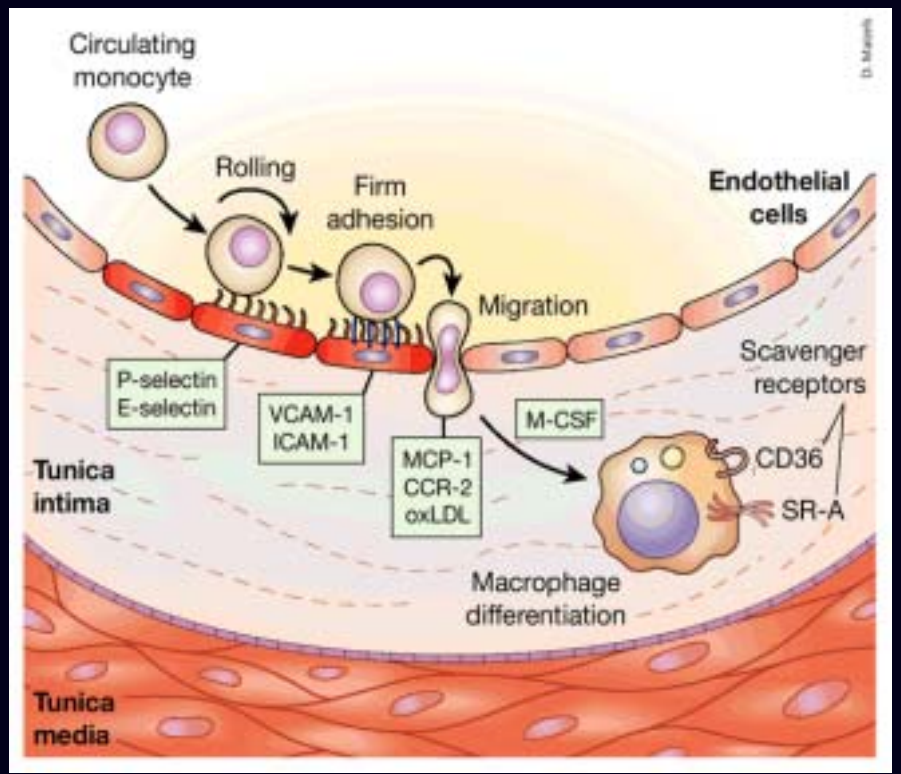
Intensive Statin Therapy

The Treating to New Targets (TNT) Study



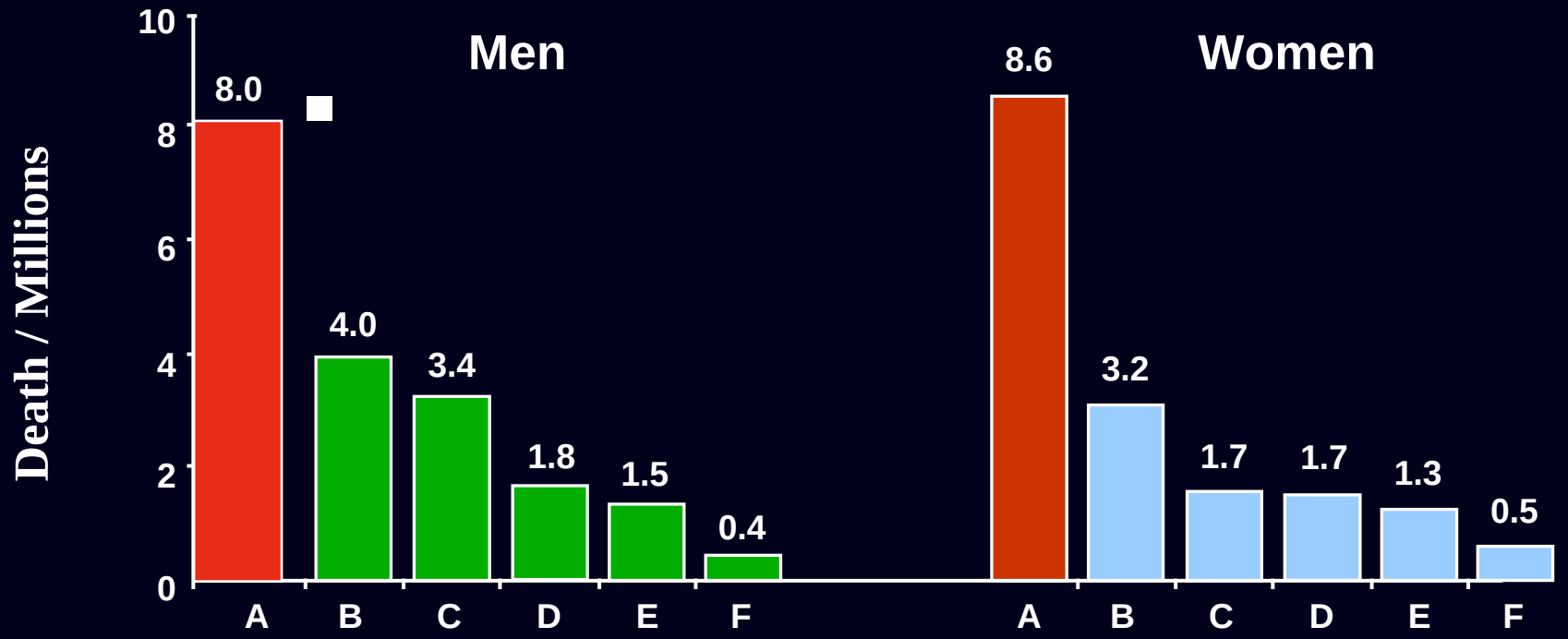
울산의대

서울아산병원

심장내과

이 철 환

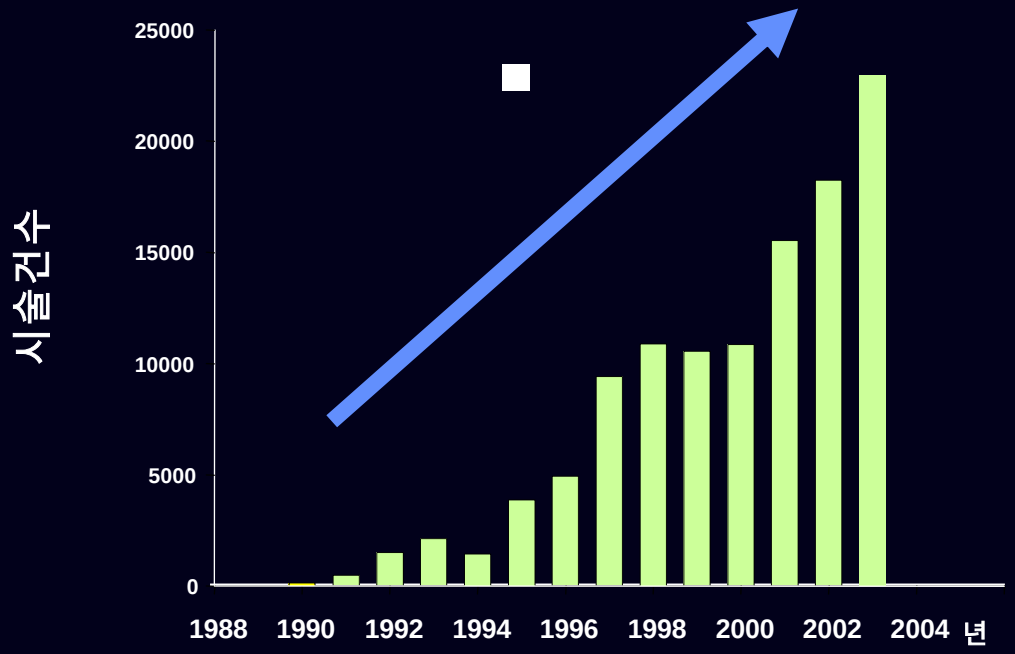
Causes of Death Worldwide, 2001



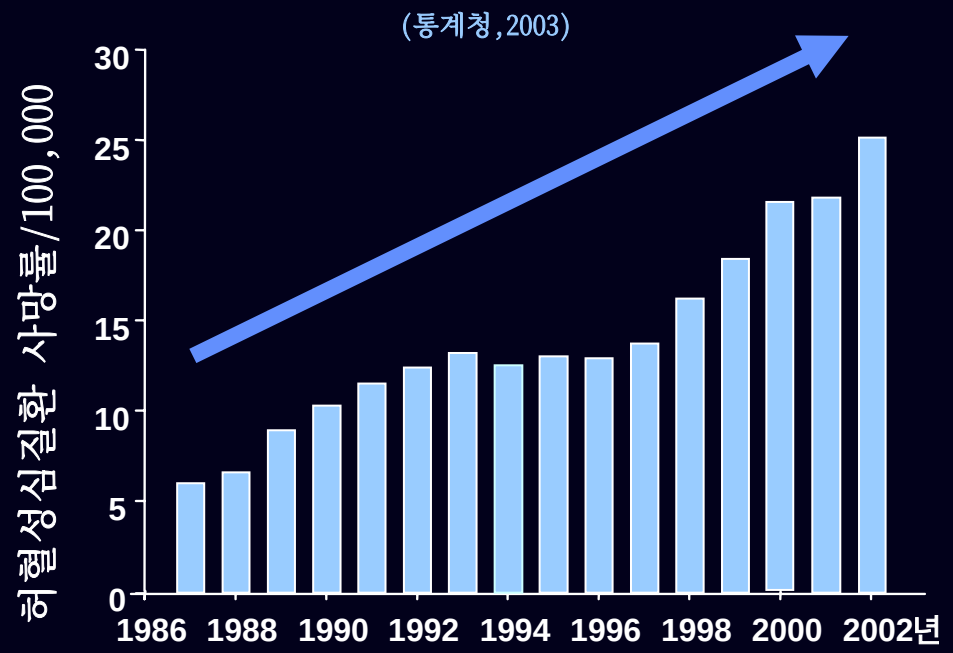
(2001, WHO)

In Korea,

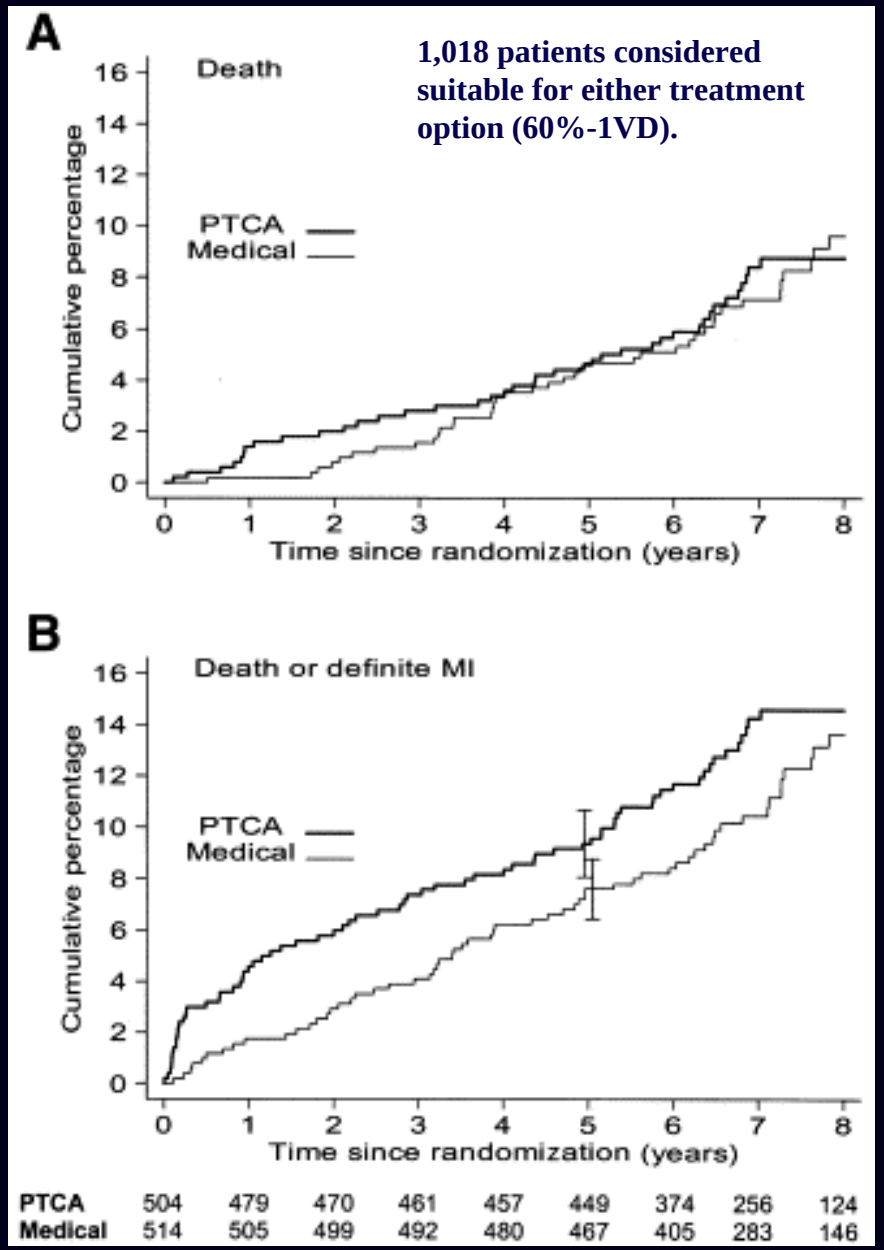
PTCA



Death due to IHD



IHD is rapidly increasing!

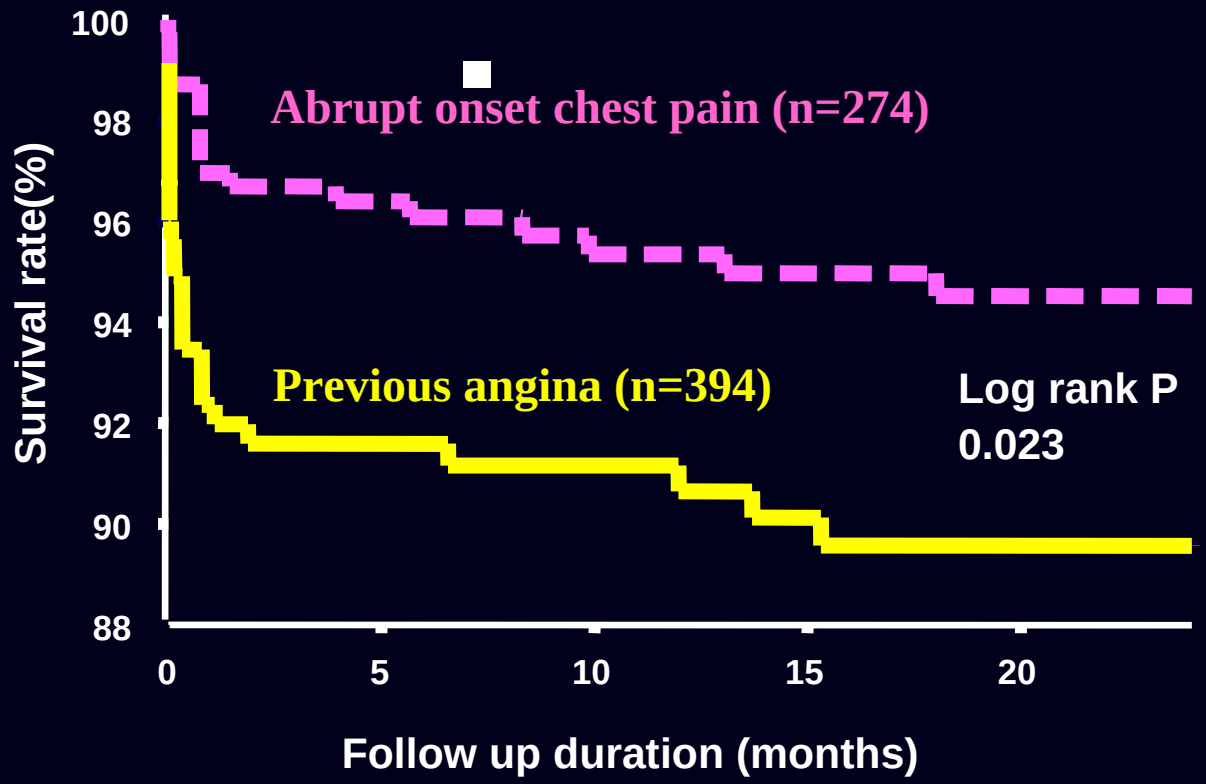


Seven-year Outcome in the RITA-2 Trial PTCA versus Medical Therapy

In RITA-2 an initial strategy of PTCA did not influence the risk of death or MI, but it improved angina and exercise tolerance.

JACC2003;42:1161

Where Should we go?

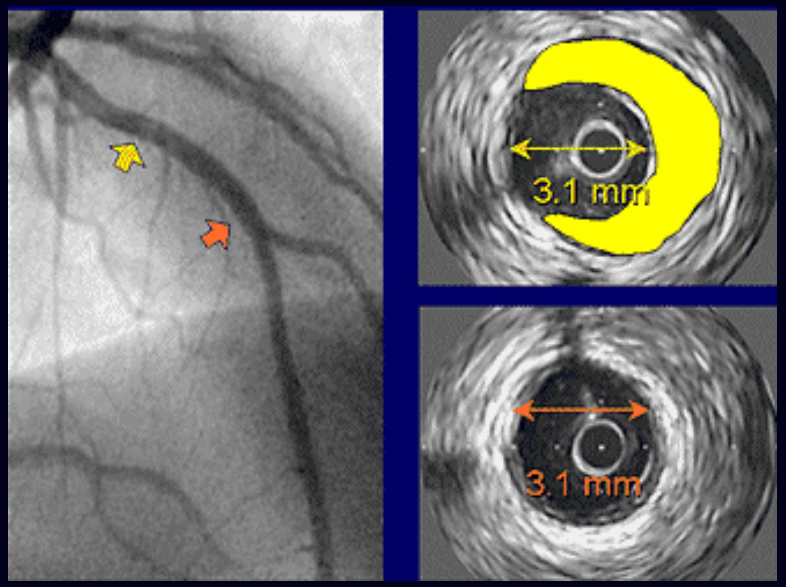


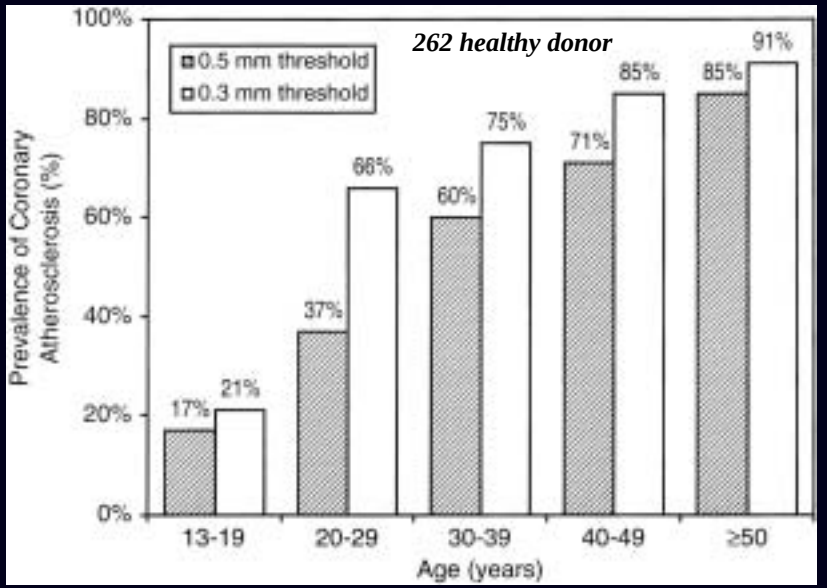
50% of patients with CAD presented with AMI or SCD.

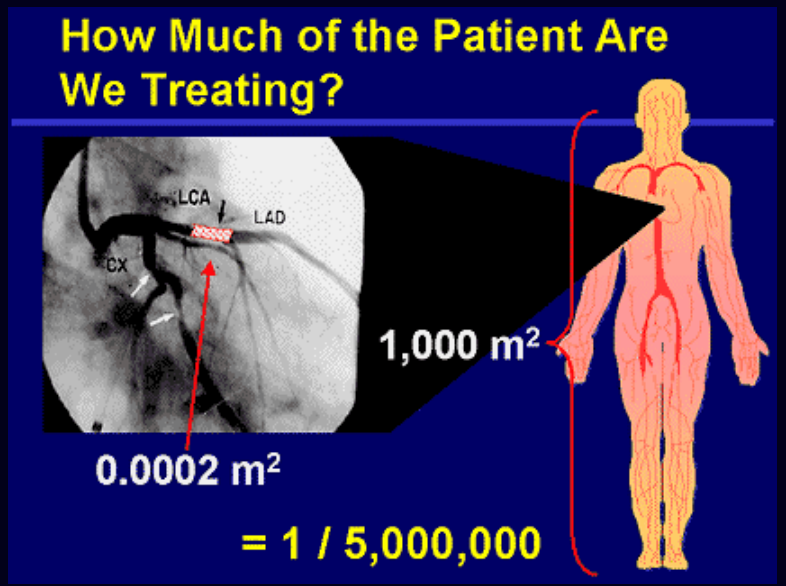
Prevention of acute coronary events must be the primary goal.

Beyond the Culprit Lesion

Lack of luminal obstruction does not mean a lack of atherosclerosis



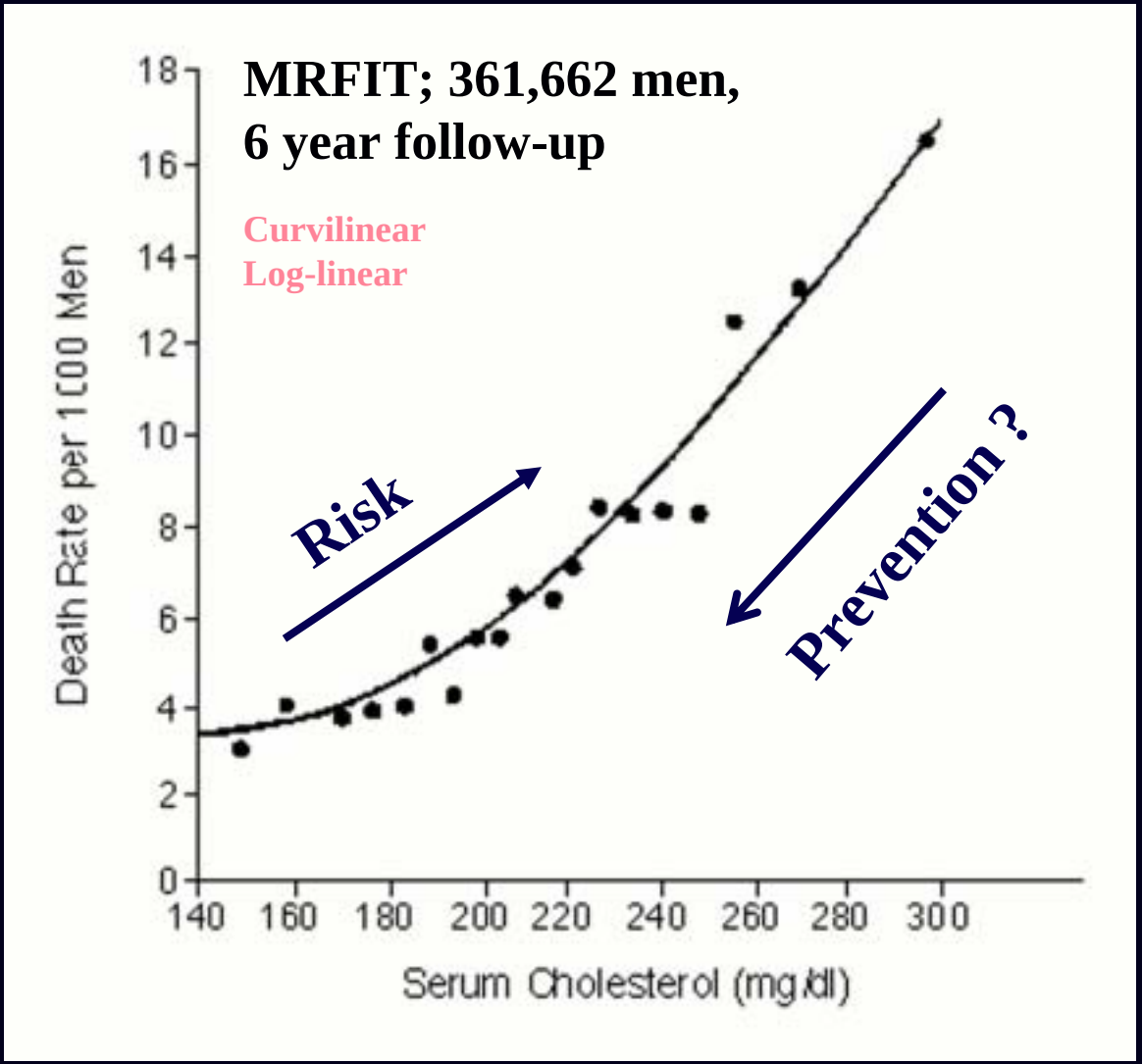




- **Atherosclerosis is a diffuse process. If you have it in your coronary vasculature, you have it in your peripheral vasculature and your cerebral vasculature.**
- **Keep in mind that you've treated only one, 5 millionth of his endothelium that's at risk for having a plaque rupture or a future event somewhere.**

Circulation 2001;103:2705

No Clear Threshold



- **ATP III Classification**

  LDL-C < 100mg/dl optimal

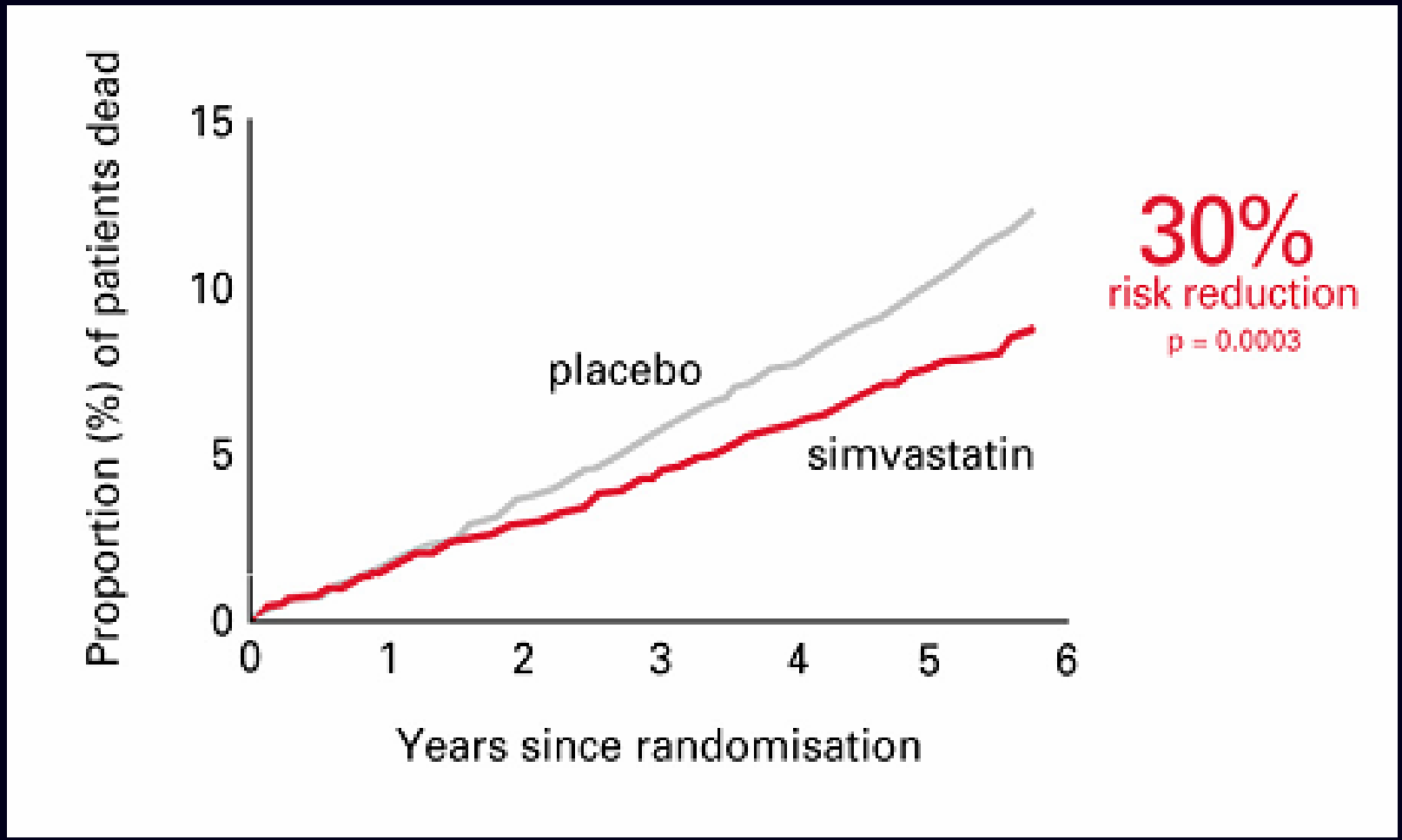
  T-Chol < 200mg/dl desirable

  HDL-C < 40mg/dl low

- **The relation between LDL-C levels and CHD risk is continuous over a broad range of LDL levels in many populations throughout the world.**

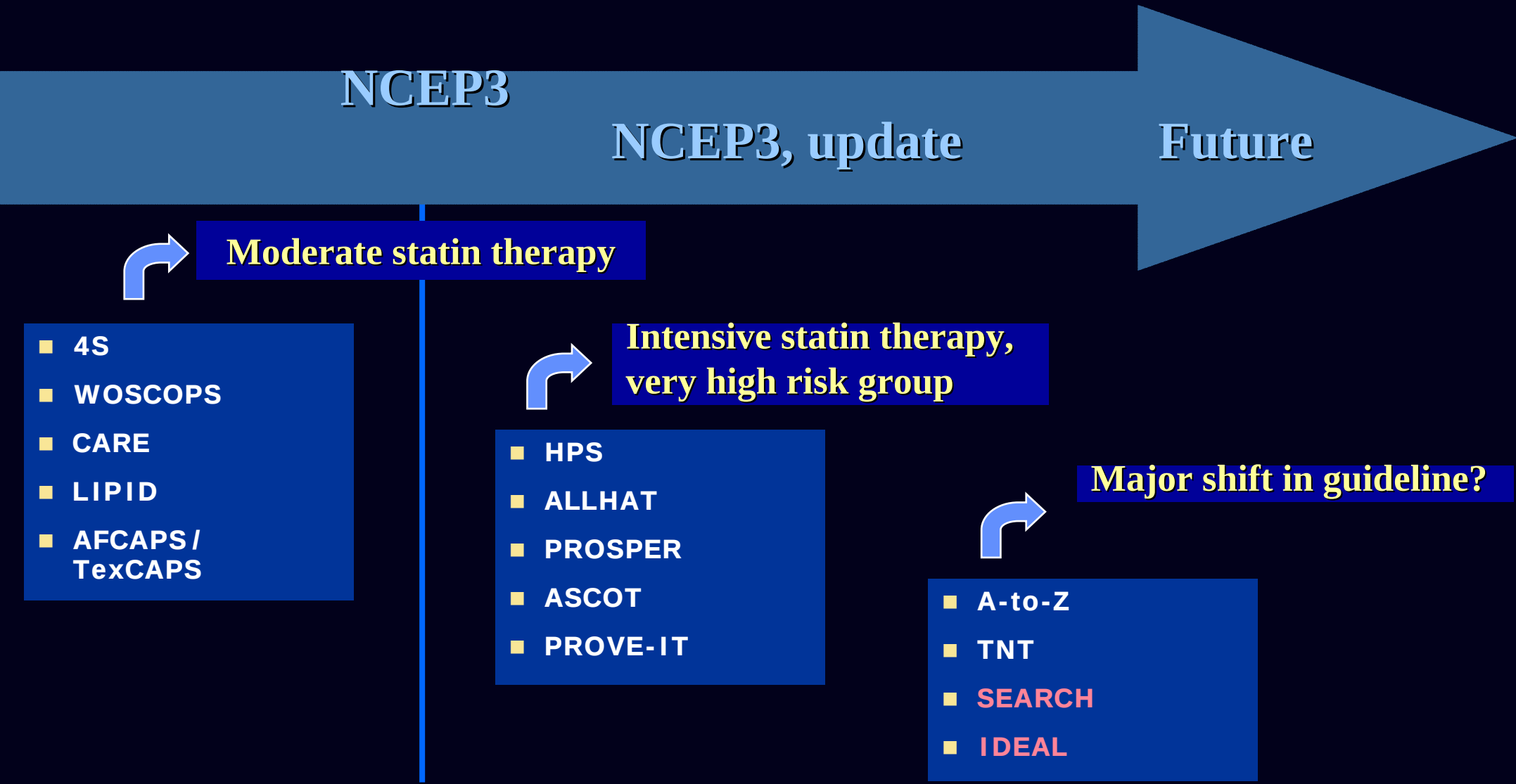
Lancet 1986:933-936.

Scandinavian Simvastatin Survival Study (4S)



Lancet 1994;344:1383

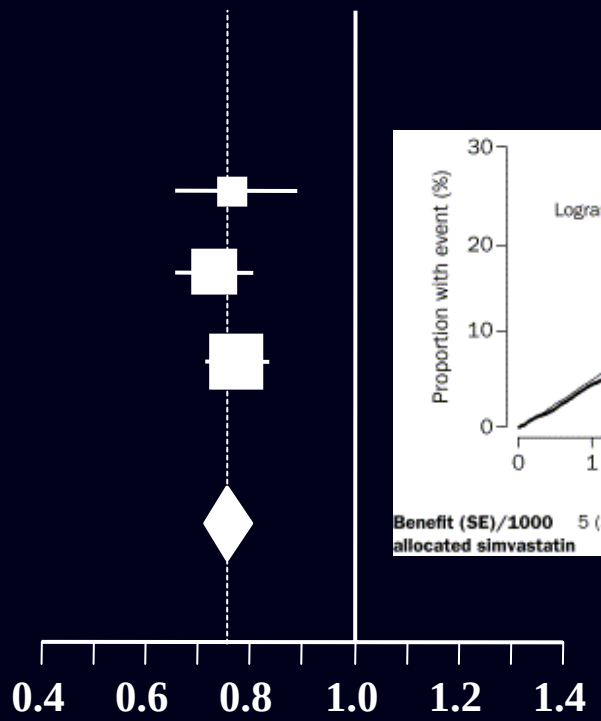
Statin Therapy in CAD



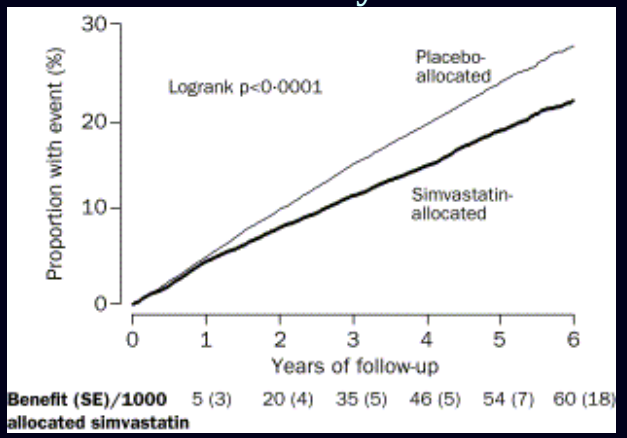
Heart Protection Study

Statins are the new aspirin.

Baseline Feature	STATIN (10269)	PLACEBO (10267)
LDL (mg/dl)		
< 100 (2.6 mmol/l)	285	360
≥ 100 < 130	670	881
≤ 130 (3.4 mmol/l)	1087	1365
ALL PATIENTS	2042 (19.9%)	2606 (25.4%)

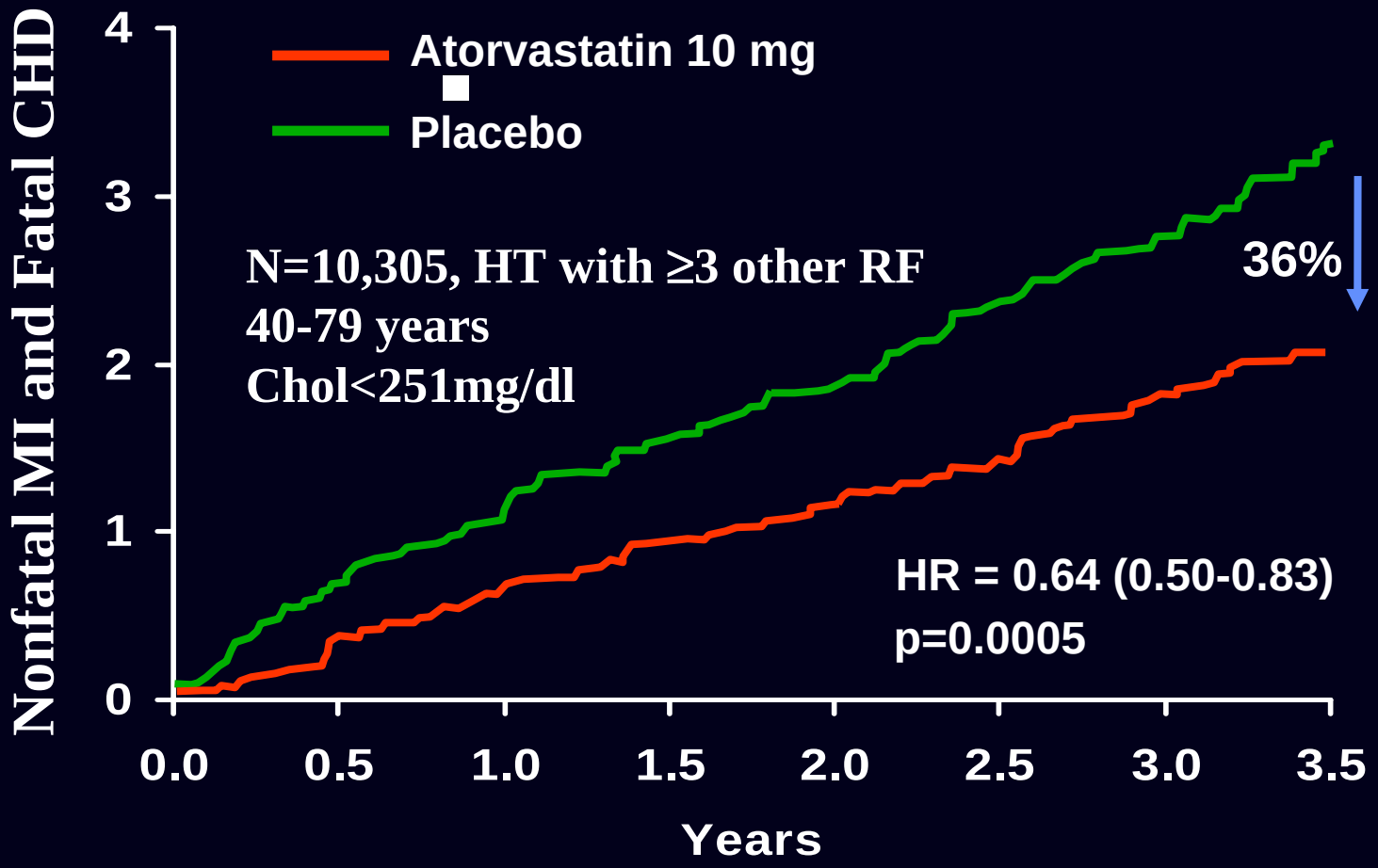


n=20,536
40-80 y



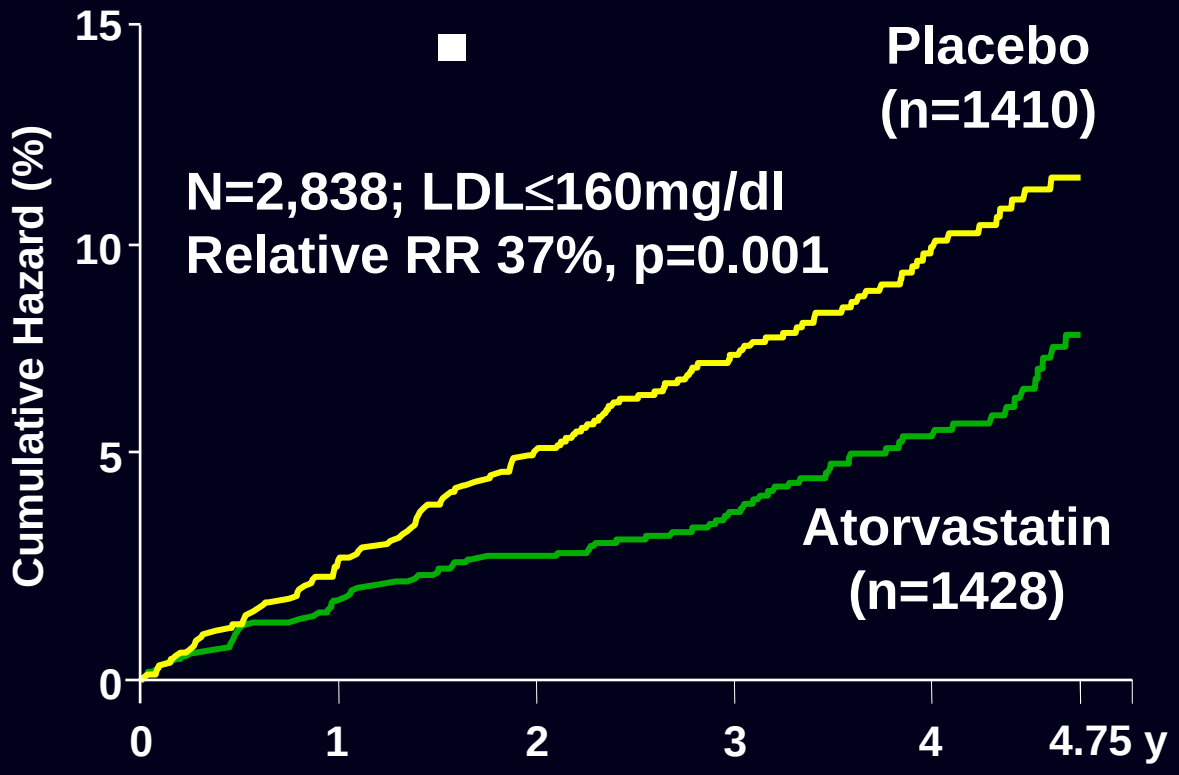
Lancet 2002;360:7

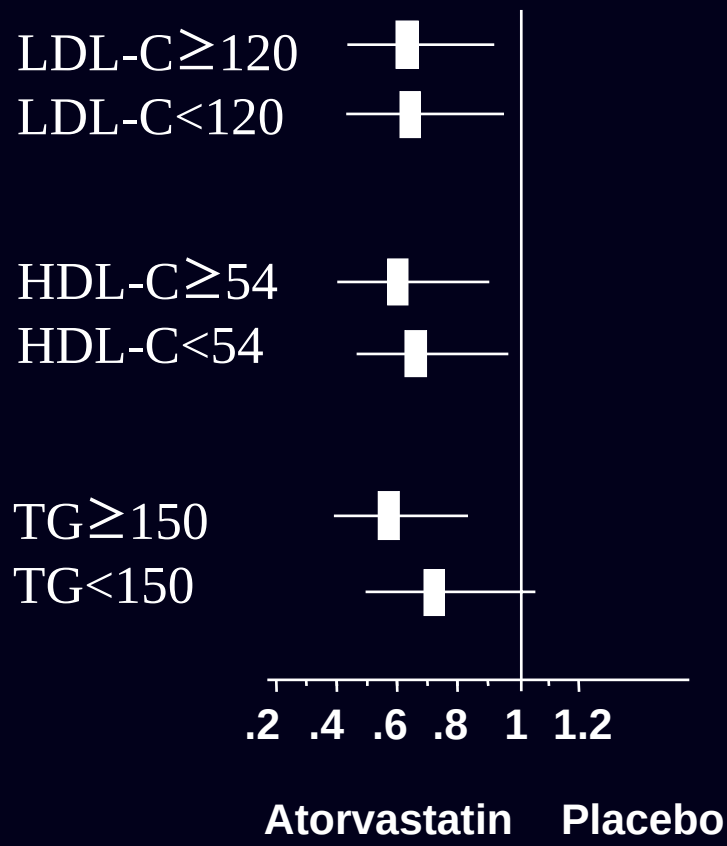
ASCOT



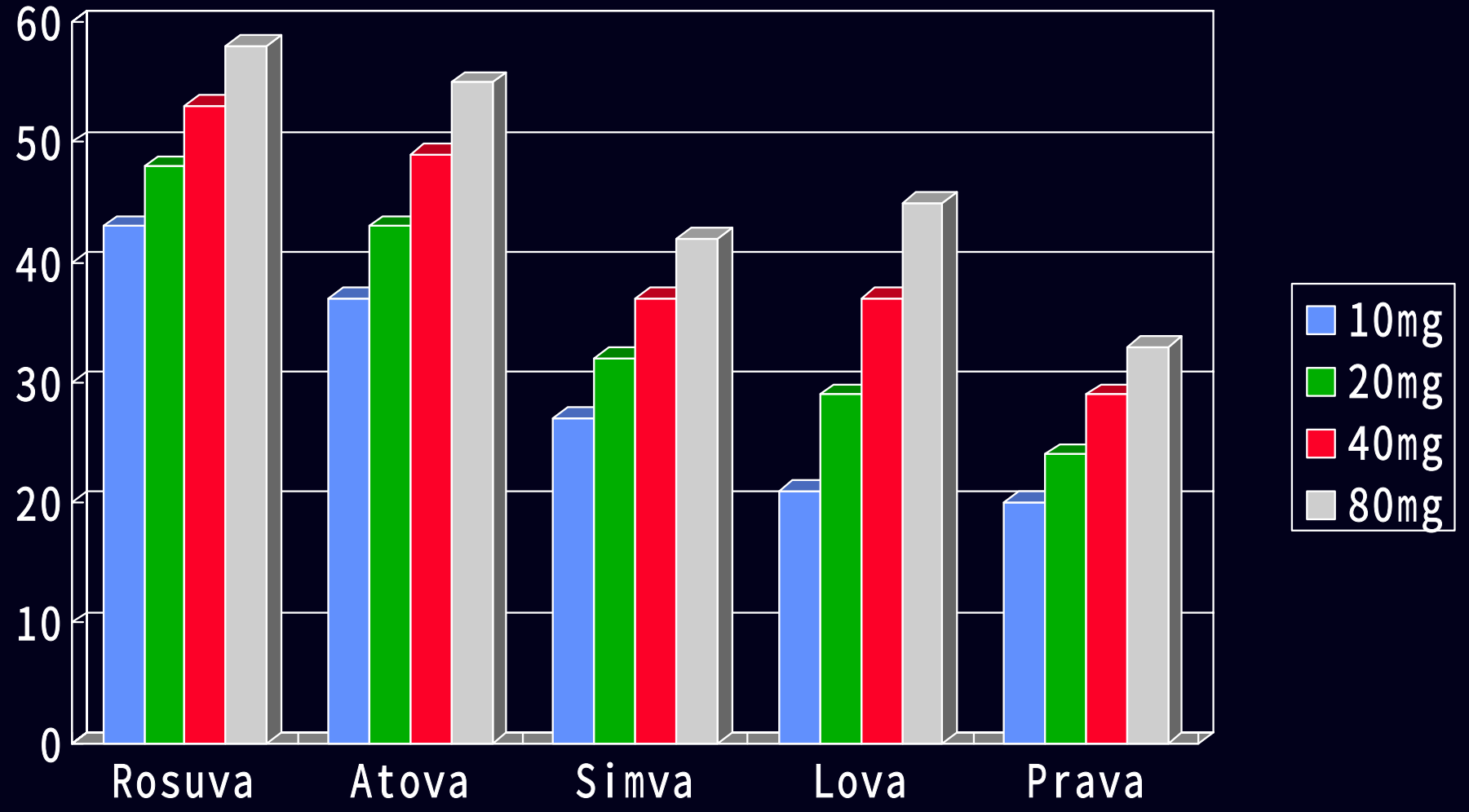
TC	HR	*P* Value
<193	0.628	0.098
193-230	0.615	0.011
231-250	0.689	0.084

Collaborative Atorvastatin Diabetes Study (CARDS, Primary Prevention)

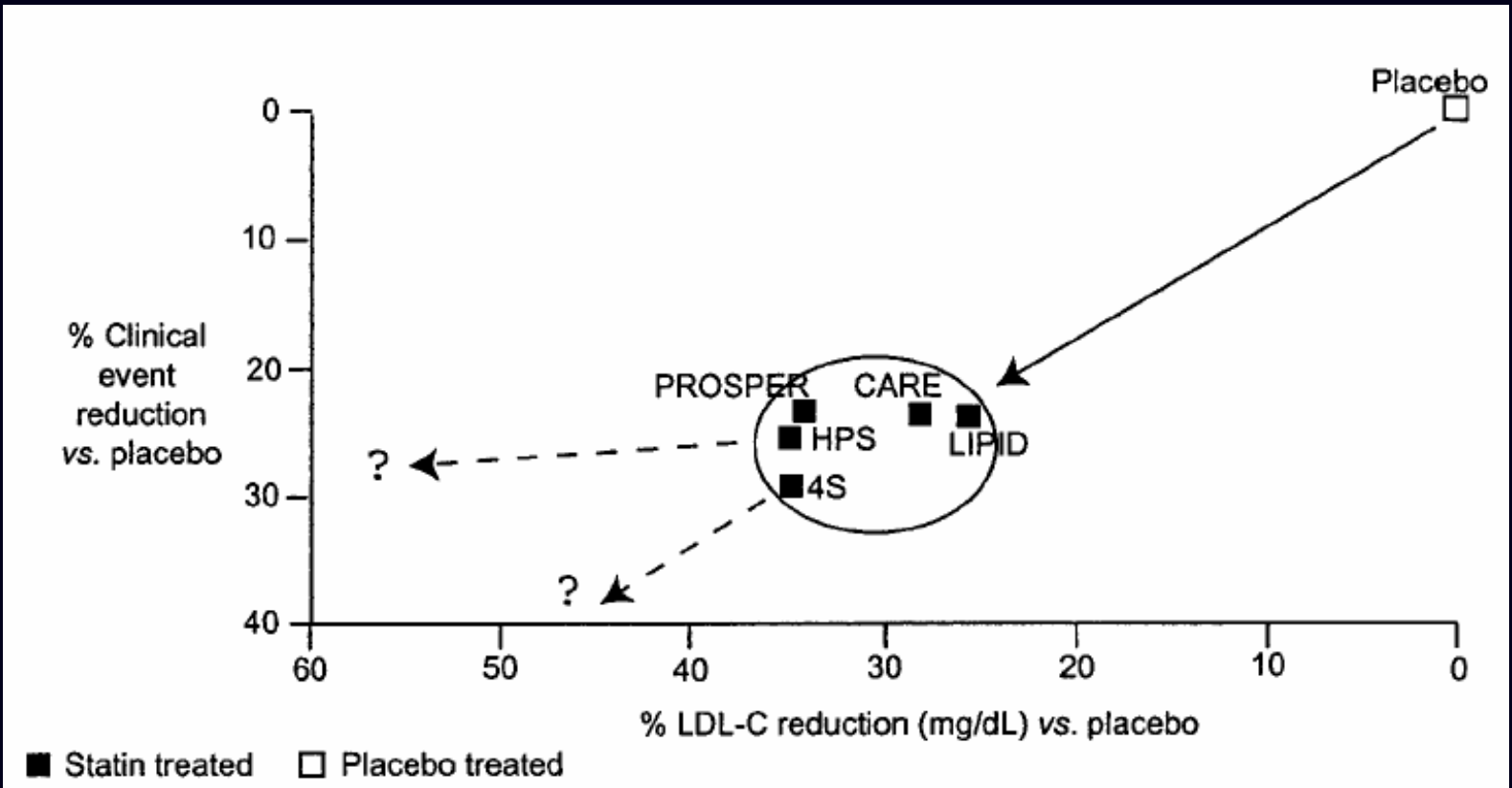




Percentage Reductions in Serum LDL-C according to Statin and Daily Dose



How Far Will the Benefits Go?

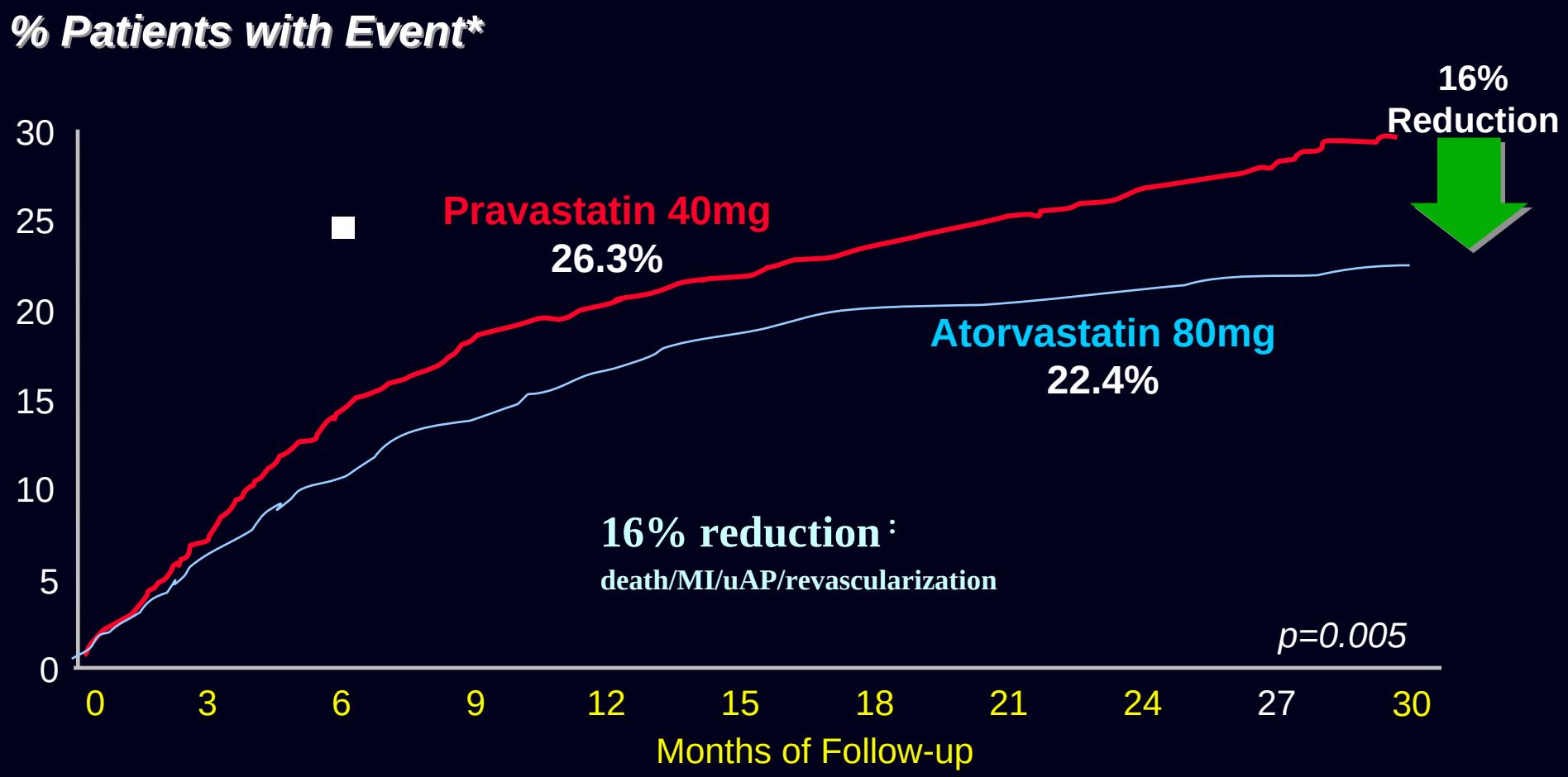


- It is not unclear whether lowering lipid levels further would increase the clinical benefit.
- HPS is not designed to answer the question of whether a lower LDL-C is better:
  The comparison (statin vs placebo) can only address the question of whether treatment better than no treatment. → We must consider treatment vs treatment.

Lower IS Better?

Setting	Acute Coronary Syndrome	Stable CAD
Studies	**PROVE-IT** **A-to-Z**	**TNT** **SEARCH** **IDEAL**
	2 year follow-up	**5 year follow-up**

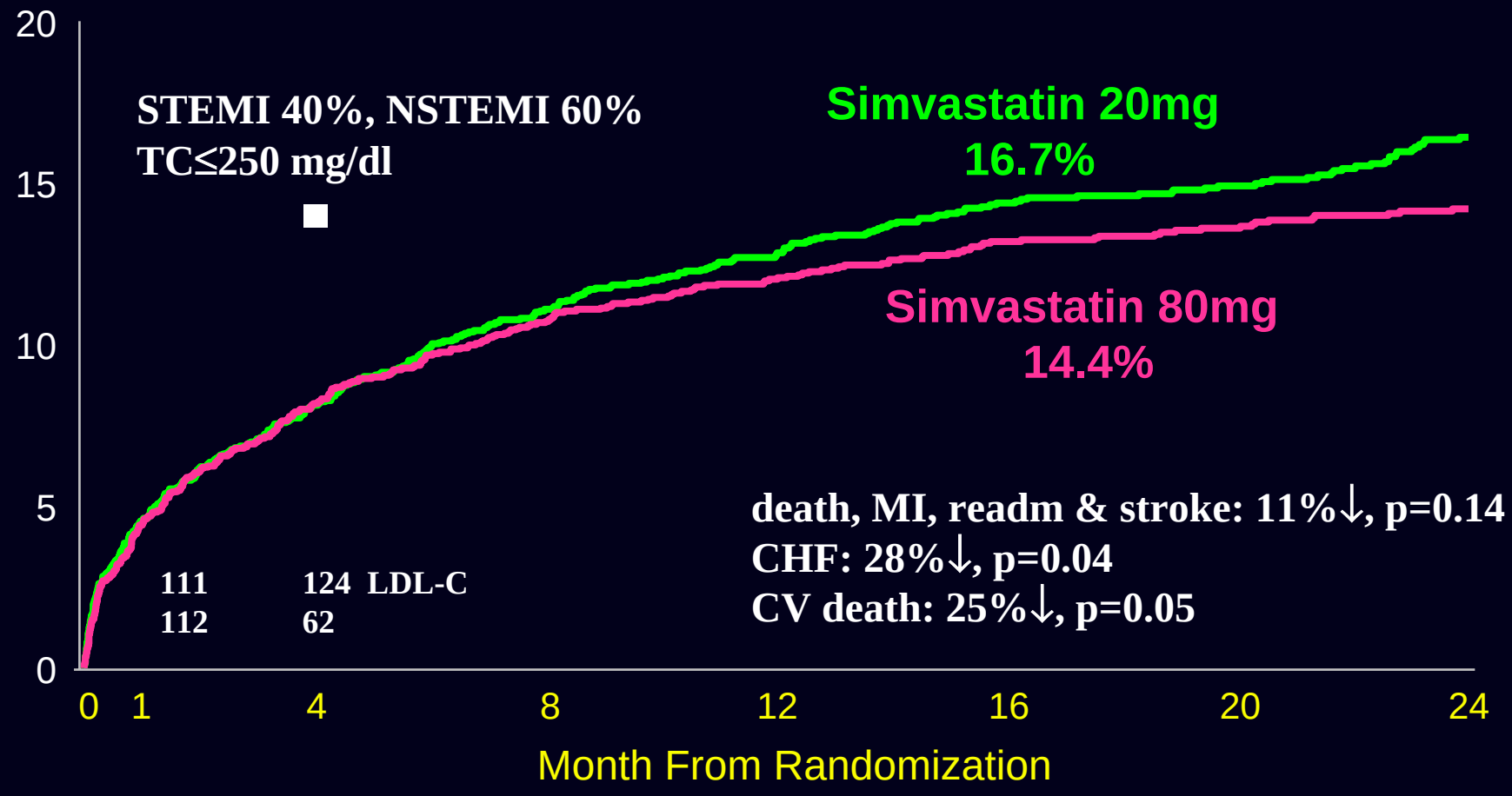
PROVE-IT



- 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

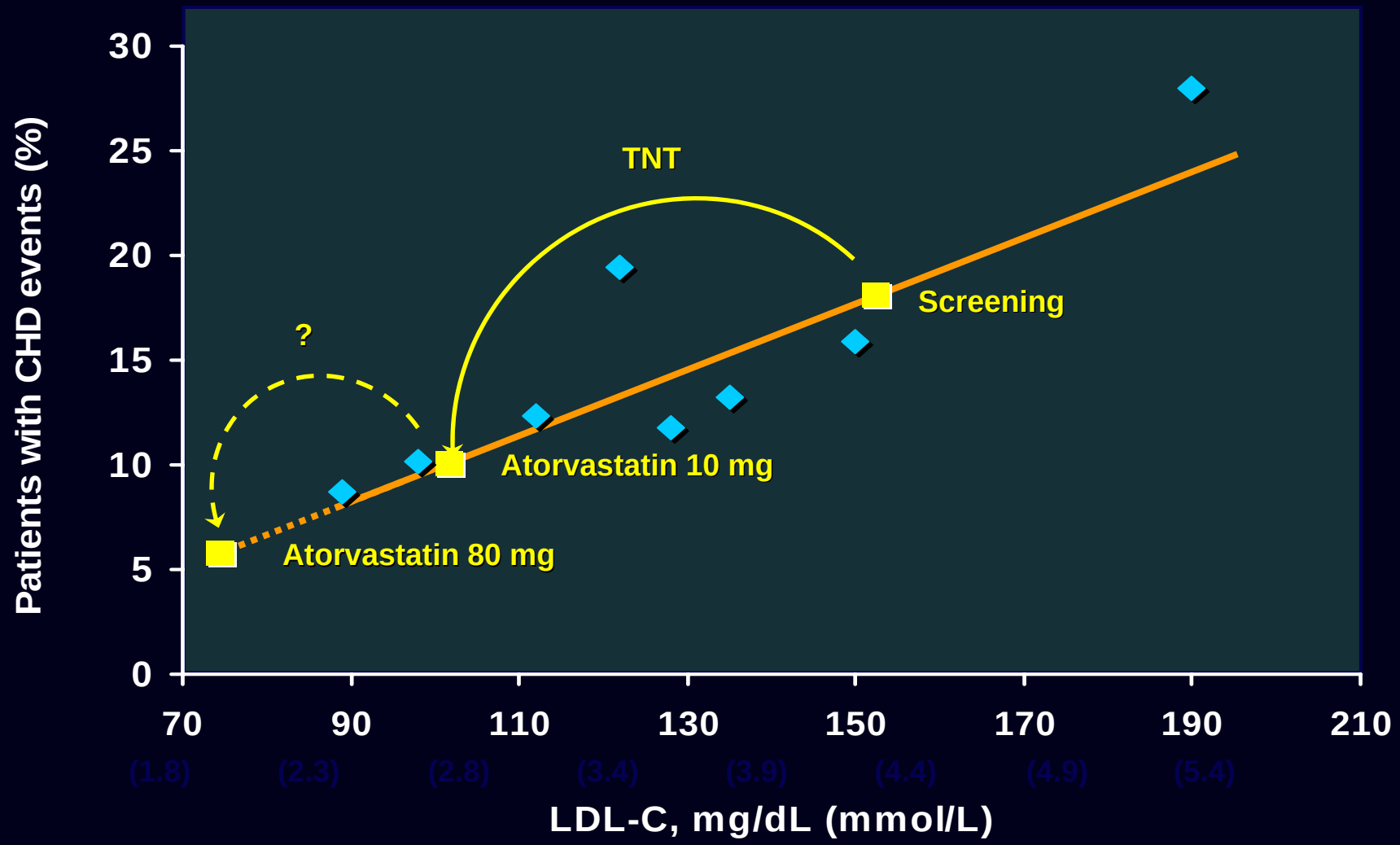
A to Z in Patients With ACS



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

JAMA2004;292:1307

The Treating to New Targets (TNT) Study: Rationale



Atherosclerosis. 1999;143(suppl 1):S17

TNT: Objective

- **TNT is the first randomized clinical trial to prospectively assess the efficacy and safety of treating patients with stable CHD to LDL-C levels significantly below 100 mg/dL**

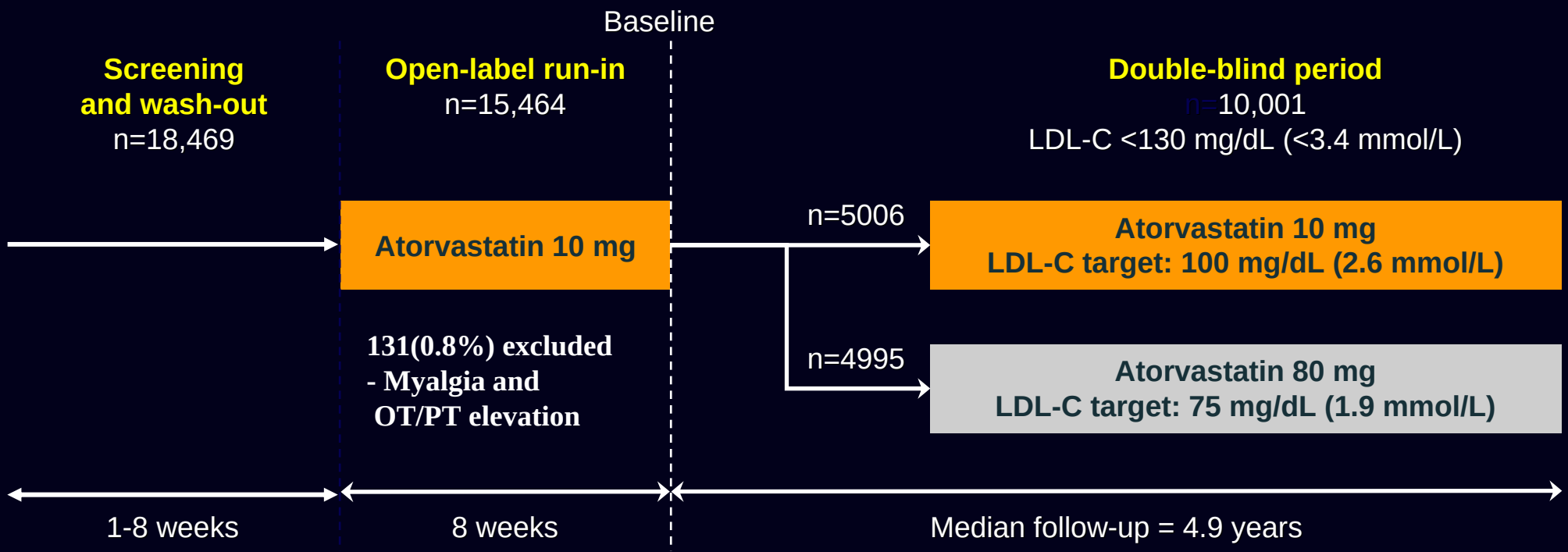
Study Design

Patient population:

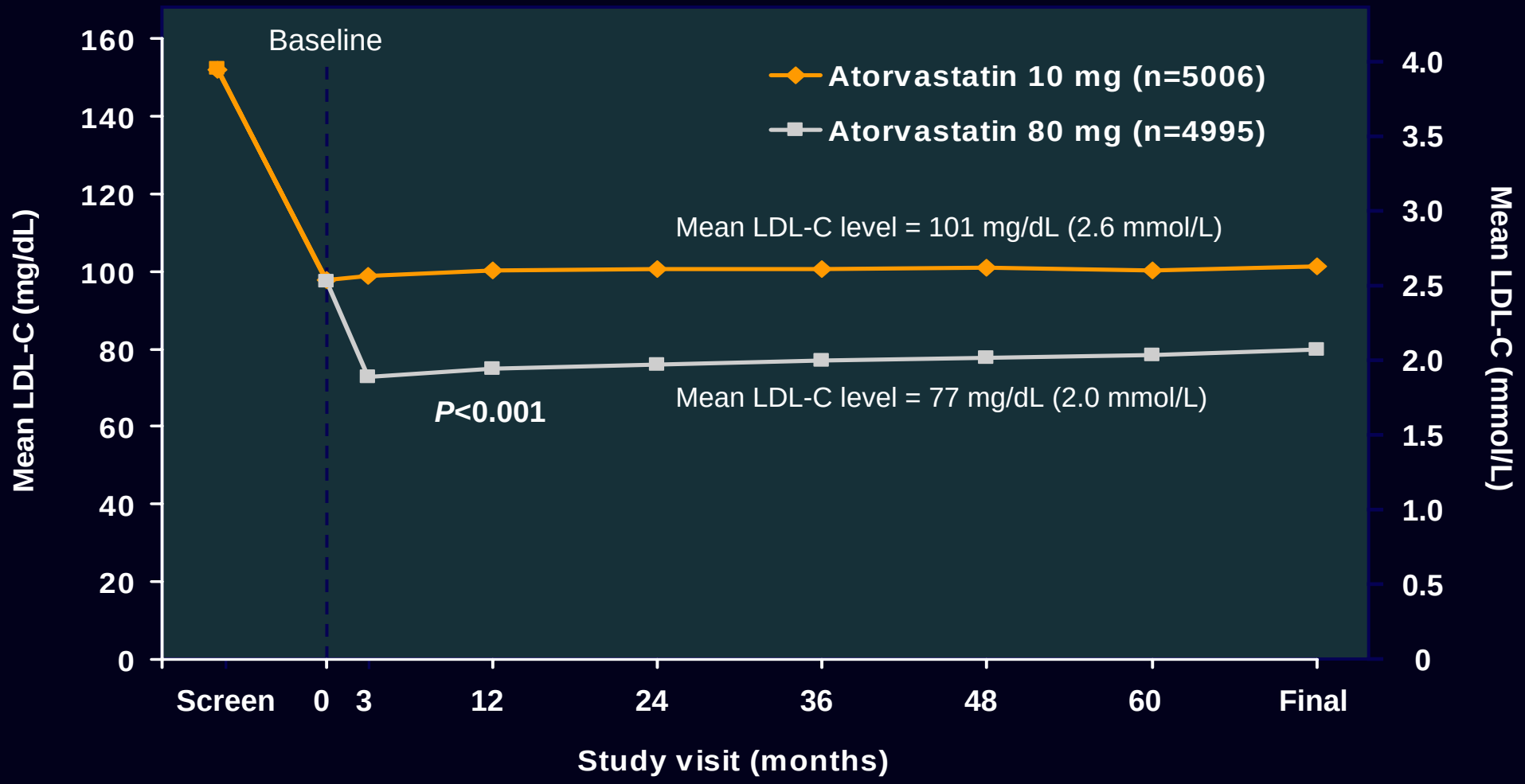
- CHD
- LDL-C: 130-250 mg/dL (3.4-6.5 mmol/L)
- Triglycerides ≤600 mg/dL (≤6.8 mmol/L)

Primary efficacy outcome measure:

- Time to occurrence of a major CV event:
  - CHD death
  - Nonfatal, non-procedure-related MI
  - Resuscitated cardiac arrest
  - Fatal or nonfatal stroke

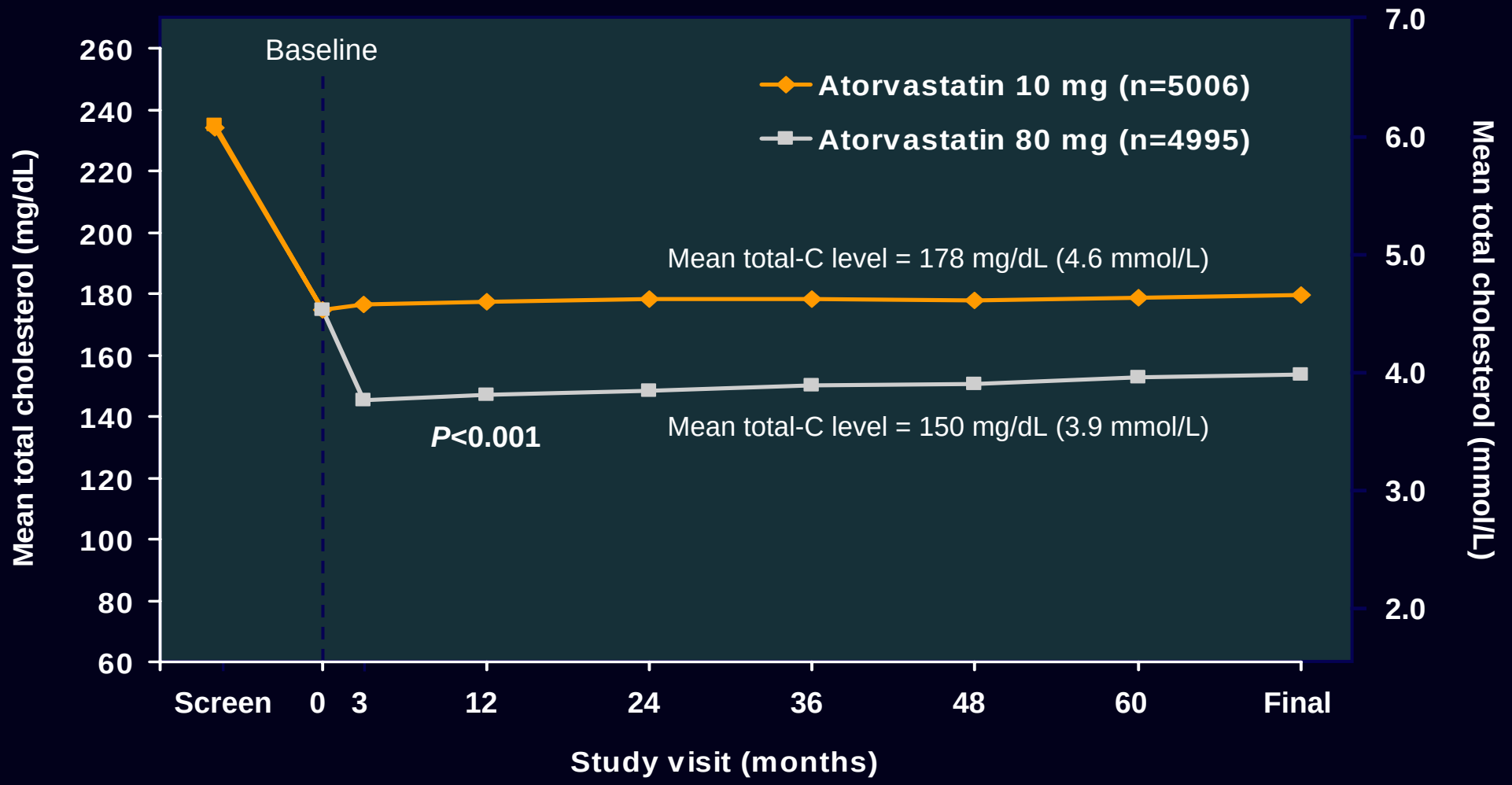


Changes in LDL-C



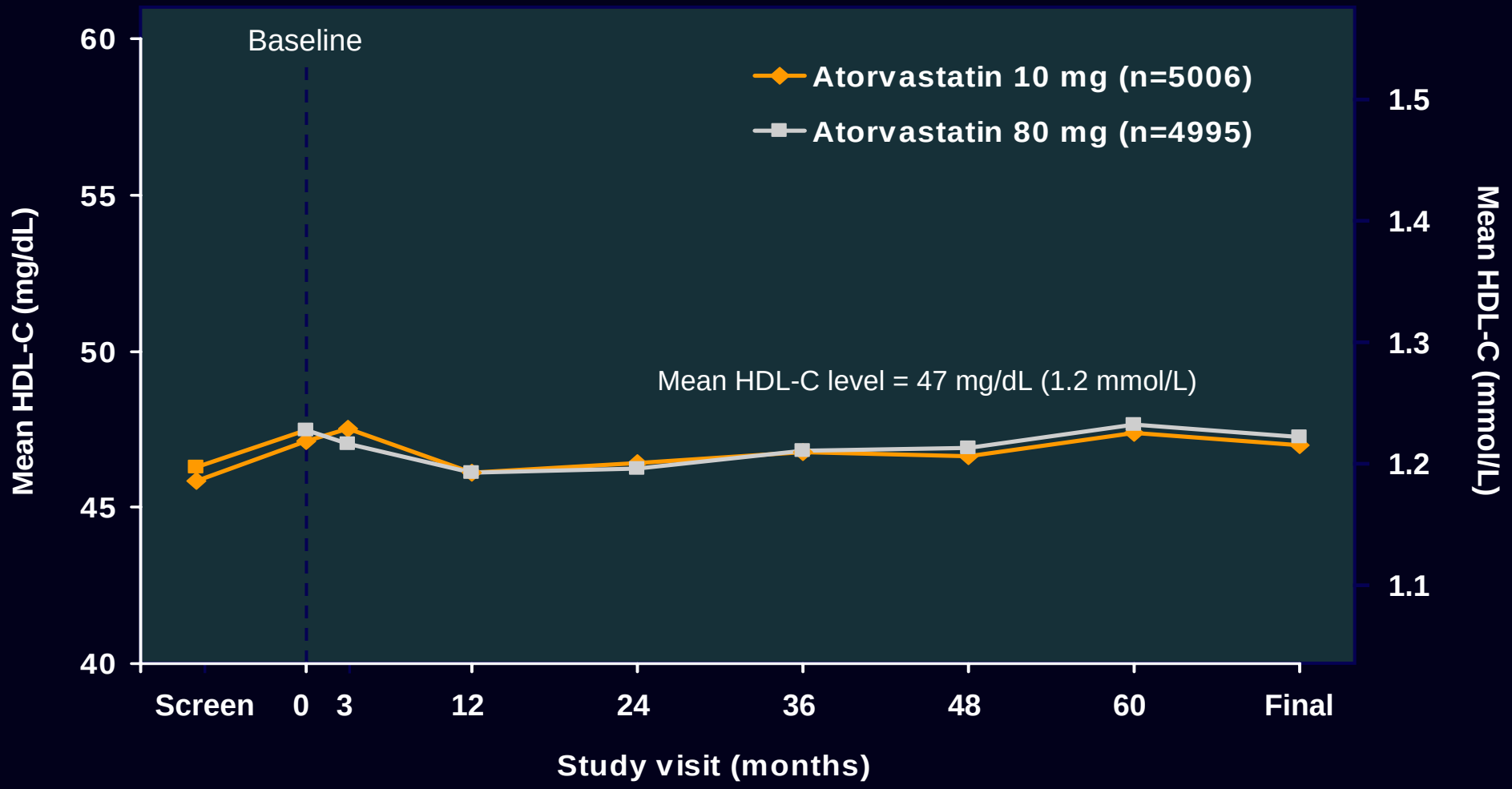
LaRosa JC, *et al*. *N Eng J Med.* 2005;352

Changes in Total Cholesterol



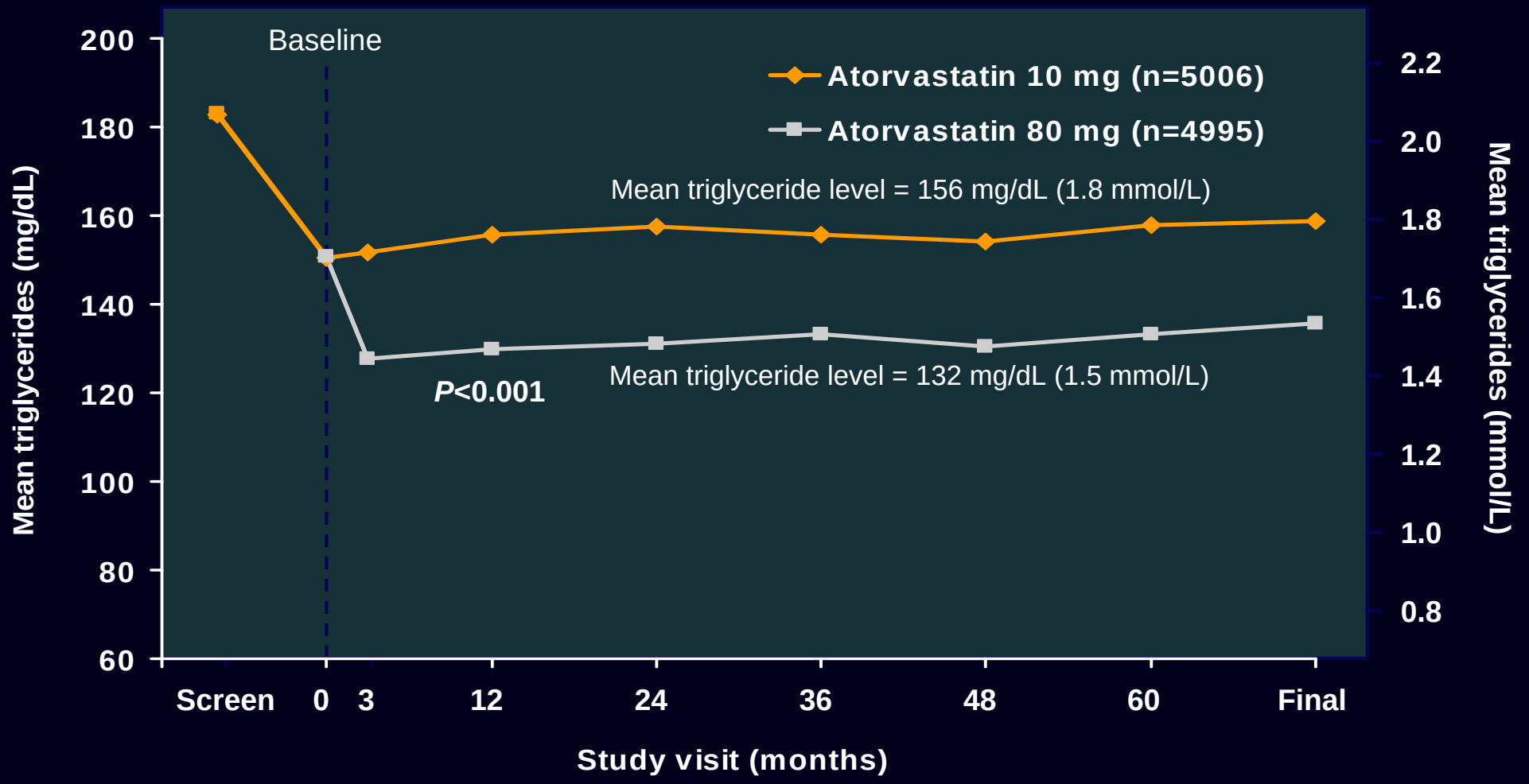
LaRosa JC, *et al. N Eng J Med.* 2005;352

Changes in HDL-C



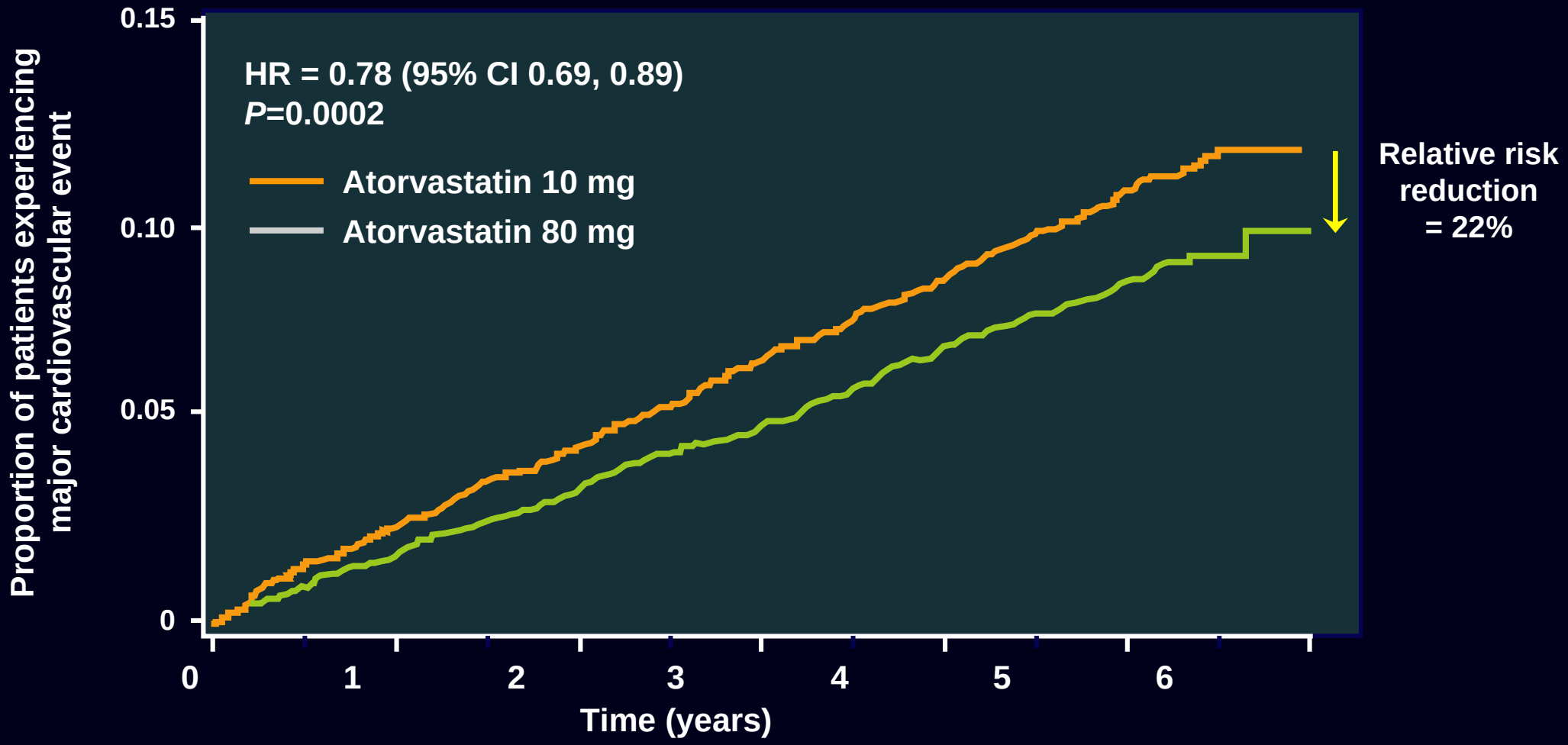
LaRosa JC, *et al. N Eng J Med.* 2005;352

Changes in Triglycerides



LaRosa JC, *et al. N Eng J Med.* 2005;352

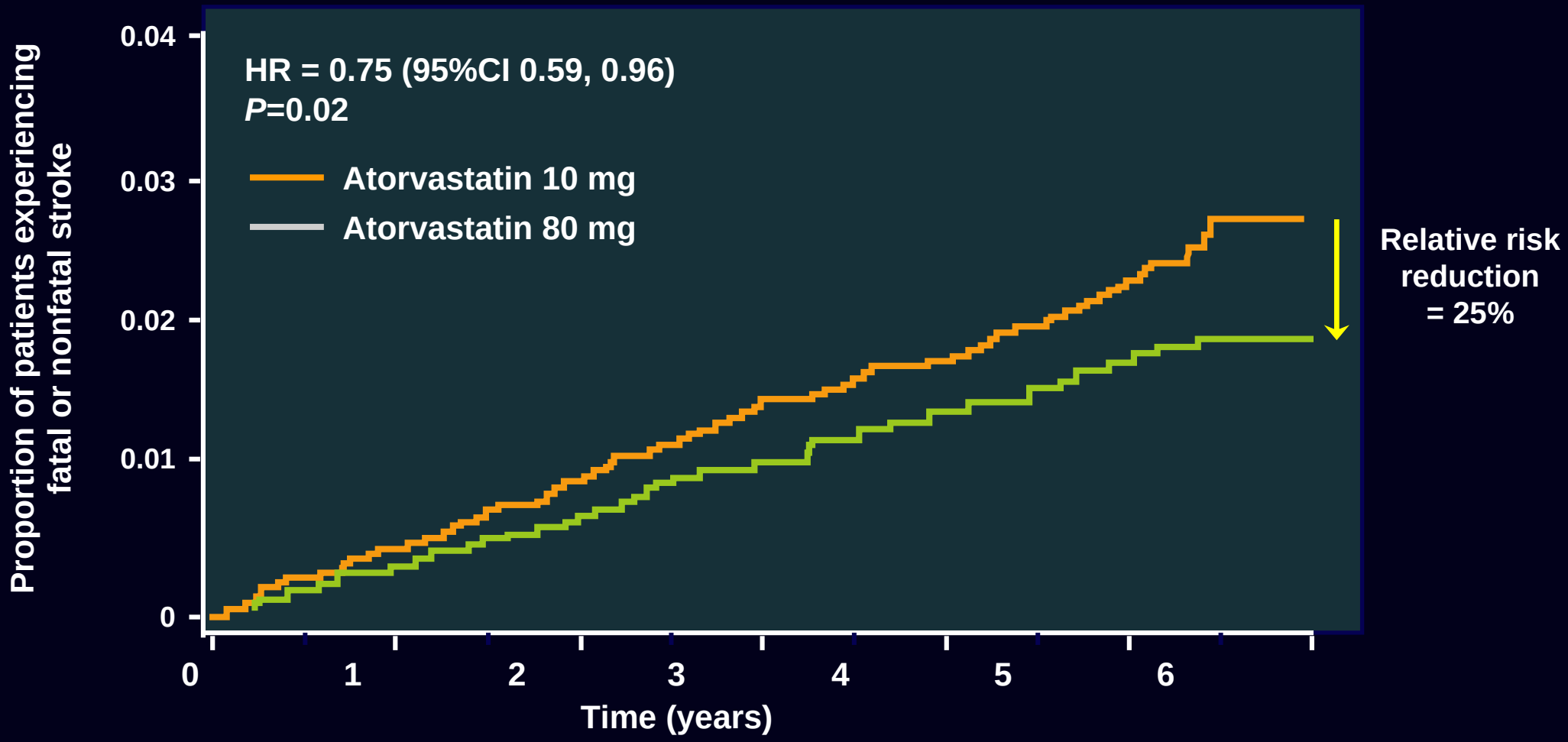
Primary Efficacy Outcome



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

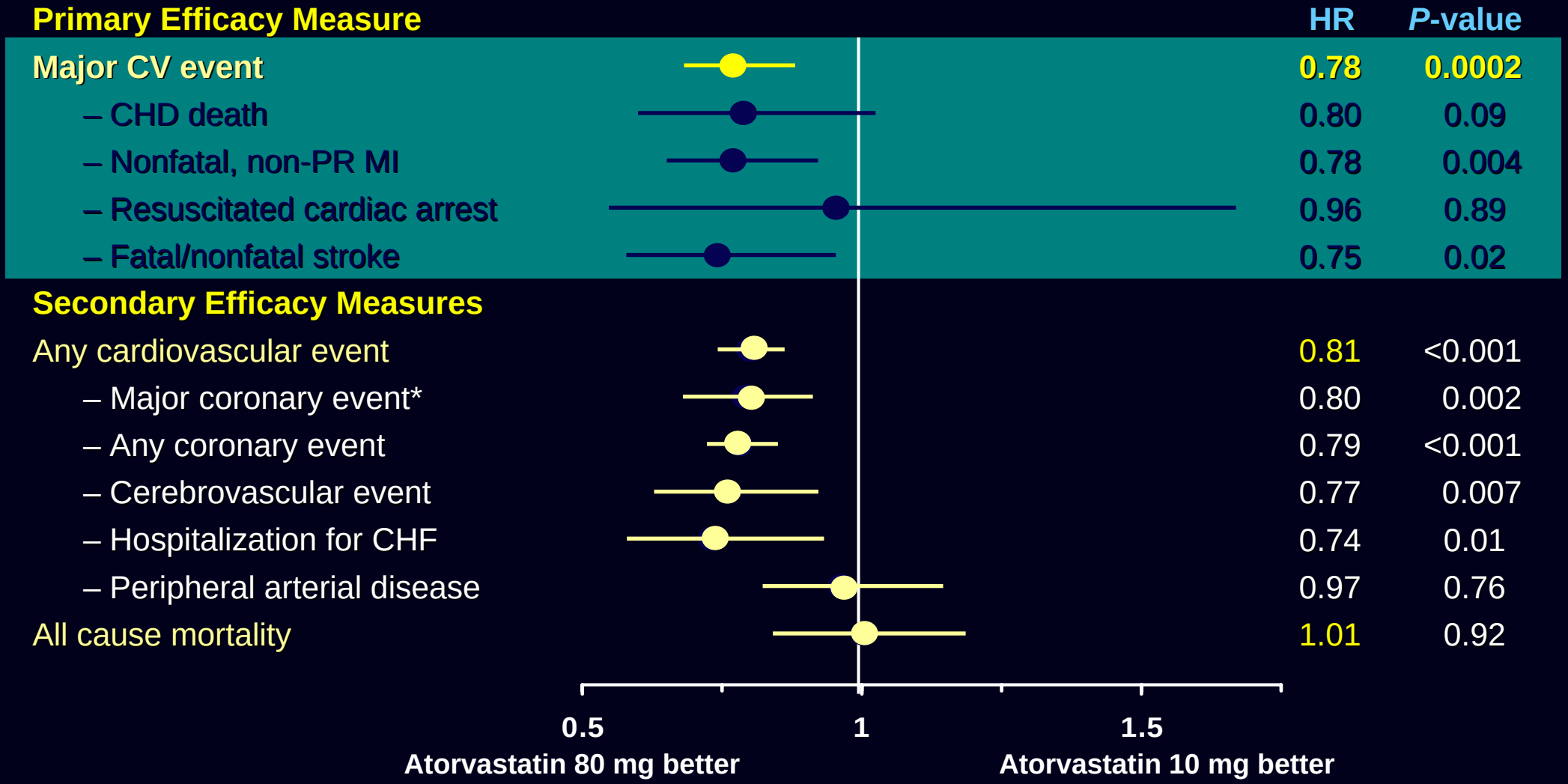
LaRosa JC, *et al. N Eng J Med.* 2005;352

Stroke (Fatal or Nonfatal)



LaRosa JC, *et al. N Eng J Med.* 2005;352

Primary and Secondary Efficacy Outcome Measures: Hazard Ratios



LaRosa JC, *et al. N Eng J Med.* 2005;352

Mortality

	No. of patients (%)	
	Atorvastatin 10 mg (n=5006)	**Atorvastatin 80 mg (n=4995)**
All-cause mortality	282 (5.6)	284 (5.7)
Cardiovascular	155 (3.1)	126 (2.5)
CHD death	127 (2.5)	101 (2.0)
Stroke death	8 (0.2)	7 (0.1)
Hemorrhagic stroke death	2 (0)	3 (0.1)
Noncardiovascular	127 (2.5)	158 (3.2)
Cancer	75 (1.5)	85 (1.7)
Trauma	9 (0.2)	15 (0.3)
Other	43 (0.9)	58 (1.2)

LaRosa JC, *et al. N Eng J Med.* 2005;352

Safety - Adverse Events

	No. of patients (%)	
	Atorvastatin 10 mg (n=5006)	Atorvastatin 80 mg (n=4995)
Total	5.8	8.1
Discontinuation	53	7.2
Myalgia	4.7	4.8
Rhabdomyolysis*	0.06	0.04
AST/ALT elevation >3 × ULN	0.2	1.2

*No cases were considered by the investigator with direct responsibility for the patient to be causally related to atorvastatin, and none met ACC/AHA/NHLBI criteria[2] for rhabdomyolysis

Conclusions

- Treatment with atorvastatin 80 mg to an LDL-C of 77 mg/dL provided significant additional clinical benefit to patients with stable CHD currently perceived to be well controlled at levels around 100 mg/dL.
- The incremental benefits observed with atorvastatin 80 mg included significant reductions in the risk of coronary events and stroke
- This improved clinical outcome was achieved without significant additional safety risk.

LaRosa JC, *et al. N Eng J Med.* 2005;352

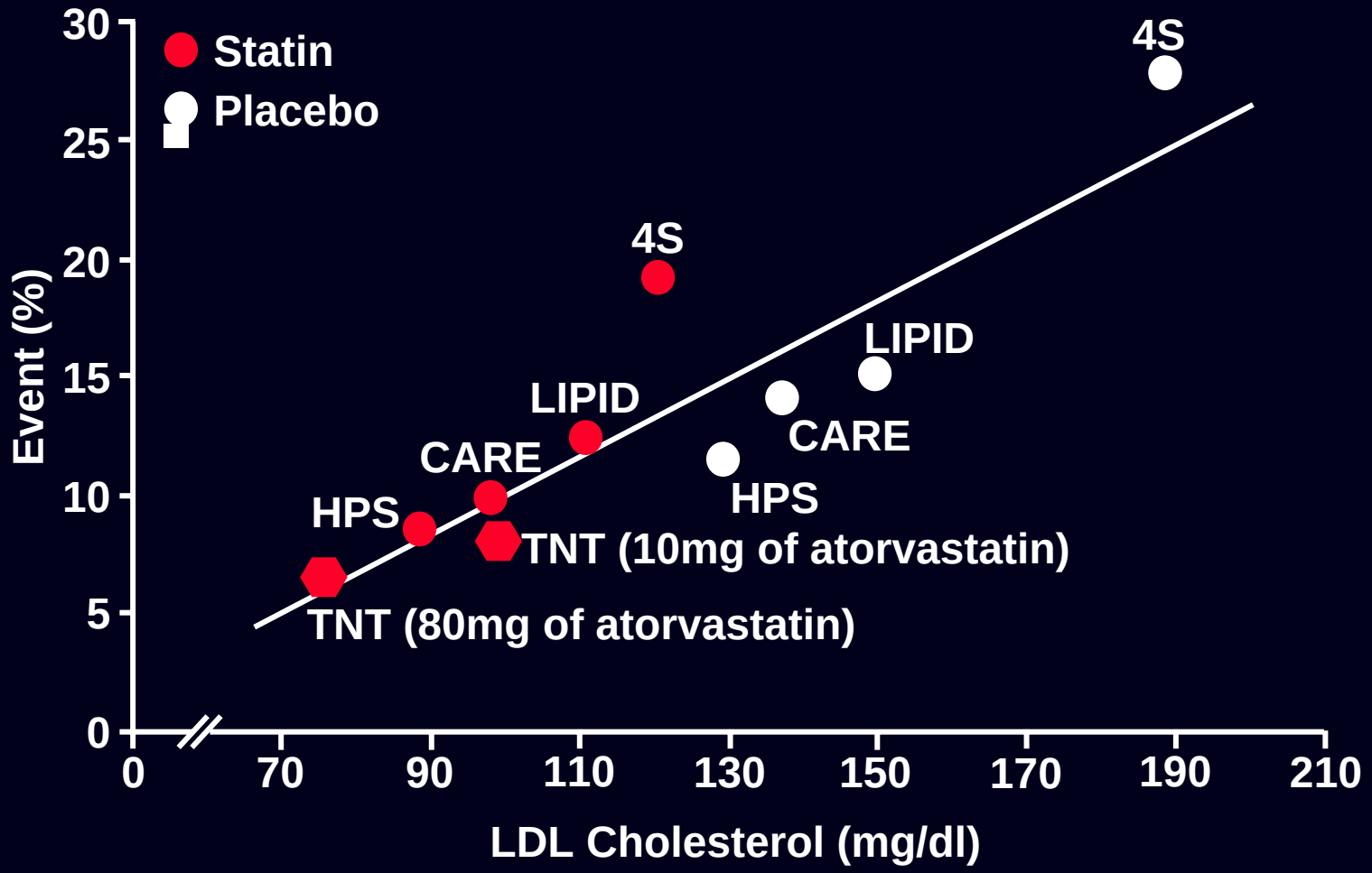
A Proof of Concept Study

- **The TNT results herald "a new era in the treatment of established coronary disease," showing that lower is better in stable CHD patients.**

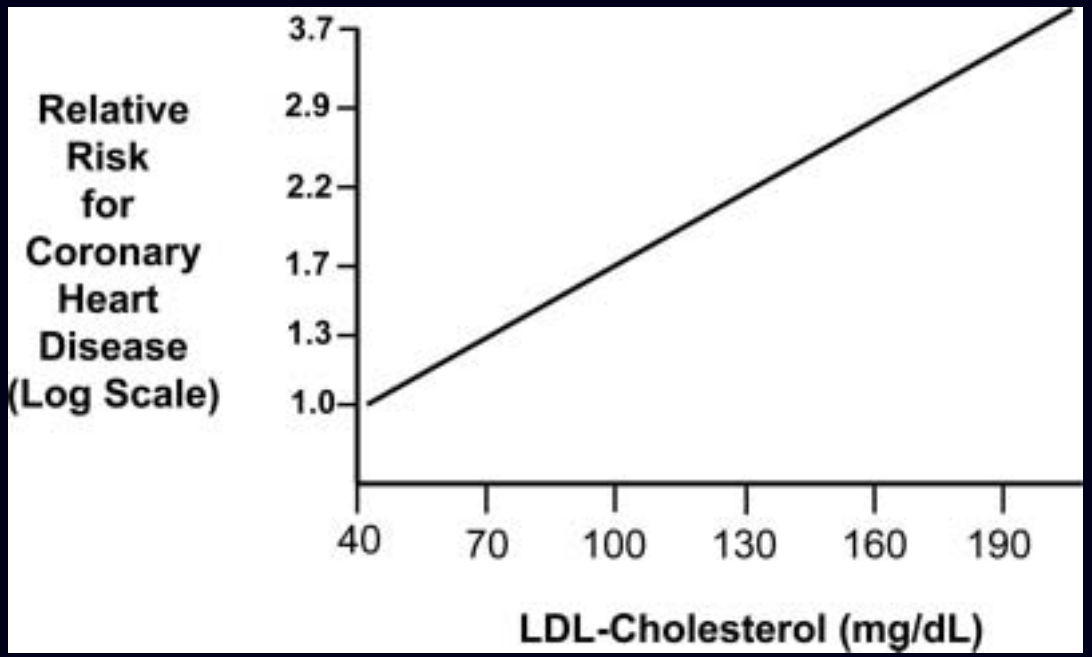
- **The absolute importance of bringing statins to patients at risk and to wider populations such as people with hypertension or with diabetes**

LaRosa JC, *et al. N Eng J Med.* 2005;352

Event Rates Plotted Against LDL-C in Secondary Prevention



No Threshold LDL-C Level Below Which No Further Reduction In Risk Occurs



	Baseline LDL	Ending LDL
Primary Prevention		
WOSCOPS	192	142
AFCAPS/TexCAPS	150	115
CARDS	119	73
ASCOT	131	90
Primary/Secondary Prevention		
HPS	131	104
PROSPER	145	95
Secondary Prevention		
4S	188	122
CARE	139	98
LIPID	150	112
PROVE-IT	106	62
TNT	98	77

At any level of LDL-C, the change in relative risk is the same as at any other LDL-C levels (log-linear relationship).

How Low Is Too Low ?

physiologically ideal range of cholesterol

- **Cholesterol is an essential component of the cell membrane and an obligate precursor for bile acid, steroid hormone, and vitamin D synthesis.**

- **People with heterozygous hypobetalipoproteinemia have total cholesterol levels as low as 80 mg/dl (LDL: 30 mg/dl). This condition is associated with longevity, presumably due to the absence of atherosclerosis, but the lack of other adverse effects that might have accompanied a low LDL level suggests that such low levels of LDL are safe.**

JACC2004;43:2142

Safety and Efficacy Regarding Lowering LDL-C Levels beyond the Set Guidelines

Endpoints	80-100 (n=256)	60-80 (n=576)	40-60 (n=631)	<40 (n=256)
Composite(%)	26.1	22.2	20.4	20.4
Death(%)	1.1	1.4	1.3	0.5
Stroke(%)	0.8	0.9	0.5	1.6
MI(%)*	10.3	6.8	4.5	6.3
CK > 10x	2.3	3.1	3.2	1
AST > 3x	3.1	0.7	1.9	2.6

The lack of an increase in side effects (myositis, altered liver function tests) and the trends toward a beneficial effect are encouraging (PROVE IT – TIMI 22 study).

Is Intensive Lipid Lowering Justified in Stable CHD Patients?

- **Fewer cardiovascular deaths were offset by more non-cardiovascular deaths:**
  - CHD death 26 ↓, Non-cardiovascular death 31↑
  → by chance or an increased risk of non-CV death?
- **Further reassurance before a major shift**
  - ongoing trials (SEARCH, IDEAL)

Intensive Statin Therapy
Shift or Wait?

- **Very-high risk group**
  - **Lower is better (NCEP III updated)**
- **Stable CAD**
  - **We need further reassurance as to the safety of this approach.**
- **Optimal LDL-C**