

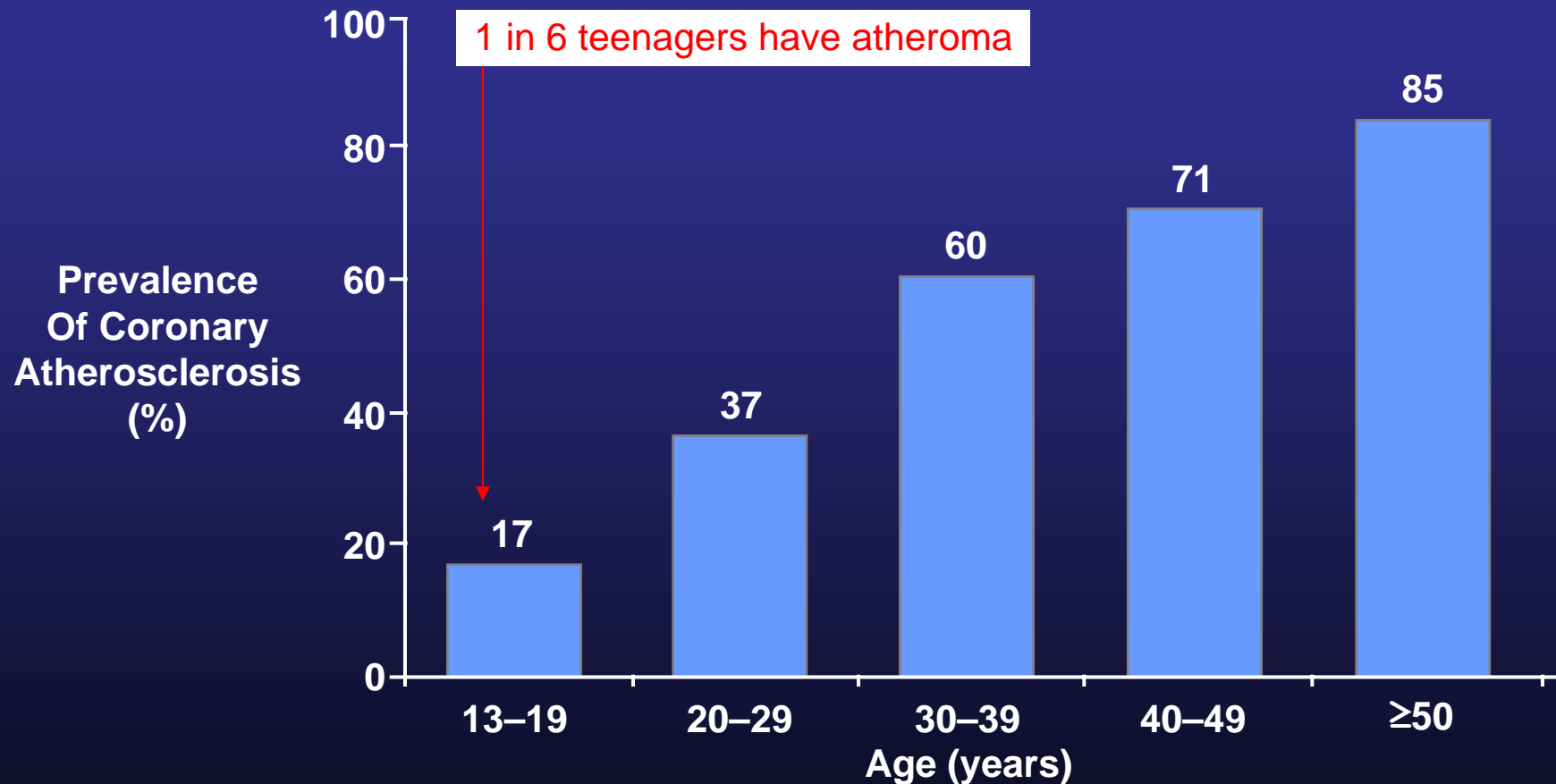
Rationale, efficacy, safety and cost of intensive LDL-C reduction in CAD

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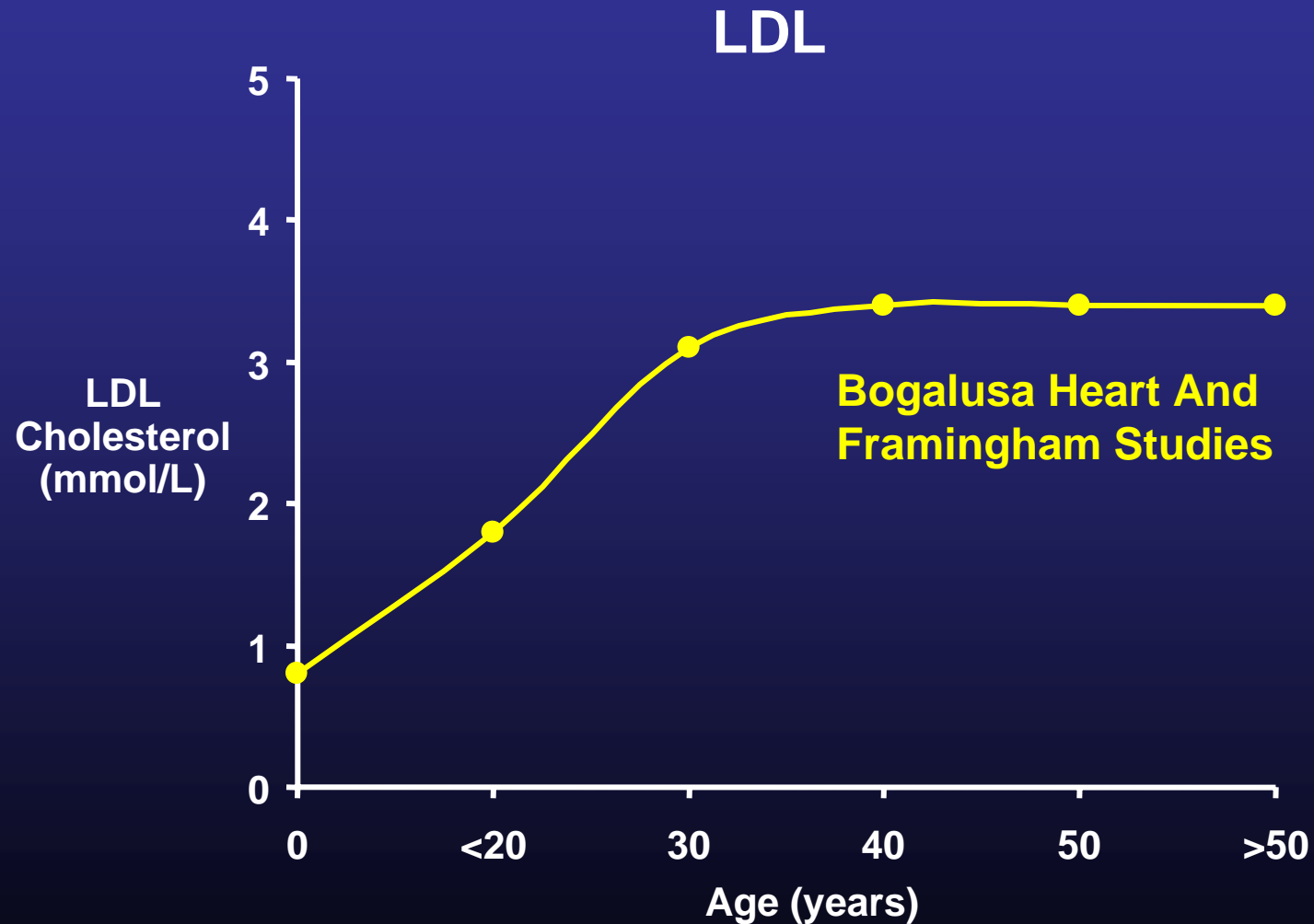
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Atherosclerosis: When Does It Begin?



Data from 262 heart transplant donors.
Sites with intimal thickness ≥ 0.05 mm were defined as atherosclerotic.

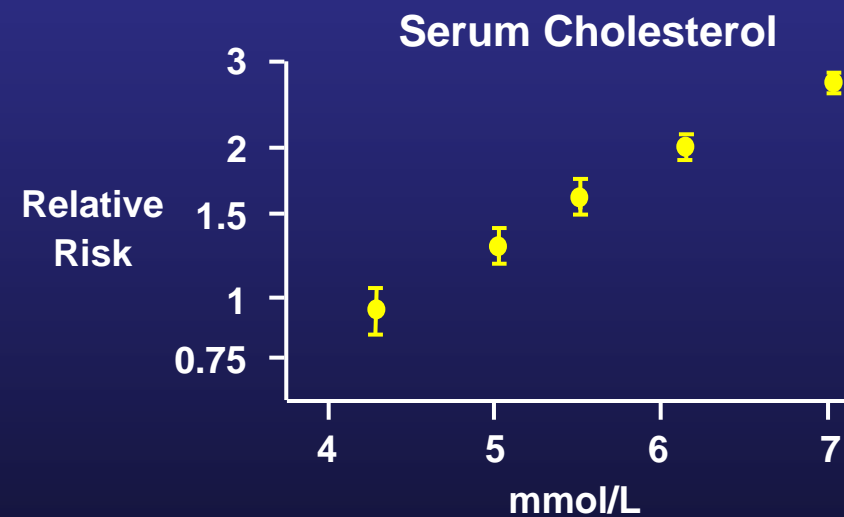
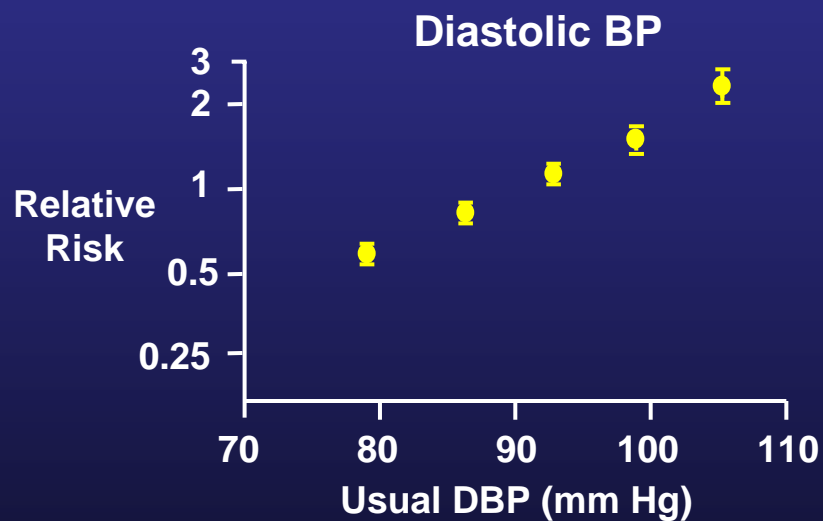
Increase In LDL Throughout Childhood And Young Adulthood



Freedman et al. *Pediatrics*. 1987;80:789.

Webber et al. *Am J Epidemiol*. 1991;133:884.

Relationship Between Risk Factor Levels And Events In Cohort Studies- no lower threshold

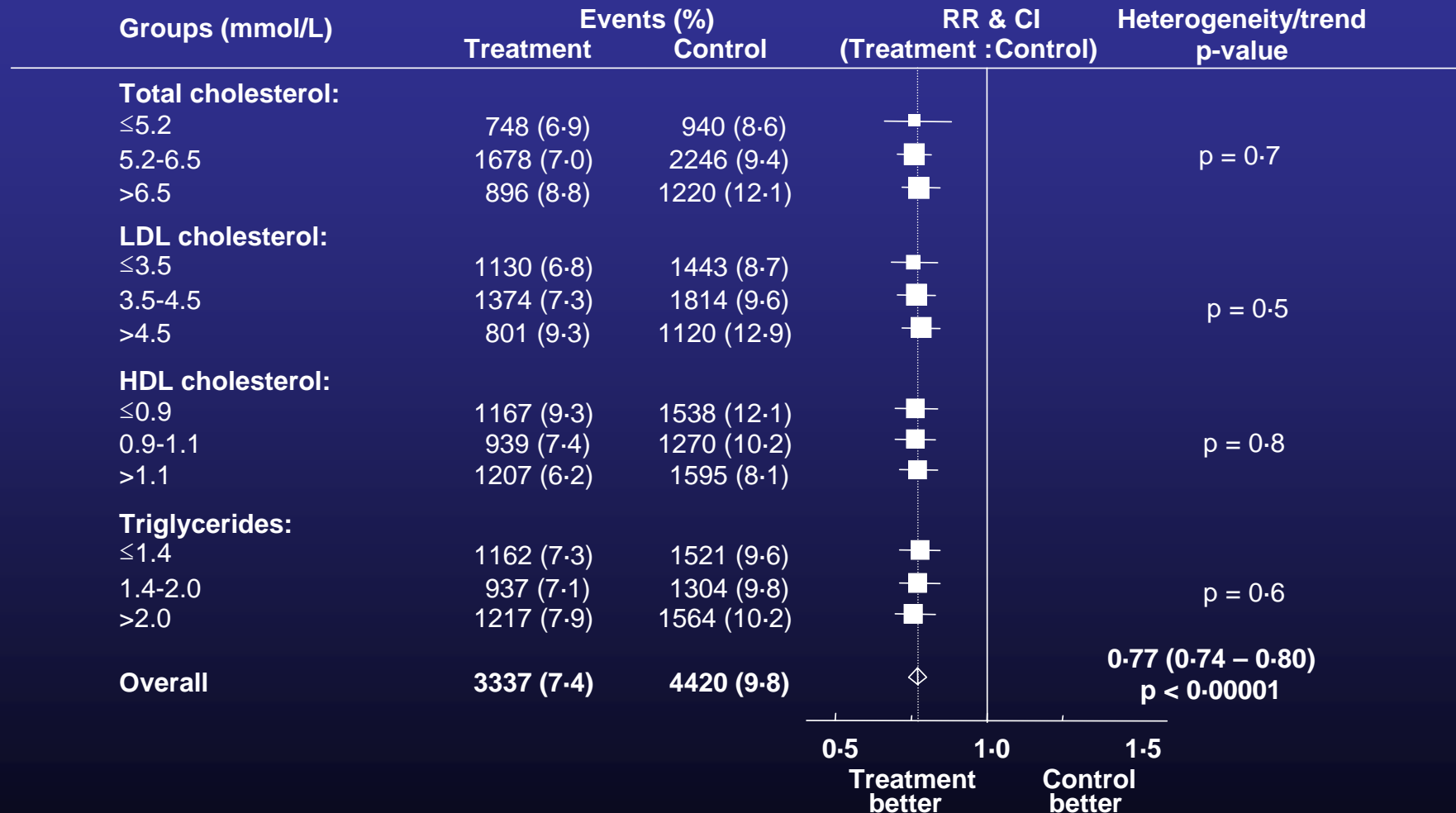


The majority of people with CAD have a “normal/low” LDL- therefore treat the level of risk in the individual and not the level of the risk factor!

Physiologic Variable	Associated Disorder	Cases In Subjects With Values >90th Percentile (%)
Systolic BP	Stroke	28
Systolic BP	Coronary disease	21
Serum cholesterol	Coronary disease	21
BMI	Coronary disease	22
BMI	Diabetes	23
BMD	Hip fracture	22

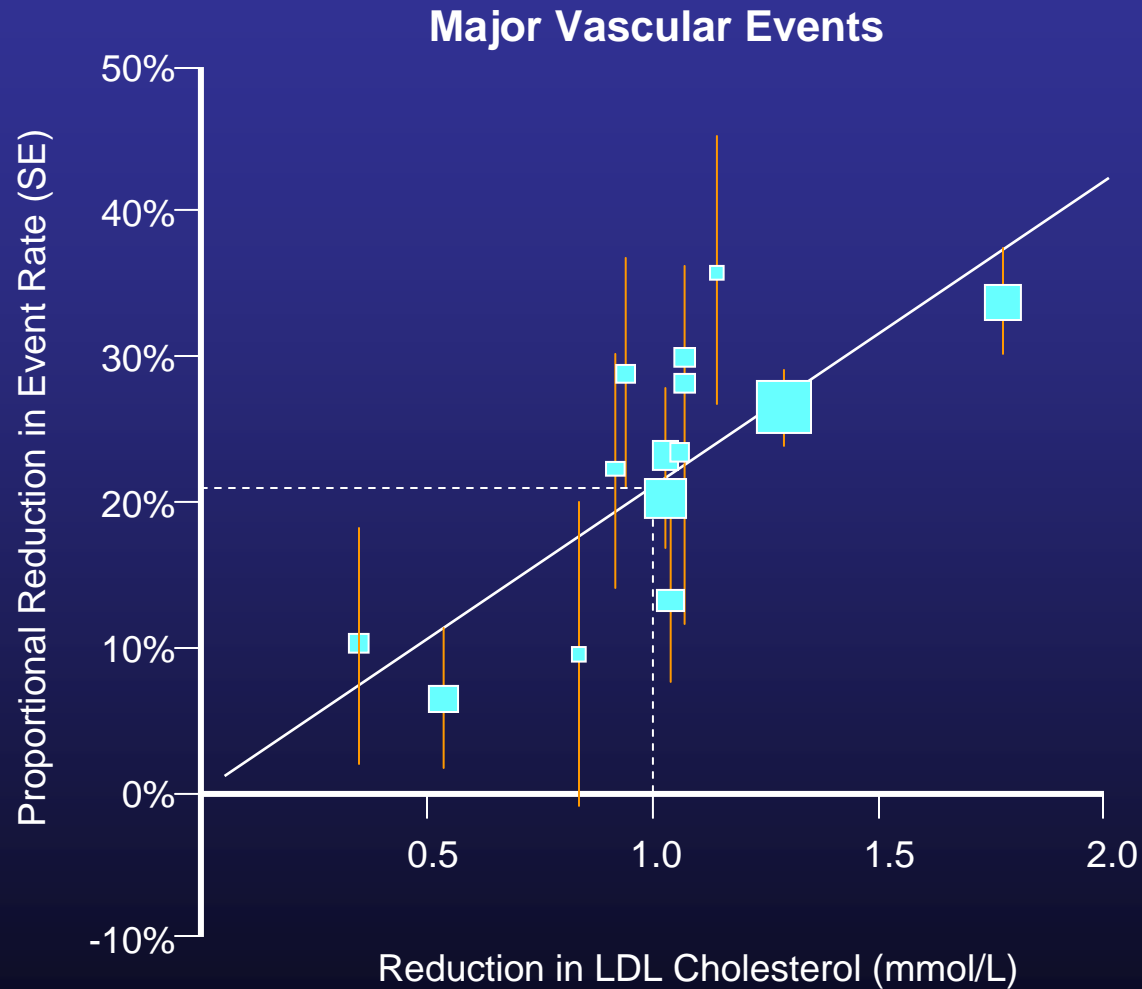
CTT Collaboration

If you have a high enough risk of CHD, baseline lipids do not matter and a statin is better than placebo- i.e. treat level of risk not level of starting lipids



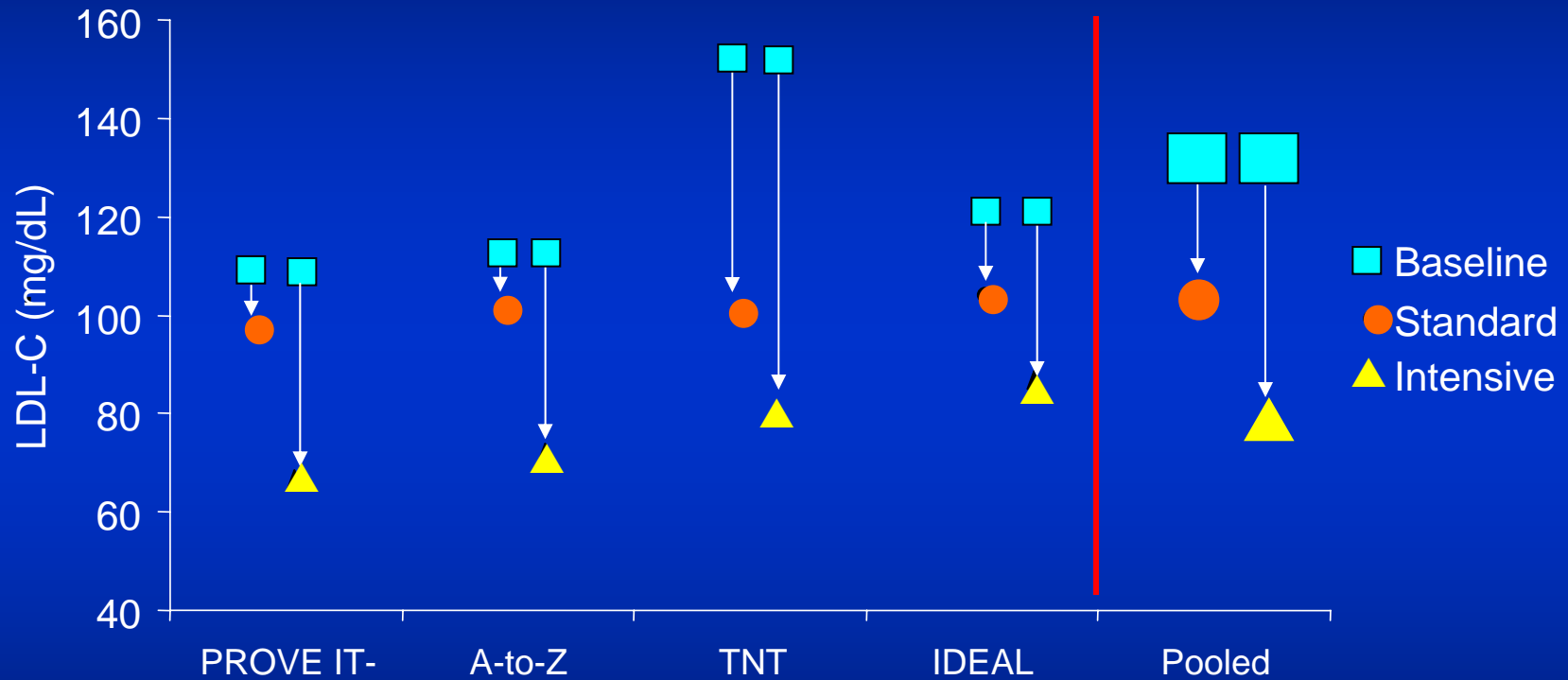
CTT-Meta-Analysis of Dyslipidemia Trials

Amount of benefit from statins is linearly related to the amount of LDL reduction and duration of therapy



Meta-Analysis of Intensive Statin Therapy LDL Cholesterol by Trial

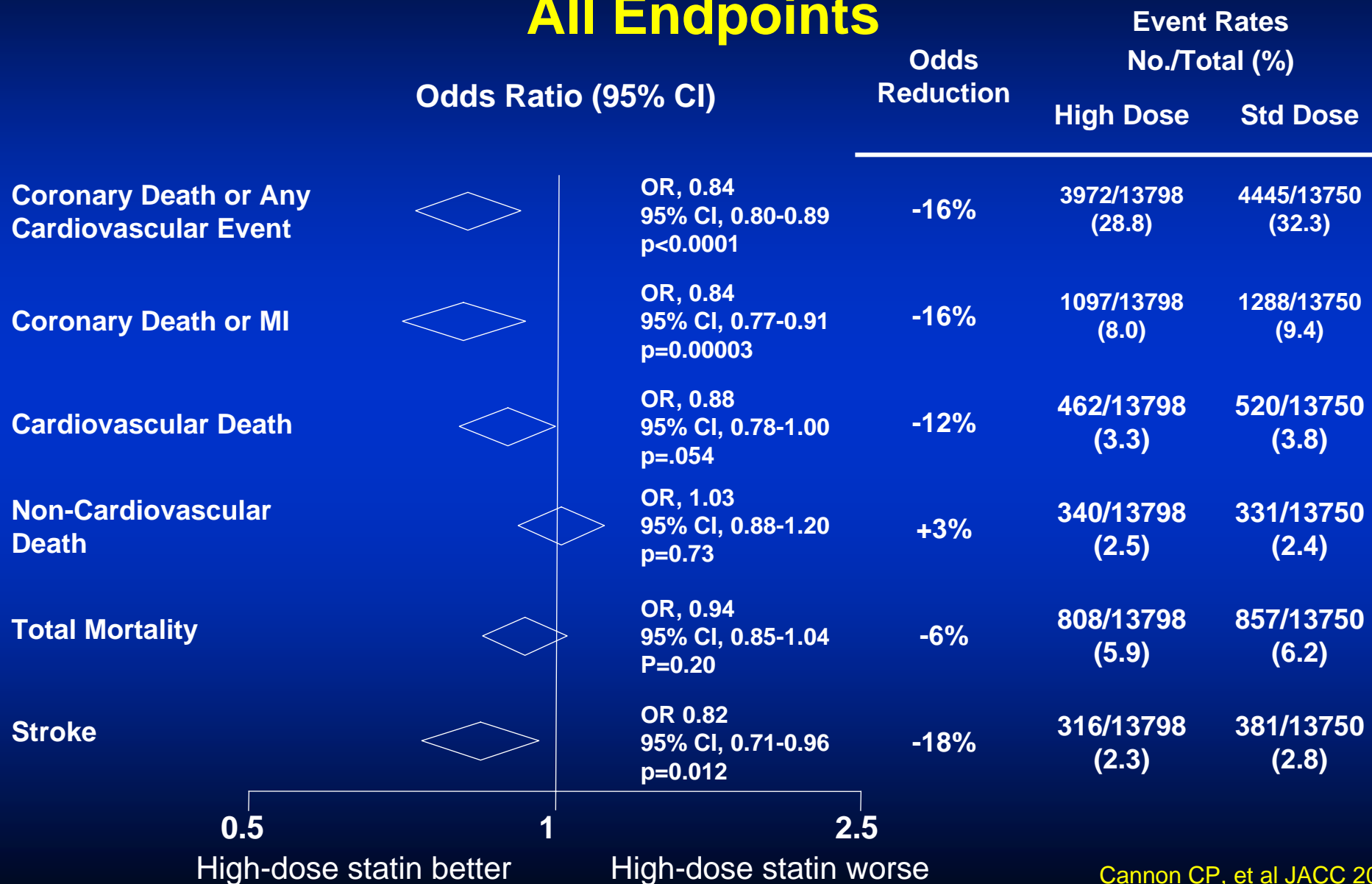
Patients	ACS		Stable CAD		Pooled
n	4162	4497	10001	8888	27548
Prior Statin Use	25.2%	0%	0%	75.5%	28.2%



	PROVE IT-TIMI 22	A-to-Z	TNT	IDEAL	Pooled
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)

Meta-Analysis of Intensive Statin Therapy

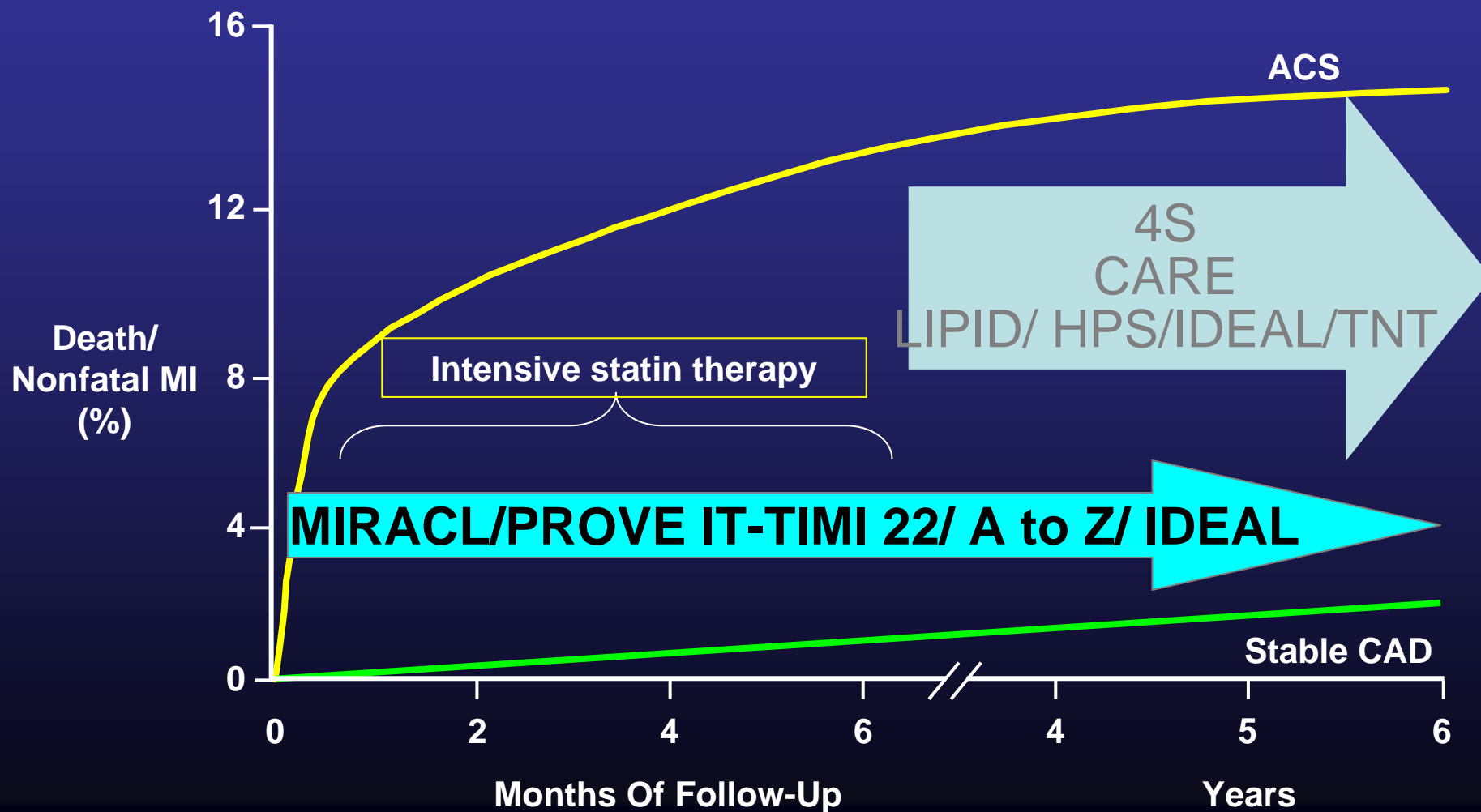
All Endpoints



In ACS intensive statin therapy and mortality

- ◆ Meta-analysis of PROVE IT and A to Z
- ◆ *Afilalo et al ESC 2006*
- ◆ About 8 500 patients with av of 2 years of FU
- ◆ 25% reduction in all cause mortality
- ◆ (0.61-0.93)
- ◆ Absolute benefit is 0.9%

Only intensive statin therapy reduces early risk after ACS

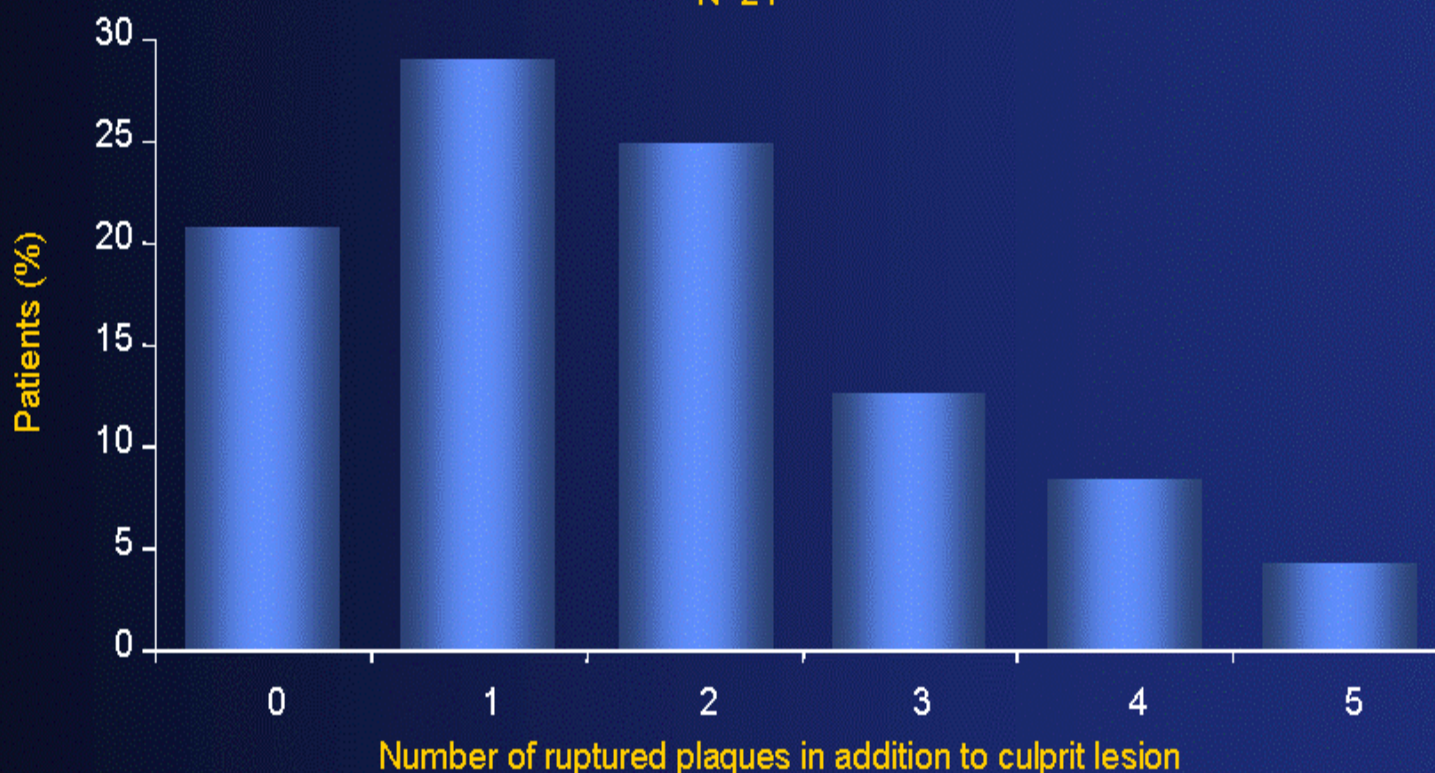




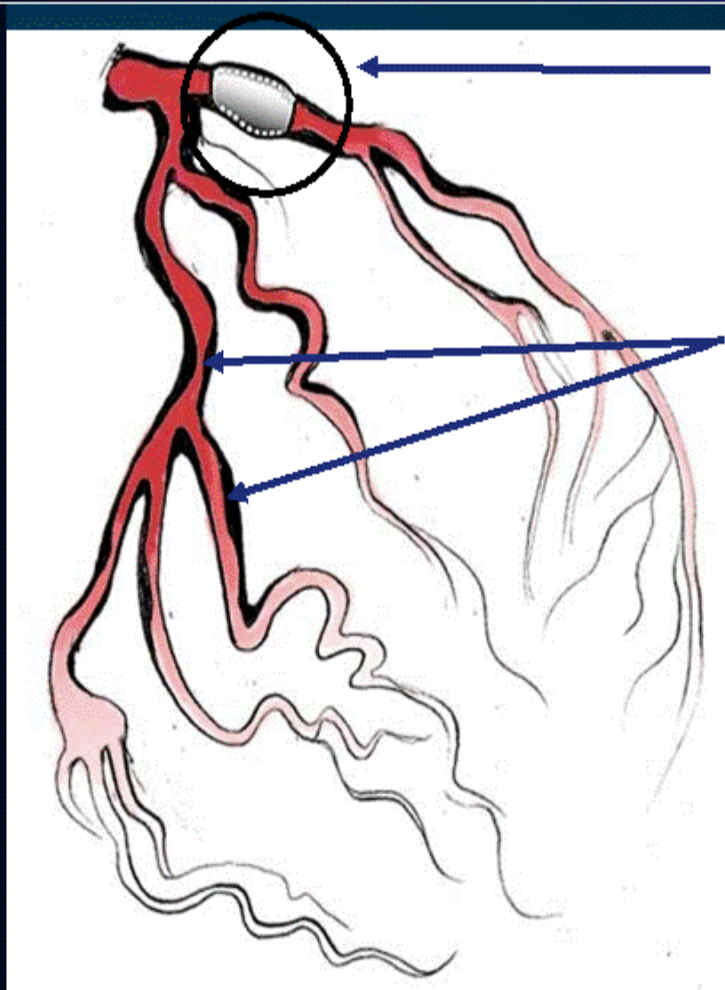
Distribution of Multiple Plaques in Patients with Acute Coronary Syndromes

80% of patients with ≥ 1 plaque

N=24



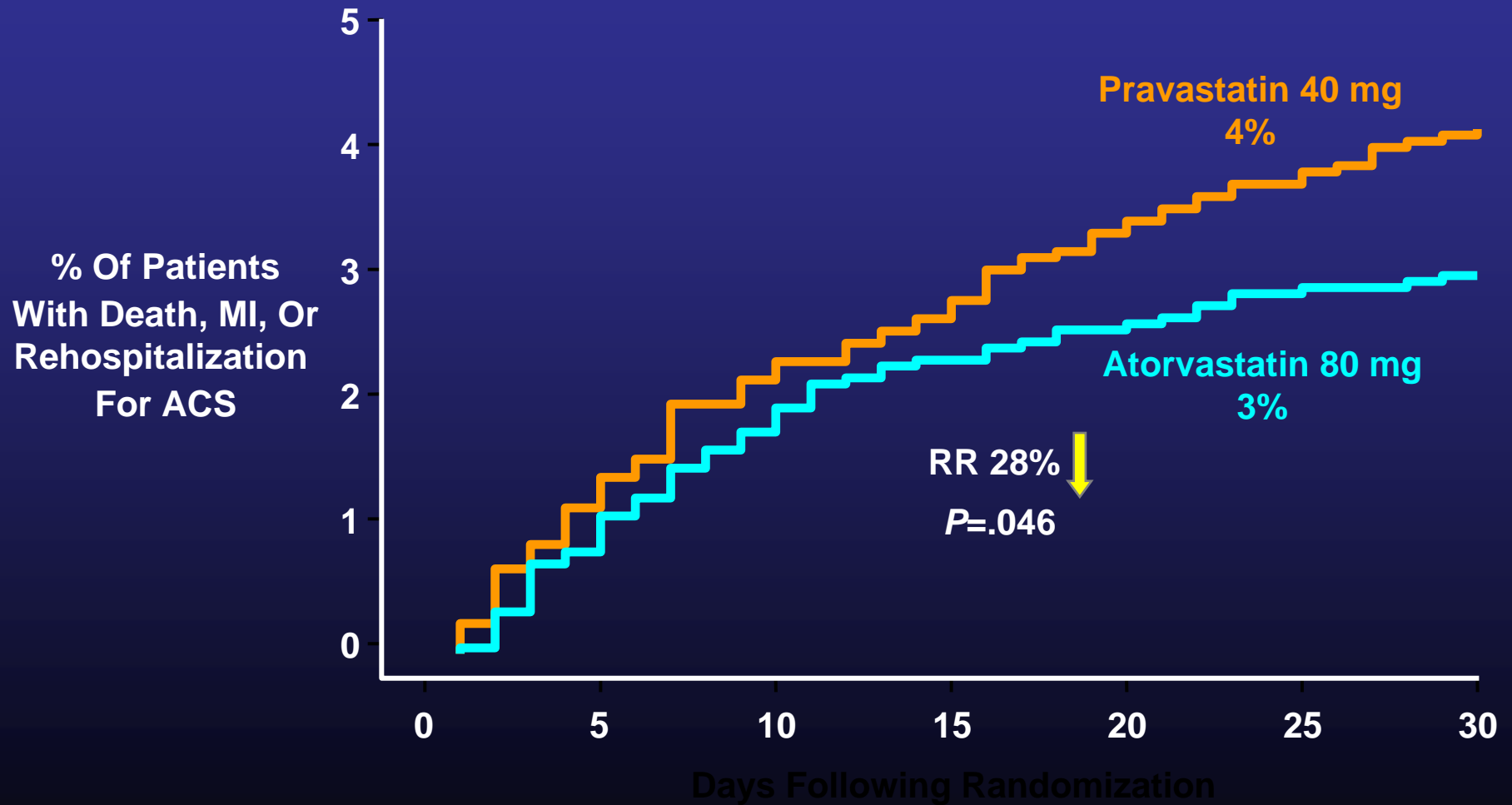
An Integrated Approach to Managing Patients With Acute Coronary Syndrome*



- **Focal** interventional treatment to stabilize ruptured plaque
 - PCI with stent
- **Systemic** medical therapy intended to stabilize plaque and inhibit clot formation, thus reducing the risk of thrombotic events (MI, stroke, or death) due to diffuse atherosclerosis
 - aspirin, clopidogrel, lipid- lowering therapy, ACE inhibitors, beta-blockers

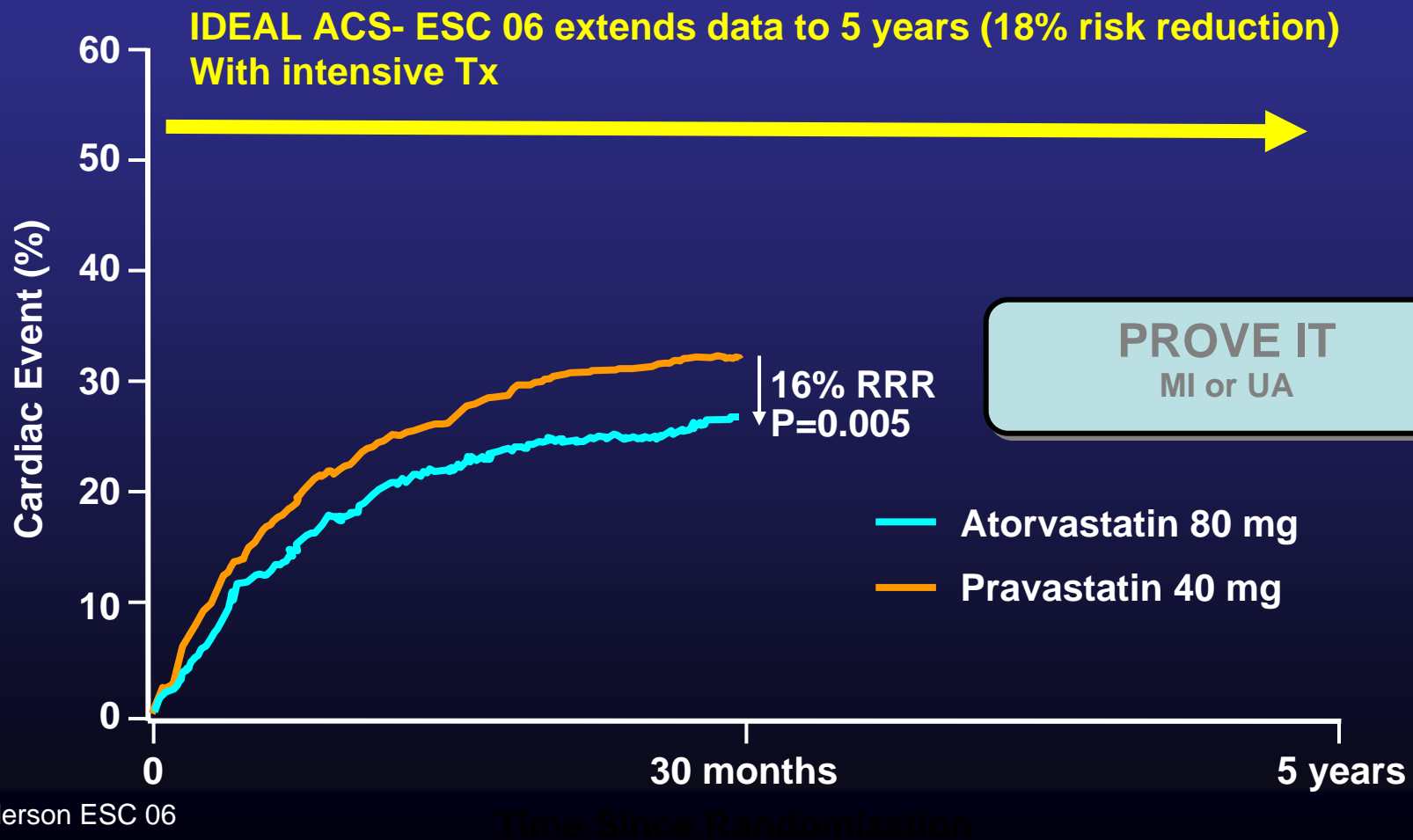
* ACS=unstable angina/non-Q-wave MI.
Ambrose JA. *Circulation*. 2002;105:2000-2004.

Rapid Early Reduction In Death, MI, Or ACS Rehospitalization With Intensive Statin Therapy at 1 month after ACS

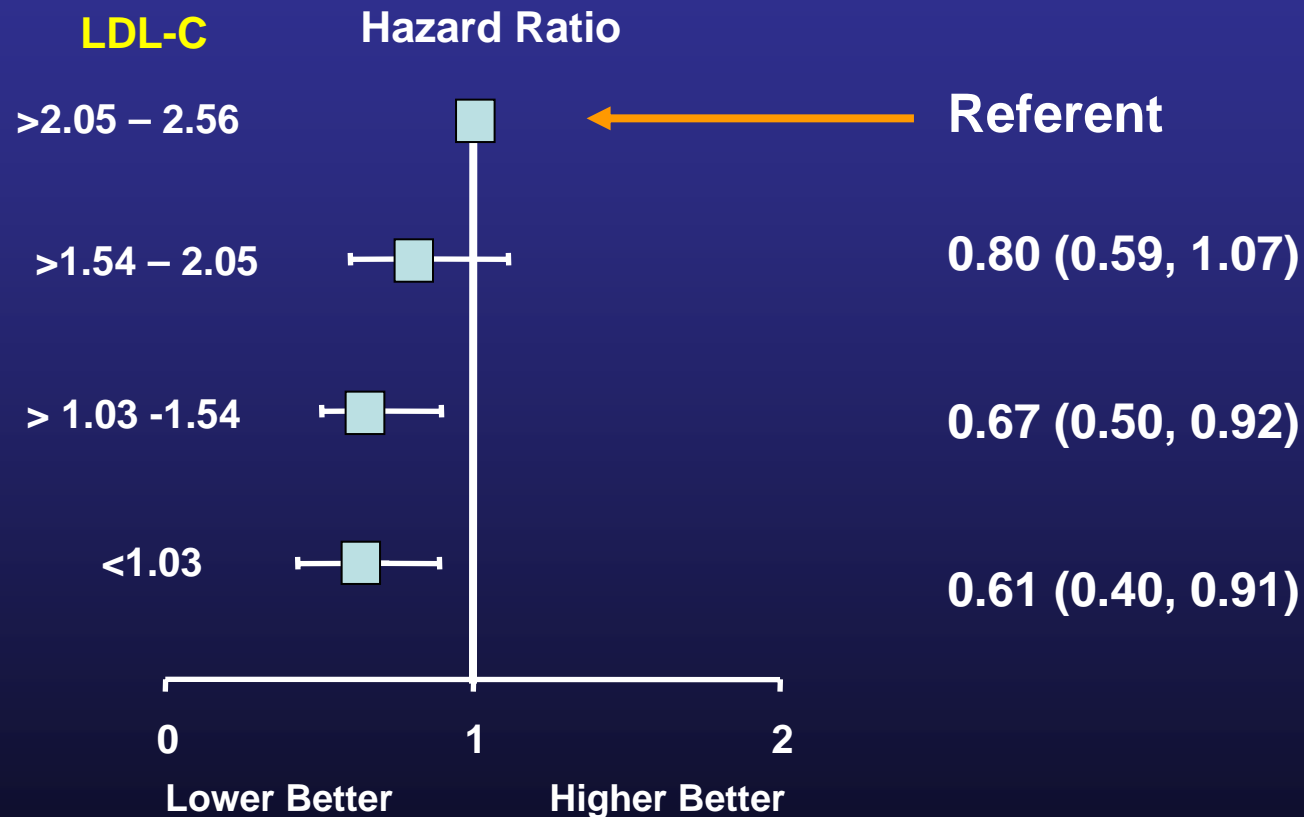


Ray et al. *J Am Coll Cardiol.* 2005.

Intensive statin Tx reduces risk of CV events



PROVE IT-TIMI 22: Relationship Between Month 4 LDL and Long-Term Risk of Death or Major CV Event (atorva 80 arm)

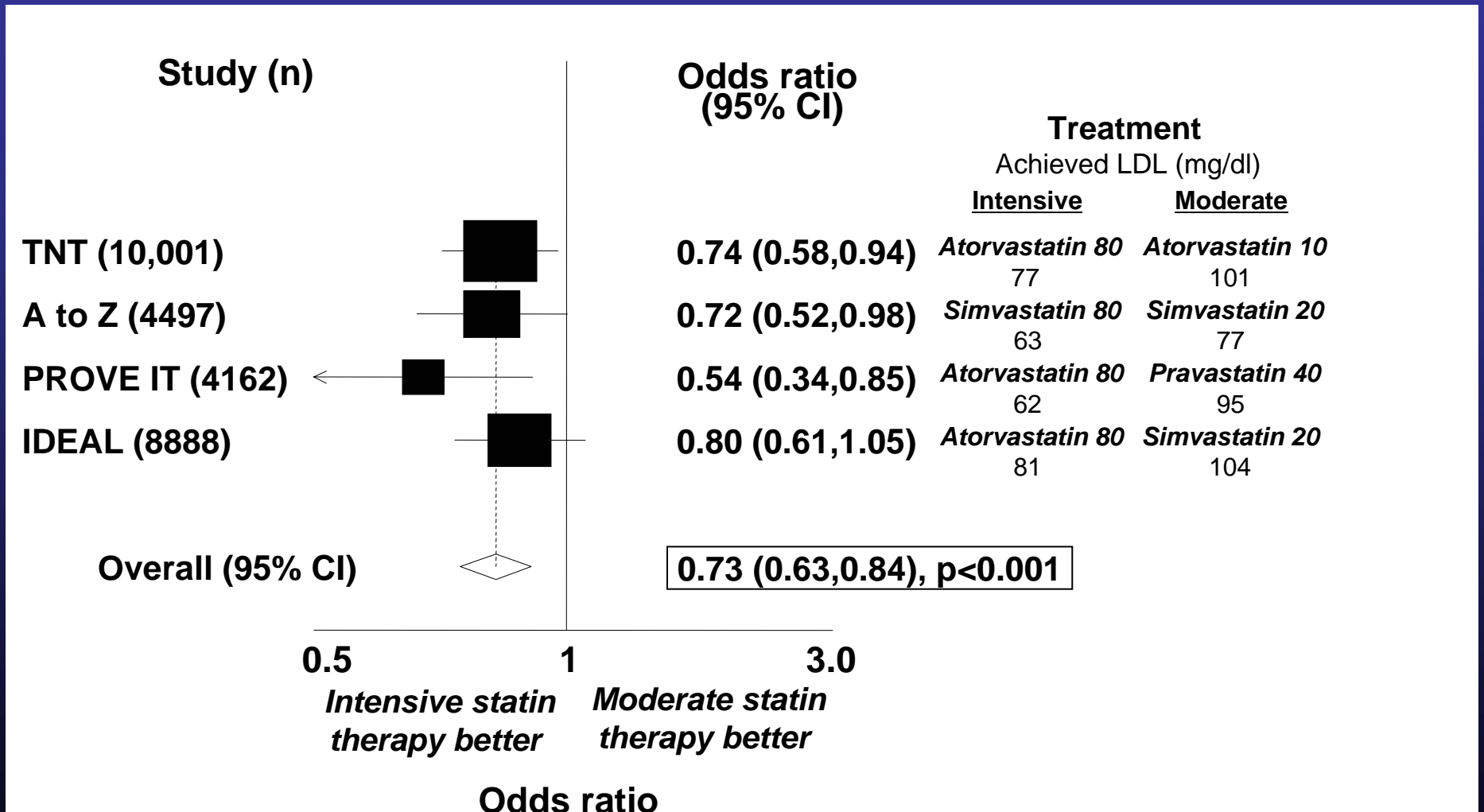


* Adjusted for age, gender, DM, prior MI, baseline LDL

If you have CAD

- ◆ A statin is better than placebo
- ◆ Intensive therapy is better than standard dose therapy
- ◆ Among those receiving intensive therapy lower LDL-C associated with lower long term risk
- ◆ i.e. Lower is better!

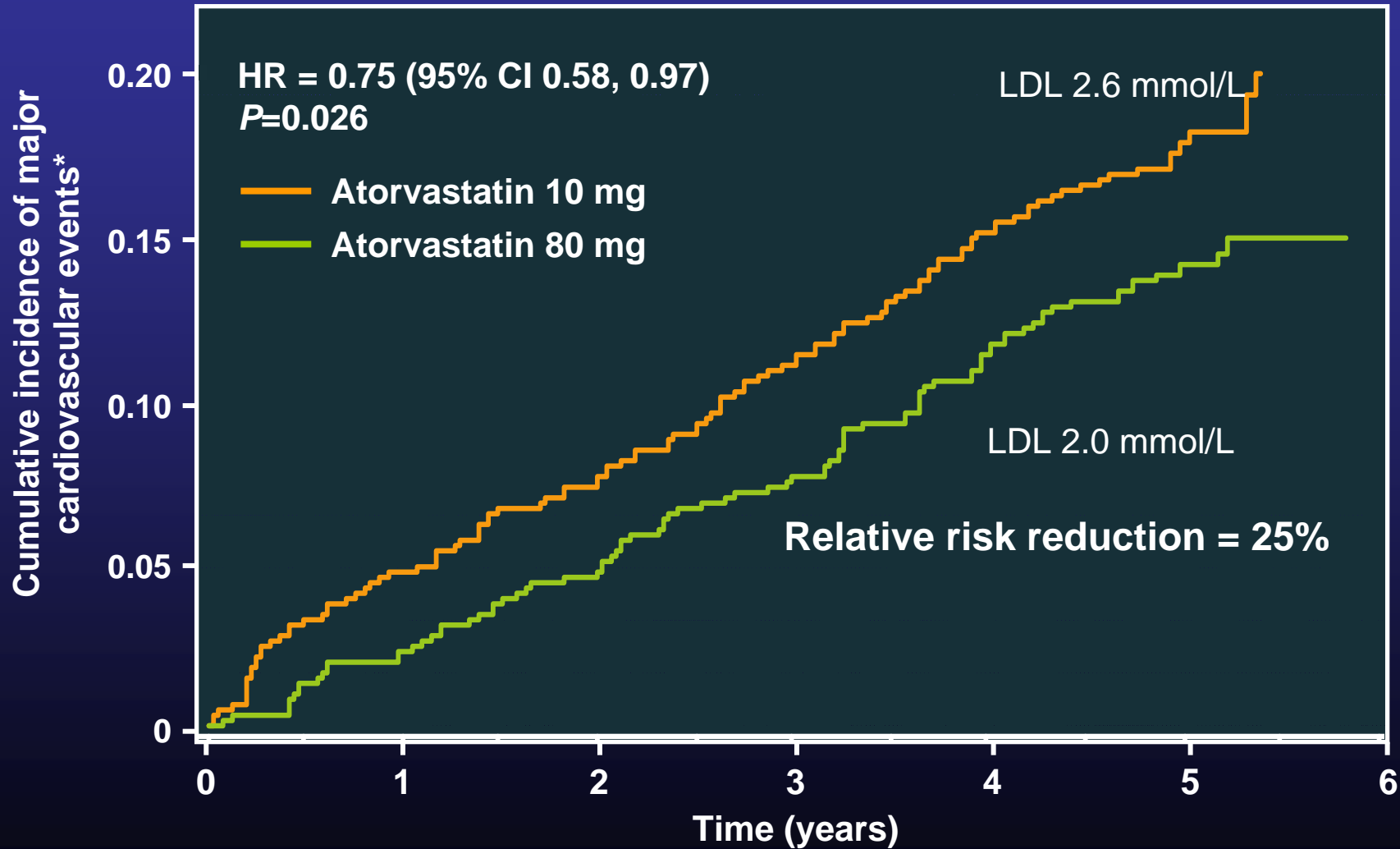
Meta-analysis of intensive vs standard therapy for reduction of heart failure



The greater the risk the greater the absolute benefit

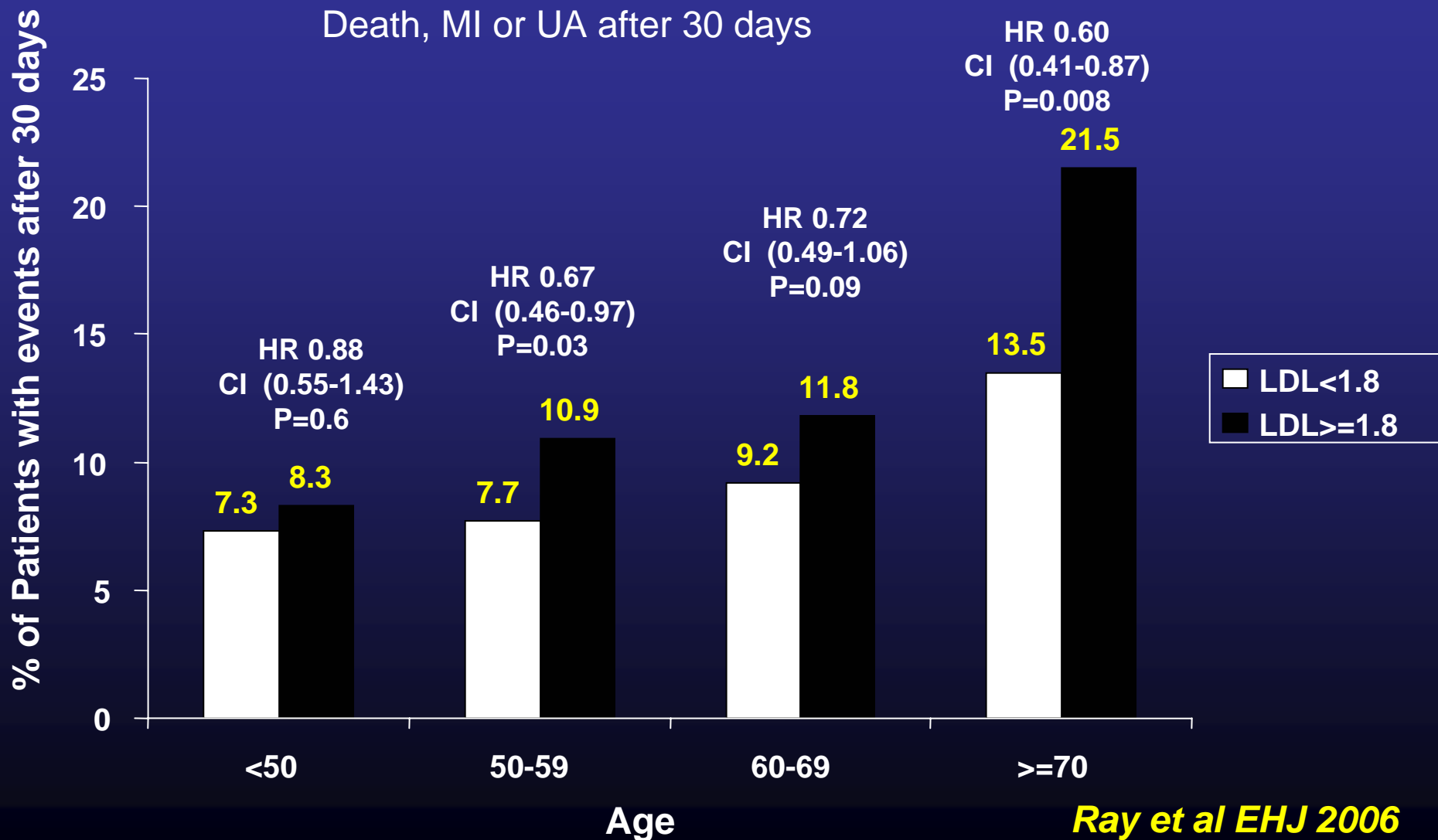
- ◆ High risk groups should be treated more intensively
- ◆ ACS/ CAD
- ◆ Diabetics
- ◆ Multiple metabolic risk factors
- ◆ Some older patients

TNT- Time to First Major Cardiovascular Event in Patients With Diabetes

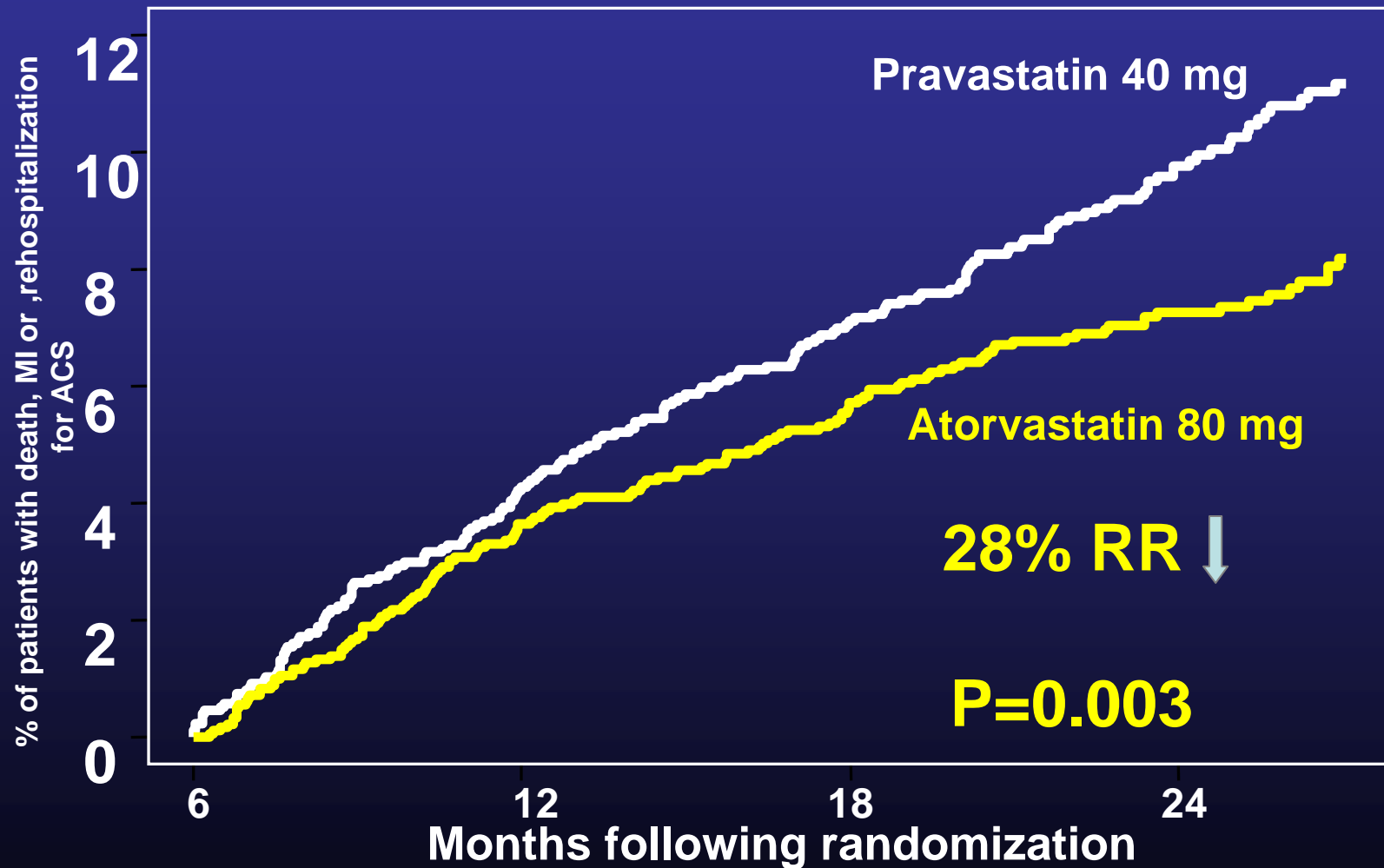


*CHD death, nonfatal non-procedure-related MI, resuscitated cardiac arrest, fatal or nonfatal stroke

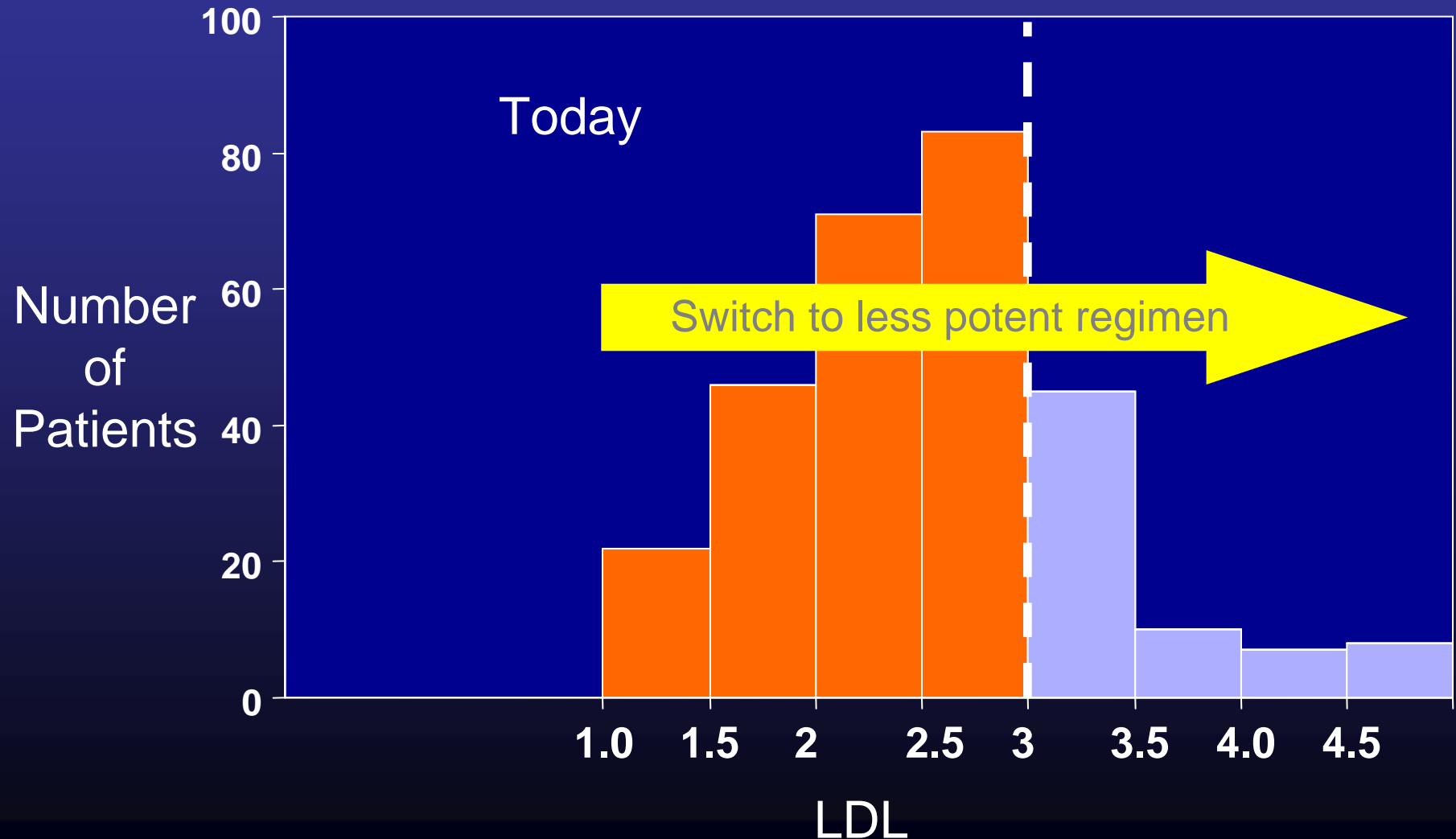
Benefit of achieving a low LDL greater with increasing age



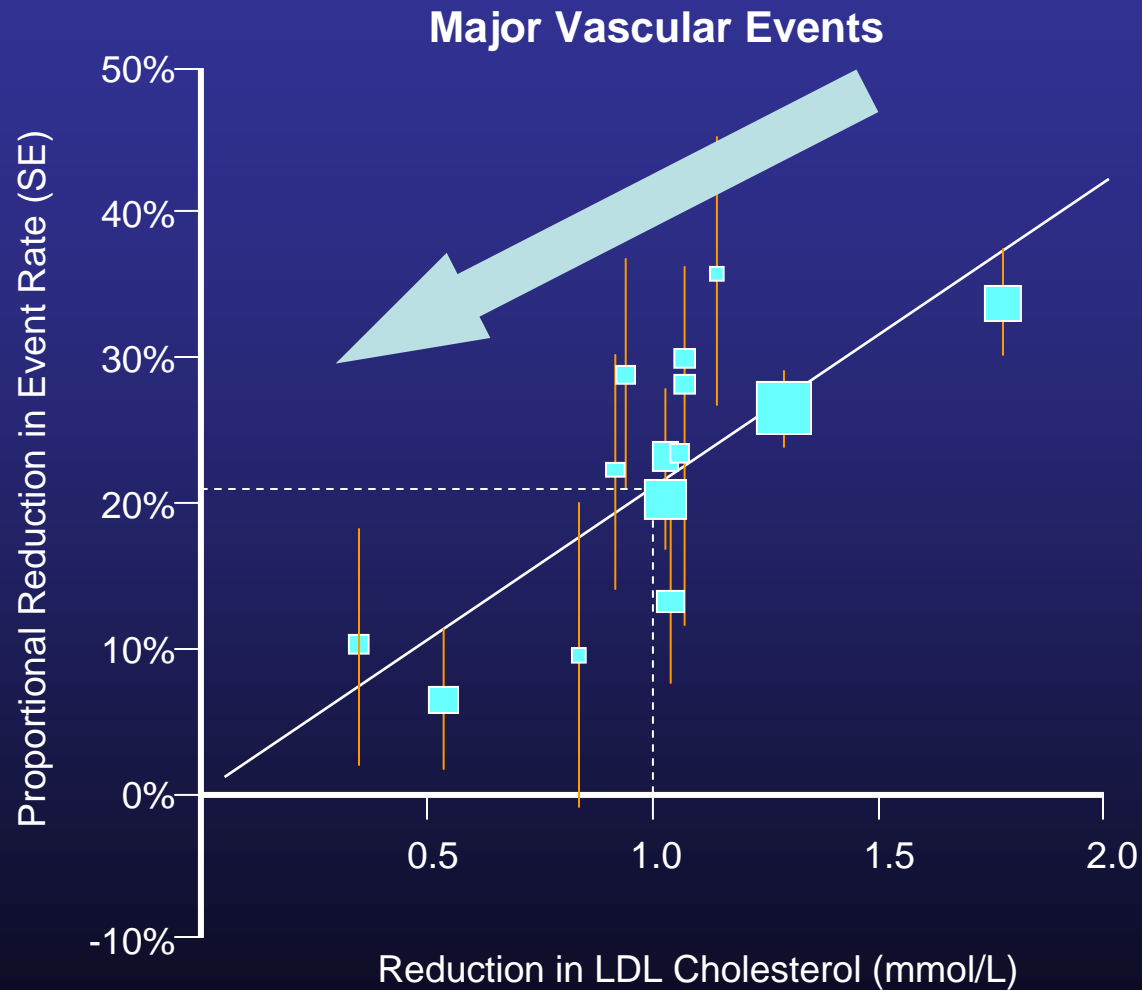
In stable patients continuation of intensive therapy further reduces Death, MI or rehospitalization for ACS i.e don't discontinue it!



Switching statins to a less potent regimen increases population LDL and thus actively increases risk!



Per population a 0.5 mmol increase in LDL using a weaker statin regimen will increase risk by 11% !



Intensive Tx with statins is cost effective in ACS patients

- ◆ As intensive therapy would reduce CABG, PCI, stroke, hospitalizations for MI and unstable angina, outpatient visits, investigations
- ◆ This would result in a **saving** of
- ◆ \$US 2.8 million per 2000pts treated for 2 years if standard dose statins **were generic**
- ◆ And
- ◆ \$US 1.99 million per 2000pts treated for 2 years if standard dose statins **were free**

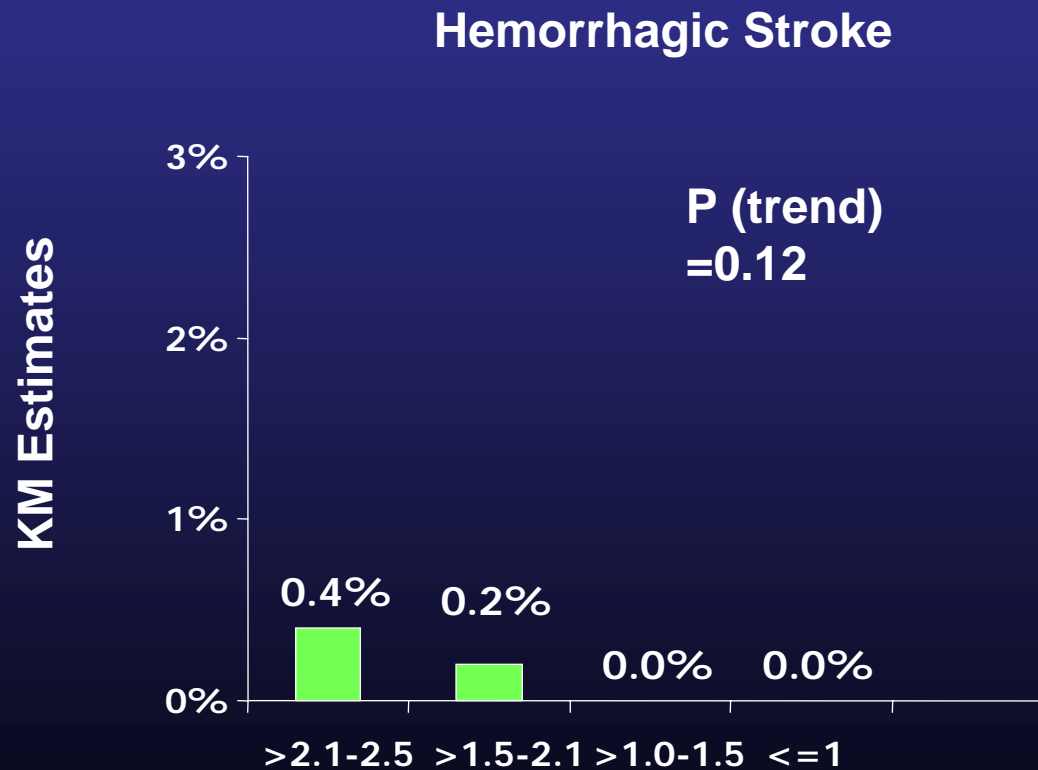
Intensive statin therapy is safe- Liver and Muscle Effects

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

PROVE IT Safety Results of ultra low LDL with atorvastatin 80mg

Atorvastatin 80 mg	LDL (mmol/L)				p value
	2.07-2.59	1.55-2.07	1.04-1.55	<1.04	
Event*					
Myositis or Myalgia (AE)	1.6	3.1	3.2	2.8	NS
CK > 3x ULN	2.3	0.7	1.9	1.0	NS
CK > 10x ULN	0.3	0	0.3	0	NS
Rhabdomyolysis	0	0	0	0	NS
ALT > 3X ULN	3.1	3.0	3.2	3.6	NS

No excess in Hemorrhagic Stroke by 4 month LDL level



Summary

- ◆ In high risk CAD patients
- ◆ The lowering LDL below current guidelines reduces adverse events over a relatively short time span
- ◆ This is safe
- ◆ This is cost effective particularly when it prevents expensive adverse events like CABG and stroke