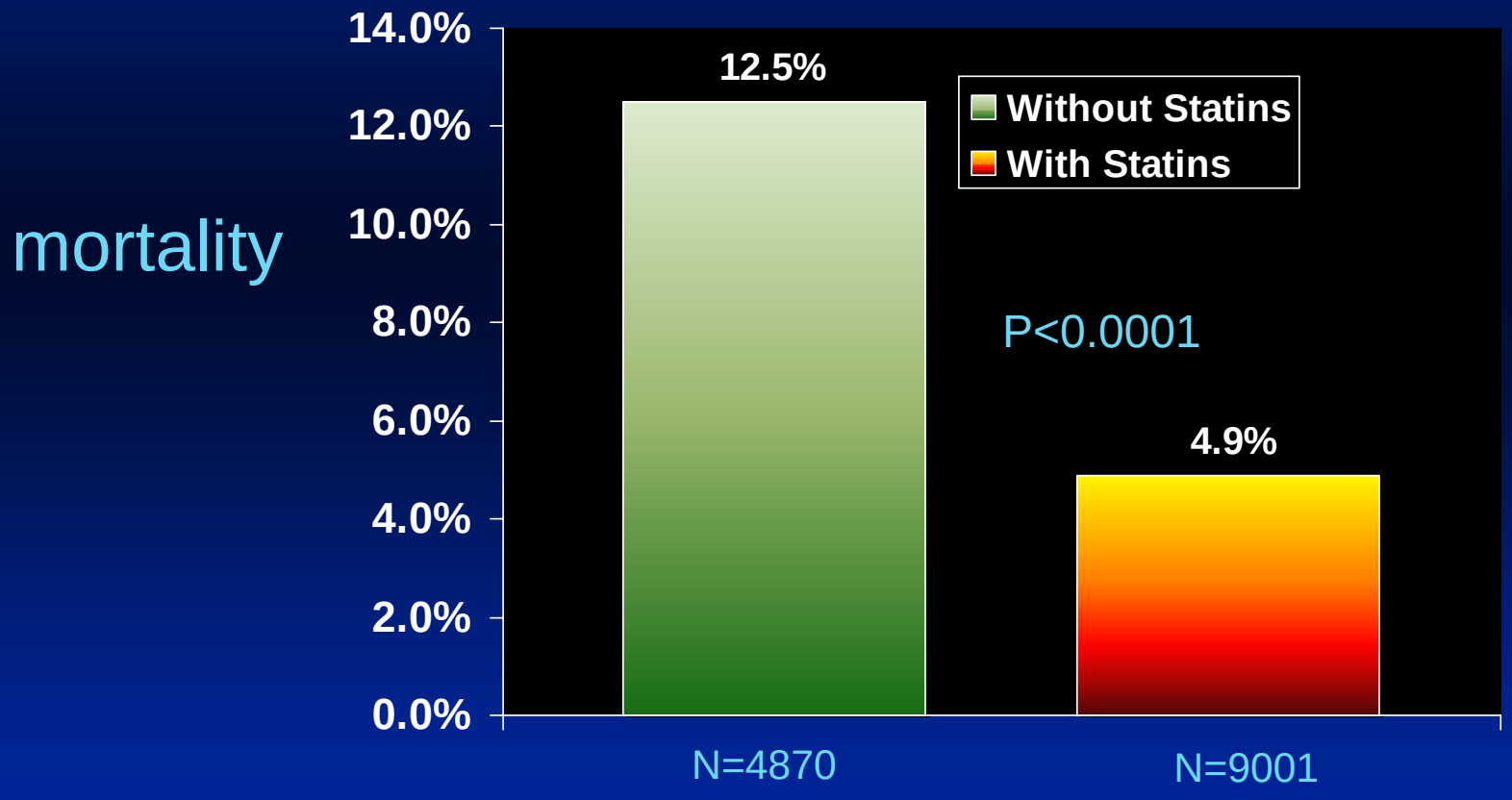
Heeschen CIRC 2002;105:1446

PRISM: Withdrawal of Statins

- Statin pretreatment in patients with acute coronary syndromes is associated with improved clinical outcome
- Discontinuation of statins after onset of symptoms completely abrogates this beneficial effect

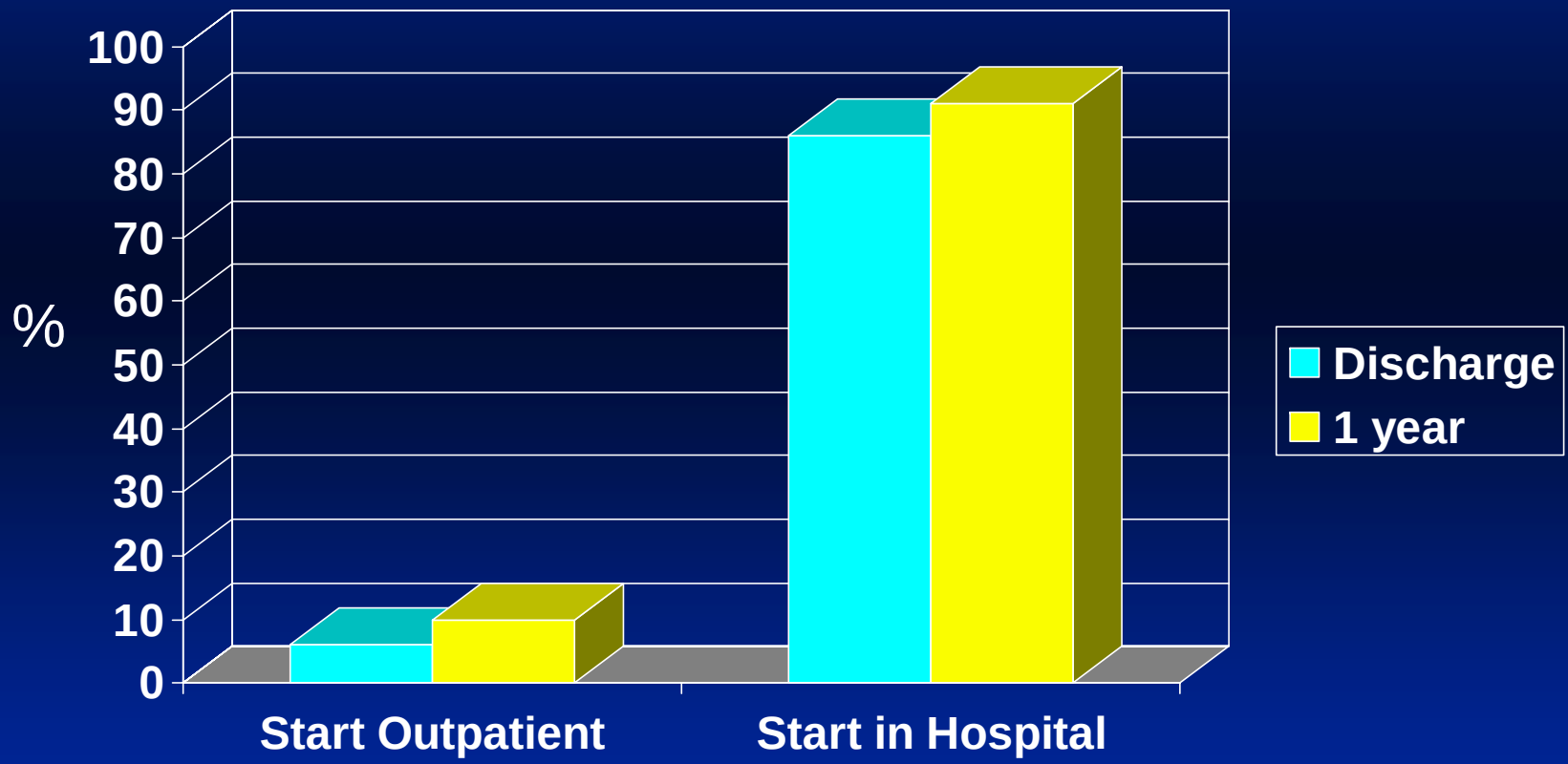
Heeschen CIRC 2002;105:1446

NRMI-4
Discontinuation of statins: mortality



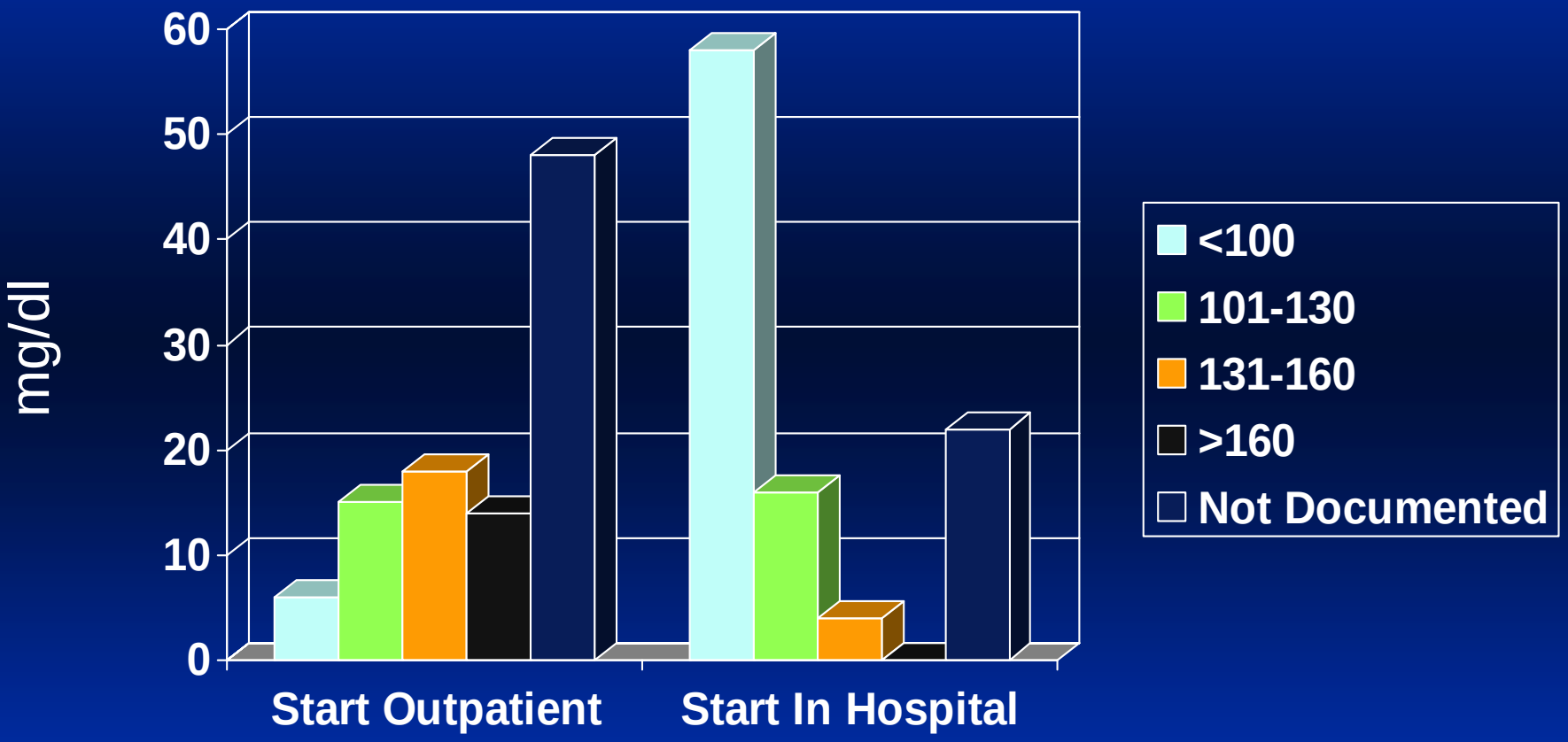
Spencer,AHA,2002

StatinTreatment Rates



Fonarow G, Gawlinski A
Am J Cardiol 2000;85:10A-17A

LDL DURING FOLLOW UP



Fonarow G, Gawlinski A
Am J Cardiol 2000;85:10A-17A

Under treatment of ACS patients
EUROASPIRE

	*Patients Receiving Medication ≥ 6 Months After CHD Event**
Antiplatelet	***81.2%***
β-blocker	***53.7%***
Lipid-lowering agent	***32.0%***

*CABG, PTCA, AMI, ,ischaemia

Eur Heart J. 1997;18:1569-1582

REVERSAL

- Double-blind comparison of atorvastatin 80mg vs pravastatin 40mg in patients undergoing catheterization
- Primary outcome was % change in atheroma volume as determined by intravascular ultrasound
- Baseline LDL was 3.9mmol/L, reduced to 2.85 in the pravastatin group and 2.05 mmol/L by atorvastatin

Nissen JAMA 2003;291:1071

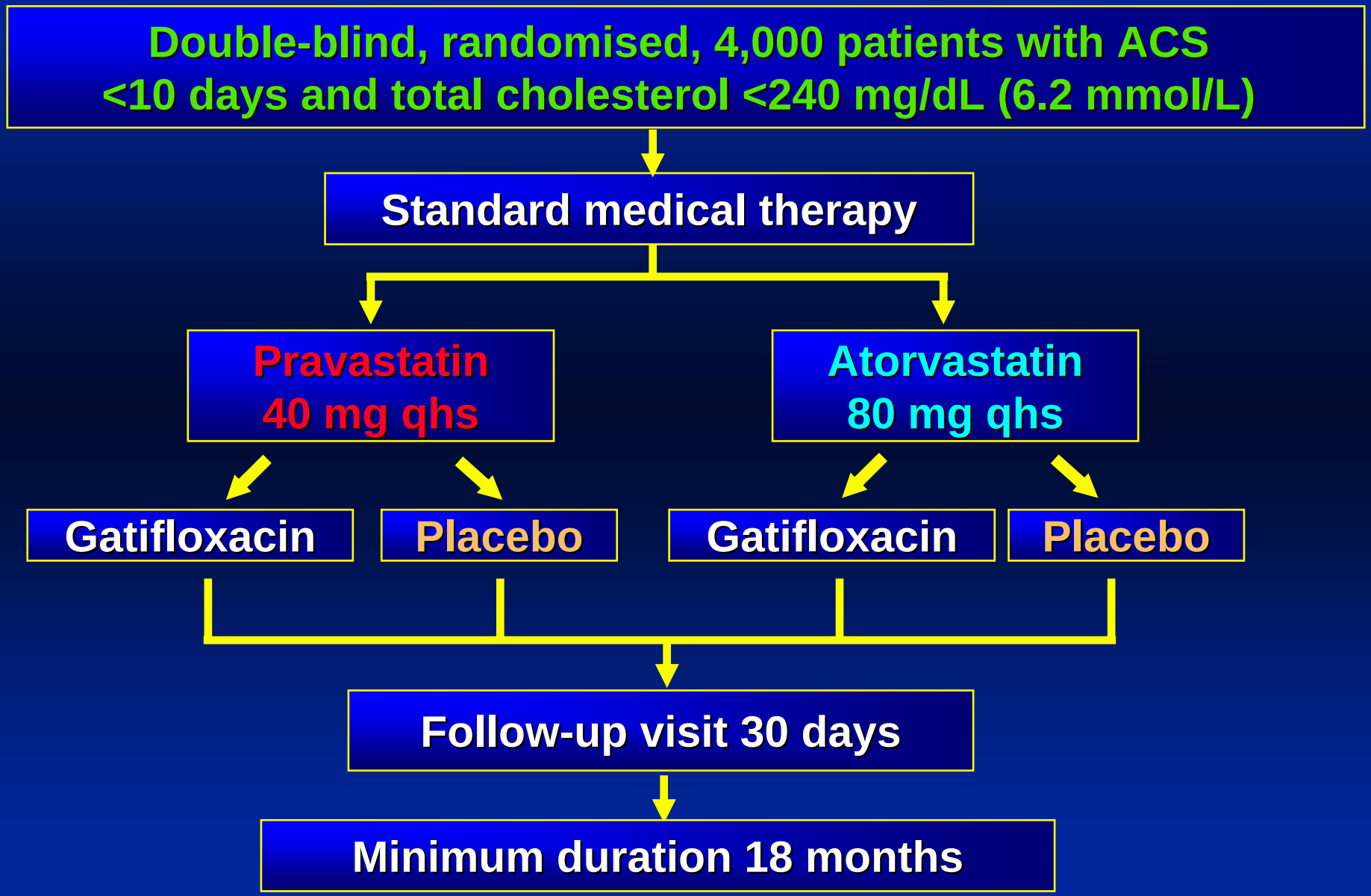
REVERSAL

- Atheroma volume and progression was decreased by atorvastatin. The lower progression rate was equivalent to an additional reduction in LDL of 20%

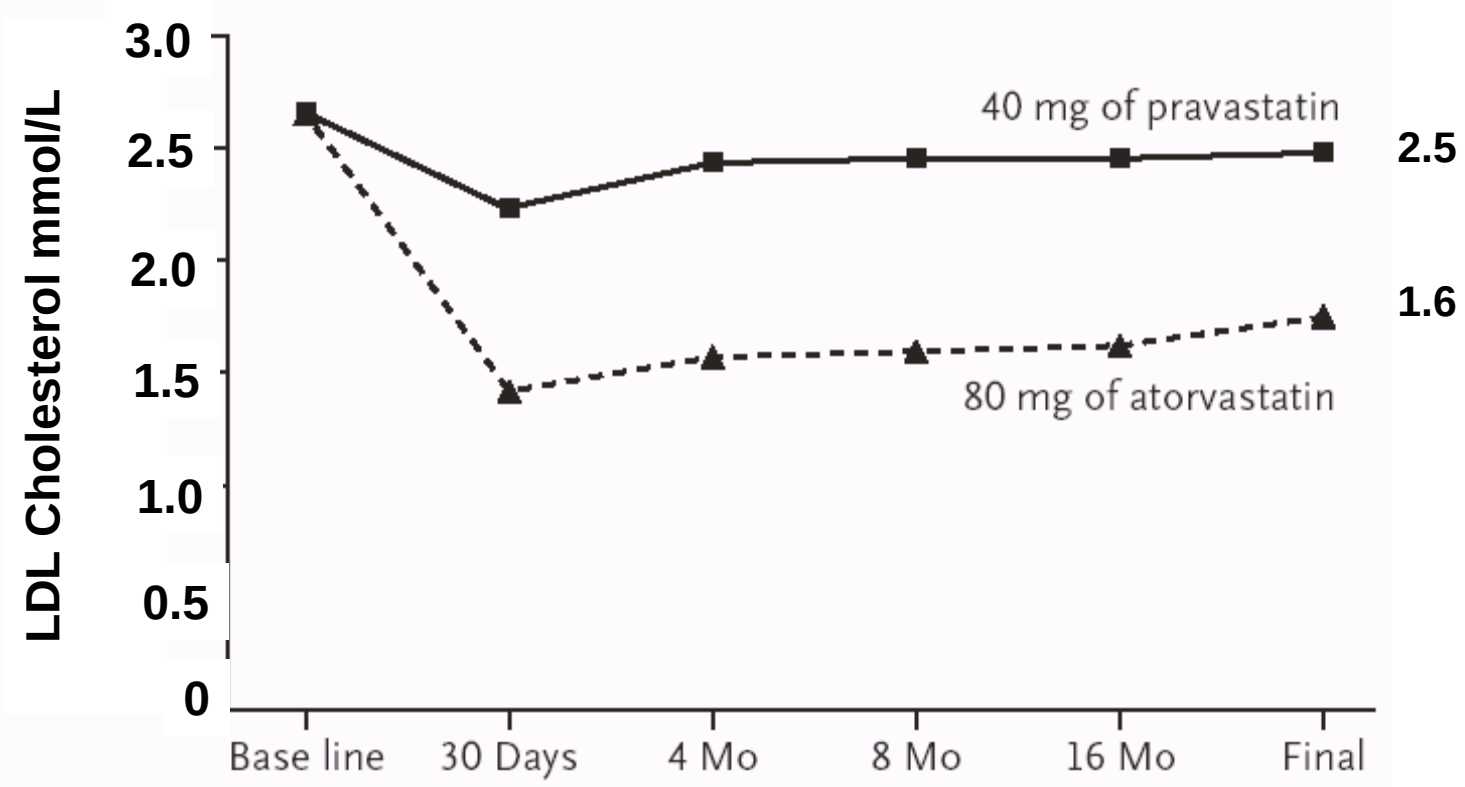
- Other changes in lipoproteins or CRP (36.4% fall with atorvastatin and 5.2% with pravastatin) could be explanations

Nissen JAMA 2003;291:1071

PROVE IT


Double-blind, randomised, 4,000 patients with ACS
<10 days and total cholesterol <240 mg/dL (6.2 mmol/L)
Standard medical therapy
Pravastatin
40 mg qhs
Atorvastatin
80 mg qhs
Gatifloxacin
Placebo
Gatifloxacin
Placebo
Follow-up visit 30 days
Minimum duration 18 months

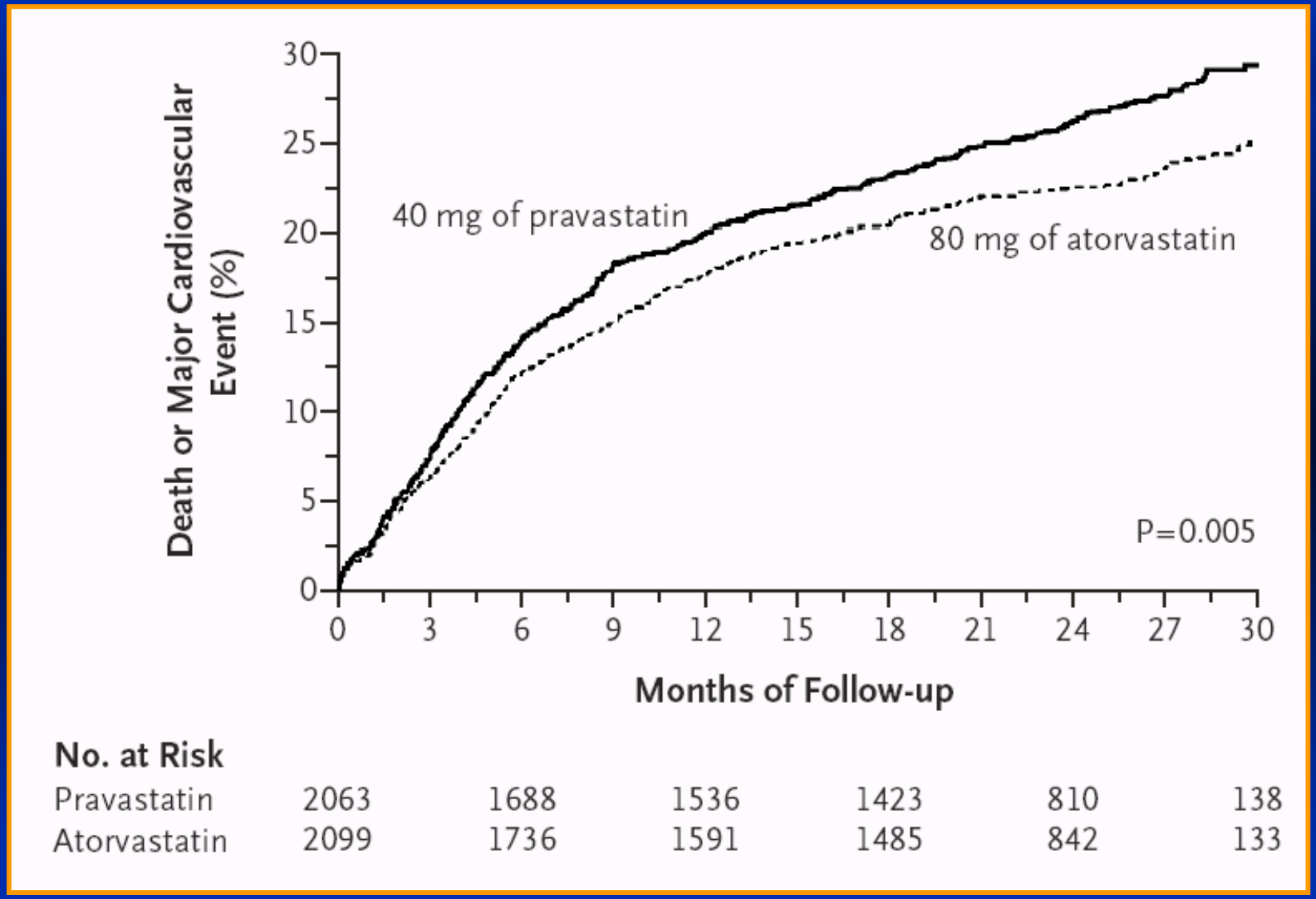
PROVE IT



No. of Patients						
Pravastatin	1973	1844	1761	1647	1445	1883
Atorvastatin	2003	1856	1758	1645	1461	1910

Cannon C, et al N Engl J Med 2004;350:15

PROVE IT



No. at Risk						
Pravastatin	2063	1688	1536	1423	810	138
Atorvastatin	2099	1736	1591	1485	842	133

Cannon C, et al N Engl J Med 2004;350:15

PROVE IT : Death or a Major Cardiovascular Event

Censoring Time	Risk Reduction	Event Rates	
		Atorvastatin	Pravastatin
		percent	
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

Cannon C, et al N Engl J Med 2004;350:15

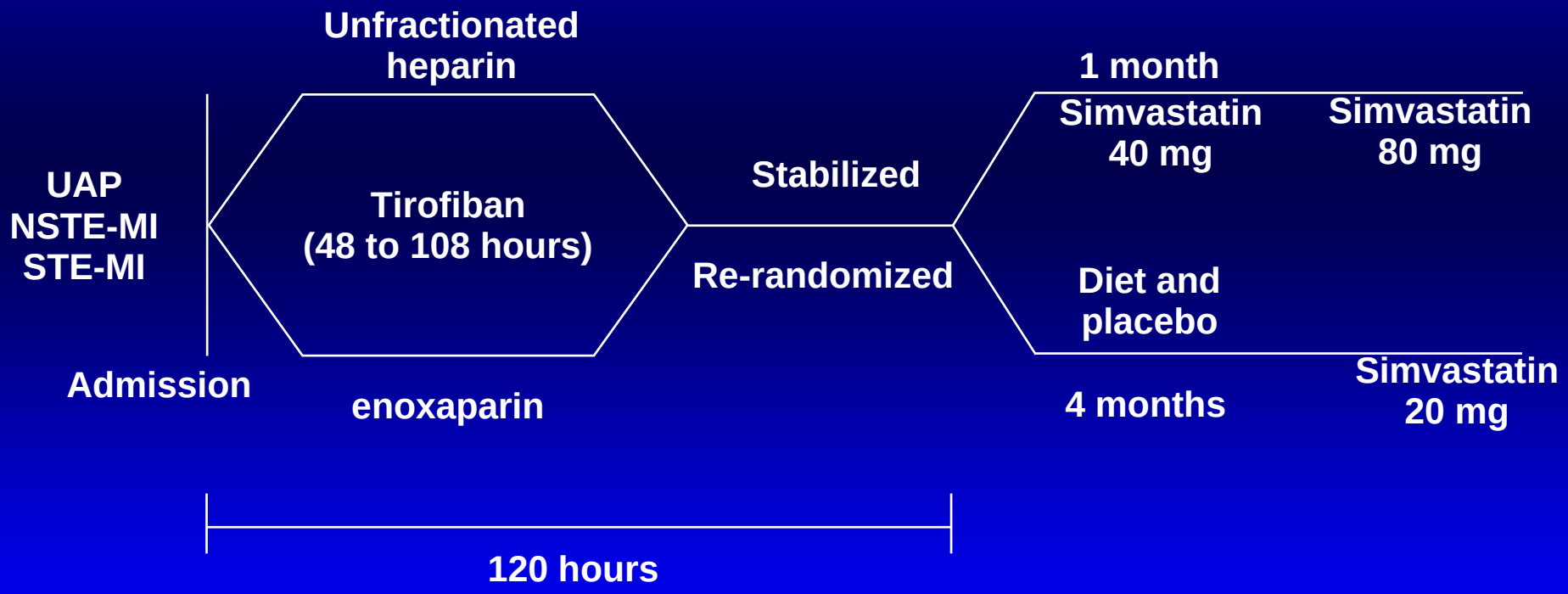
PROVE-it

- Most likely the difference in therapies is explained by differences in LDL
- Pleotrophic effects could also be important
- Atorvastatin has been shown to have a greater anti-inflammatory effect with a much larger reduction in CRP
- The target LDL should now be 1.6mmol/L

A-Z Study Design

- A Phase
- (open-label)

Z Phase
(double-blind)



Z-Phase Qualifying Event and Characteristics

Event	Z-Phase N=4395	MIRACL N=3086
STE-MI	39.9%	
Non-STE ACS	58.4%	100.0%
MI	76.7%	53.5%
Non-MI	23.3%	46.5%

Characteristics

Median Age (yrs)	61.0	65.0
Male gender	75.1%	65.0%

Differences between MIRACL and A to Z

- MIRACL excluded patients requiring PCI during the index hospitalization or in whom PCI was planned whereas A to Z allows patients treated with PCI

- MIRACL had few patients treated with IIb/IIIa receptor antagonists whereas A to Z tests acute lipid lowering in conjunction with the best contemporary practice.

Differences between MIRACL and A to Z

- MIRACL compared 80mg of atorvastatin to placebo whereas A to Z compares 40mg-80mg simvastatin with placebo for 4 months followed by 20mg of simvastatin.
- Follow-up in MIRACL was for only 16 weeks whereas it is 1-2 years in A to Z.
- MIRACL only included non-ST elevation ACS patients whereas A to Z also includes patients with ST elevation ACS.

A to Z: Continuing Relevance and Questions Addressed

Z-phase

- **Will early aggressive therapy with simvastatin reduce early and longer term cardiovascular event rates?**
- **Will there be benefits in patients across the spectrum of ACS?**
- **Will there be consistent benefits in patients undergoing or not undergoing revascularization?**
- **What will be the event rates in patients treated with this combination of therapies?**

A to Z, MIRACL and PROVE IT

	A-Z	MIRACL	PROVE IT
Patients	4500 (Z phase)	3000	4000
Diagnosis	NSTE ACS, STE-MI	NSTE ACS	NSTE ACS, STE-MI
Cholesterol	<6.4 mmol/L	< 7.0 mmol/L	3.9-6.2 mmol/L
Intervention	PCI	none allowed	after PCI
Therapy	Simvastatin 40-80 mg placebo 4 Months	Atorvastatin 80mg placebo 4 Months	Pravastatin 40mg Atorvastatin 80mg
Start of Therapy	2-5 days	1-4 days	<10 days
Follow-up	~18 months end-point driven	4 months	2 years
Therapy			
NSTE ACS	Aggrastat/Heparin/Enox	not defined	not defined
STE-MI	ASA/Heparin/Fibrinolysis	N/A	not defined

Rationale for Early Statin Therapy

- Clinical Need
  - Recurrent events occur early after index presentation
- Pathophysiologic rationale
  - Restores endothelial function
  - Reduces markers of inflammation
  - Improves thrombotic “profile”
- Improves Compliance
- Clinical Data

Conclusions

- *Evidence from retrospective analyses of clinical trials and registries suggest that early statin usage is beneficial*

- *Given the heterogeneity of risk in patients with ACS and the multiple therapies that must be selectively applied, prospective therapeutic trials to determine the impact of early statin use on outcomes have been required*

- *A to Z will contribute important information to our understanding of the role of statins early in ACS*