# Statin Therapy in Acute Coronary Syndromes

**The Earlier, The Better !**

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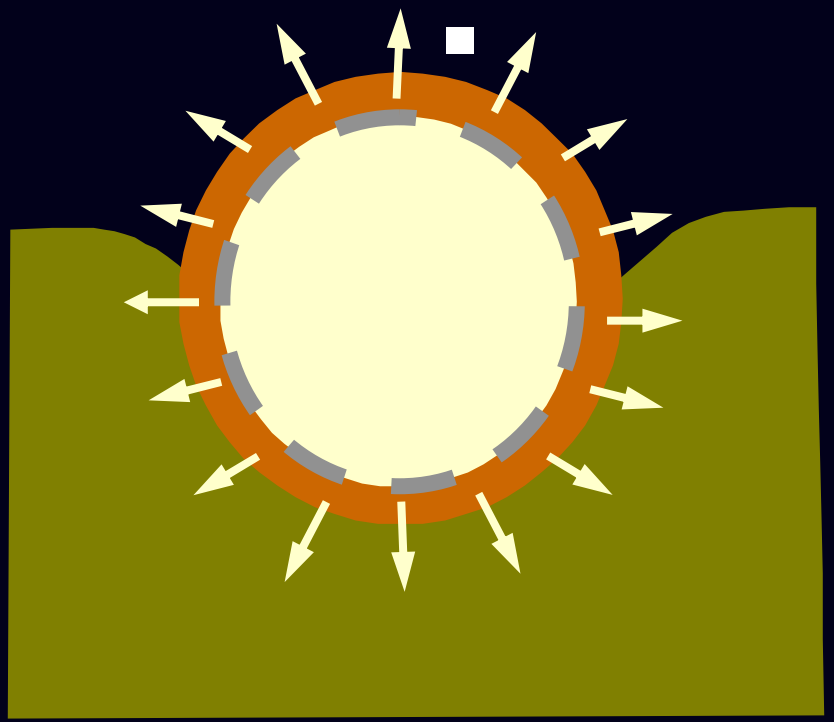
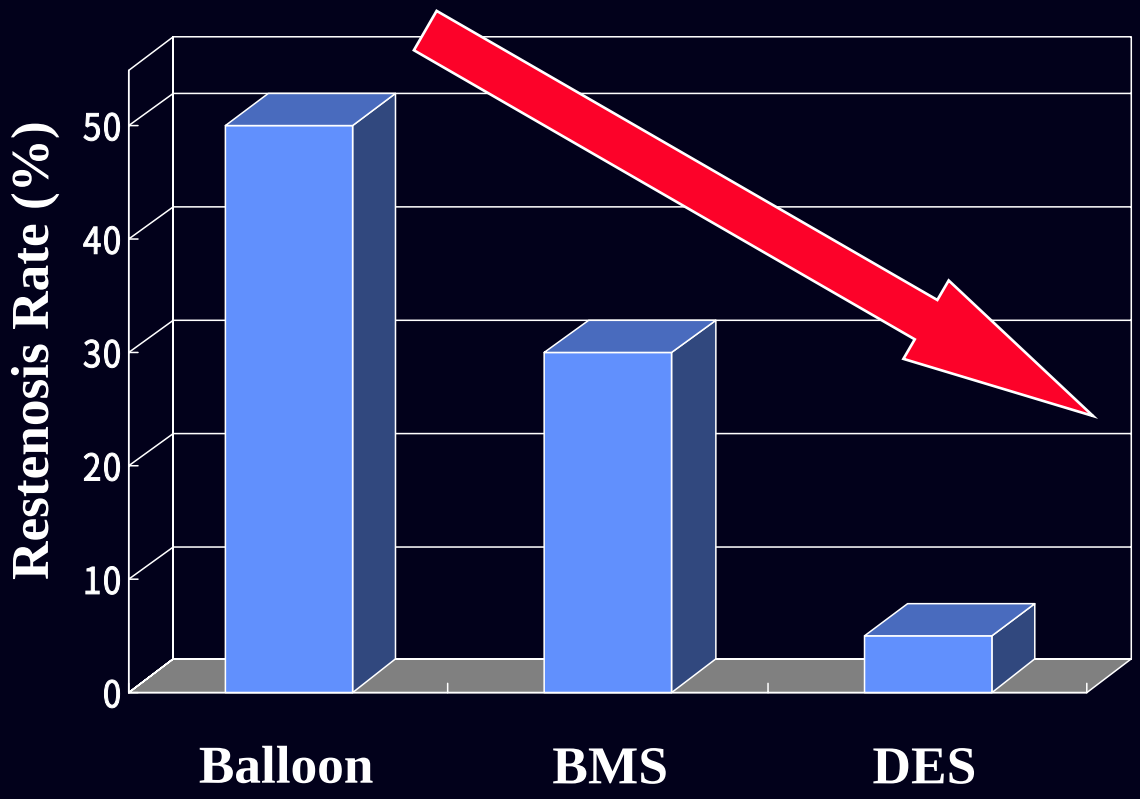
# Drug-Eluting Stents





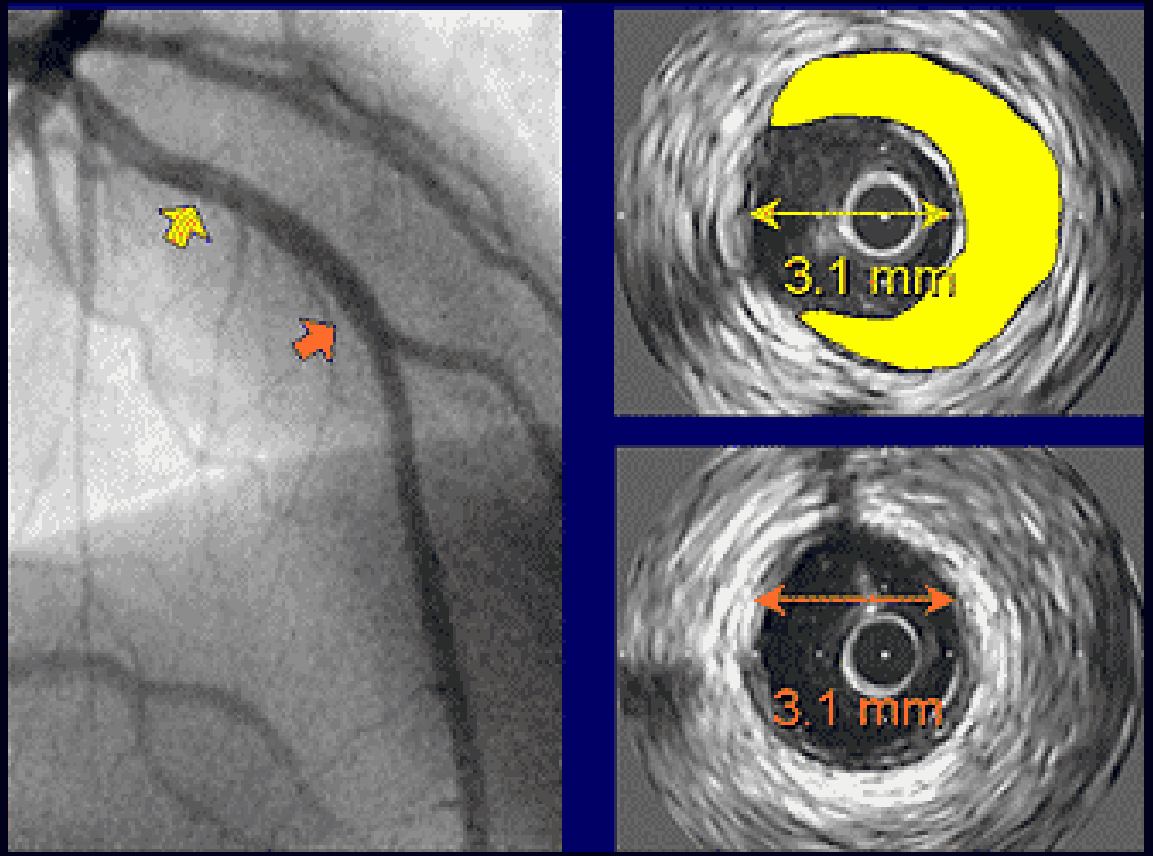
# A New Opportunity to Decrease Morbidity and Mortality from CAD

- **DES and CABG:**
  **consume billions of dollars, but, in most cases, do not prevent myocardial infarction and death.**

- **Non-stenotic vulnerable plaques:**
  **cannot be detected with current imaging techniques, are in most cases, the cause of MI and death.**

# Beyond the Culprit Lesion

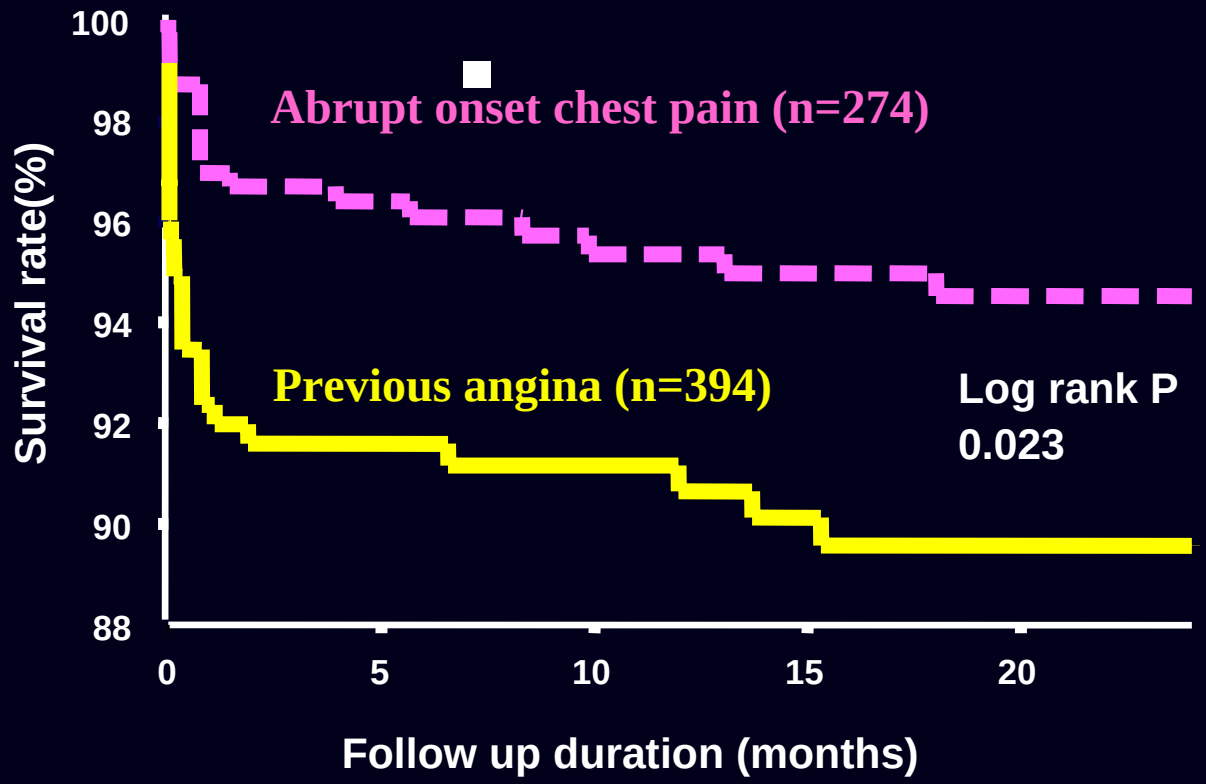
262 healthy donor




- **Atherosclerosis is a diffuse process.**
- **Lack of luminal obstruction does not mean a lack of atherosclerosis**

*Circulation 2001;103:2705*

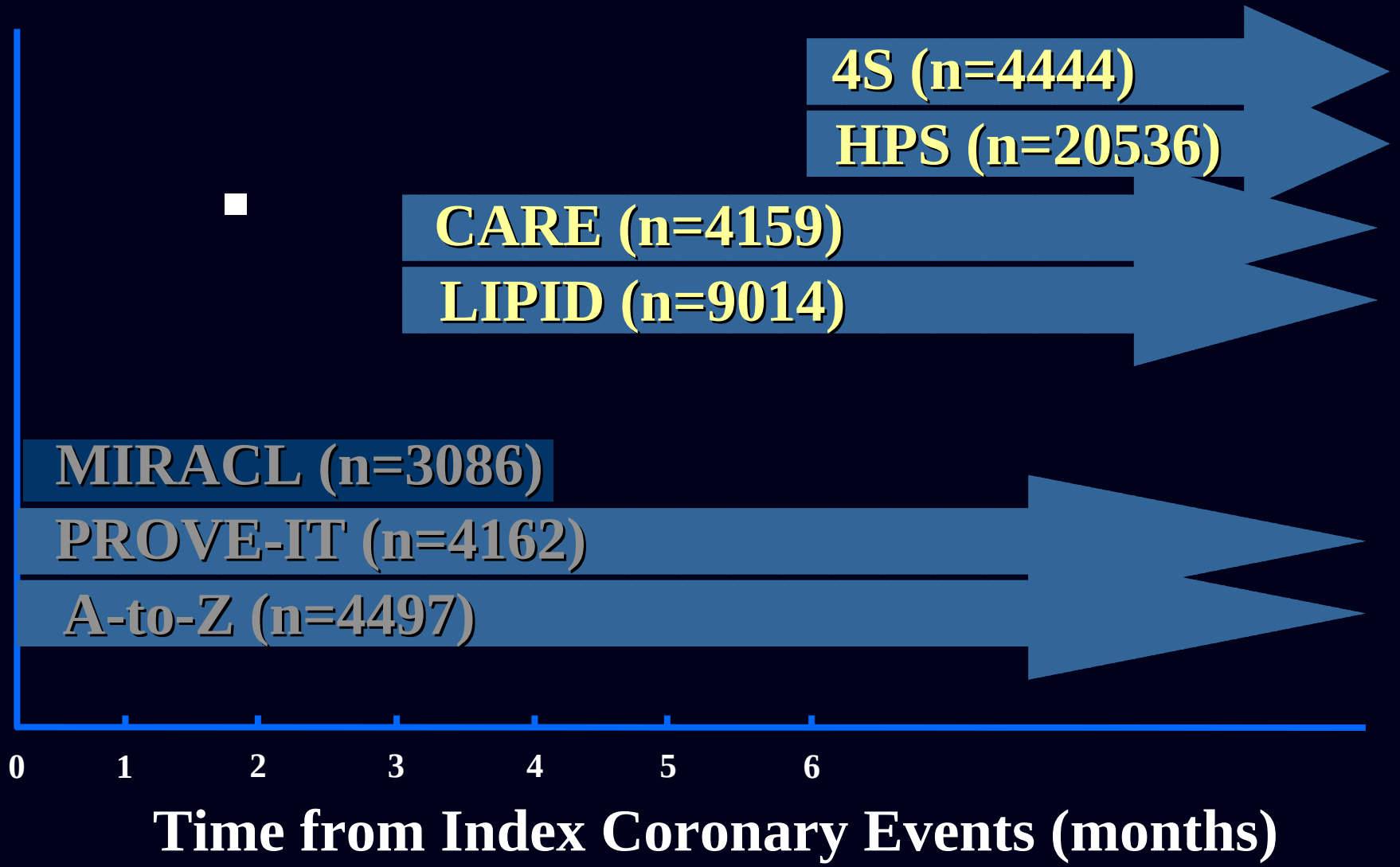
# Where Should we go?



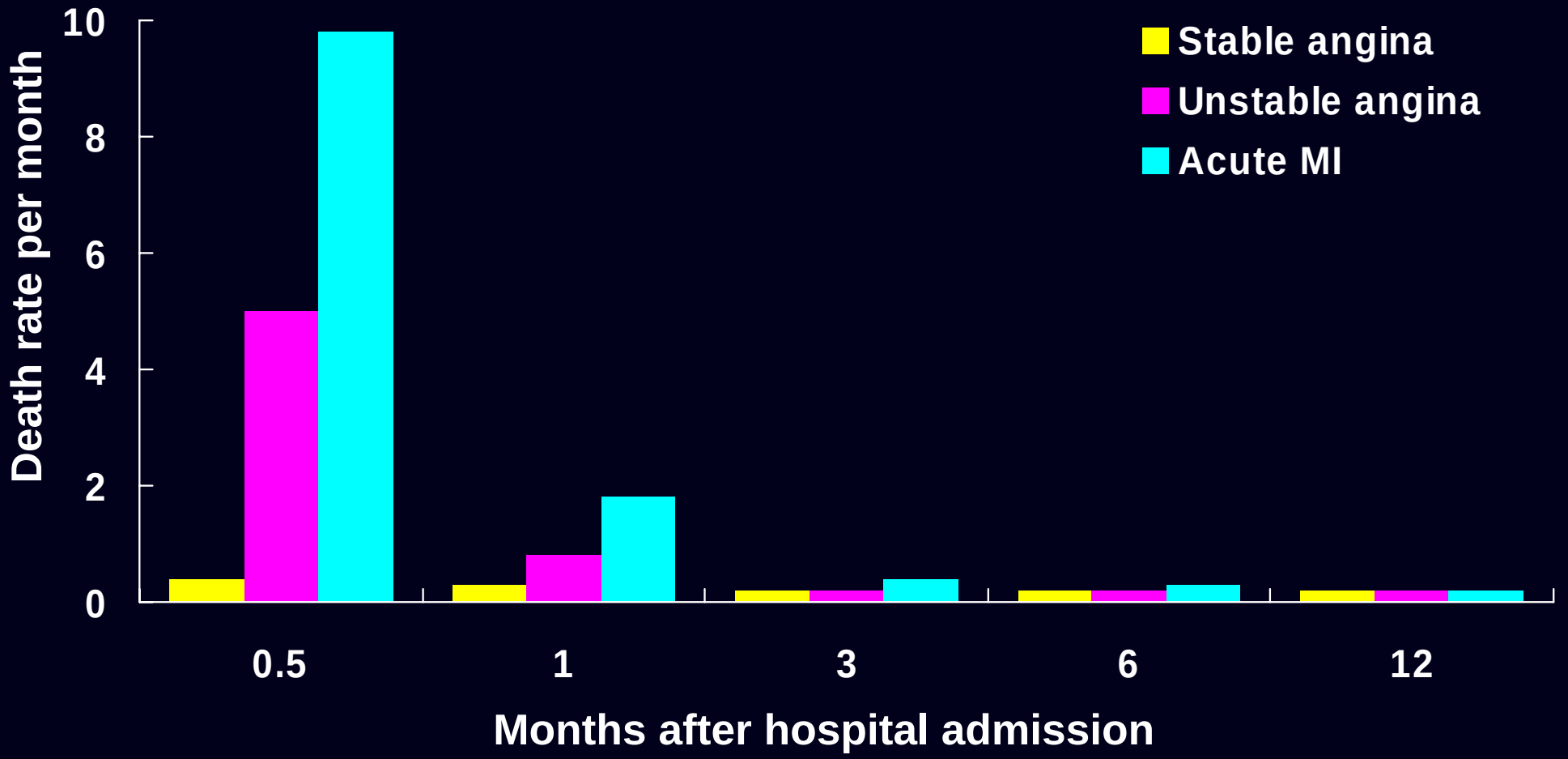

**50% of patients with CAD presented with AMI or SCD.**

**Prevention of acute coronary events must be the primary goal.**

# Statin Therapy in CAD



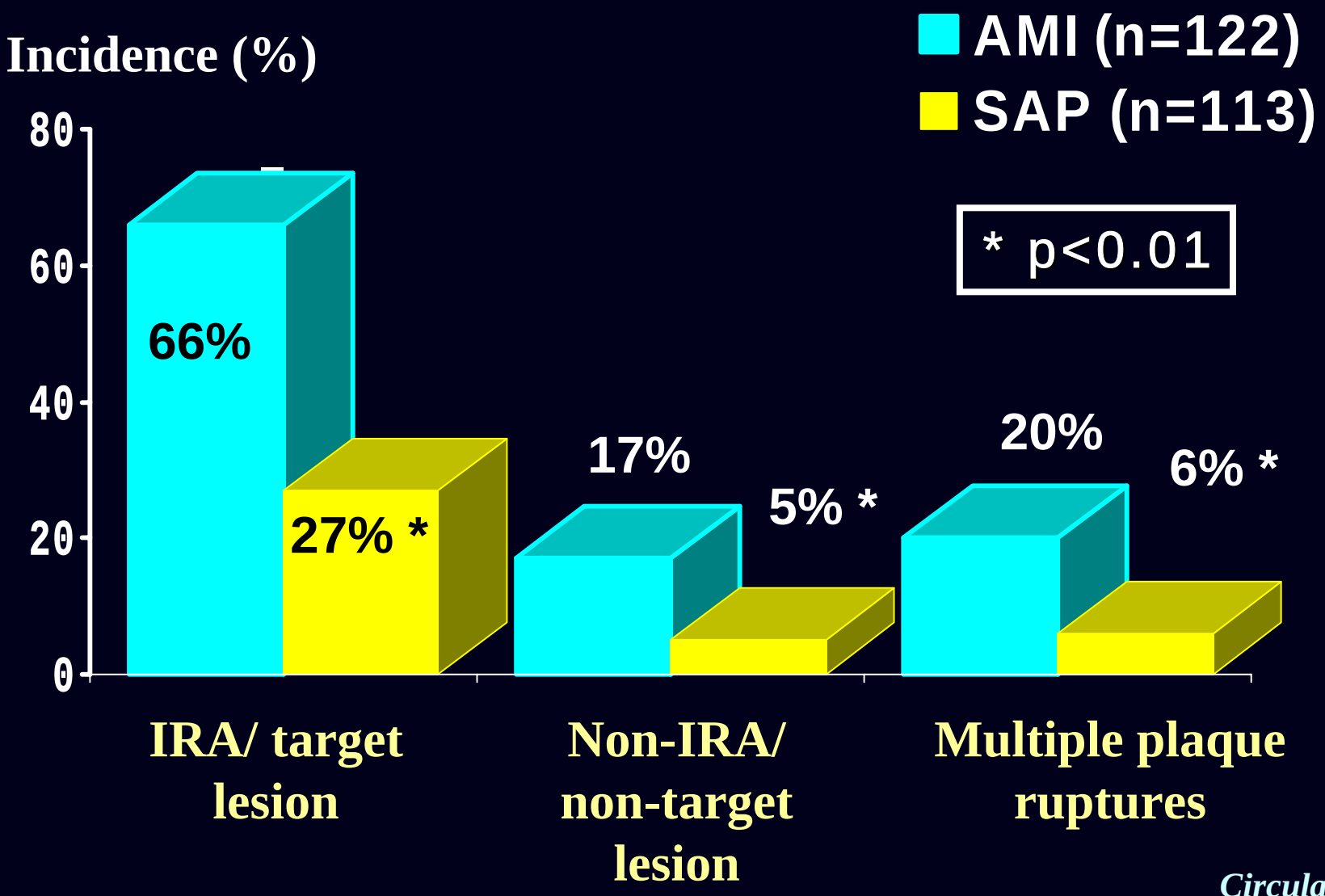
# CV Mortality after ACS




*Heart 2003;89:1268*

*AMC Data*

# Multiple Plaque Rupture




*Circulation2004;110:928*

# Statin Therapy in ACS

- **Are statins beneficial early post ACS?**
- **Does the degree of LDL lowering matter?**

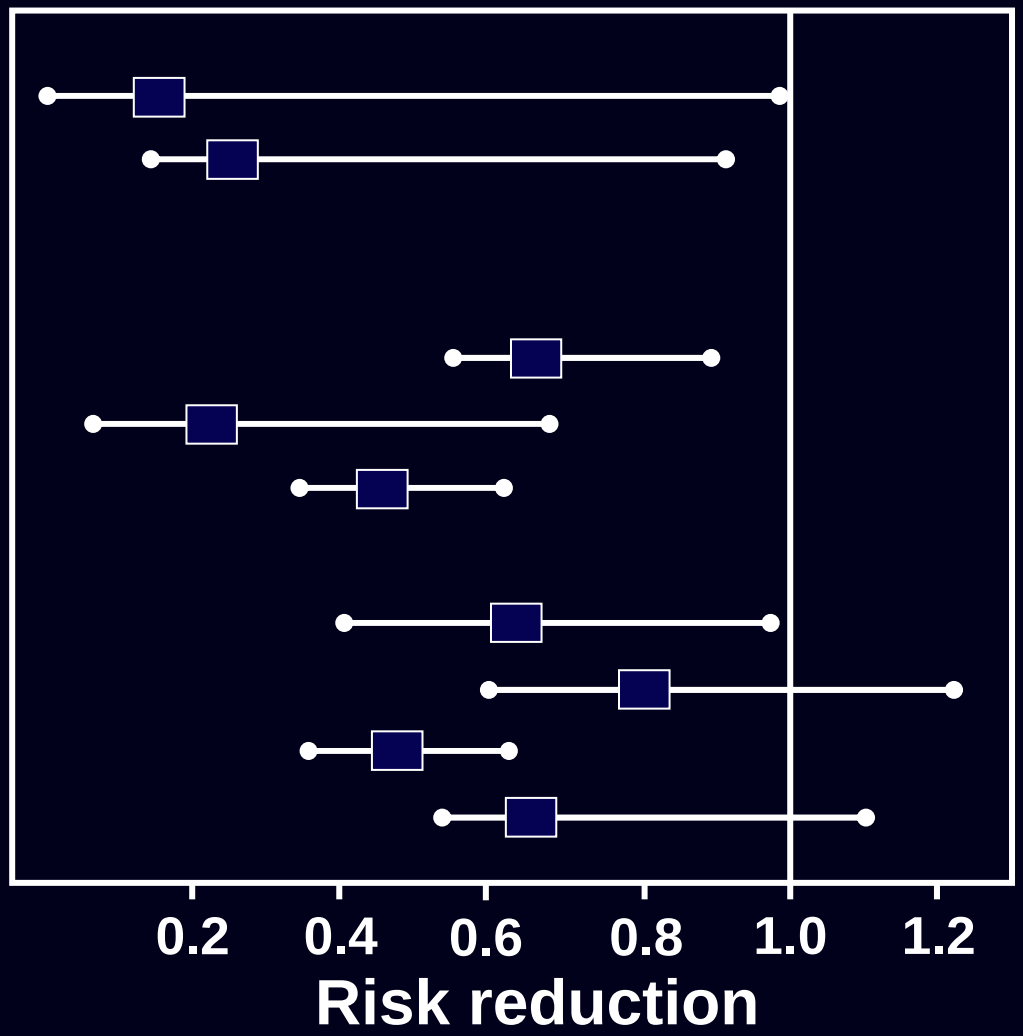
# Risk reduction in patients with an ACS treated with lipid-lowering therapy.

**Early benefit (in-hospital)**
- **Mayo Clinic**
- **PRISM trial** ■

**Late benefit (16 wk to 1y)**
- **Swedish Study**
- **Mayo Clinic**
- **PURSUIT/Gusto IIB**
- **In TIME II**
  - **prior lipid treatment**
  - **no prior lipid treatment**

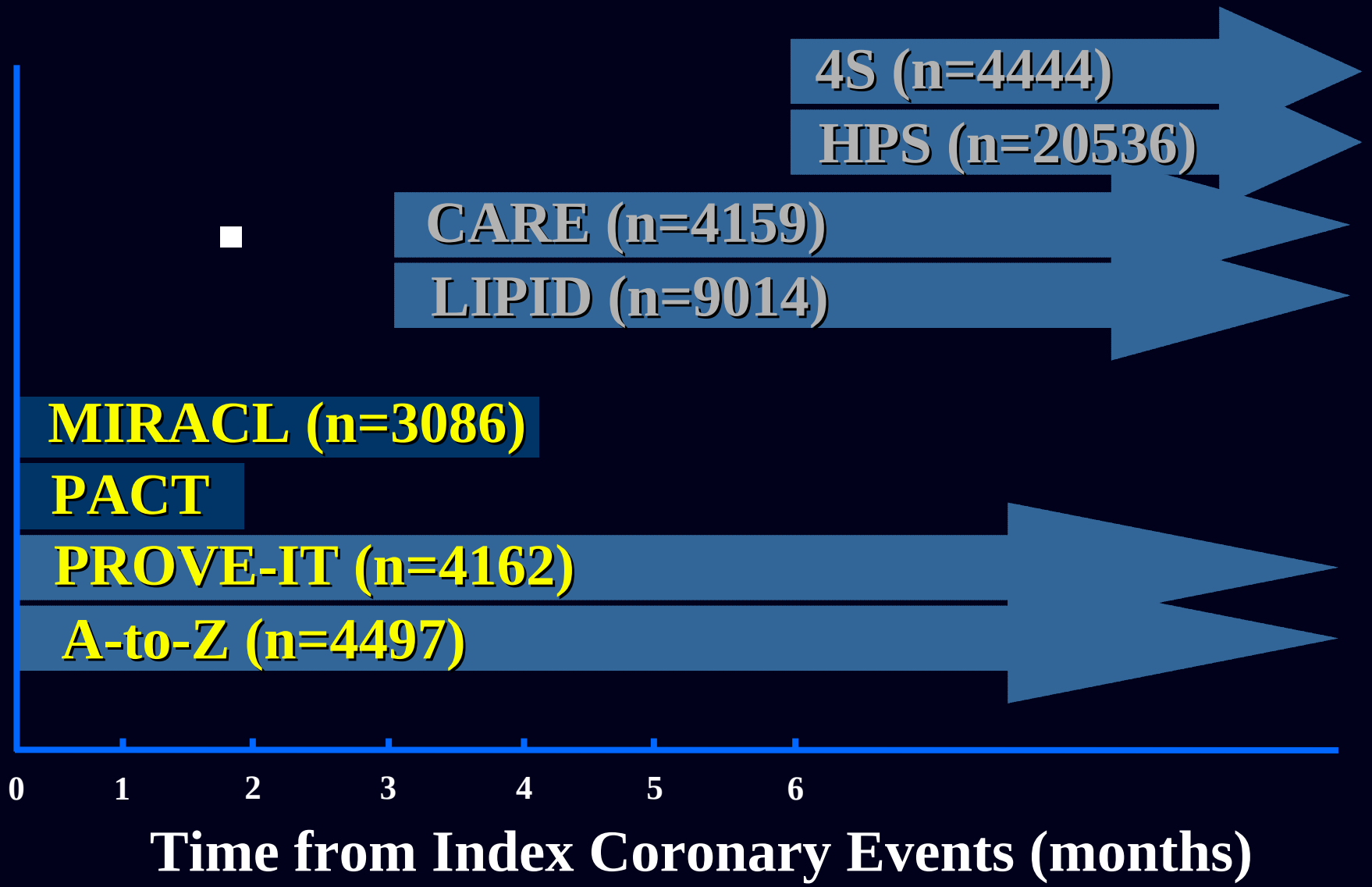
**OPUS/TIMI 16**

**SYMPHONY**



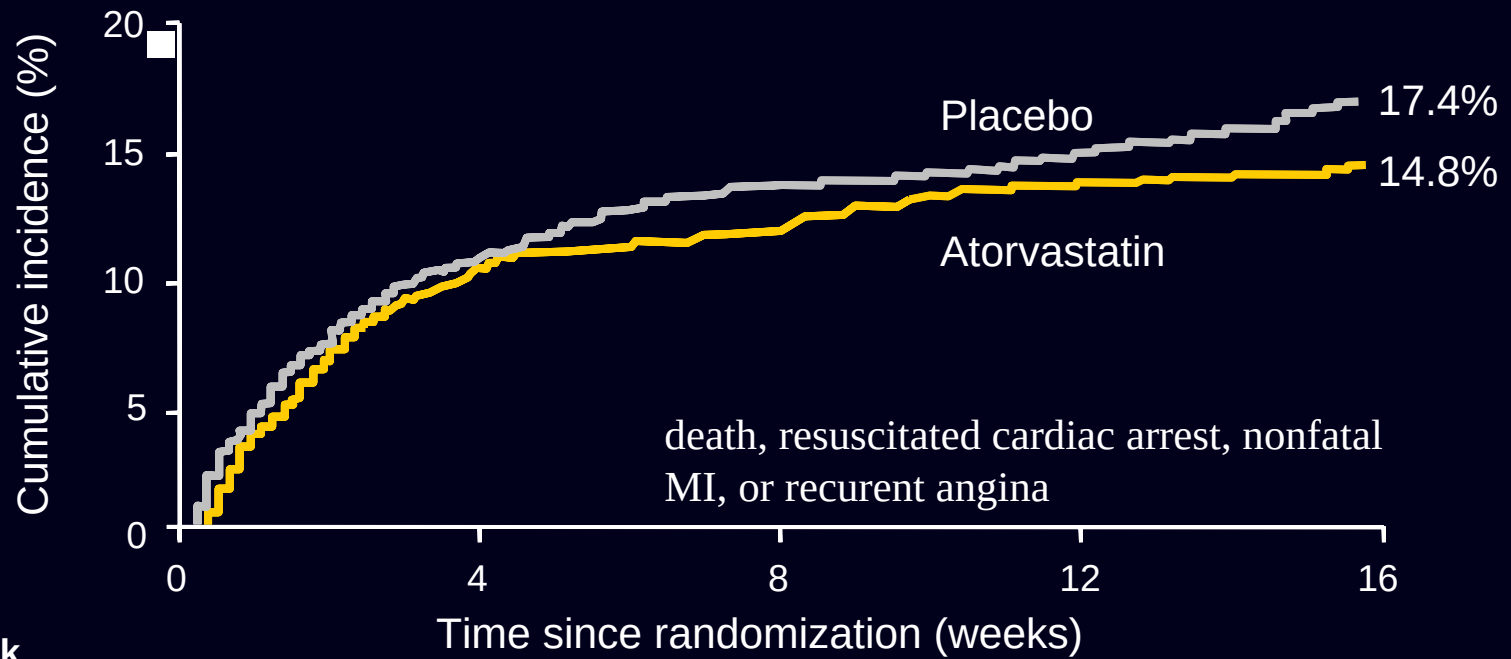

*Eur Heart J 2004;6:A32*

# Early Statin Therapy in ACS



# MIRACL: Reductions in Recurrent Ischemic Events

**Atorvastatin 80 mg/d over 16 weeks in ACS patients (n=3086)**



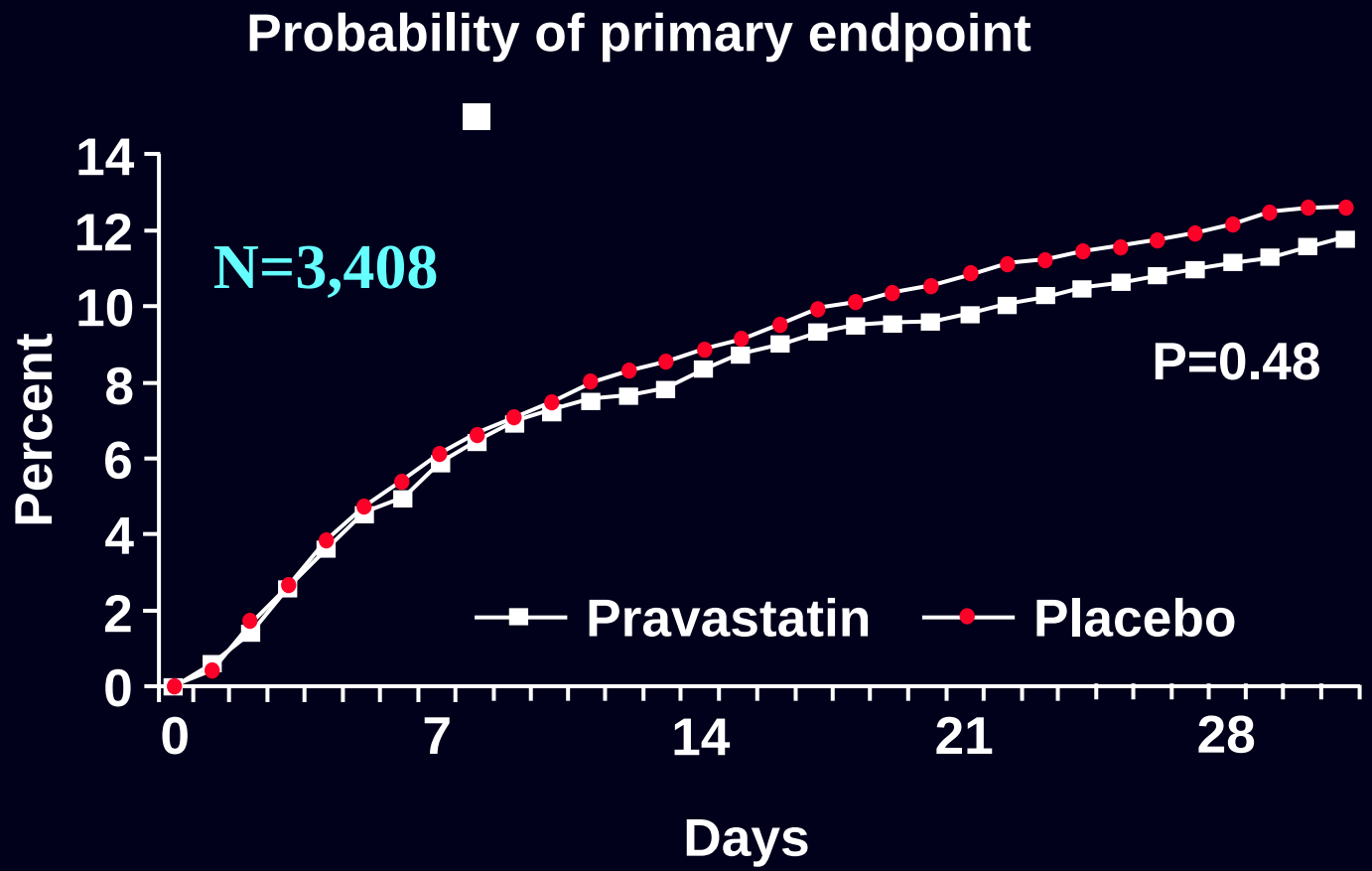

**Number at Risk**

| | | | | | |
|---|---|---|---|---|---|
| Atorvastatin | 1538 | 1381 | 1351 | 1323 | 518 |
| Placebo | 1548 | 1384 | 1338 | 1318 | 473 |


Schwartz GG, et al. *JAMA.* 2001;285:1711-1718.
Kinlay S, et al. *Circulation*. 2003;108:1560-1566.

# Effect of Pravastatin Compared With Placebo Initiated Within 24 h of Onset of AMI or uAP

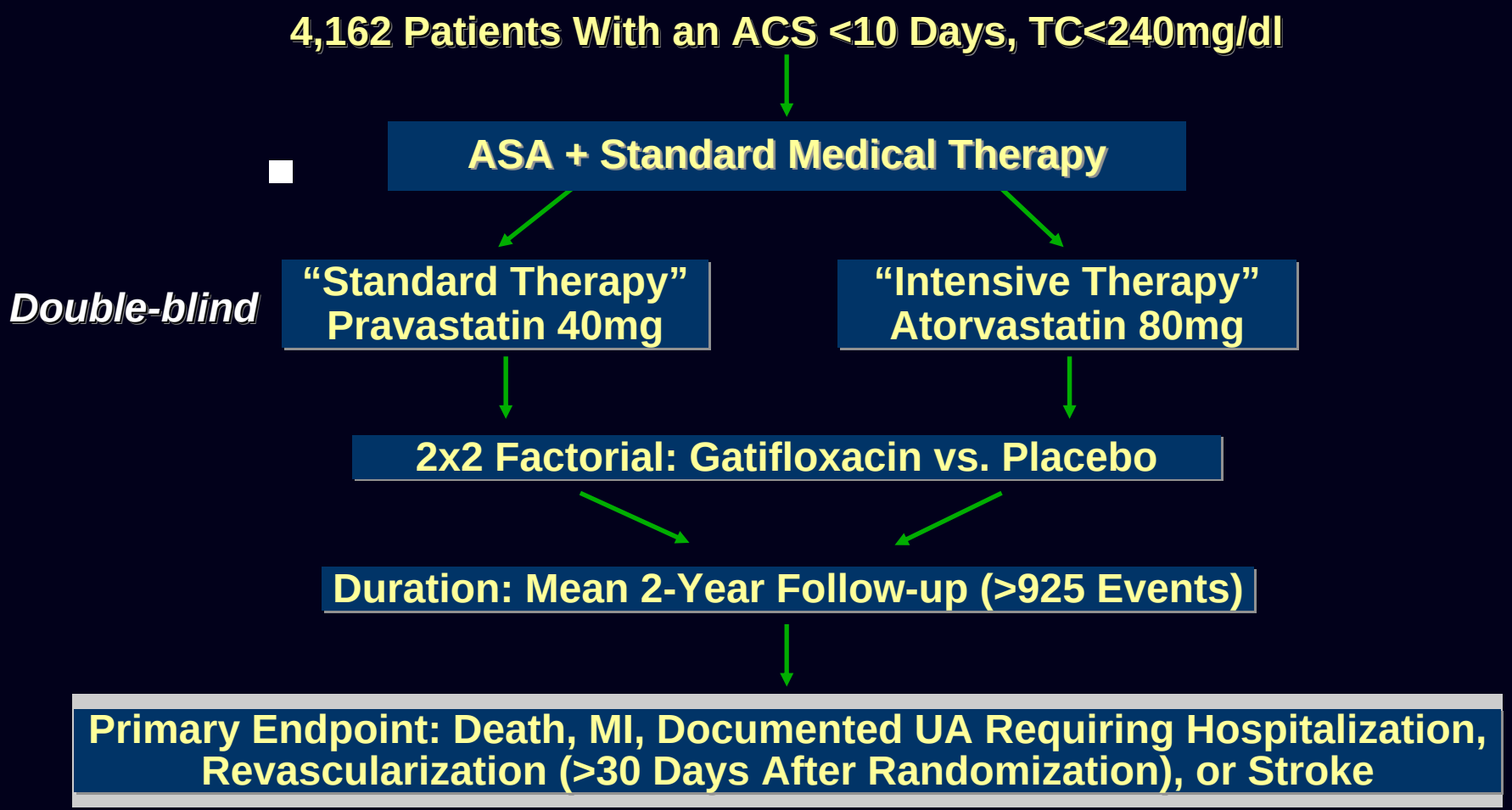
## The Pravastatin in Acute Coronary Treatment (PACT) trial



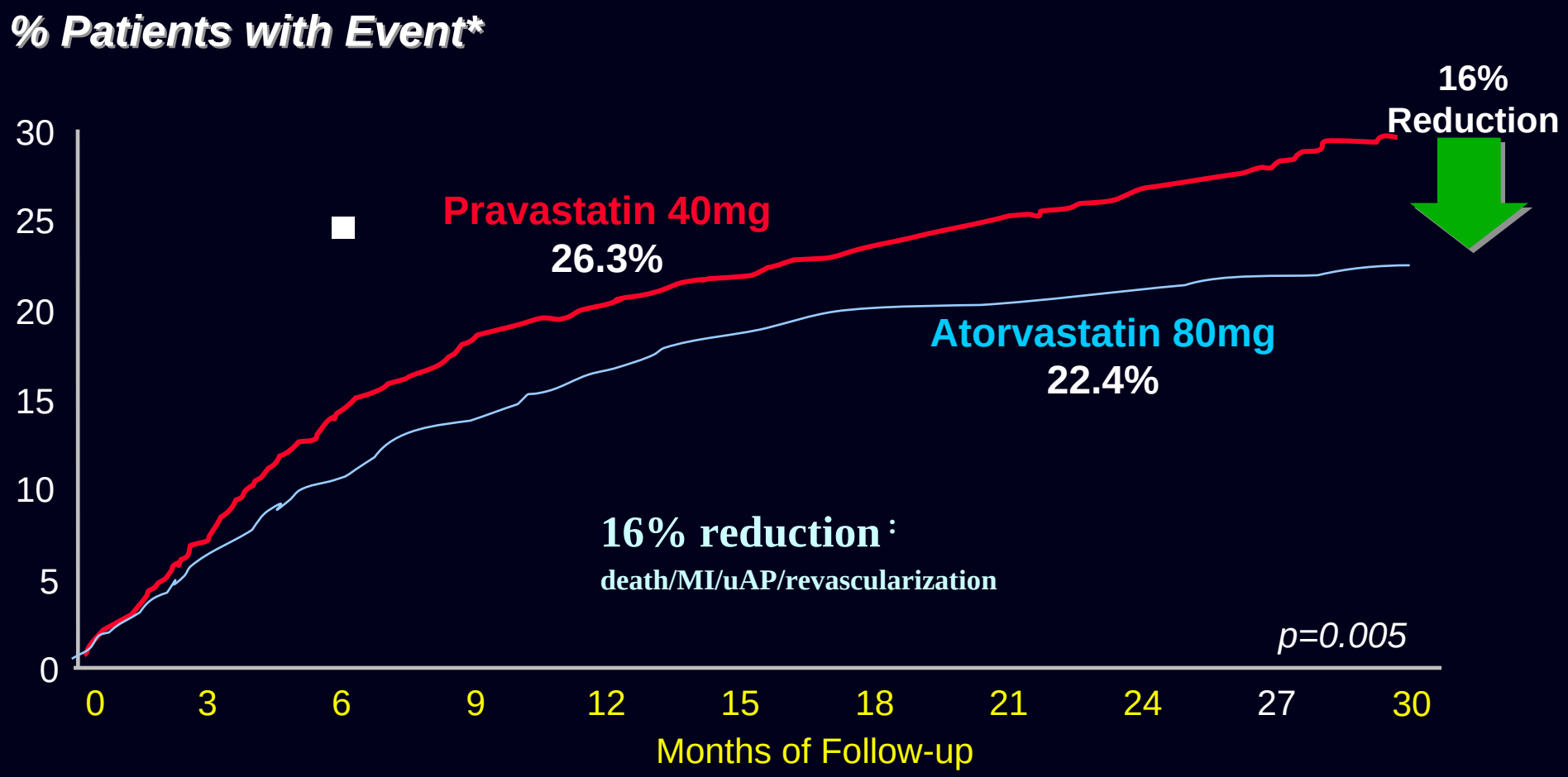

**Pravastatin can be safely administered within 24h of the onset of symptoms of an ACS, with a favorable but not significant trend in outcome at 30 days compared with placebo.**

*AHJ2004:148(1):e2*

# PROVE-IT


4,162 Patients With an ACS <10 Days, TC<240mg/dl
ASA + Standard Medical Therapy
Double-blind
"Standard Therapy"
Pravastatin 40mg
"Intensive Therapy"
Atorvastatin 80mg
2x2 Factorial: Gatifloxacin vs. Placebo
Duration: Mean 2-Year Follow-up (>925 Events)
Primary Endpoint: Death, MI, Documented UA Requiring Hospitalization, Revascularization (>30 Days After Randomization), or Stroke

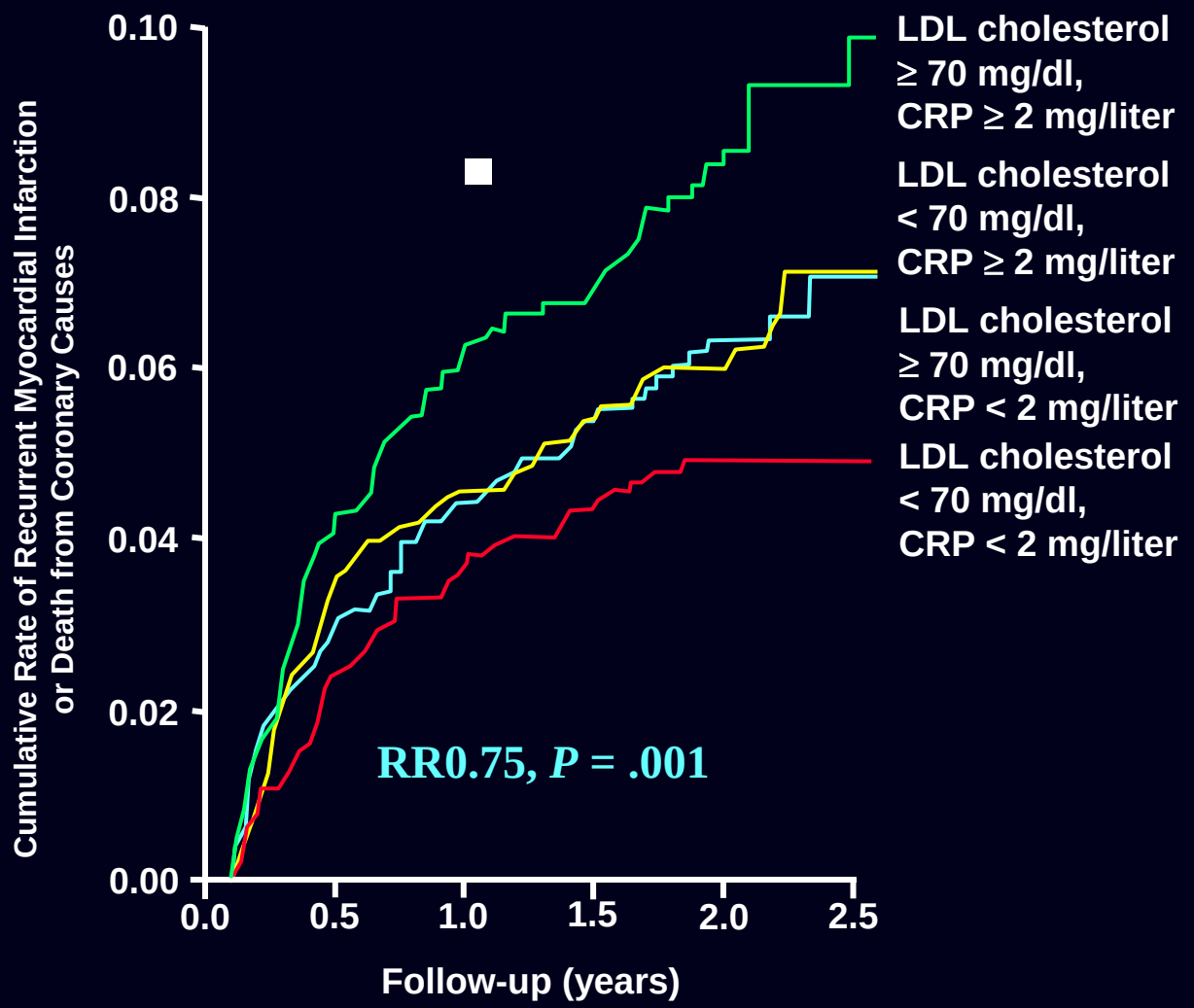
# PROVE-IT




- N=4,162 ACS (early invasive-3/4; multiple medications)
- Among patients who have recently had an ACS, an intensive lipid-lowering statin regimen provides greater protection against death or major cardiovascular events than does a standard regimen.

*NEJM 2004;350:1495*

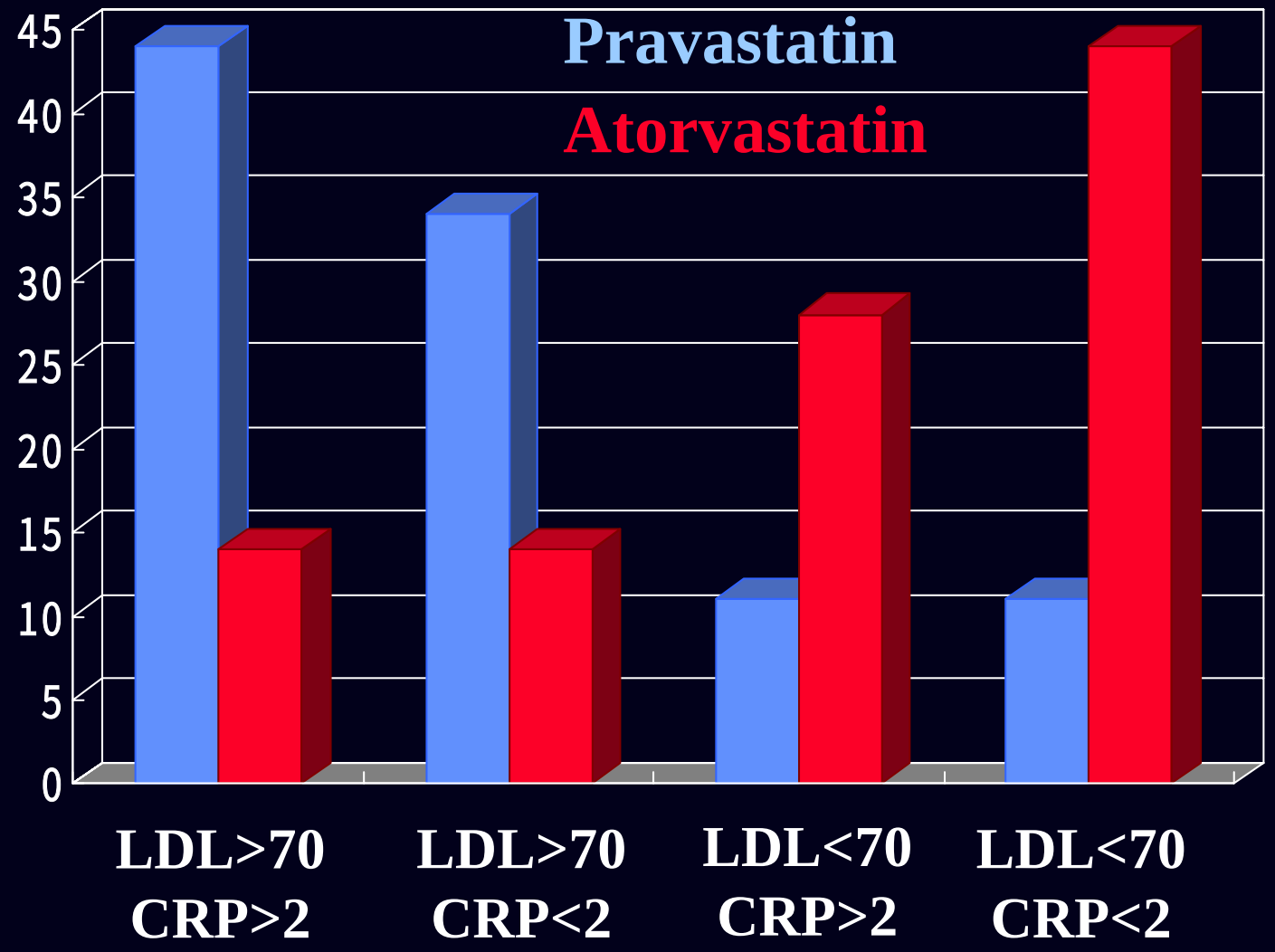
# PROVE-IT: CRP Analysis



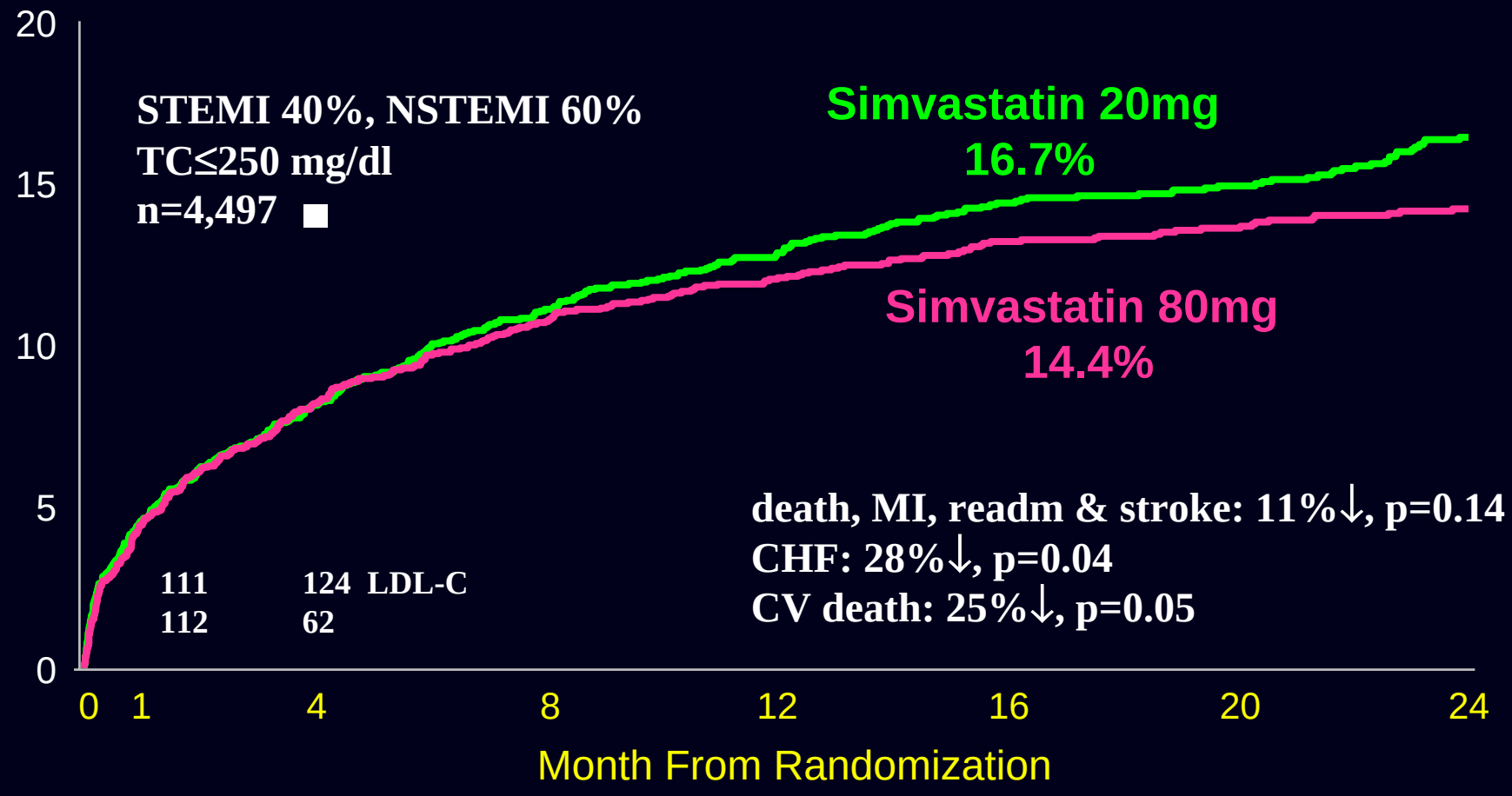

**Patients who have low CRP levels after statin therapy have better clinical outcomes than those with higher CRP levels, regardless of the resultant level of LDL cholesterol.**

*N Engl J Med 2005;352:20*

# PROVE-IT: CRP Analysis



# A to Z in Patients With ACS




- No early divergence in even rates despite differences in LDL-C
- A favorable trend toward reduction of MACE.

*JAMA2004;292:1307*

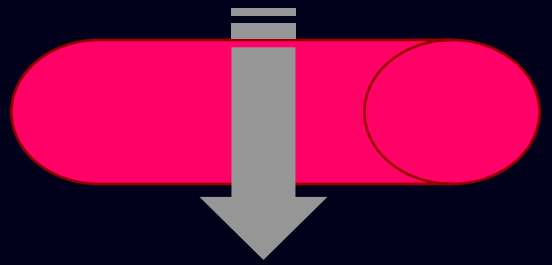
# Intensive Statin Therapy in ACS

| | A to Z | MIRACL | PROVE-IT |
|---|---|---|---|
| No. of Patients | 4,497 | 3,086 | 4,162 |
| Δ LDL-C, mg/dl | | | |
| Early | 62 | 63 | 33 |
| Late | 15 | NA | 28 |
| Δ CRP, % | 17 | 34 | 39 |
| Event reduction, % | | | |
| Early | 0 | 16 | 18 |
| Late | 11 | NA | 16 |
| Myopathic event* | 9(0.4%) | 0 | 0 |

*CK higher than 10 times the upper limit of normal

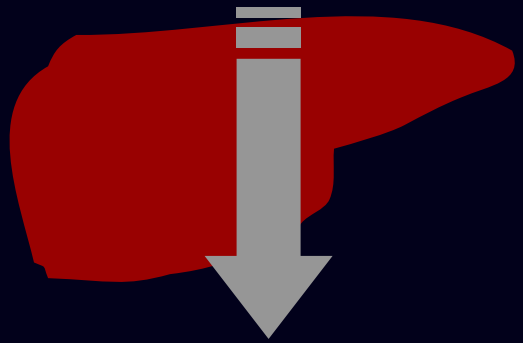
# Effects of Statin

**Vascular action**



**Anti-inflammatory**
**Anti-oxidant**
**Anti-thrombotic**
**Endothelial function**

**Hepatic action**

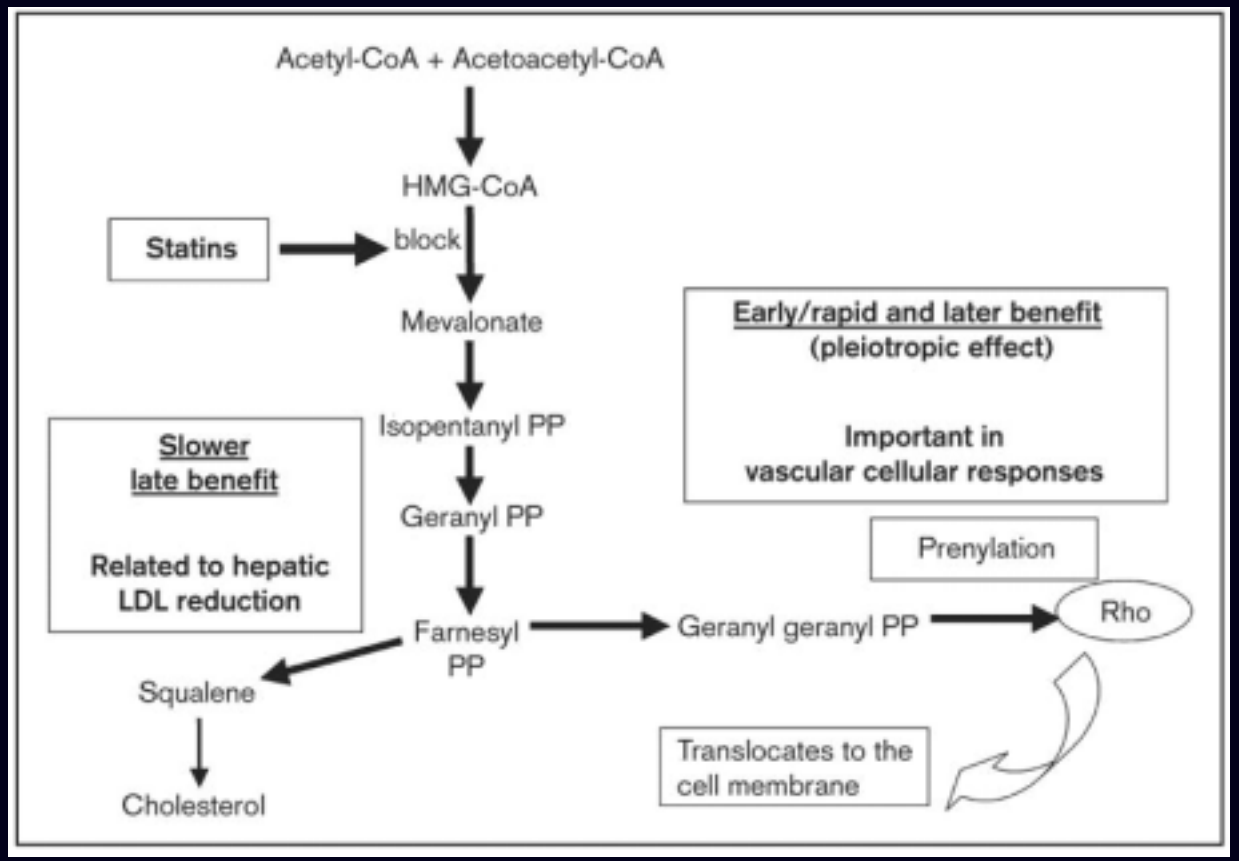


**LDL-lowering**
**Others**

**Plaque stabilization**

**Prevent CV events**

# Intensive inhibition of HMG-CoA reductase

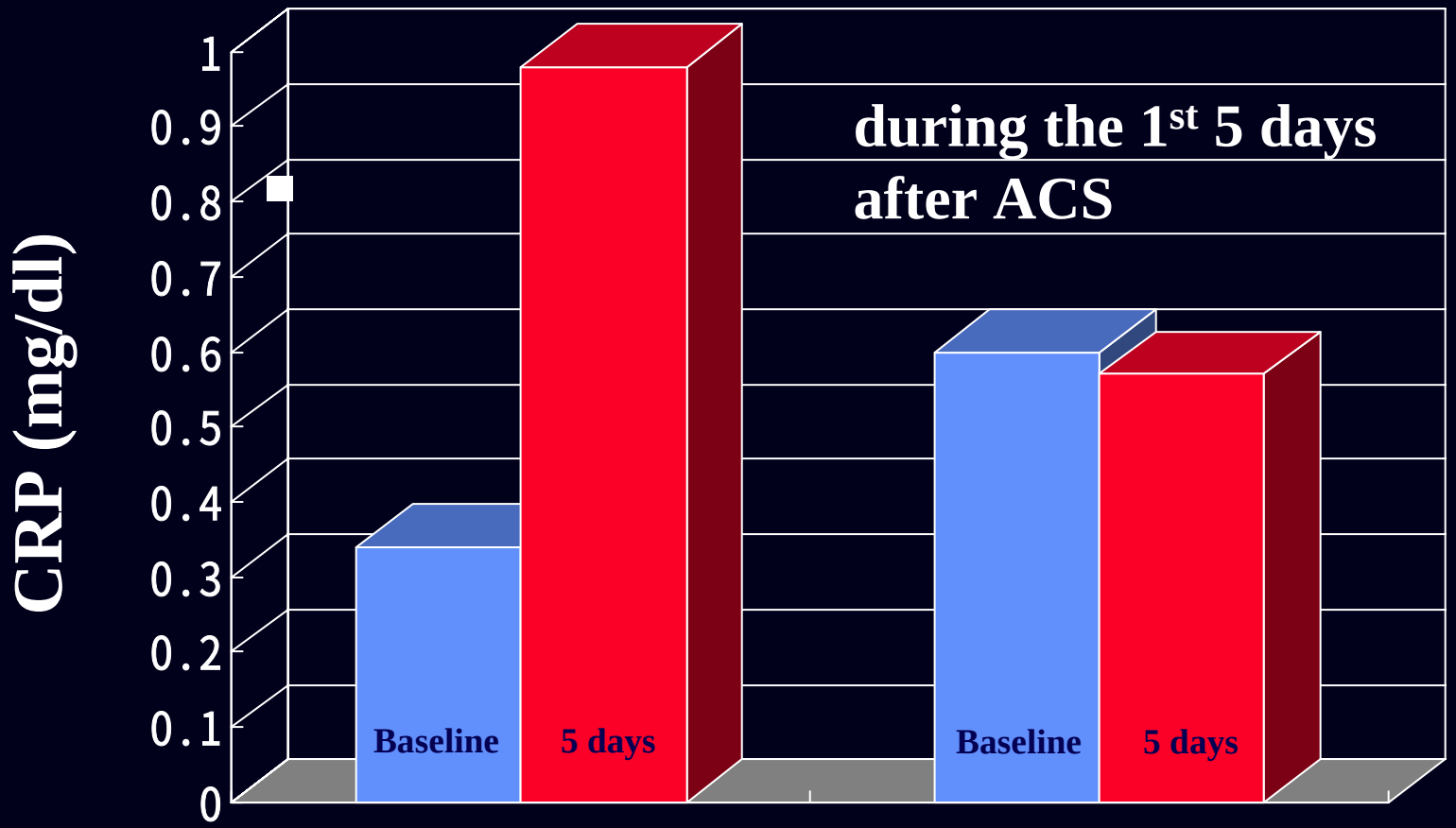



**HMG-CoA reductase is an ubiquitous enzyme which is present in vascular and inflammatory cells as well as in hepatocytes.**

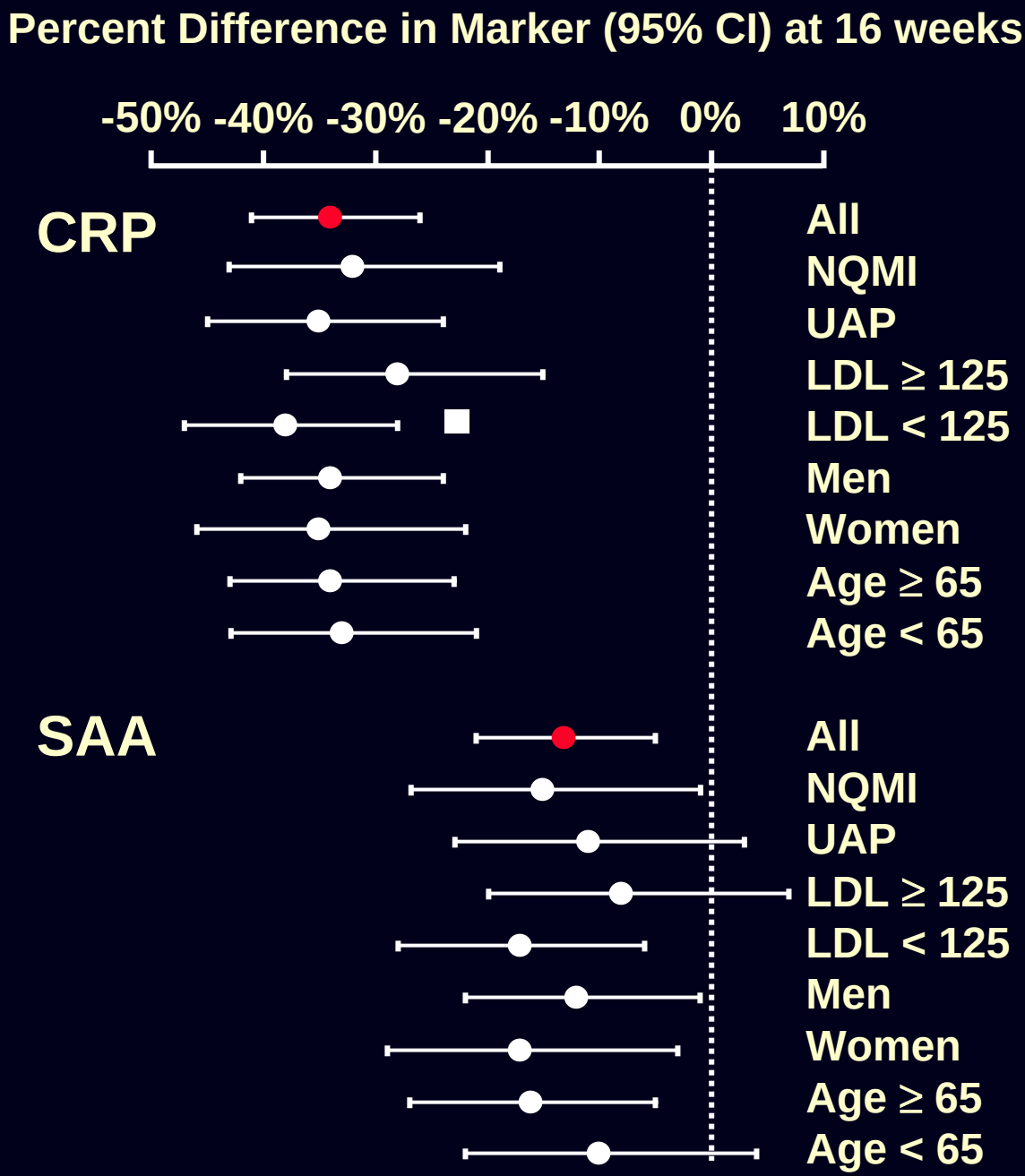
***Isoprenoids bind a number of G-proteins such as Rho and Ras by prenylation. Rho activates a number of nuclear TF such as NFkB.***

*Curr Opinion Lipidol 2004;15:637*

# Anti-inflammatory Effect of *Atorvastatin (80mg)* in Unstable Angina and NQMI




*AJC2003;92:298*




# High-Dose Atorvastatin in the MIRACL Study

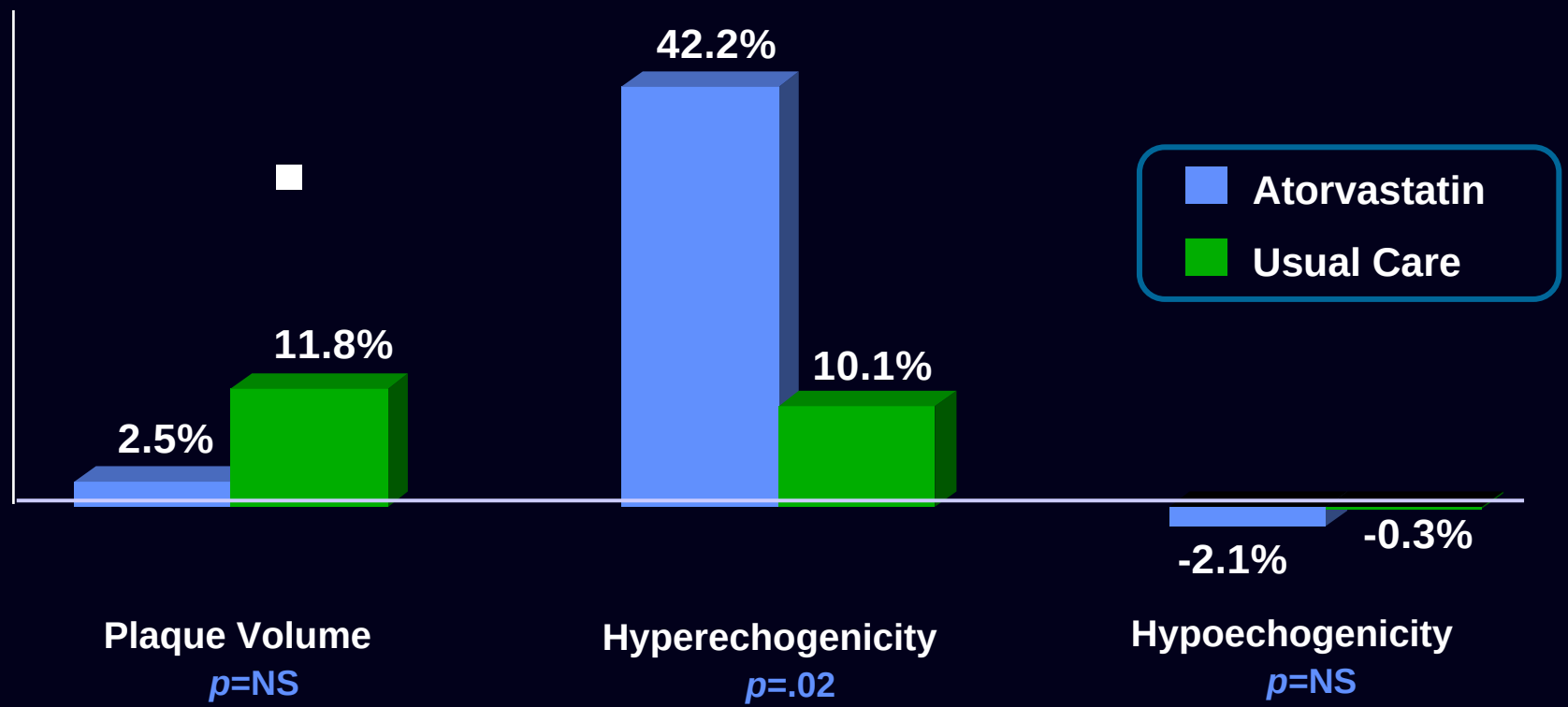
**Compared with placebo, atorvastatin significantly reduced CRP and SAA at 16 weeks follow-up.**

**High-dose atorvastatin potentiated the resolution of inflammation after ACS, reinforce the concept of early lipid lowering soon after ACS.**

*Circulation 2003;108:1560*

# Gain Trials

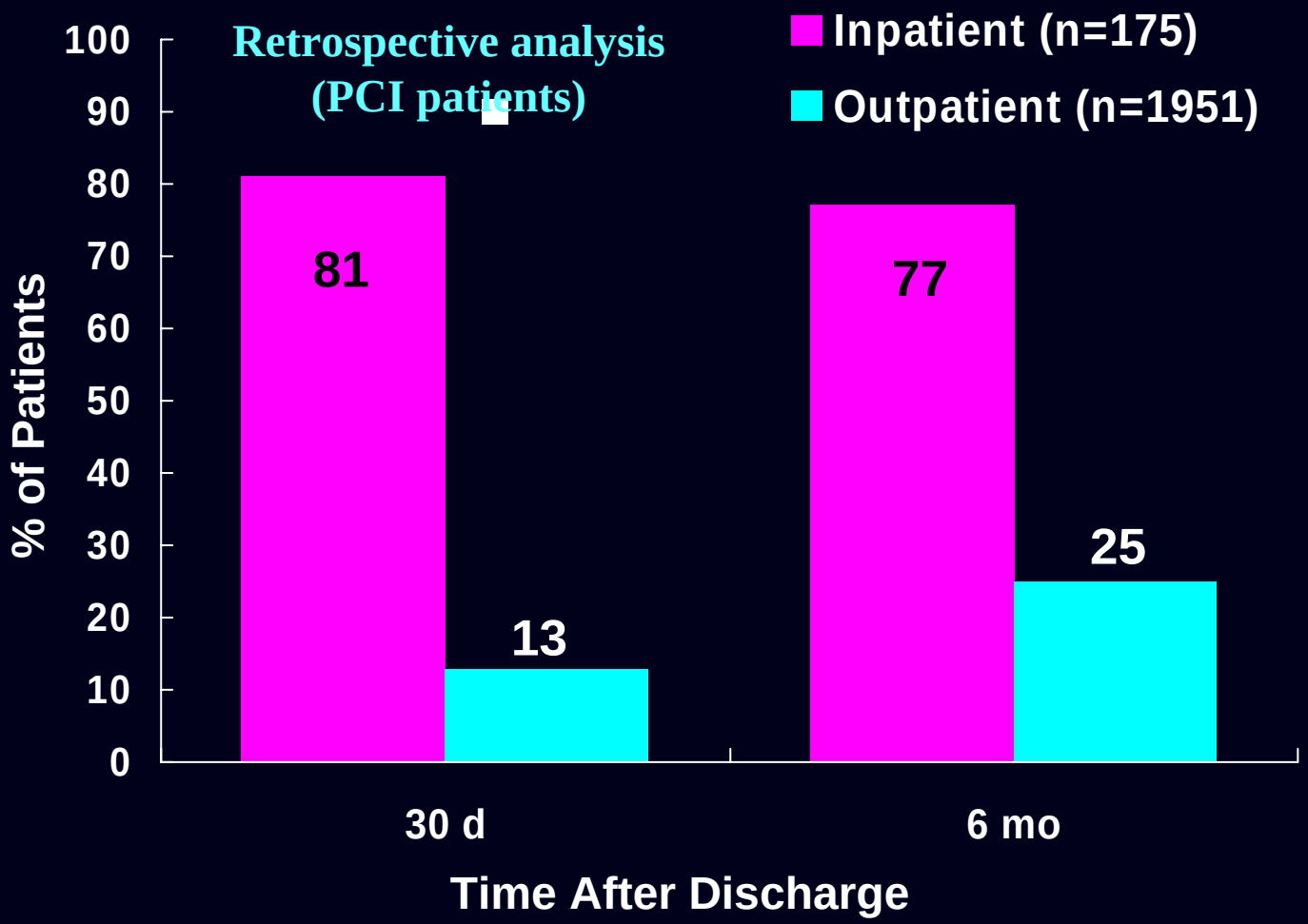
***Change After 12 Months of Therapy (%)***




**The impact of aggressive therapy with atorvastatin (LDL goal of <100 mg/dL) vs moderate therapy (usual care with various statins) on plaque volume and content using ICUS**

*Circulation* 2001;104:387

# In-Hospital Initiation of Lipid-Lowering Therapy After Coronary Intervention as a Predictor of Long-term Utilization




**Inpatient initiation of lipid-lowering therapy is a strong and independent predictor of subsequent use.**

*Arch Intern Med 2003; 163: 2576*

# Current Guidelines in ACS

- **NCEP III**
  - **start therapy on admission or within 24 h**

- **ACC/AHA**
  - **start therapy 24-96 h after admission**

*towards zero events*

# Conclusions

- **Overall, statin therapy should be initiated in the setting of ACS, regardless of plasma lipid values.**
- **The results of recent clinical trials herald the beginning of a new era of intensive statin therapy.**

# Thank You.

**Starting today,**
**every patient going home with a heart attack!**

***We have to move***
***beyond LDL-C.***

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