The role of statins- New Approaches

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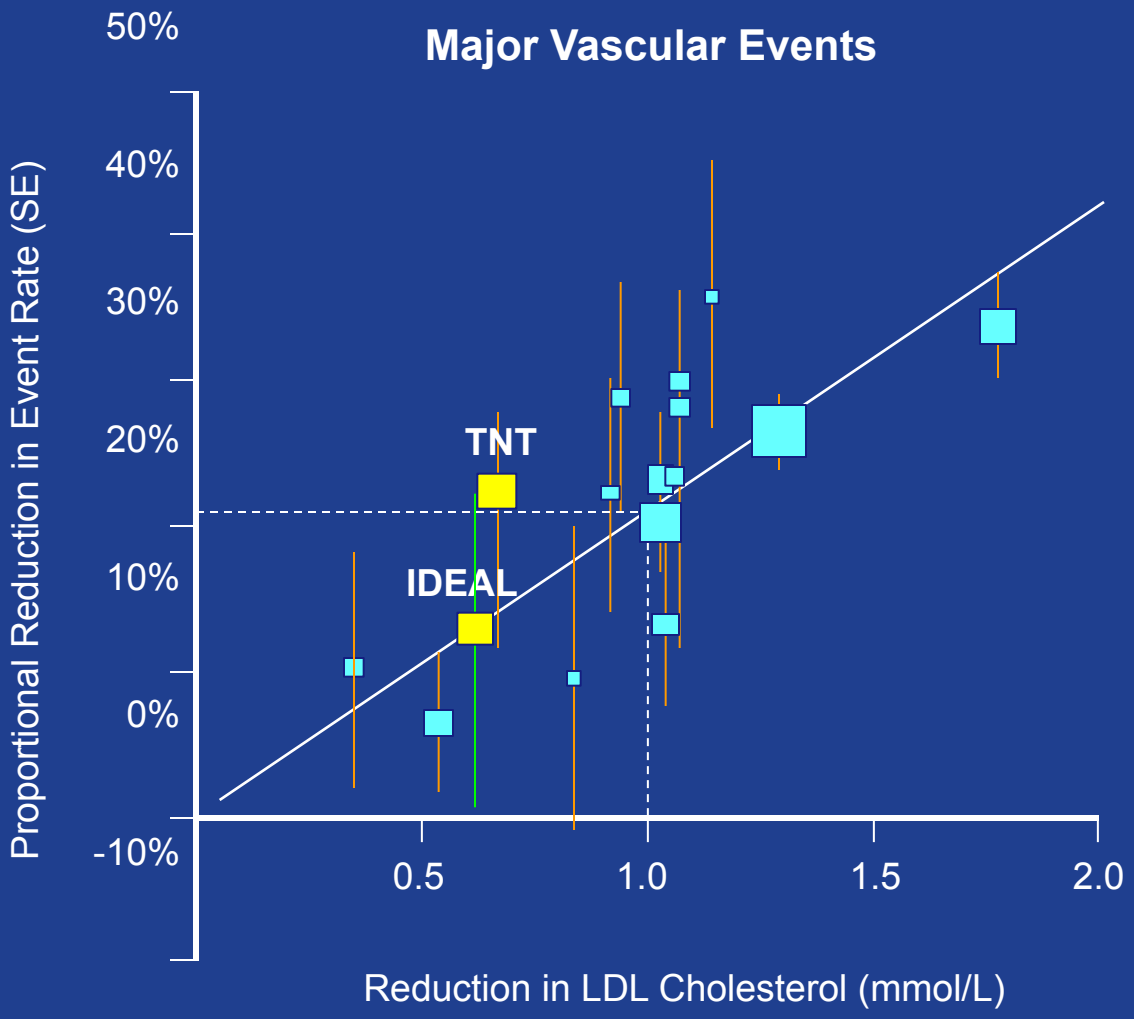
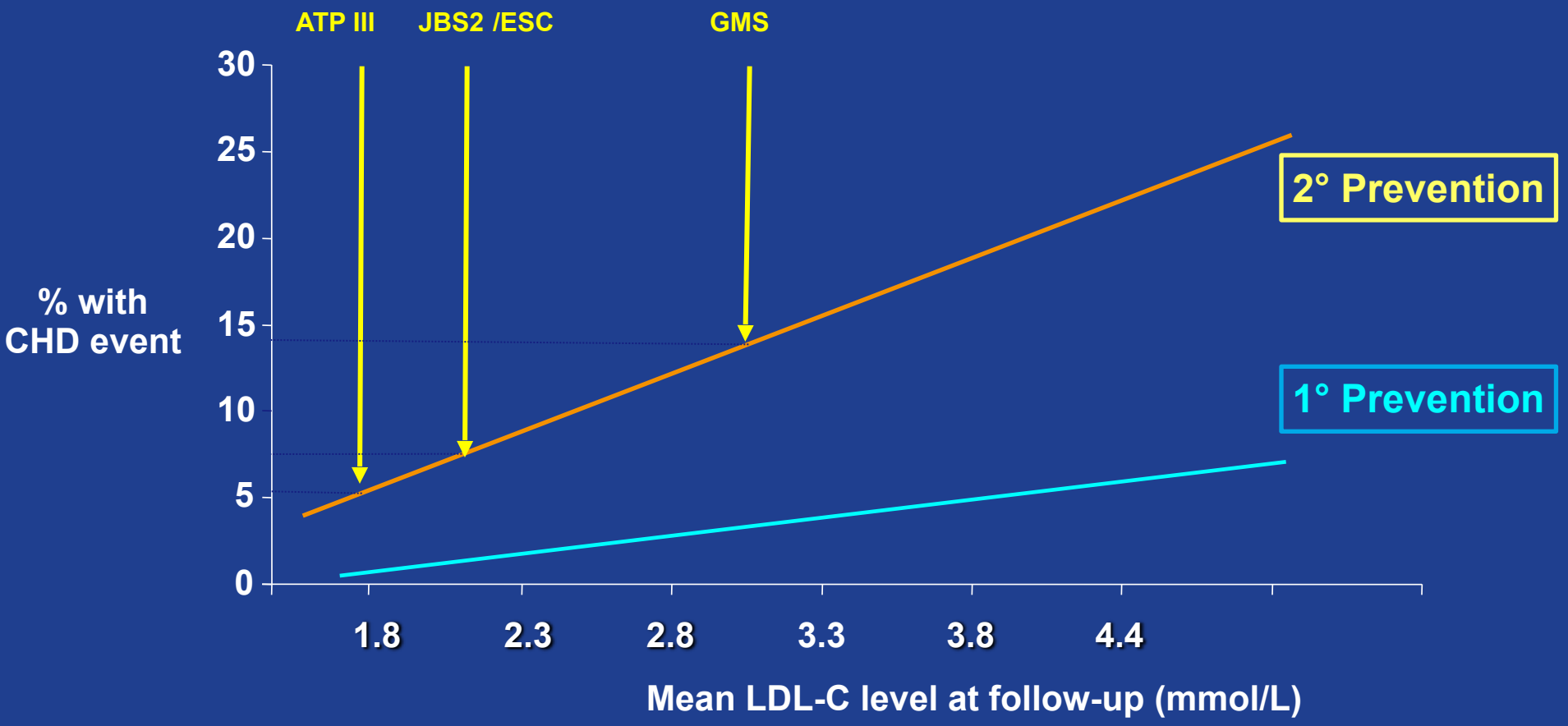
Meta-Analysis of Dyslipidemia Trials



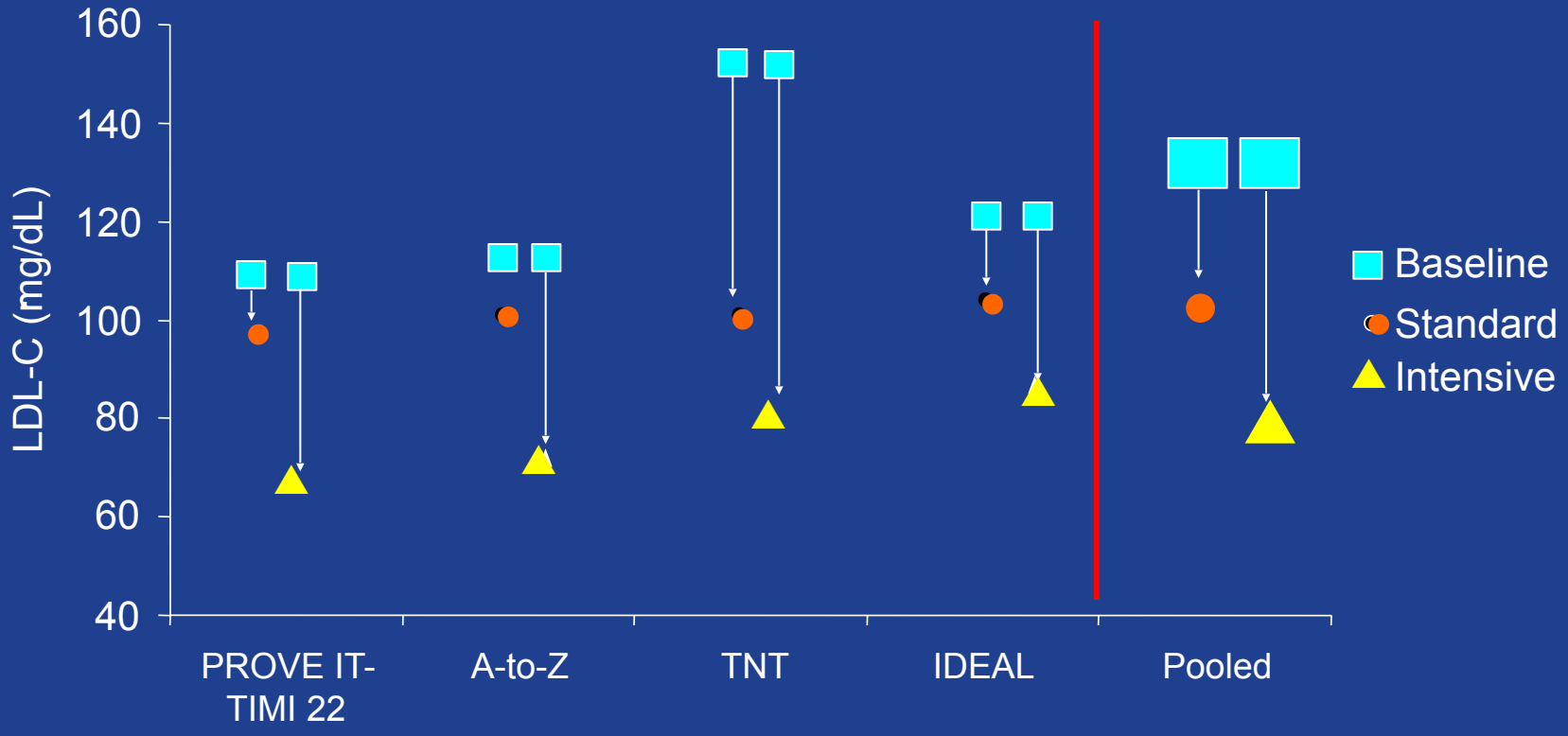
Adapted from CTT Collaborators. *Lancet.* 2005; 366:1267-78

Greater absolute benefit in secondary vs primary prevention with more intensive Tx



Meta-Analysis of Intensive Statin Therapy
LDL Cholesterol by Trial

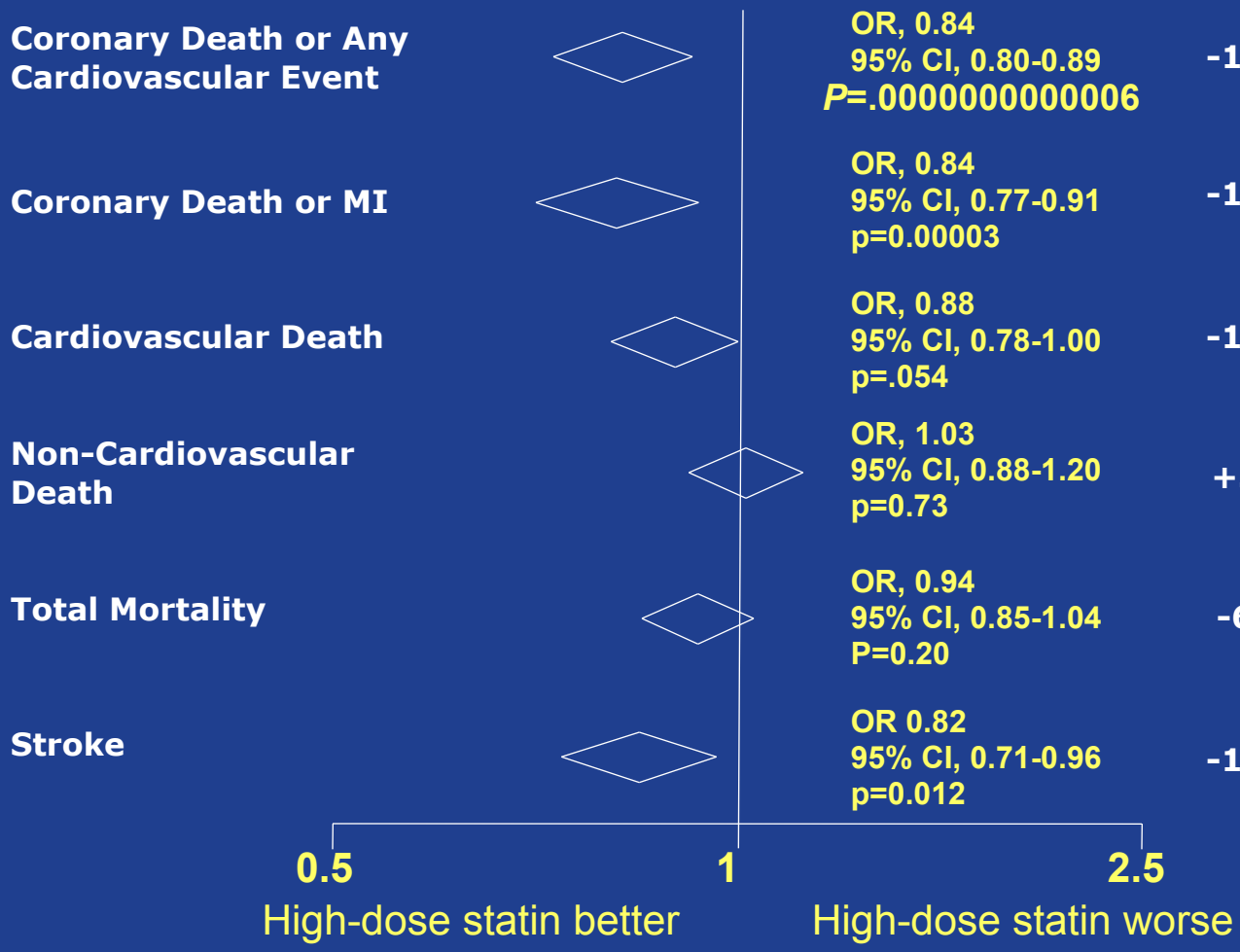
Patients	ACS		Stable CAD		Pooled
n	4162	4497	10001	8888	27548
Prior Statin Use	25.2%	0%	0%	75.5%	28.2%



Baseline*	**108.4**	**112.9**	**152**	**121.5**	**129.6 (3.32)**
Standard*	**97.1**	**101**	**101**	**104**	**101.4 (2.6)**
Intensive*	**65.5**	**69.1**	**77**	**81**	**75.4 (1.93)**

Cannon CP, et al. JACC 2006; 48: 438 - 445.

Meta-Analysis of Intensive Statin Therapy
All Endpoints



	Odds Ratio (95% CI)	Odds Reduction	Event Rates No./Total (%)	
			High Dose	Std Dose
Coronary Death or Any Cardiovascular Event	OR, 0.84 95% CI, 0.80-0.89 *P*=.0000000000006	-16%	3972/13798 (28.8)	4445/13750 (32.3)
Coronary Death or MI	OR, 0.84 95% CI, 0.77-0.91 p=0.00003	-16%	1097/13798 (8.0)	1288/13750 (9.4)
Cardiovascular Death	OR, 0.88 95% CI, 0.78-1.00 p=.054	-12%	462/13798 (3.3)	520/13750 (3.8)
Non-Cardiovascular Death	OR, 1.03 95% CI, 0.88-1.20 p=0.73	+3%	340/13798 (2.5)	331/13750 (2.4)
Total Mortality	OR, 0.94 95% CI, 0.85-1.04 P=0.20	-6%	808/13798 (5.9)	857/13750 (6.2)
Stroke	OR 0.82 95% CI, 0.71-0.96 p=0.012	-18%	316/13798 (2.3)	381/13750 (2.8)

Cannon CP, et al JACC 2006

In ACS intensive statin therapy and mortality

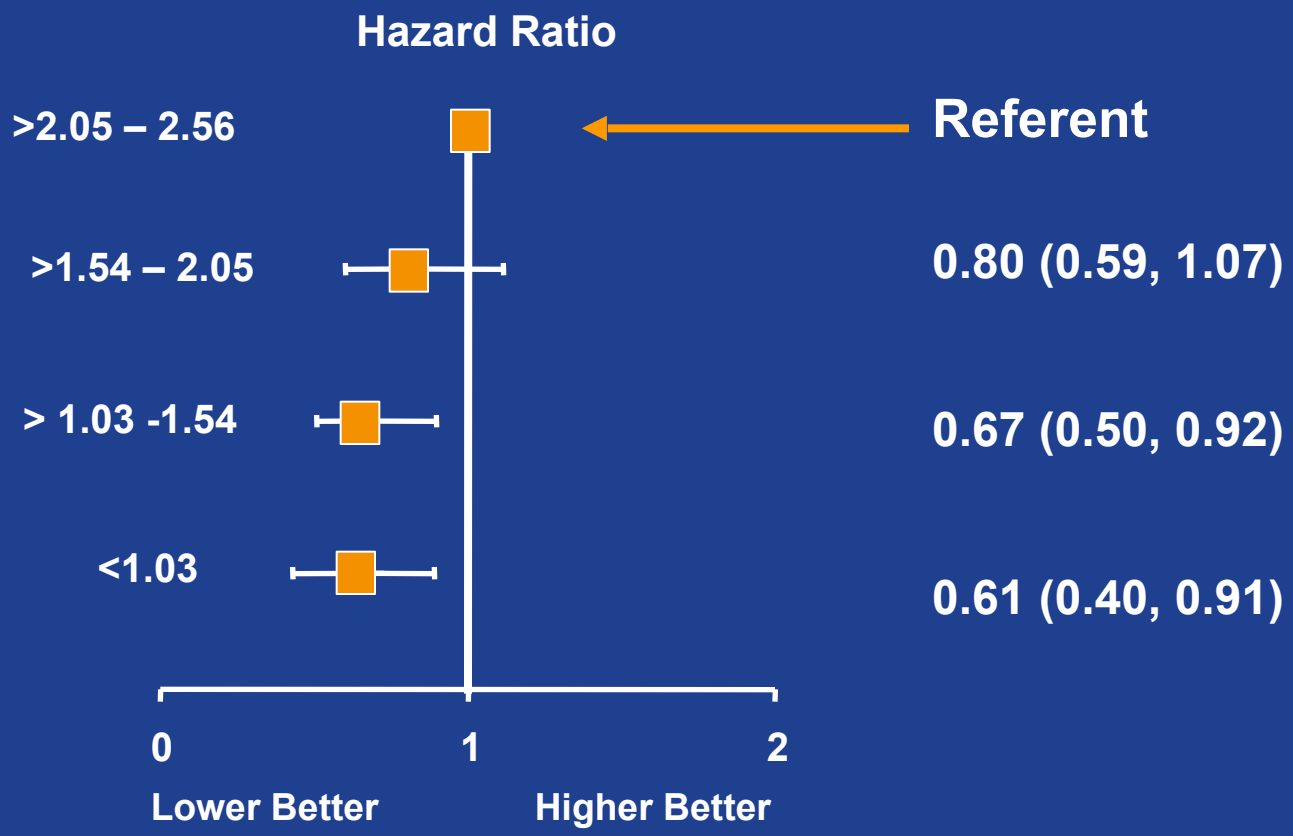
- Meta-analysis of PROVE IT and A to Z
- *Afilalo et at Heart 2007*

- About 8 500 patients with av of 2 years of FU

- 25% reduction in all cause mortality
- (0.61-0.93)

- Absolute benefit is 1.2%

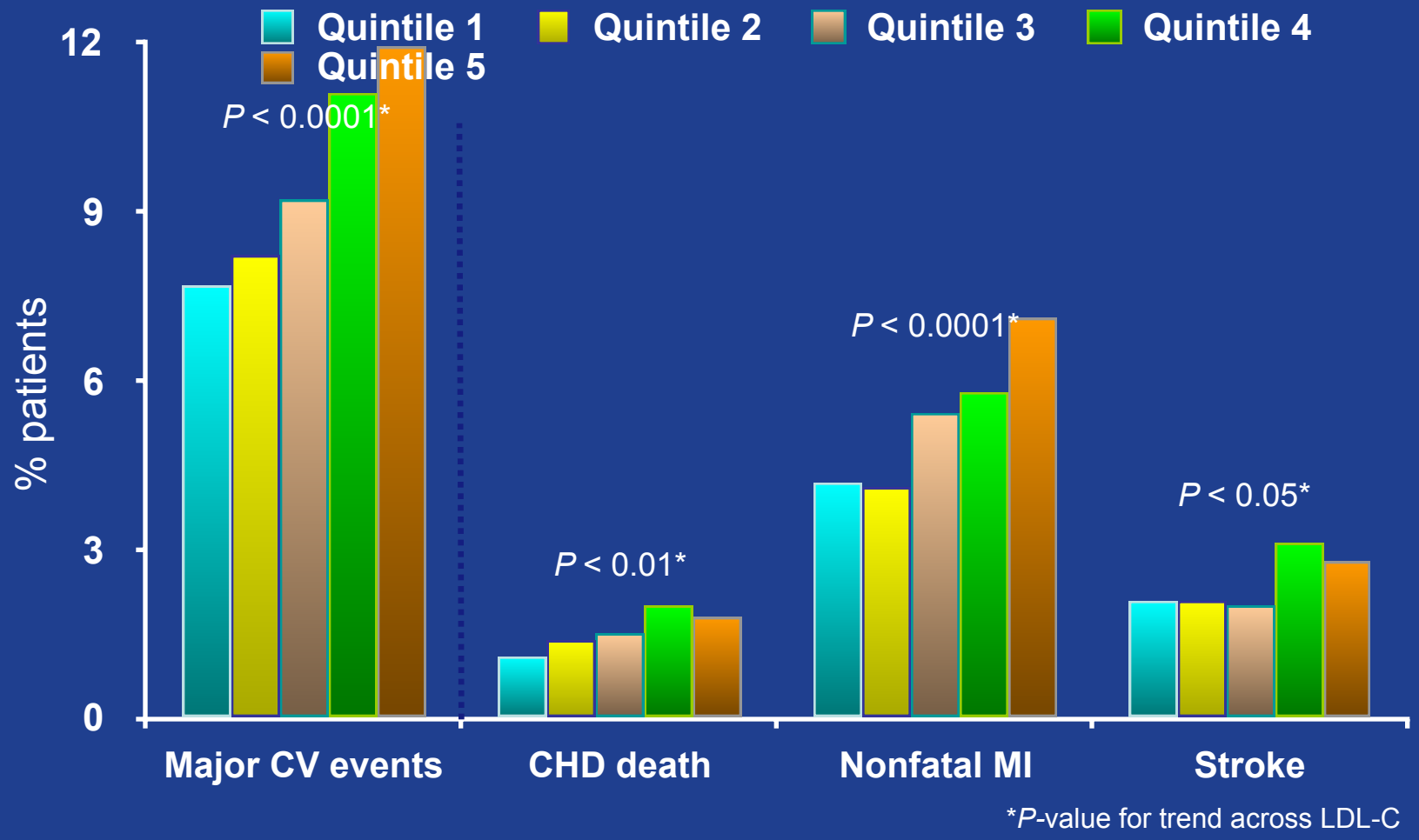
PROVE IT-TIMI 22: Relationship Between Month 4 LDL and Long-Term Risk of Death or Major CV Event



*Adjusted for age, gender, DM, prior MI, baseline LDL

Wiviott SD, et al. JACC. 2005

TNT: Incidence of First Major Cardiovascular Events Across Quintiles



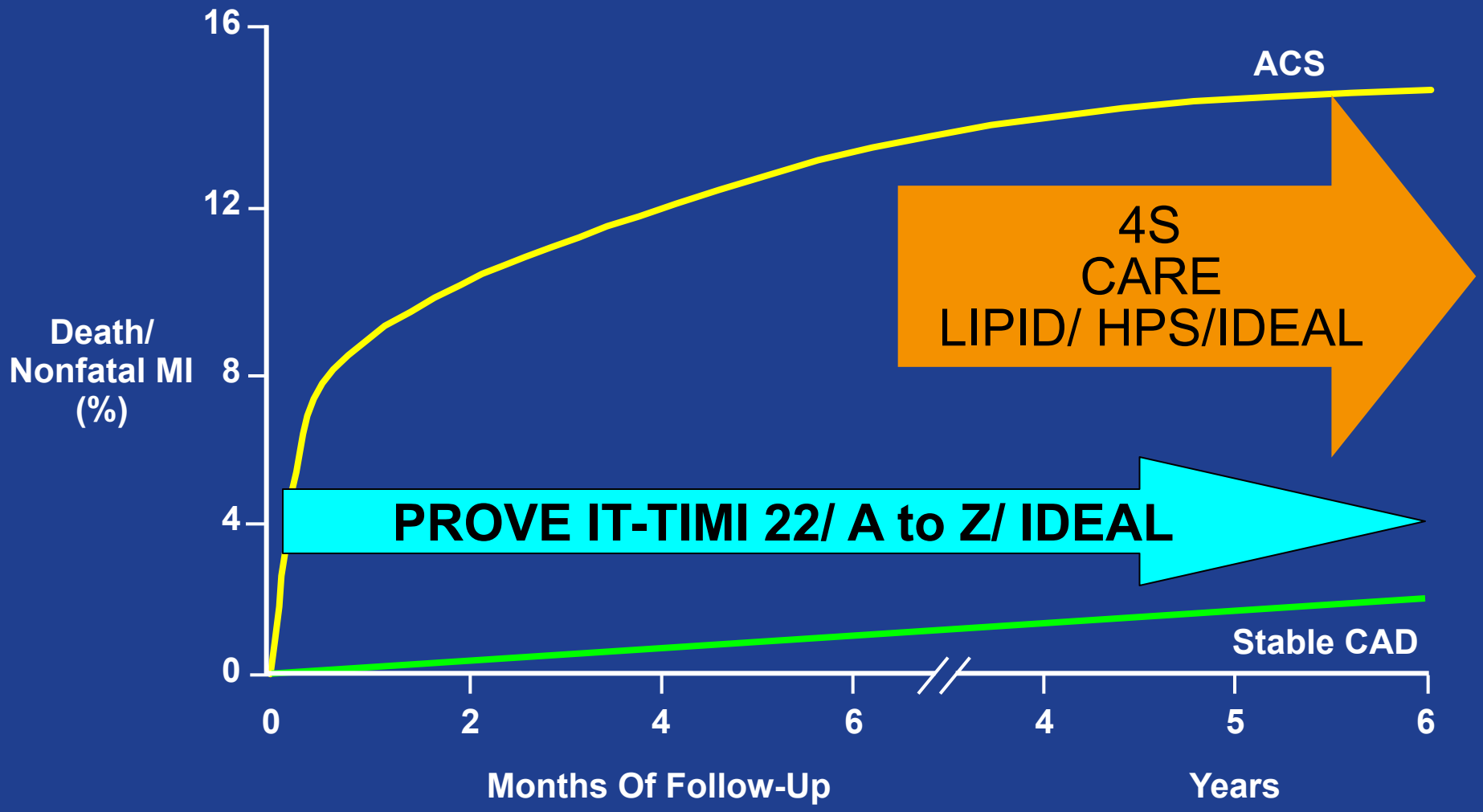
*P-value for trend across LDL-C

LaRosa JC. AJC. 2007

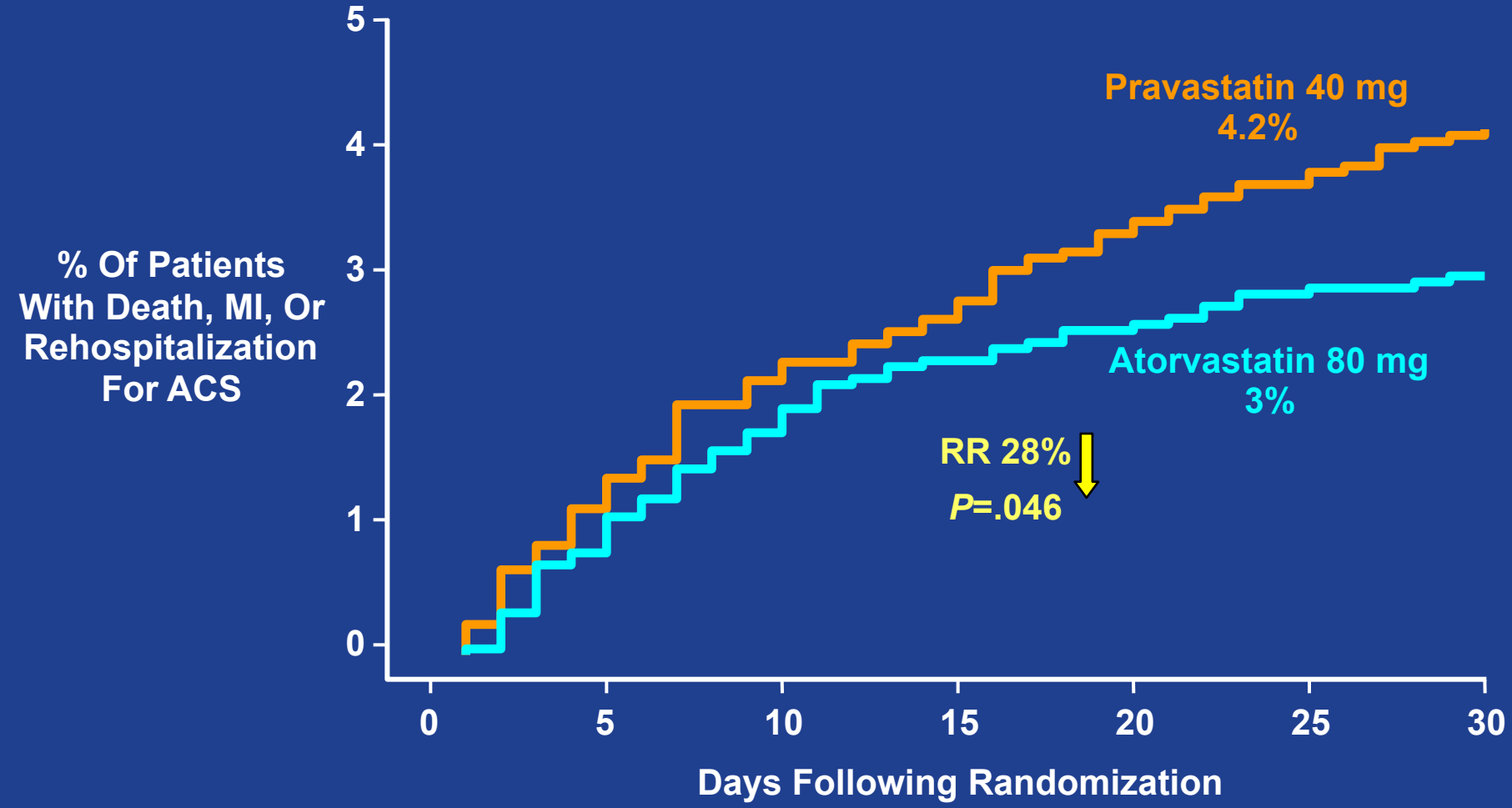
Interpretation

- Lower is better
- In stable CHD titrate statin to achieve a lower LDL-C
- <1.8mmol/L North American guidelines
- <2.0mmol/L in European guidelines

Can we afford to delay intensive statin Tx in ACS?



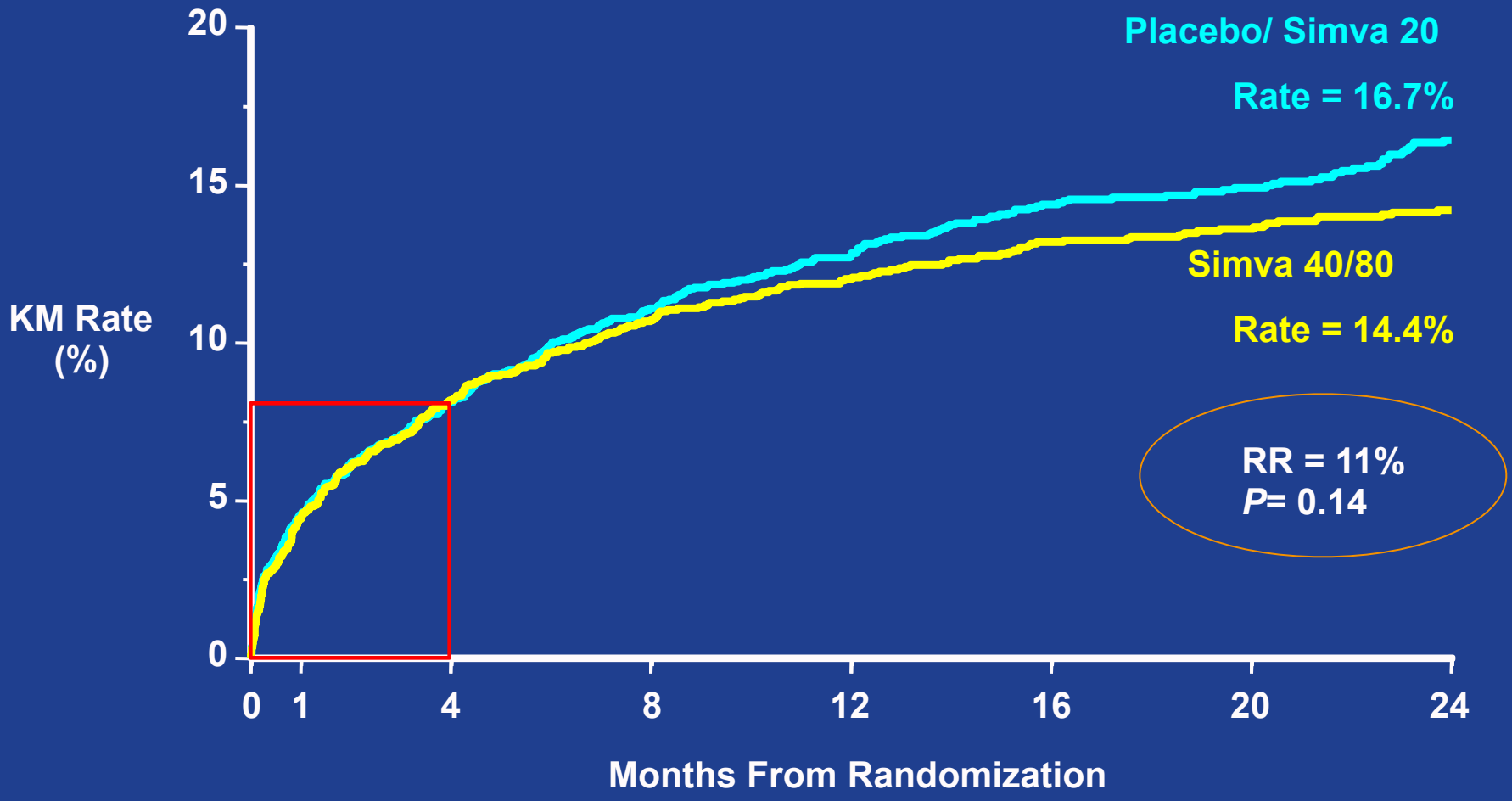
Rapid early reduction in Death, MI or ACS With Intensive statin Tx <1 month



Ray et al. J Am Coll Cardiol. 2005.

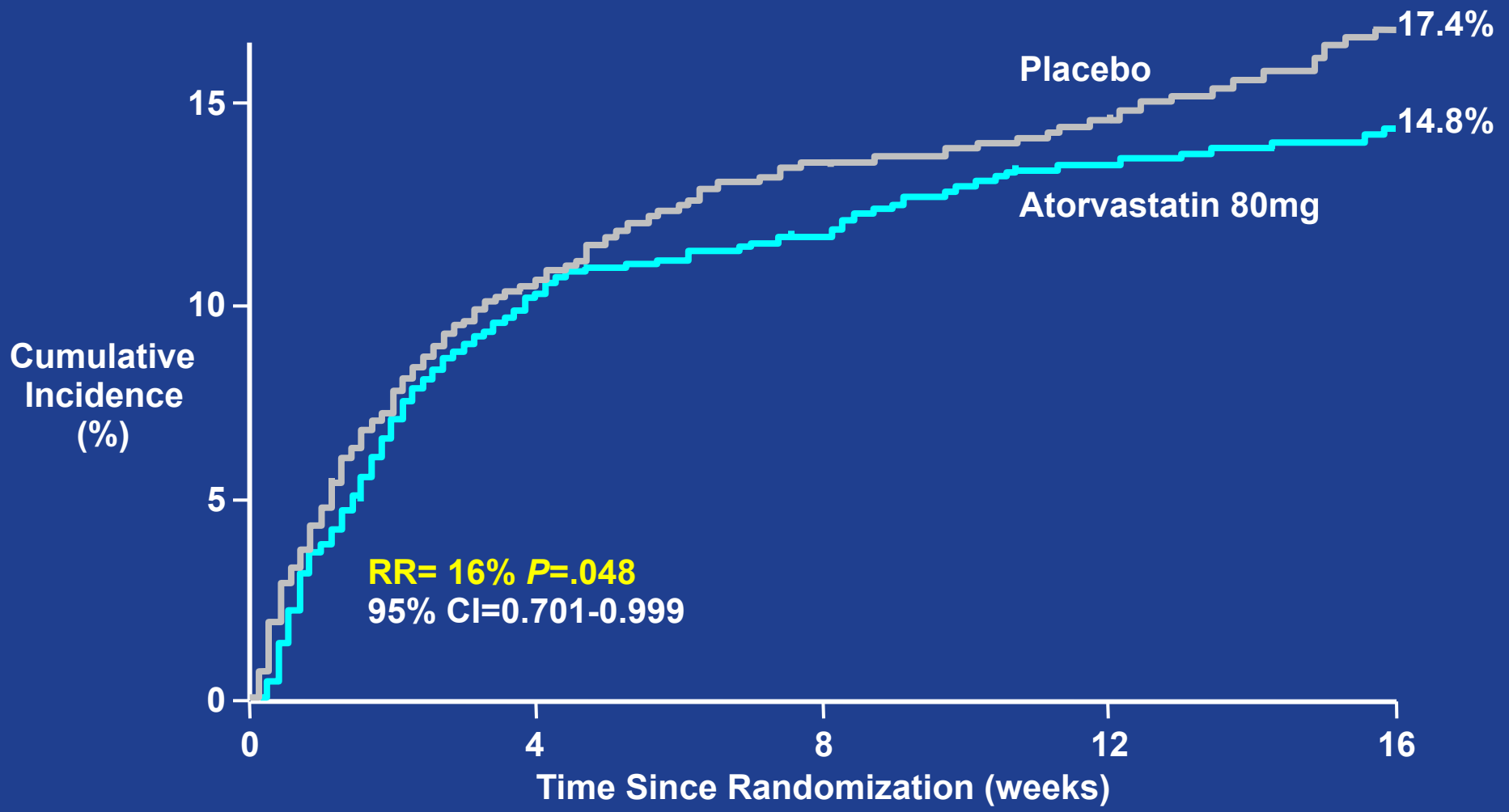
A To Z Primary End Point

CV Death, MI, Readmission ACS, Or Stroke



De Lemos et al. *JAMA*. 2004;292:1307.

MIRACL: Primary Efficacy Measure: Time To First Event*



*Death (any cause), nonfatal MI, resuscitated cardiac arrest, worsening angina with new objective evidence, and urgent rehospitalization.

PROVE IT-TIMI 22 And MIRACL: CRP Appears To Be Driving The Early Time To Benefit With Intensive Atorvastatin Therapy

	A-to-Z	MIRACL	PROVE IT
Number of patients randomized	4497	3086	4162
Early* LDL achieved on treatment, mmol/l	1.6	1.85	1.6
Early* LDL cholesterol differential, mmol/l	1.6	1.6	0.85
CRP differential, %	17	34	38
Early event reduction, %	0*	16*	18†

* Measured 120 days after randomization.

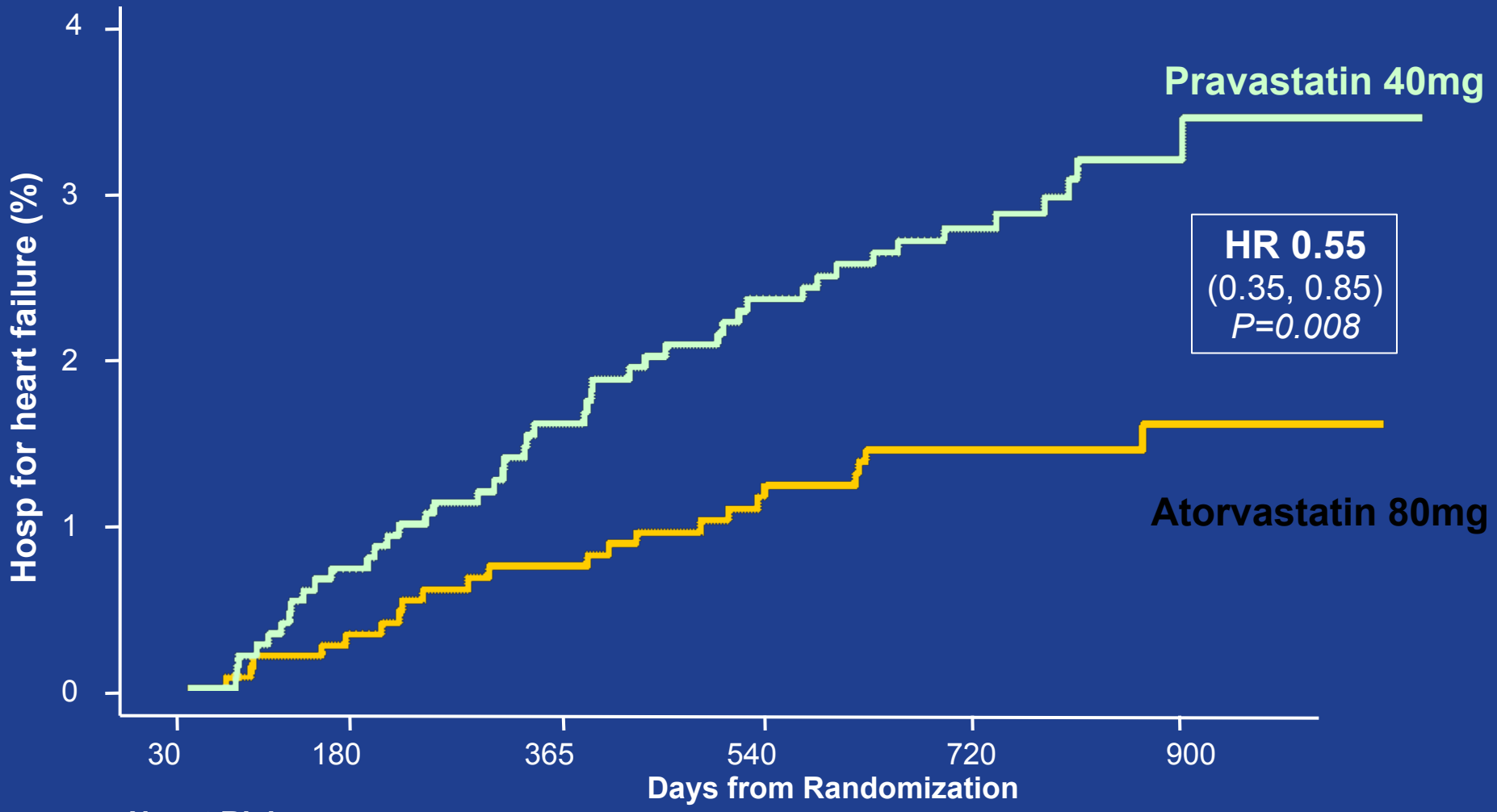
† Measured 90 days after randomization.

Adapted from Nissen. *JAMA*. 2004;292:1365.

Interpretation

- Only intensive statin therapy produces early benefits after ACS
- The early benefit appears to be poorly related to LDL-C reduction
- Early benefits may reflect a reduction in inflammation by pleiotropic effects

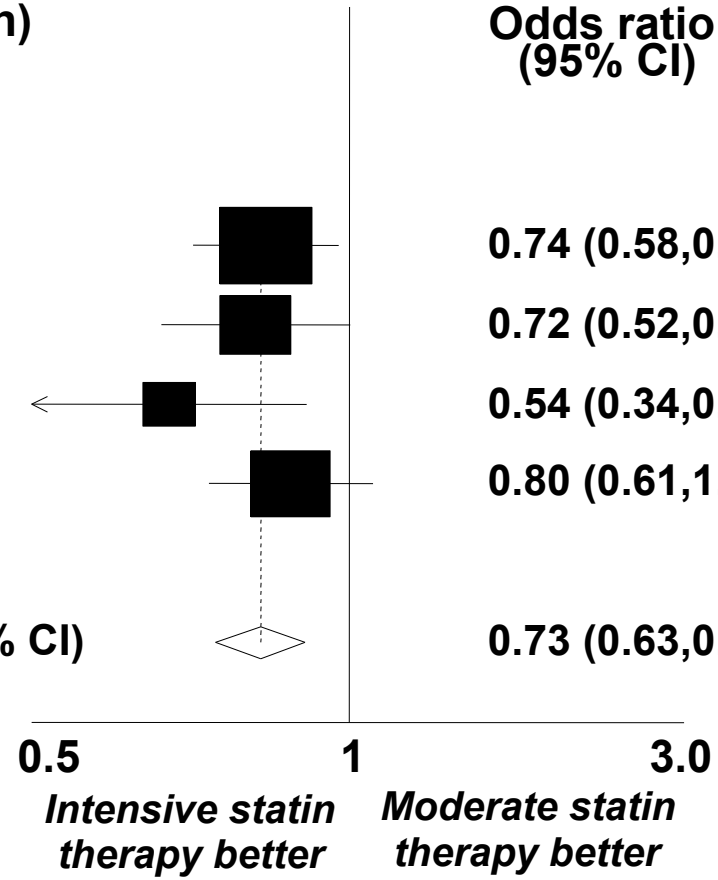
Risk of heart failure and statin therapy



No. at Risk						
Prava	2063	1930	1846	1785	866	342
Atorva	2099	1959	1869	1826	869	339

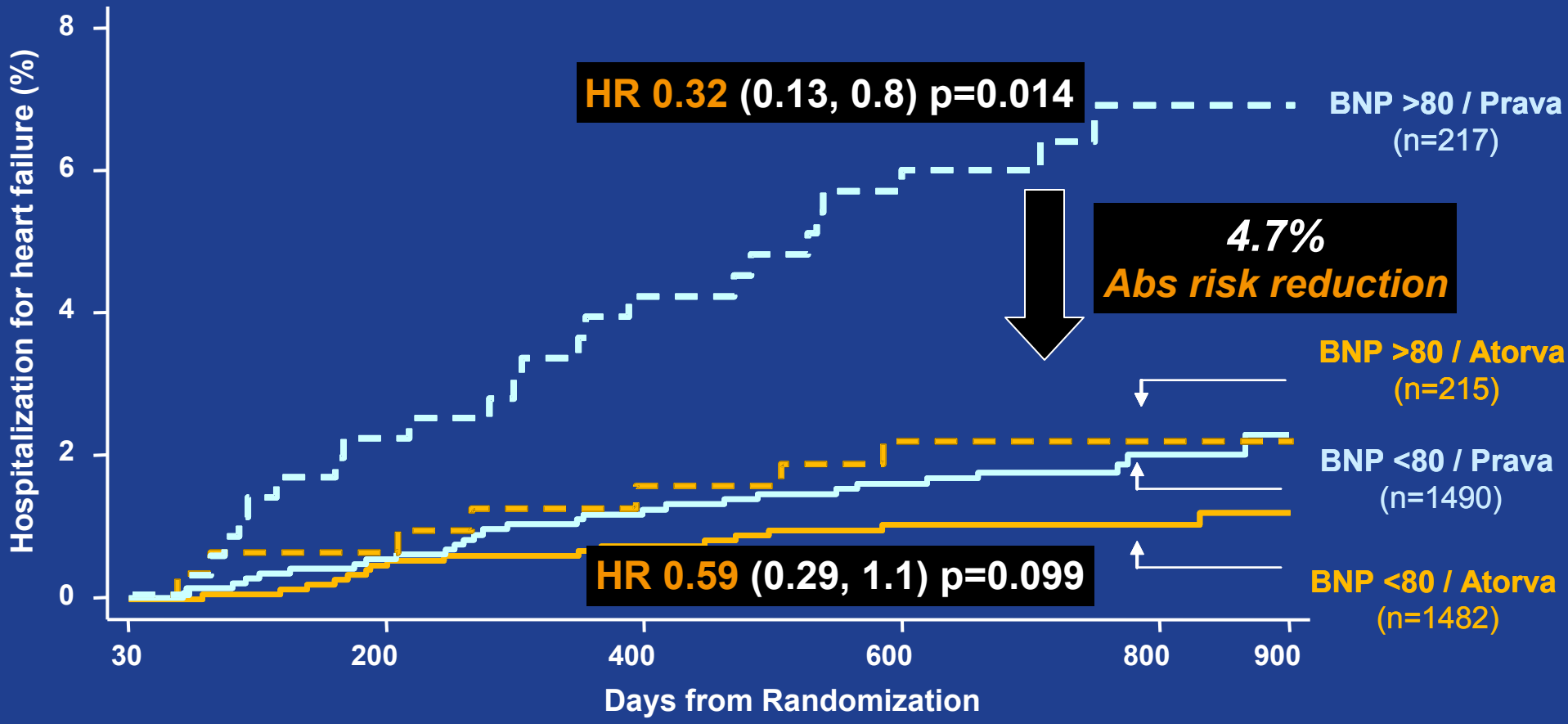
Scirica et al, JACC 06

Meta-analysis of intensive vs standard therapy for reduction of heart failure



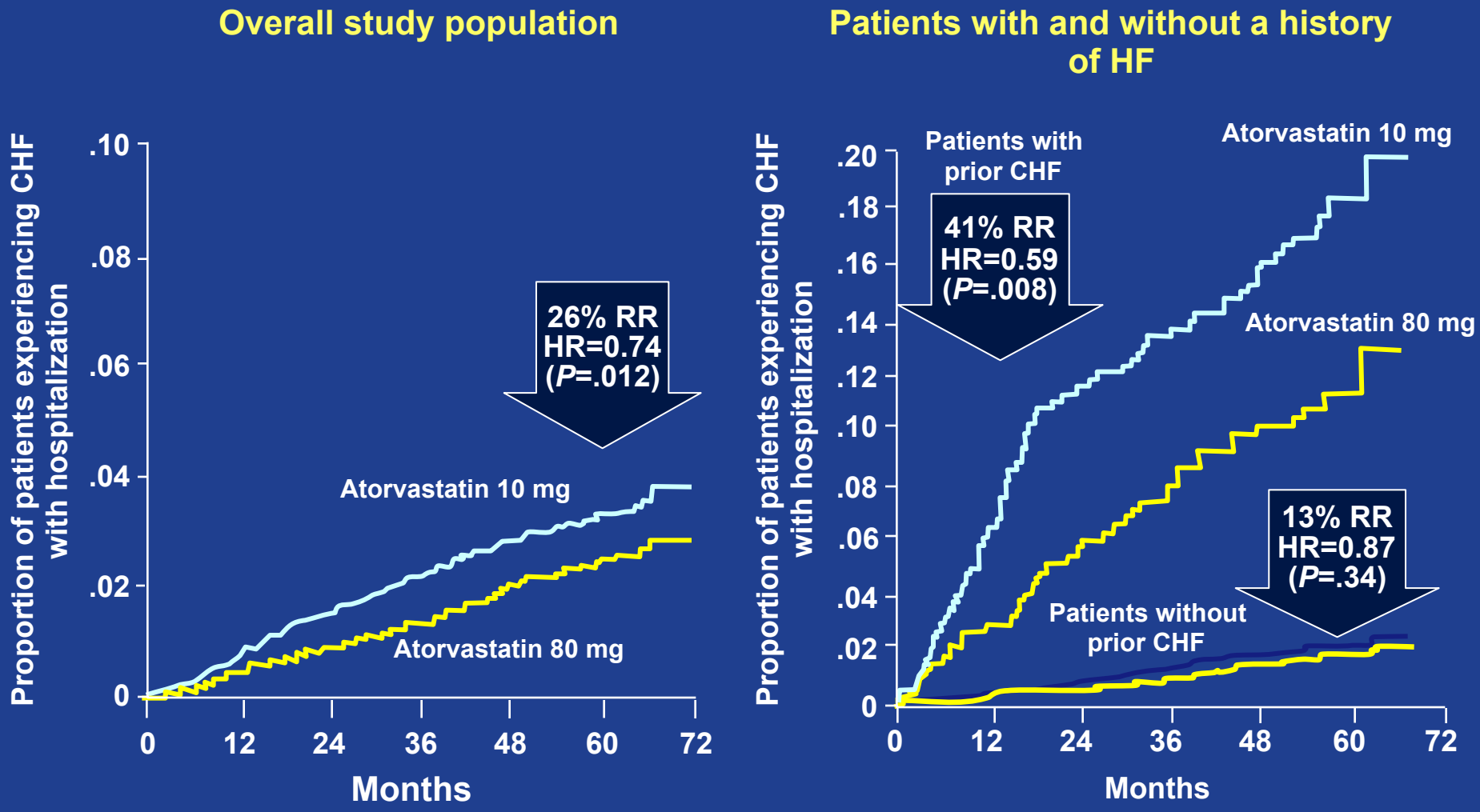
Scirica, Morrow, Ray et al JACC 2006

Risk of heart failure according to BNP and intensity of statin therapy



Scirica et al, JACC 2006;47:2326-31

TNT: High-dose Atorvastatin Reduced Hospitalizations for HF



The Treating to New Targets (TNT) study followed 10,001 patients with stable CAD randomized to treatment with atorvastatin 80 mg or 10 mg for a median of 4.9 years. A history of HF was present in 7.8% of patients. Patients with known ejection fraction <30% and advanced HF were excluded from the study. Hospitalization for HF was a predefined secondary end point.

Khush KK et al. *Circulation.* 2007;115:576-583.

Conclusion

- In patients with CHD there is incremental benefit in achieving a lower LDL-C target with intensive statin therapy
- Among patients on intensive statin therapy the lowest LDL-C levels are associated with lowest risk
- i.e. Lower is better

- In ACS patients intensive statin therapy initiated early after ACS is associated with early benefits

- Early benefits are incompletely explained by LDL-C changes and may reflect pleiotropic effects

- Intensive Tx reduces hospitalization for heart failure especially in those with prior history of heart failure or higher BNP levels