

Lipids and Guidelines.
For my Patient I want more Simplicity
LDL less Than 60 and Pay attention to HDL, OK?

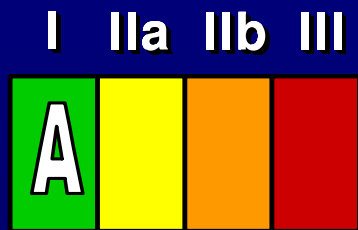
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ACC's West Coast Cardiovascular Forum
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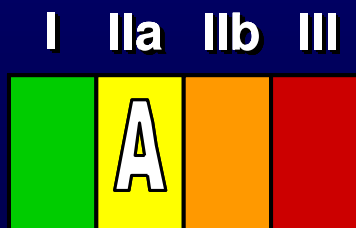
Updated ATP III LDL-C Goals for Therapy

Risk Category	Goal	LDL-C (mg/dL)	
		Initiation Level for TLC	Consideration Level for Drug Therapy
High risk: CHD or CHD risk equivalents (10-yr risk >20%)	<100 (optional: <70)	≥100	≥100 (<100: consider drug options)
Moderately high risk: 2+ risk factors (10-yr risk 10–20%)	<130 (optional:<100)	≥130	≥130 (100–129: consider drug options)
Moderate risk: 2+ risk factors (10-yr risk <10%)	<130	≥130	≥160
Lower risk: 0–1 risk factor	<160	≥160	≥190 (160–189: LDL-C-lowering drug optional)

Secondary Prevention Lipid Goals



LDL-C should be less than 100 mg/dL



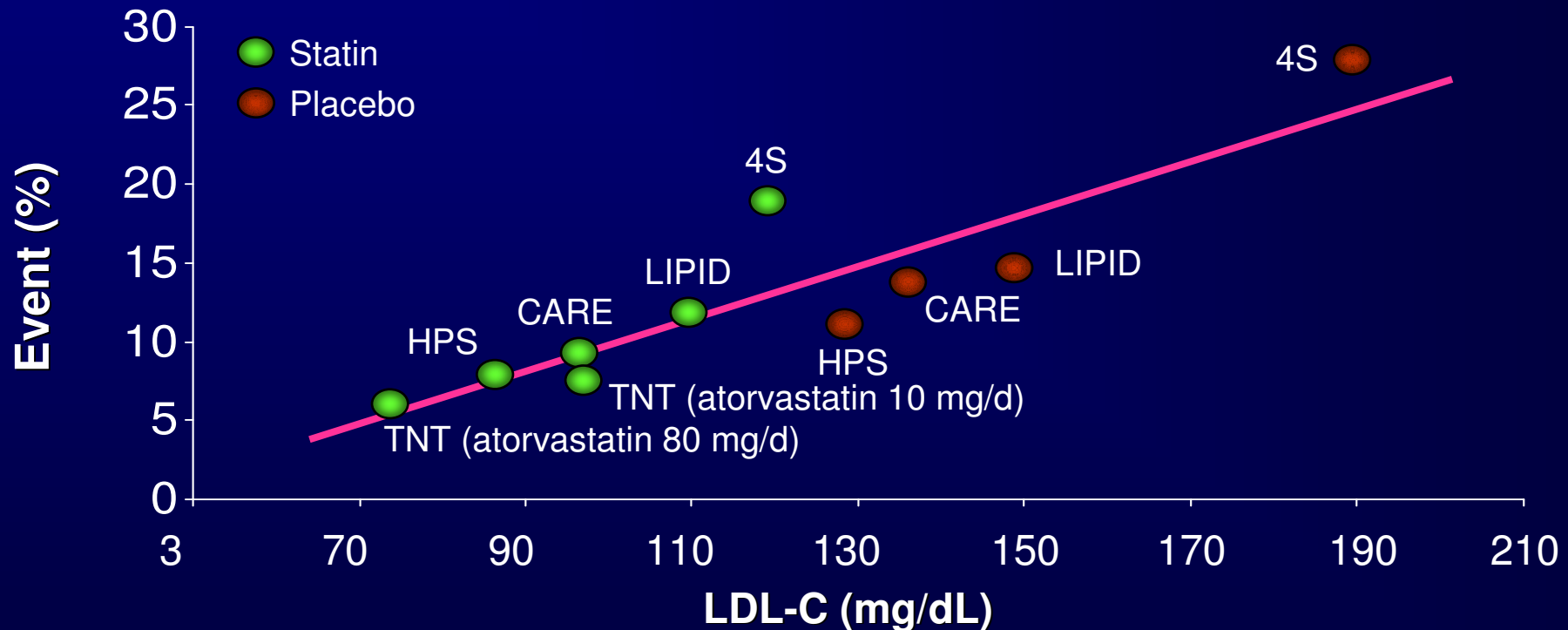
Further reduction to LDL-C to < 70 mg/dL is reasonable

If TG ≥ 200 mg/dL, non-HDL-C should be < 130 mg/dL*

*Non-HDL-C = total cholesterol minus HDL-C

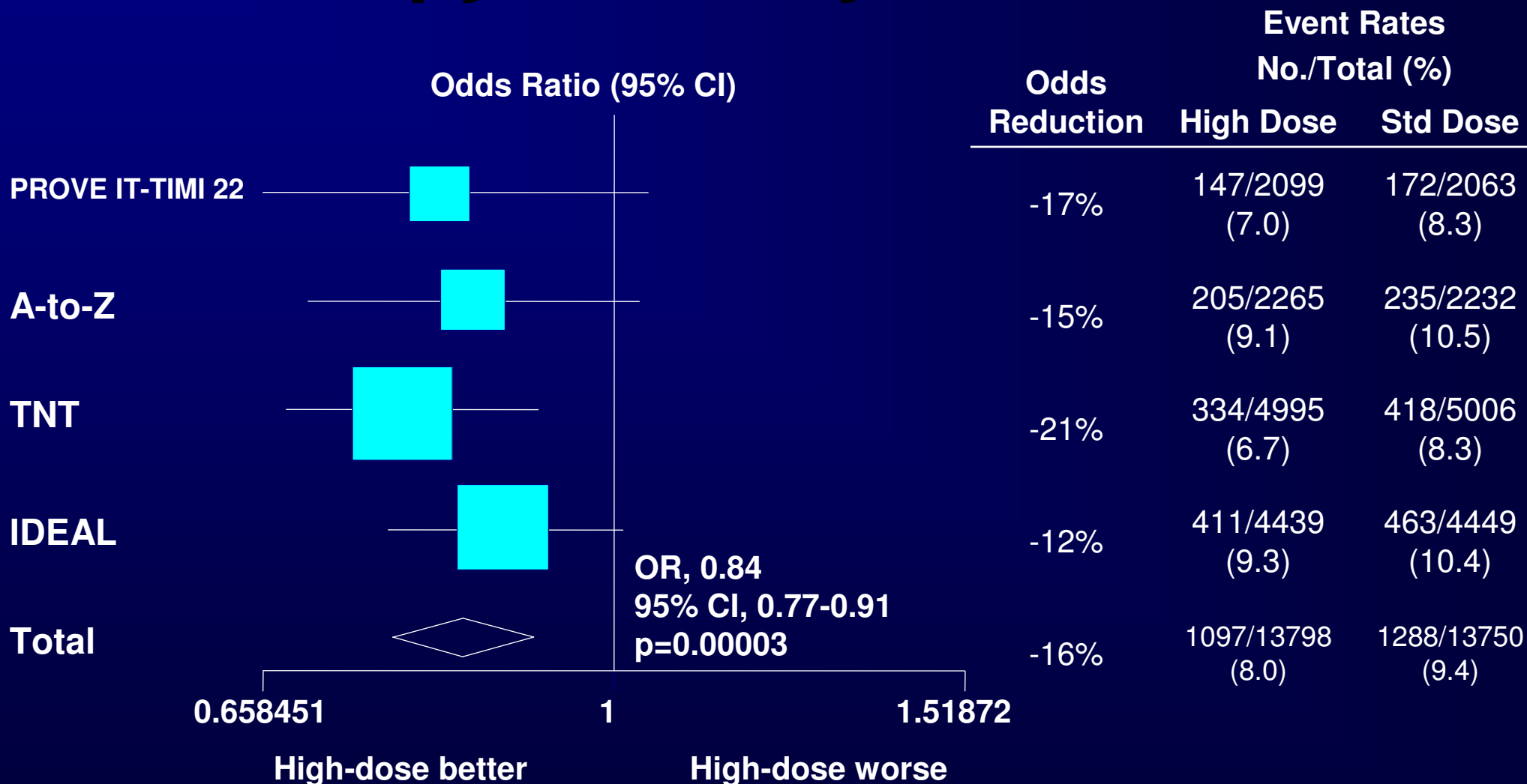
Statin: Secondary Prevention

Relationship between LDL-C Levels and Event Rates in Secondary Prevention Trials of Patients with Stable CHD

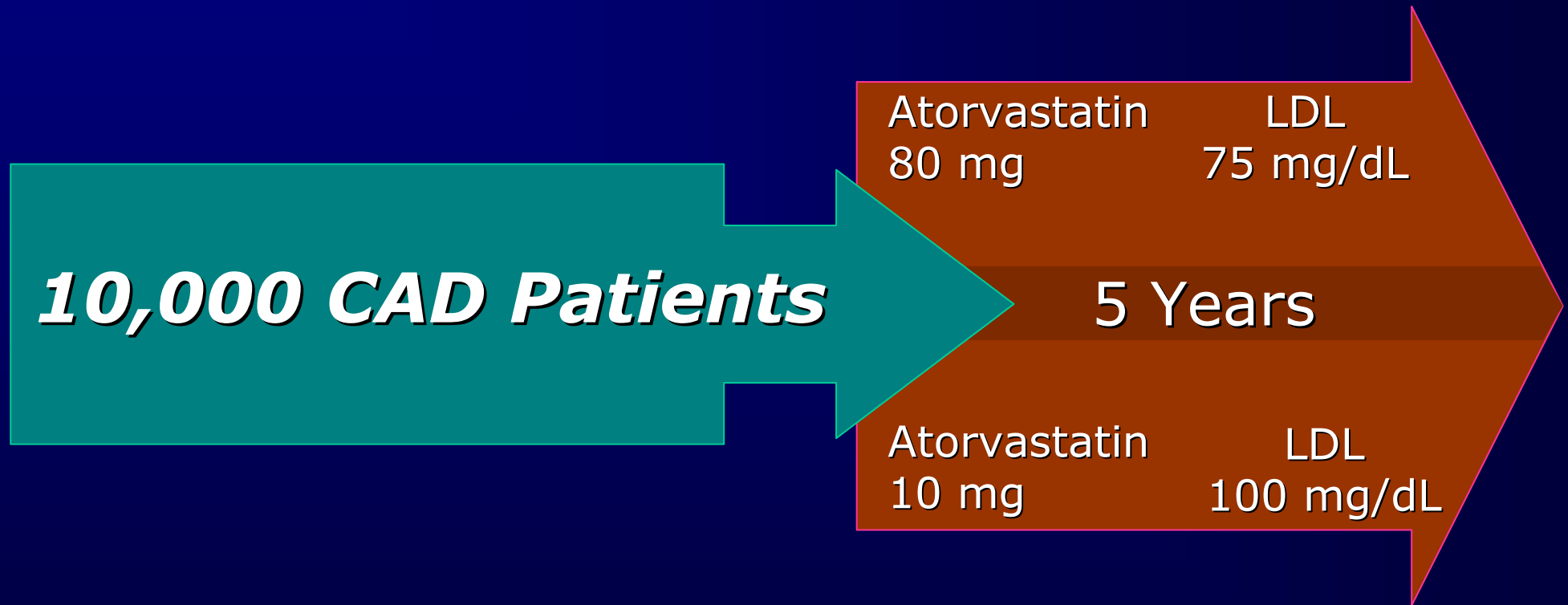


LDL-C=low-density lipoprotein cholesterol; CHD=coronary heart disease; TNT=Treating to New Targets; HPS=Heart Protection Study; CARE=Cholesterol and Recurrent Events Trial; LIPID=Long-term Intervention with Pravastatin in Ischaemic Disease; 4S=Scandinavian Simvastatin Survival Study.

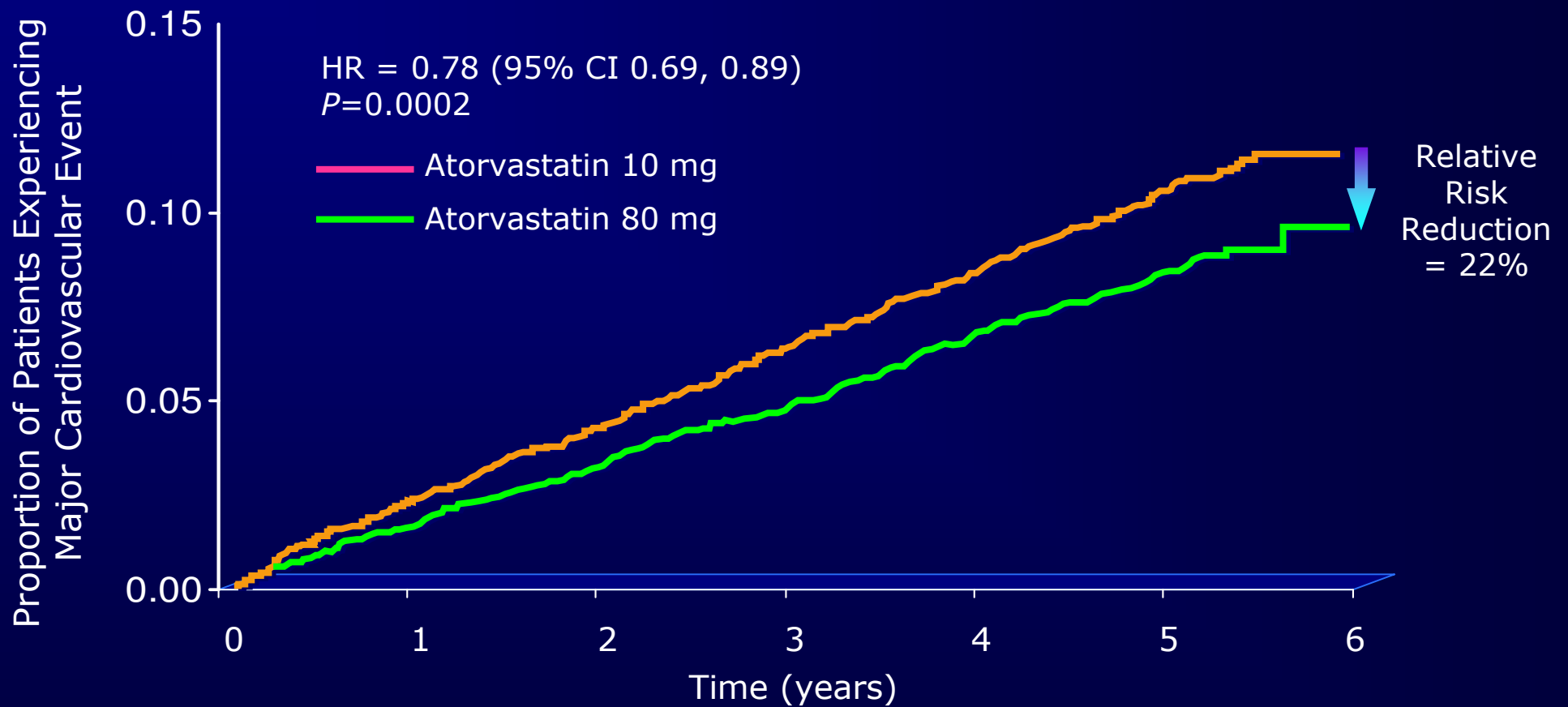
Meta-Analysis of Intensive Statin Therapy Coronary Death or MI



Endpoint Studies: Treating to New Targets (TNT): Study Design

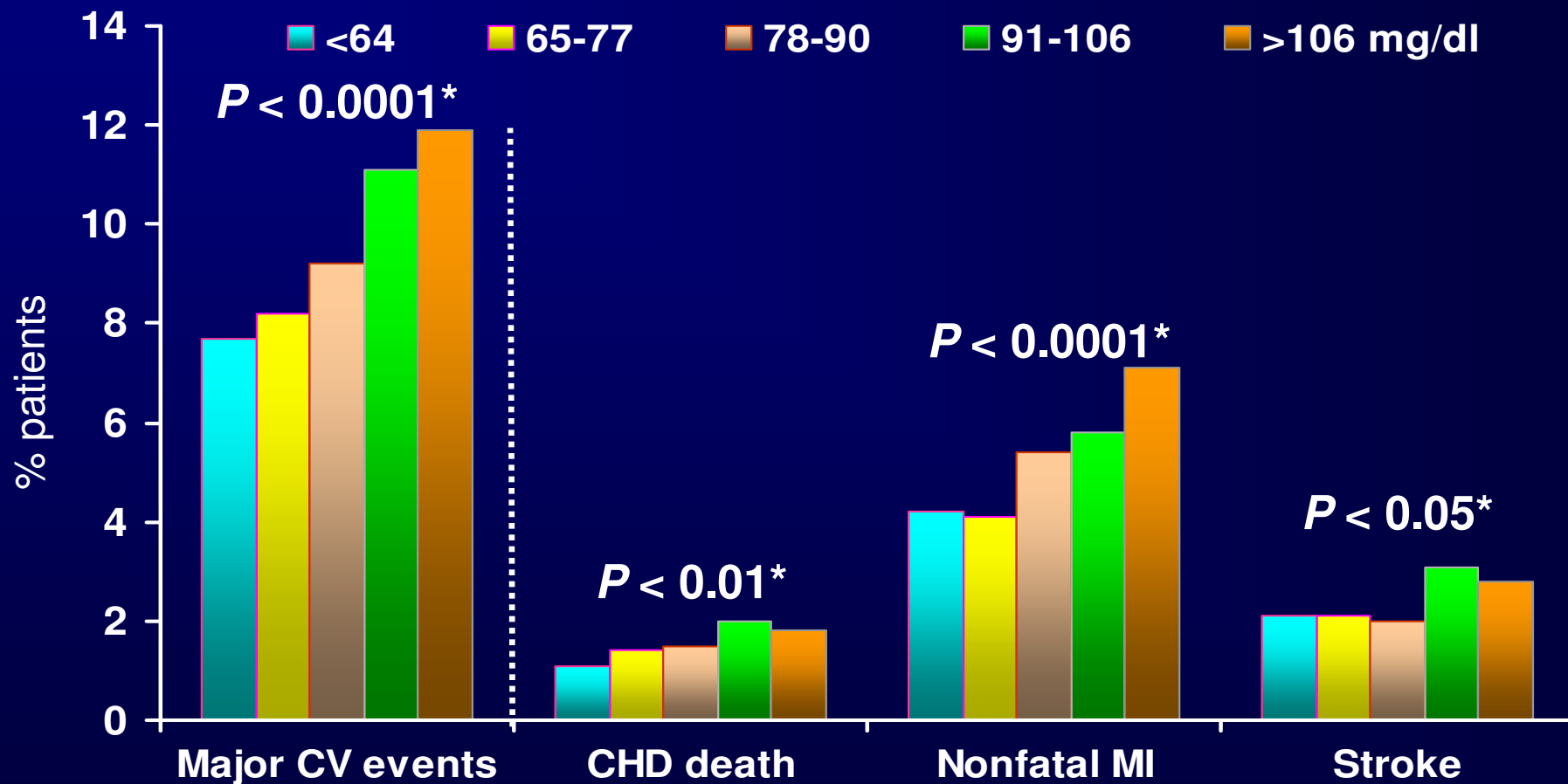


Treating to New Targets (TNT): Primary Efficacy Outcome Measure First Major Cardiovascular Event*



* Coronary heart disease death, nonfatal non-procedure-related myocardial infarction, resuscitated cardiac arrest, fatal or nonfatal stroke

Major CV Events Across Quintiles of Achieved LDL



*P-value for trend across LDL-C

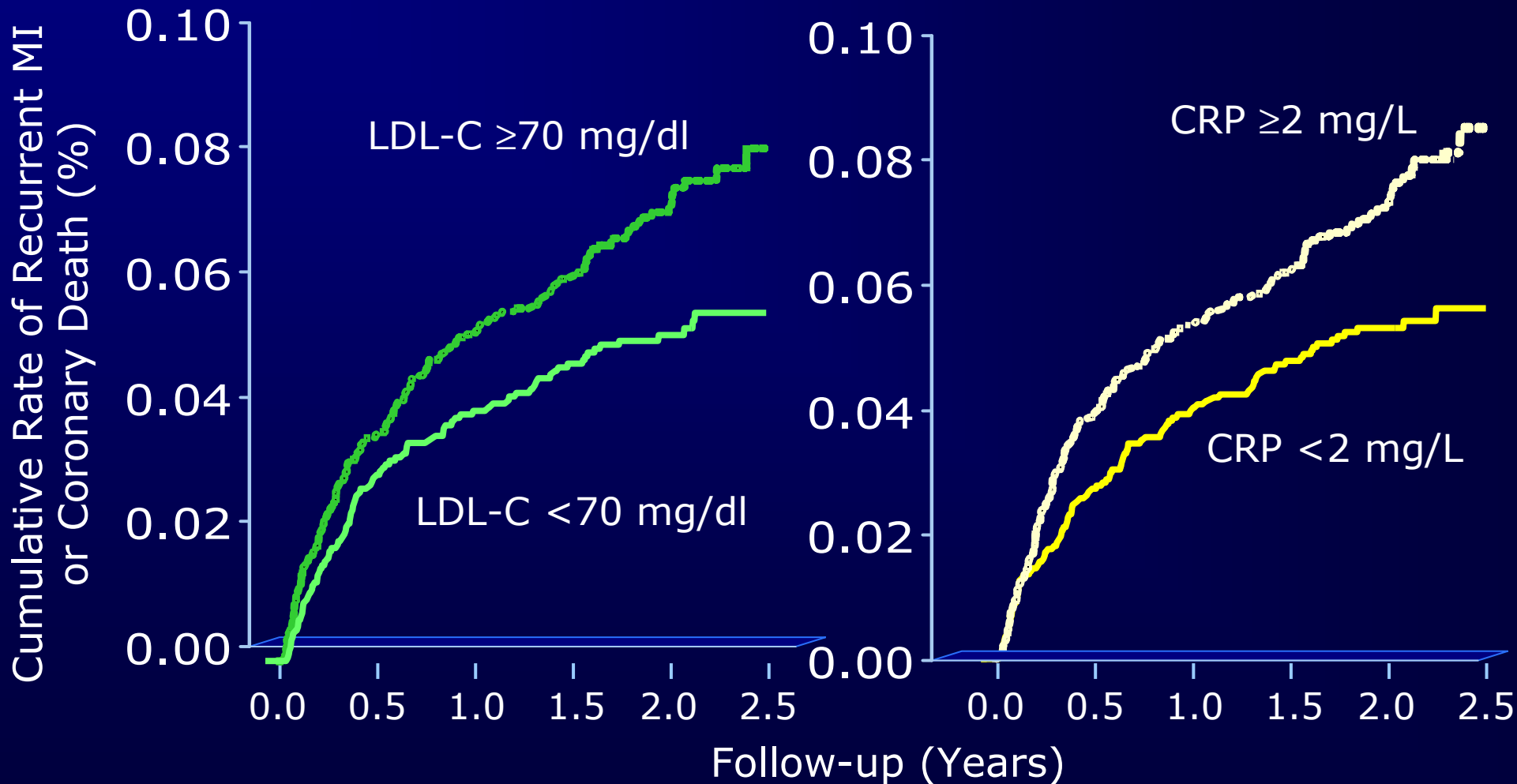
Relative Risks of Recurrent Coronary Events following Treatment with Statin Therapy, according to Achieved LDL-C and Achieved CRP Levels: PROVE IT–TIMI 22

	Quartile				P
	1	2	3	4	
Achieved LDL-C, mg/dl	<54	54–71	72–94	>94	
Age-adjusted	1.0	1.1	1.3	1.8	<.001
Risk factor–adjusted*	1.0	1.1	1.3	1.7	<.001
Achieved CRP, mg/L	<0.9	0.9–1.9	2.0–4.2	>4.2	
Age-adjusted	1.0	1.5	1.5	1.9	<.001
Risk factor–adjusted*	1.0	1.5	1.4	1.8	<.001

*Adjusted for age, sex, smoking status, diabetes, hypertension, and BMI.

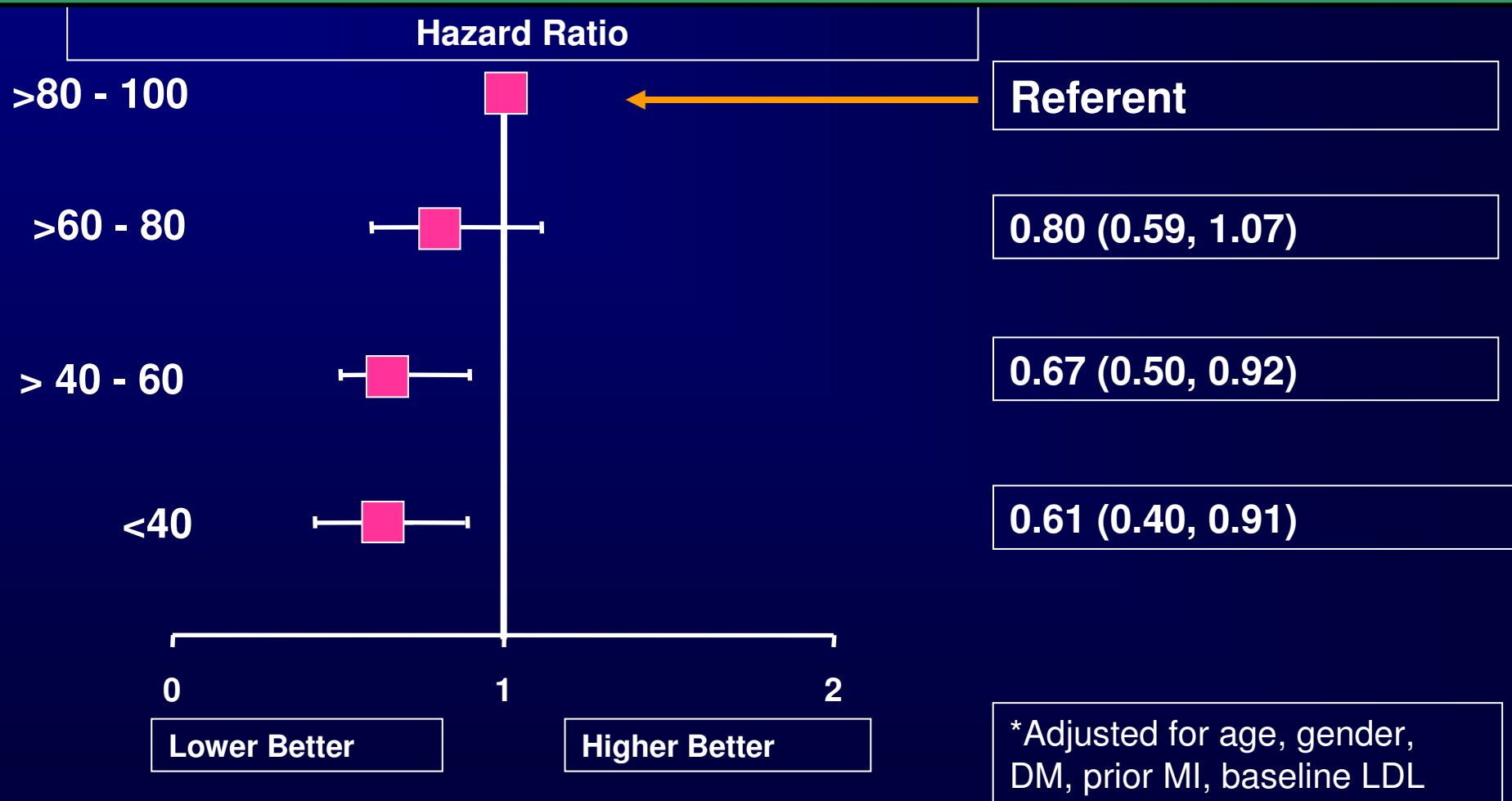
No change in results with additional adjustment for Killip class, peak level of creatine kinase, and use or nonuse of early revascularization.

Clinical Relevance of Achieved LDL-C and Achieved CRP after Treatment with Statin Therapy: PROVE IT-TIMI 22



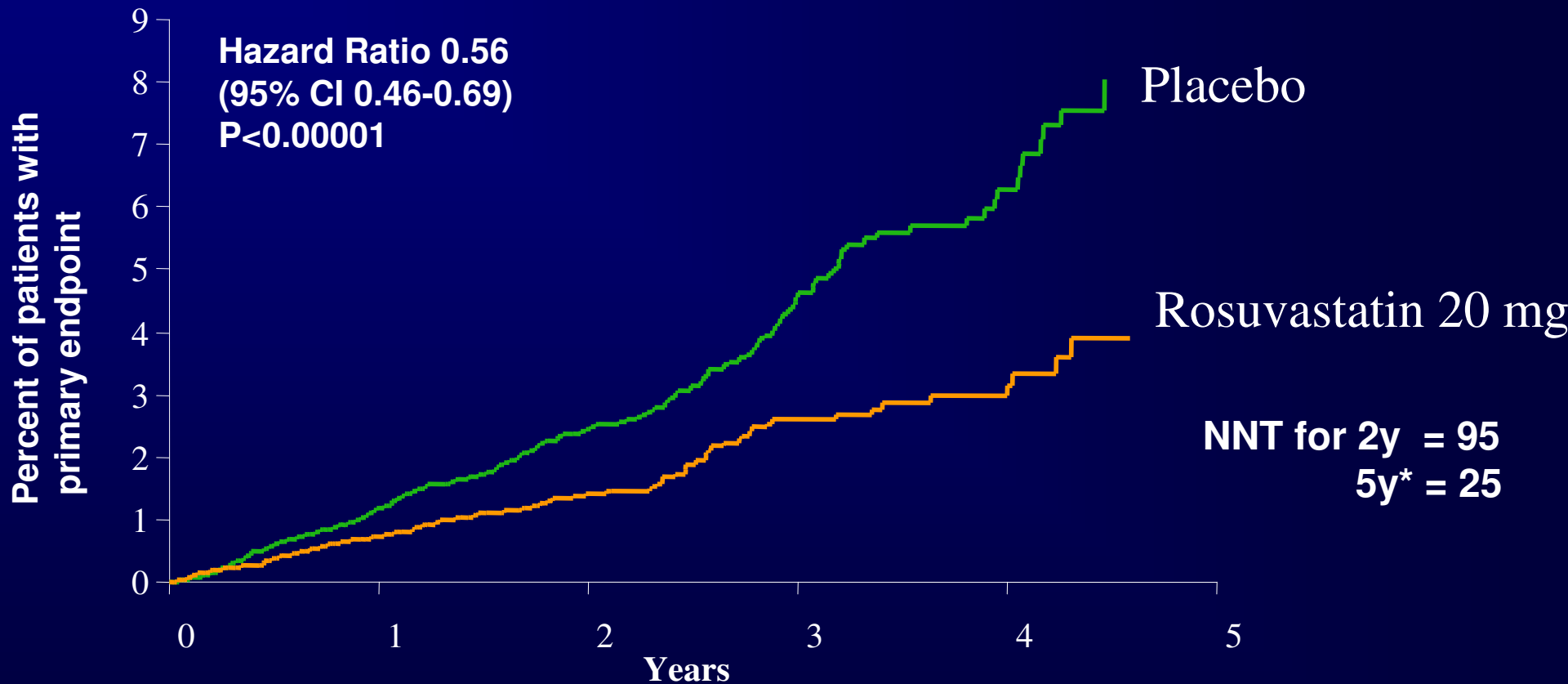


Month 4 LDL and Long-Term Risk of Death or Major CV Event



JUPITER - Primary Endpoint

Time to first occurrence of a CV death, non-fatal stroke, non-fatal MI, unstable angina or arterial revascularization



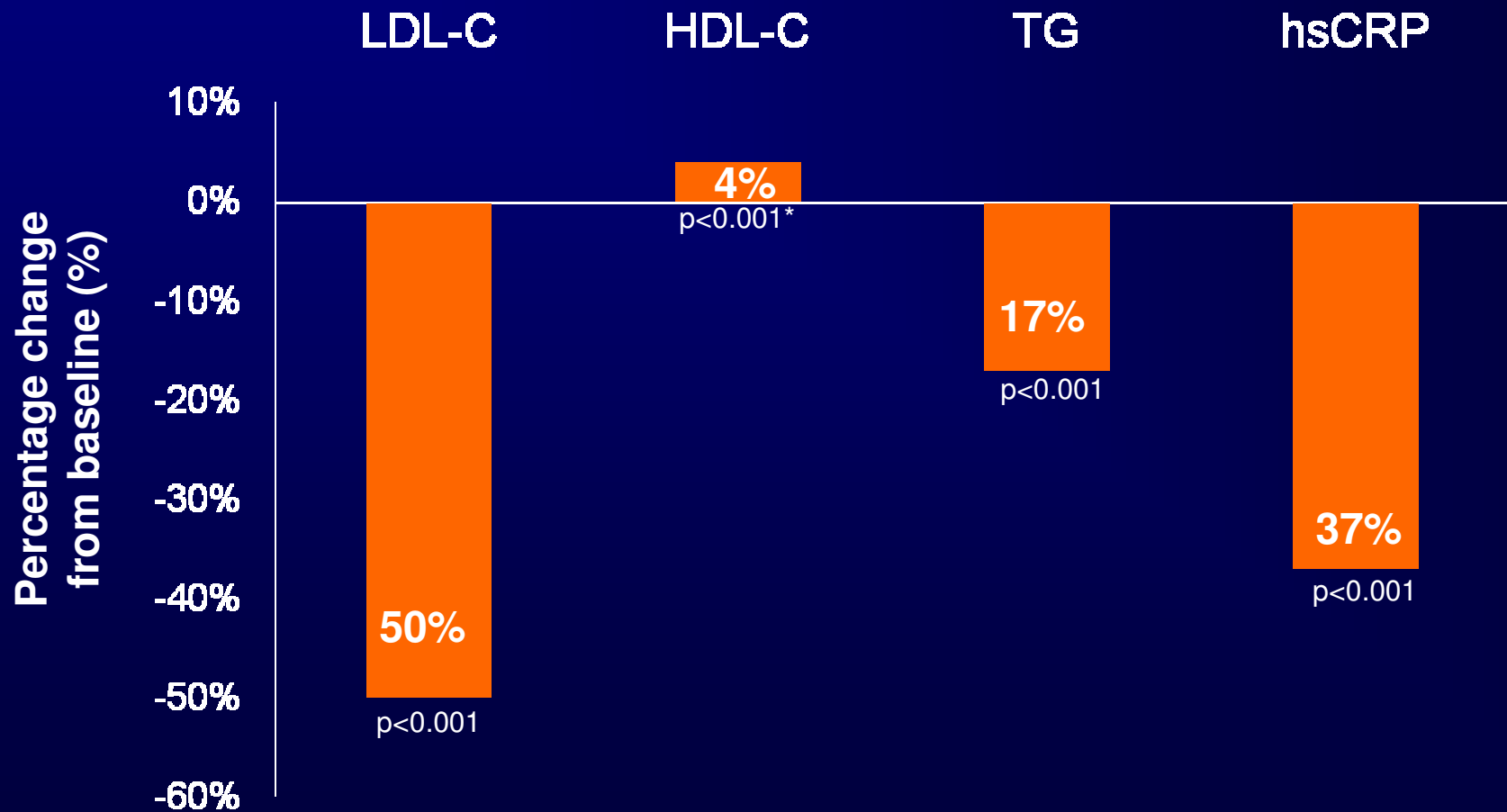
Number at risk

RSV	8901	8412	3893	1353	538	157
Placebo	8901	8353	3872	1333	531	174

*Extrapolated figure based on Altman and Andersen method

JUPITER

Effects on LDL-C, HDL-C, TG and hsCRP at 12 months;
Percentage change between rosuvastatin and placebo



*P-value at study completion (48 months) = 0.34

Ongoing Clinical Trials Of LDL-Lowering

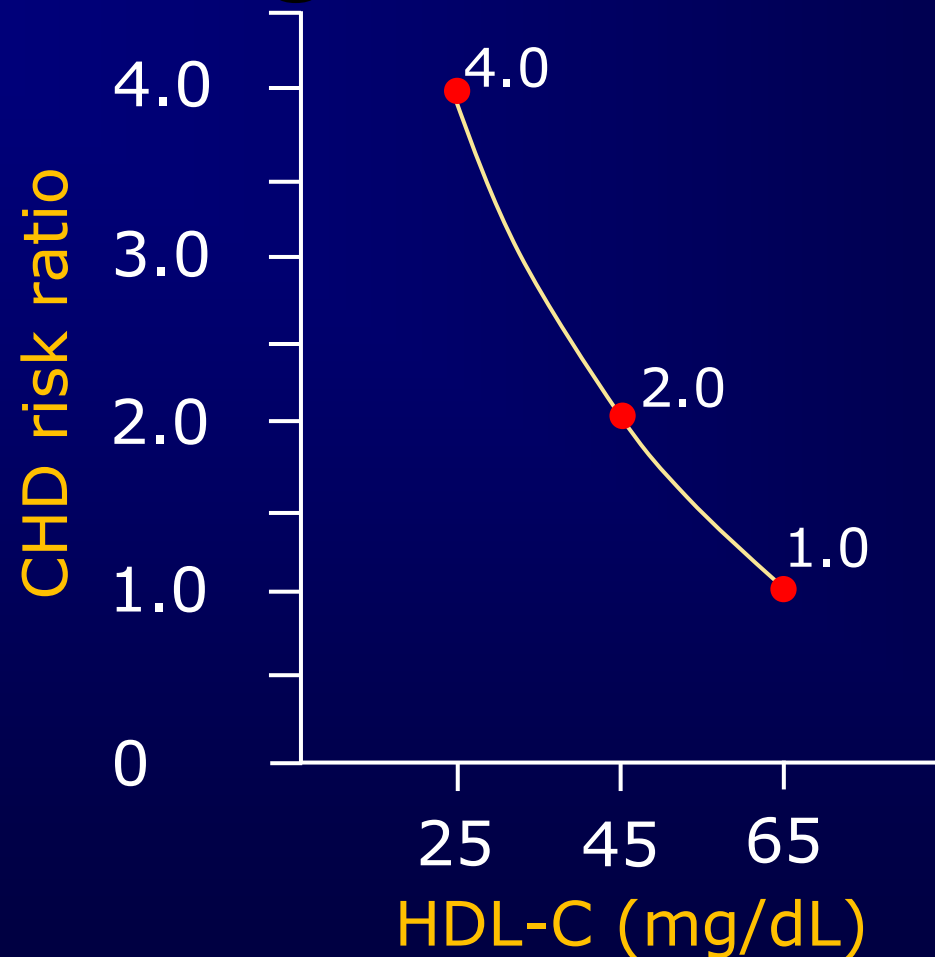
- **IMPROVE IT:** Improved Reduction of Outcomes: Vytorin Efficacy International Trial

Patient

- A 48-year-old overweight male with family hx of CAD and hypertension comes to you with known CAD, s/p stent placement for angina, seeking your advice.
- **Pre-Rx Lipids:** LDL-C: 125 mg/dL, HDL-C: 33 mg/dL, and TG: 185 mg/dL. You start atorvastatin 20 mg.
- **6-week follow-up:** TC: 155 mg/dL, LDL-C: 88 mg/dL, HDL-C: 36 mg/dL, TG: 160 mg/dL, non HDL-C 120 mg/dL.

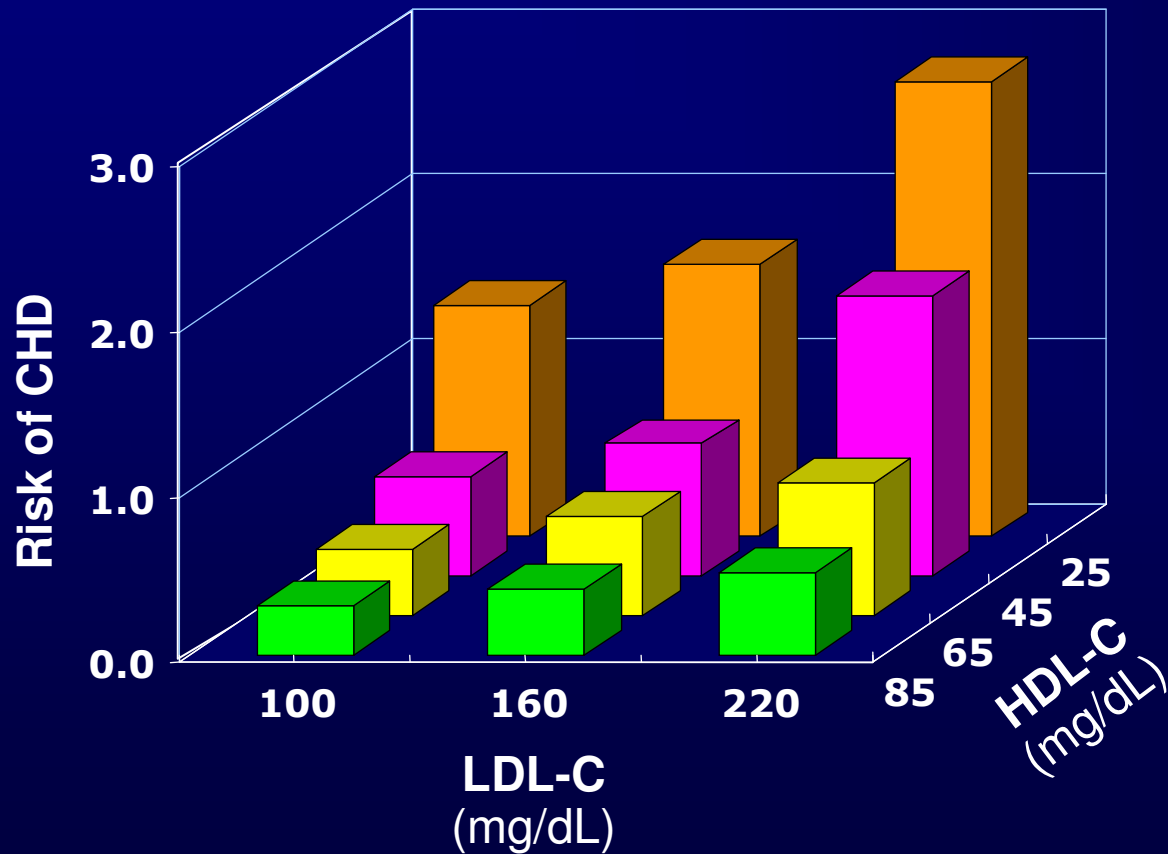
NCEP Targets: LDL-C <100, TG <200, non HDL-C <130mg/dL, HDL-C *Not Specified*

CHD Risk According to HDL-C Framingham Heart Study



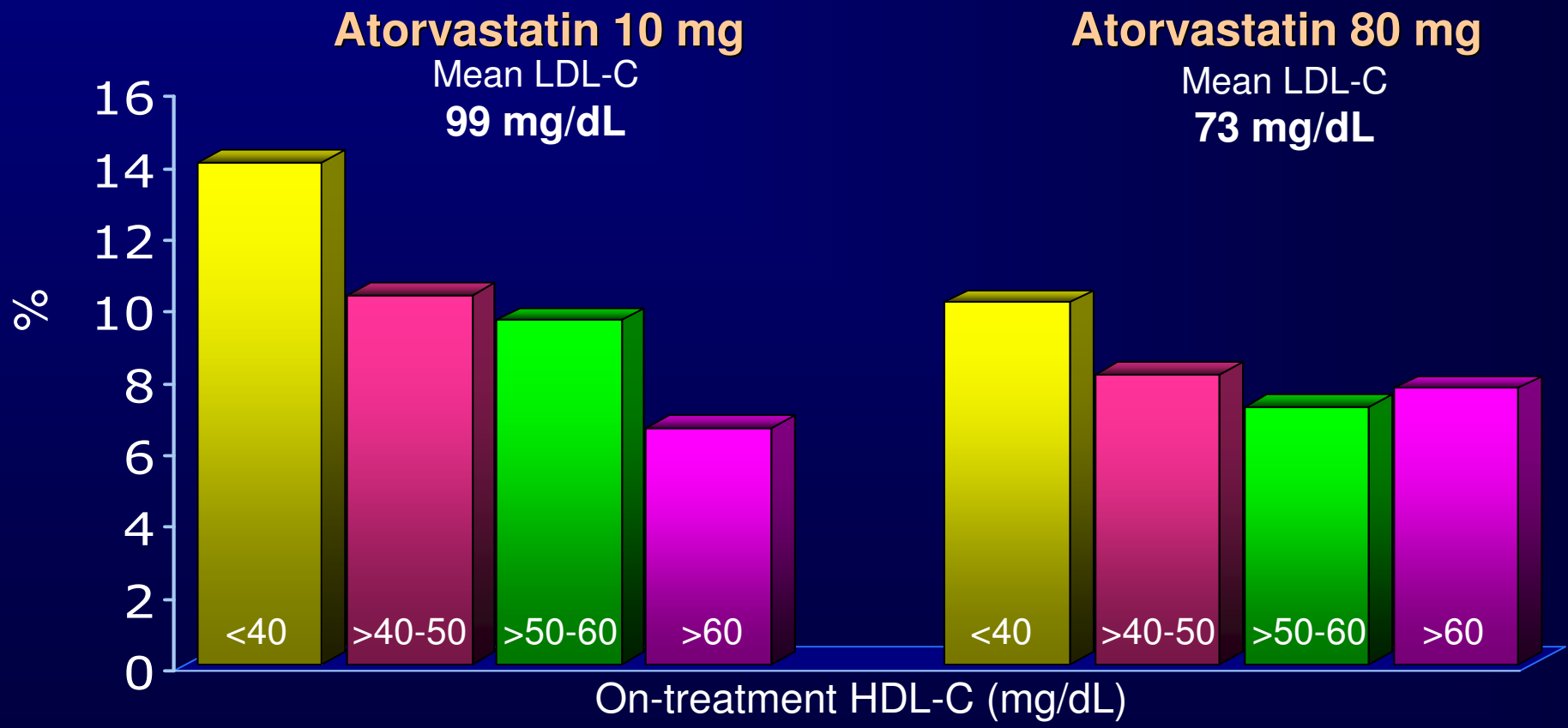
CV Risk: HDL-C and LDL-C Interaction

Data From Framingham Study



- For any level of LDL-C, HDL-C is inversely related to CHD risk
- Rule of 1's
 - For every 1% shift in HDL-C or LDL-C, event rates are ~1% lower

Major Cardiovascular Events According to On-treatment HDL-C: Treating to New Targets (TNT) Trial

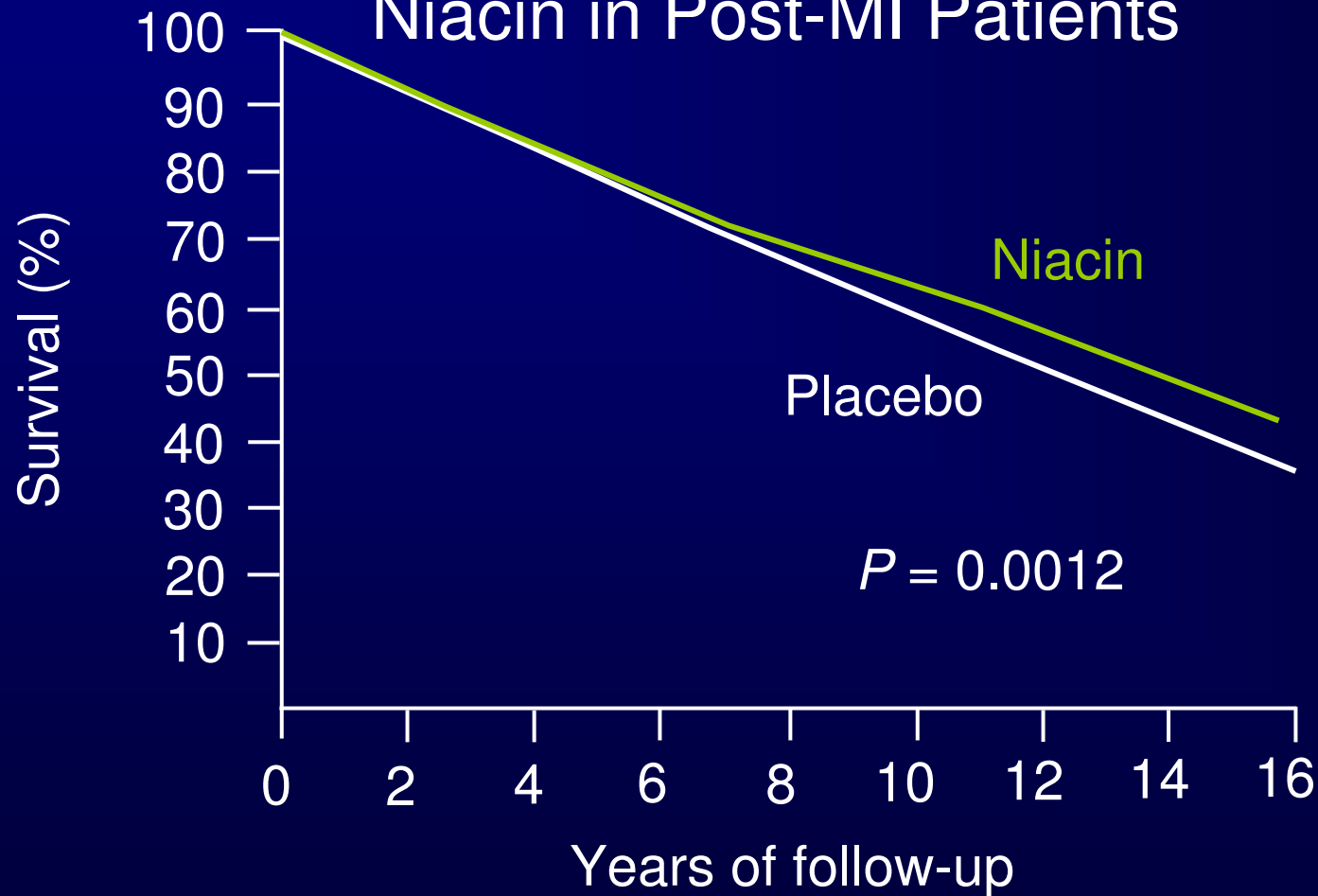


Coronary Drug Project

- Long-term efficacy and safety of five lipid-influencing drugs
 - Niacin, clofibrate, dextrothyroxine, and two estrogen regimens
- 8,341 men (aged 30–64 y) with previous MI
- Initial study conducted between 1966 and 1975 (mean follow-up: 6.2 y)
- At end of study, 6,008 survivors followed for additional mean 8.8 y

Coronary Drug Project

Long-Term Mortality Benefit of Niacin in Post-MI Patients



HDL Atherosclerosis Treatment Study: HATS

Simvastatin Plus Niacin versus Placebo

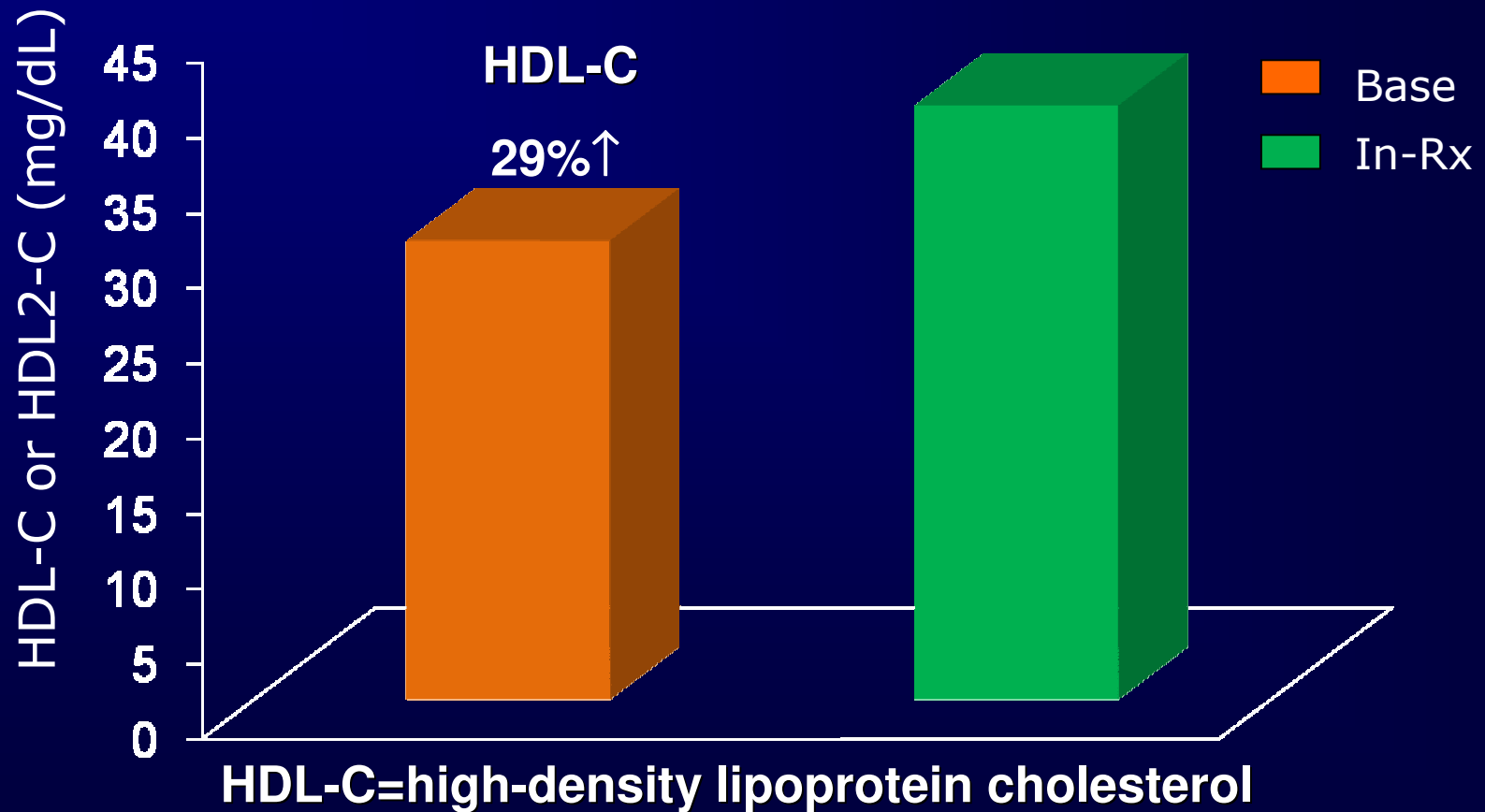
Baseline Characteristics:

- 160 patients with clinical and angiographic CAD, mean HDL-C: 31 mg/dL, LDL-C: 127 mg/dL, and TG: 202 mg/dL, age: 53.

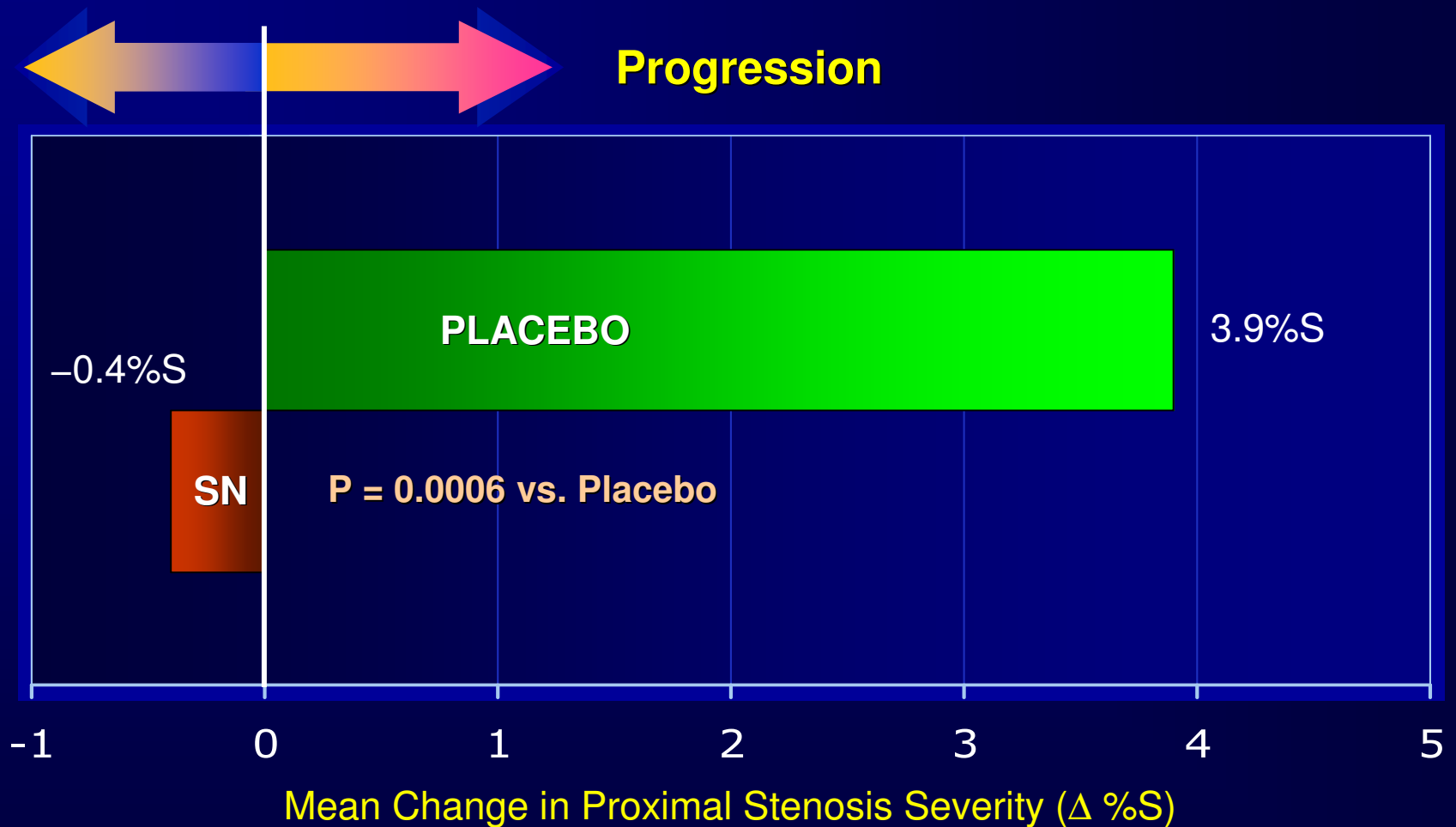
On-Treatment Results:

- Lipid and lipoprotein response
- Coronary stenosis changes (by quantitative coronary angiography)
- Clinical endpoint reduction

HATS: HDL-C Response to Niacin Plus Simvastatin



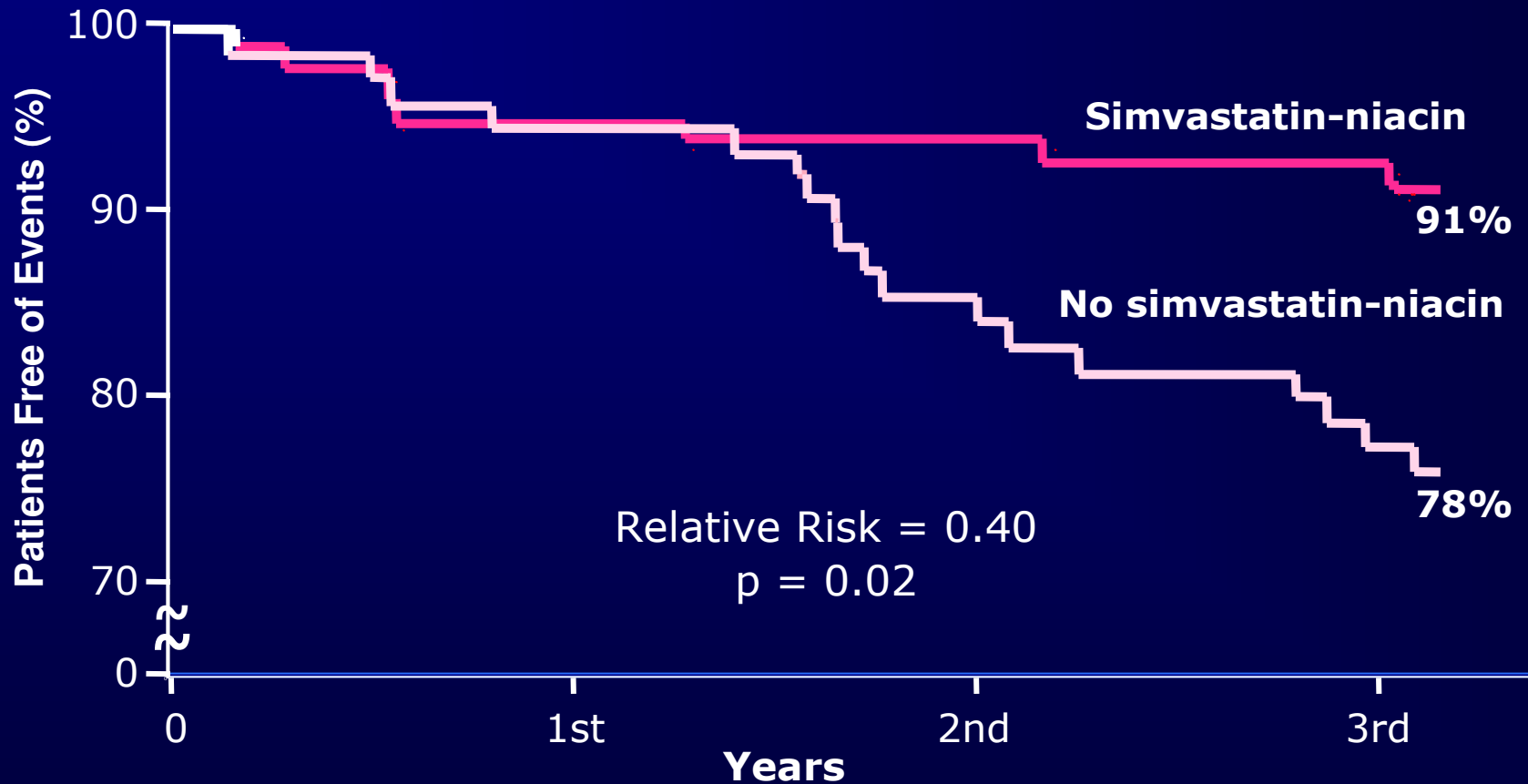
HATS QCA Results



HATS=HDL-atherosclerosis treatment study; QCA=quantitative coronary angiography; Reg'n=regression;
SN=simvastatin and niacin

HATS: *Primary Clinical Endpoint*

CAD Death, Non-fatal MI, Stroke or Revascularization



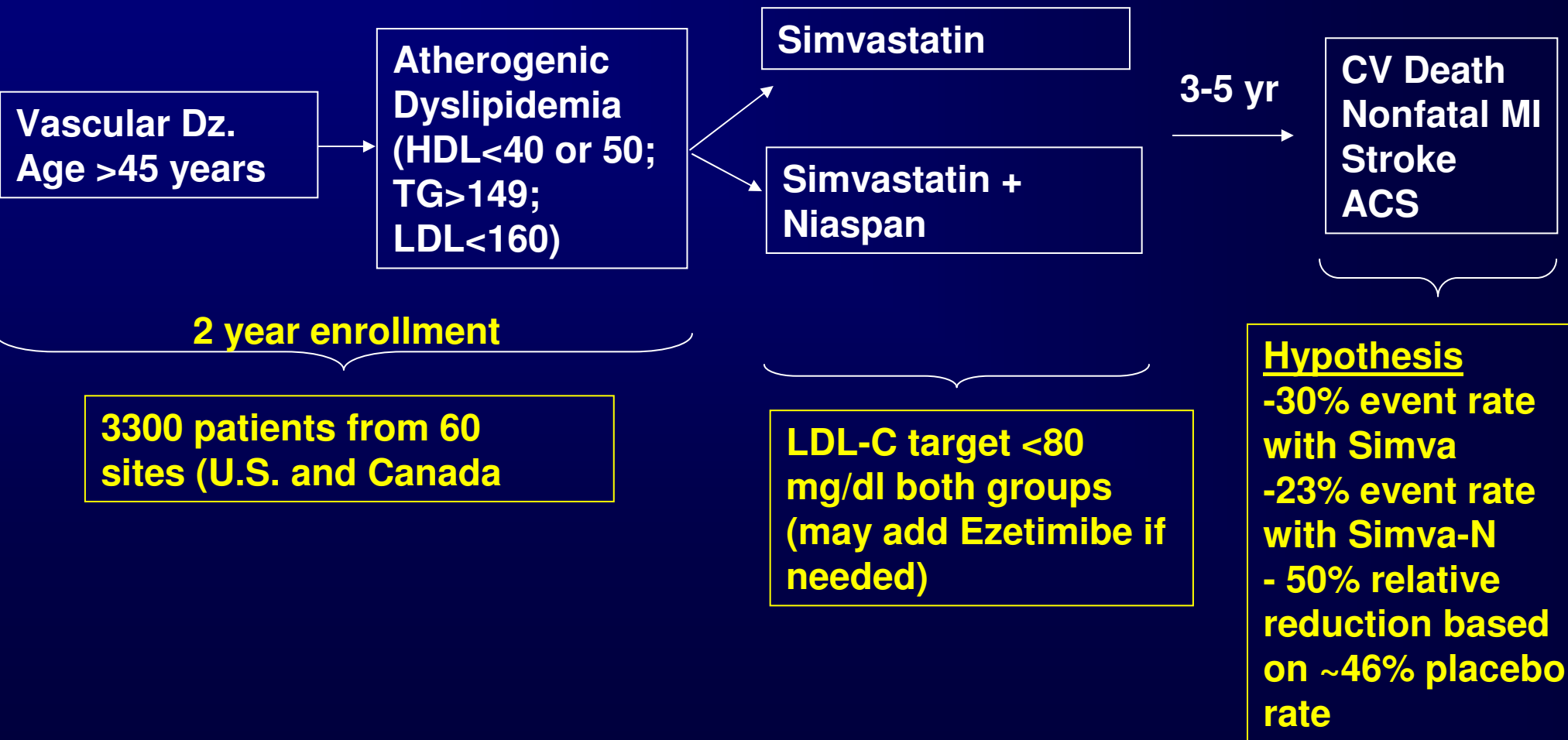
Summary: Niacin plus Statin

- Exceeds statin effects on LDL, HDL, TG, and LDL particle size/density
- Stops stenosis progression
- Magnitude of benefits predicted by epidemiology, (% HDL-C and % LDL-C change), and supported by 23-trial meta-analysis
- Clinical proof: 2010

Ongoing Outcomes Trials of Combined LDL-C Lowering and HDL-C Raising

Study	Sponsor	Rx vs. Control	N total*	\$ total (mil)*	Median Follow	Finish Year*
ACCORD	NIH & Pharma	Feno + St vs. Statin	5900	300 M	5.6 years	Q3-'09
AIM-HIGH	NIH & Kos	Nia + Sim vs. Sim	3300	42 M	4.0 years	Q3-'10
HPS-THRIVE	Merck, USA	Nia + Sim + Fl† vs. Sim	20000	????	4+ years	Q4-'12

AIM-HIGH Study Overview



CETP Inhibition with Torcetrapib: Cardiovascular Events and mortality in the ILLUMINATE trial at termination of the trial on Dec 02, 2006

Atorvastatin Group=A (n=7534)
Torcetrapib/Atorvastatin Group=T/A (n=7533)

Compared to A, T/A increased HDL-C by 72% and reduced LDL-C by 25%

	A	T/A	
Major cardiovascular events	373	464	(p=0.001)
Deaths	59	93	(p=0.006)

Lipid Monotherapy Options: Clinical and Lipid Outcomes

Drug Class	CV Event Reduction (%)	LDL-C Decrease (%)	HDL-C Increase(%)
Statins	25% - 35% (4S, CARE, LIPID)	+++++	+ 5%
Niacin	16% - 35% (CDP, Stockholm)	++	+++++ 30%
Fibrates	11% - 24% (FIELD, VA-HIT)	+	++ 10%
Torcetrapib	61%↑	+	+++++ 40%

Conclusions

- In high risk patients, An LDL target of <60 mg/dL is feasible and safe and associated with the best cardiovascular results. We should shoot for this target
- Statin therapy should be maximized prior to adopting other therapies; HOW WE GET TO TARGET IS IMPORTANT. Hold on for IMPROVE-IT
- HDL raising therapy is less established and the topic of exciting research and again, HOW WE GET TO TARGET IS IMPORTANT. Niacin is underutilized and the outcomes trials are coming