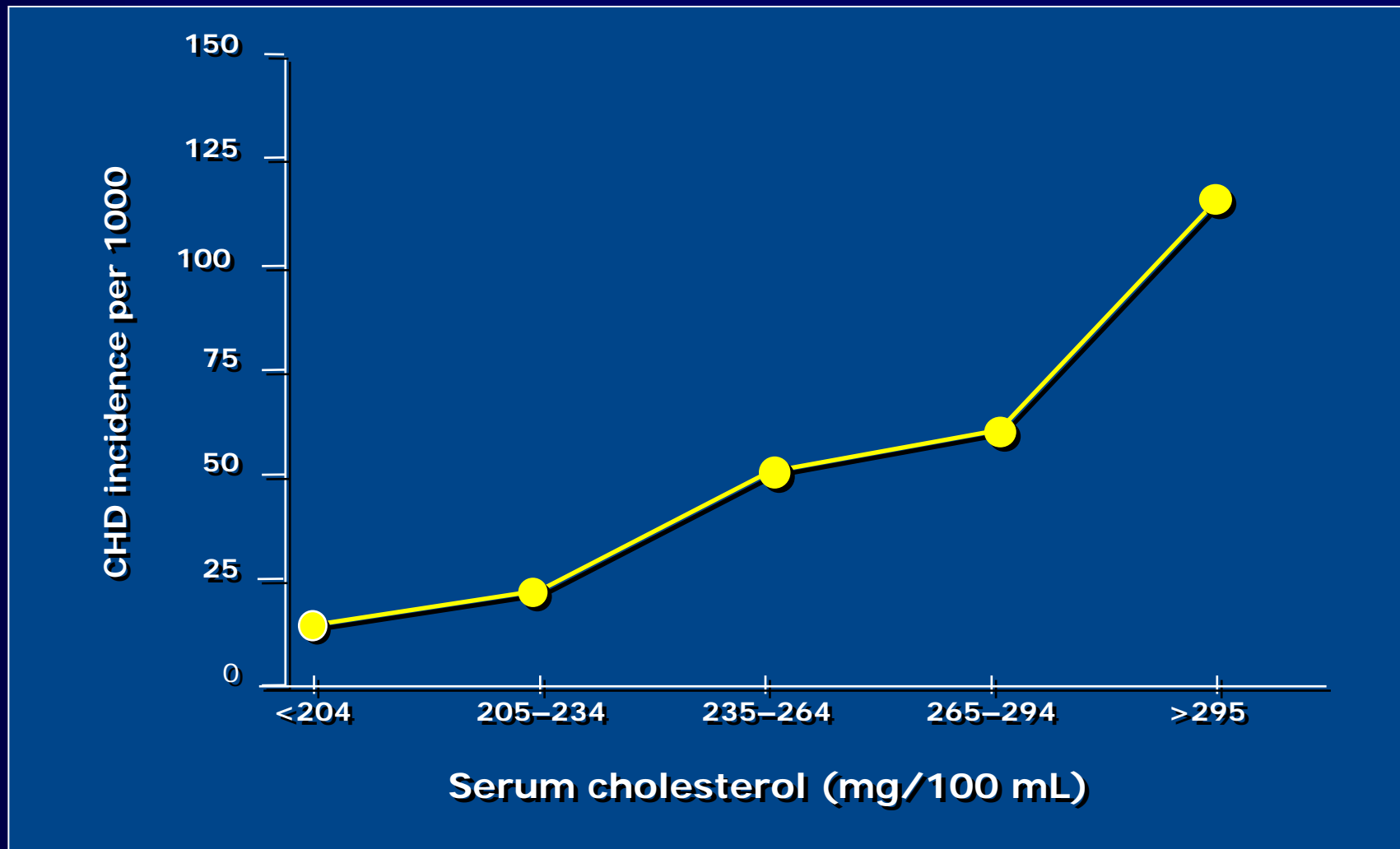


Cardiovascular Outcomes Through Statin Treatment

: Evidence based Outcomes

Dong-Ju Choi, MD, PhD
Cardiovascular Center
Bundang Hospital
Seoul National University

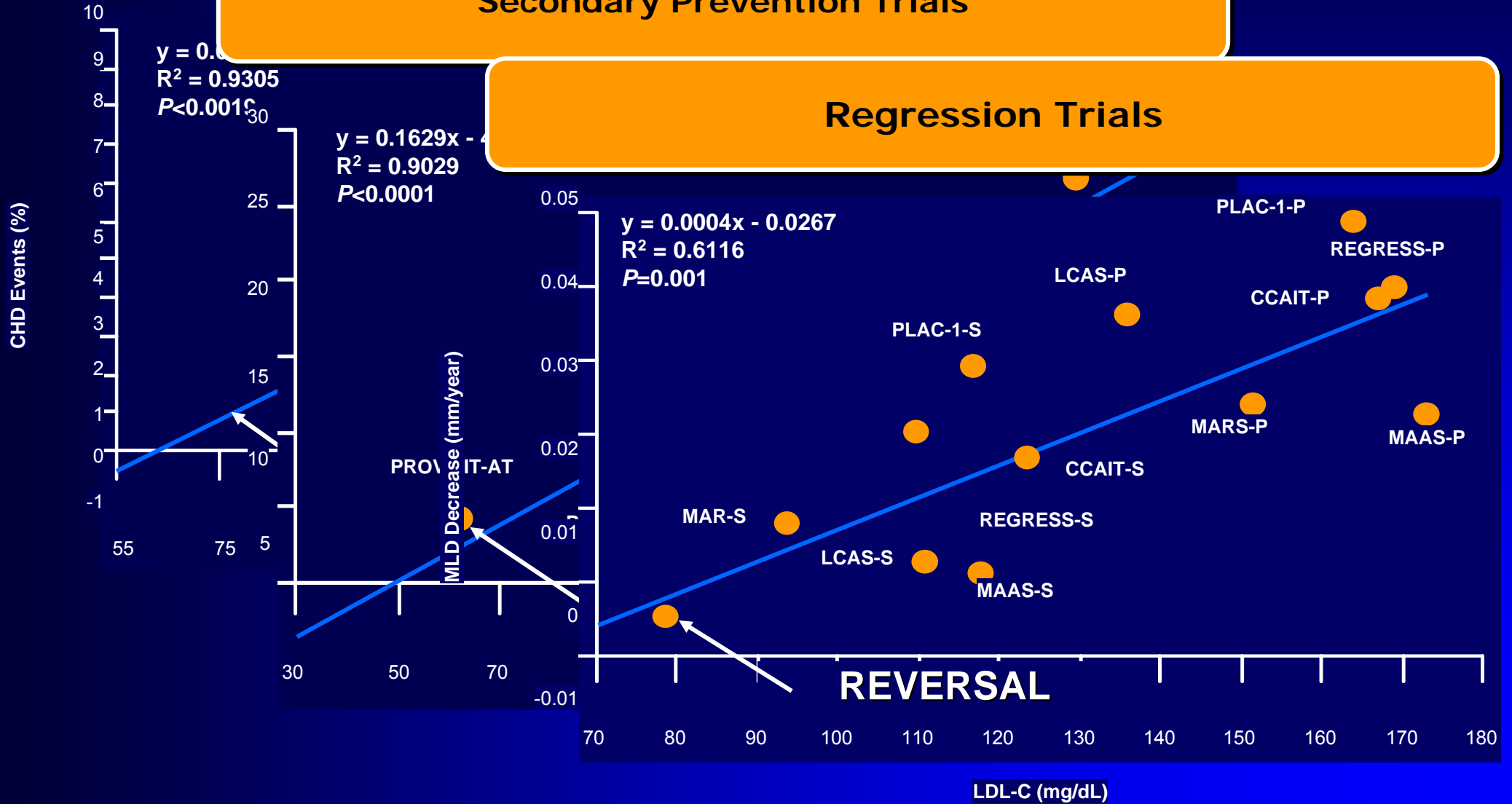
The Framingham Study: Relationship Between Cholesterol and CHD Risk



Primary Prevention Trials

Secondary Prevention Trials

Regression Trials

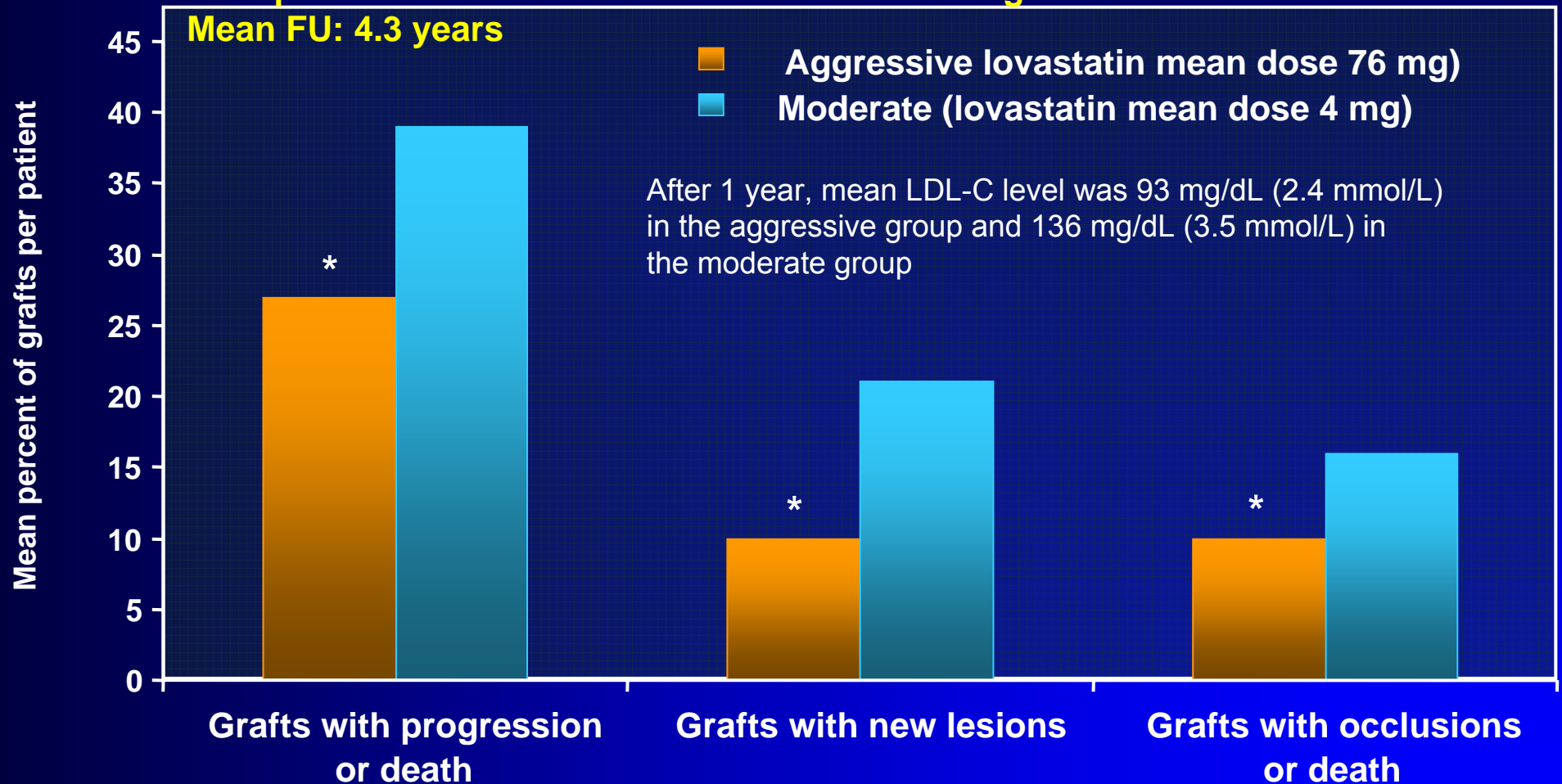


Why lower ?

Post CABG Trial: Aggressive Lipid Lowering Had More Favorable Outcomes Than Moderate Lipid Lowering

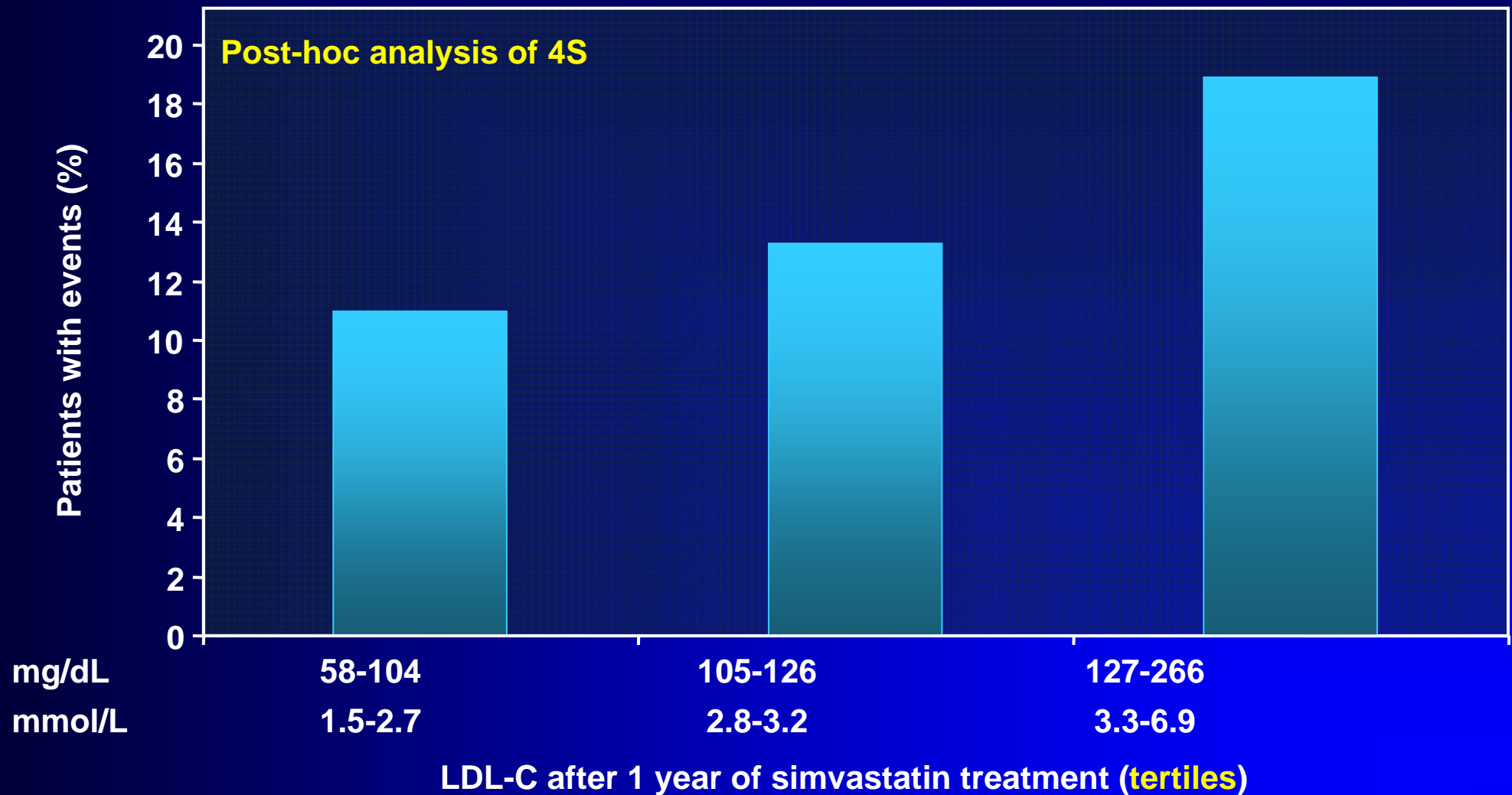
1351 patients with an LDL-C level of 130 to 175 mg/dL

Mean FU: 4.3 years



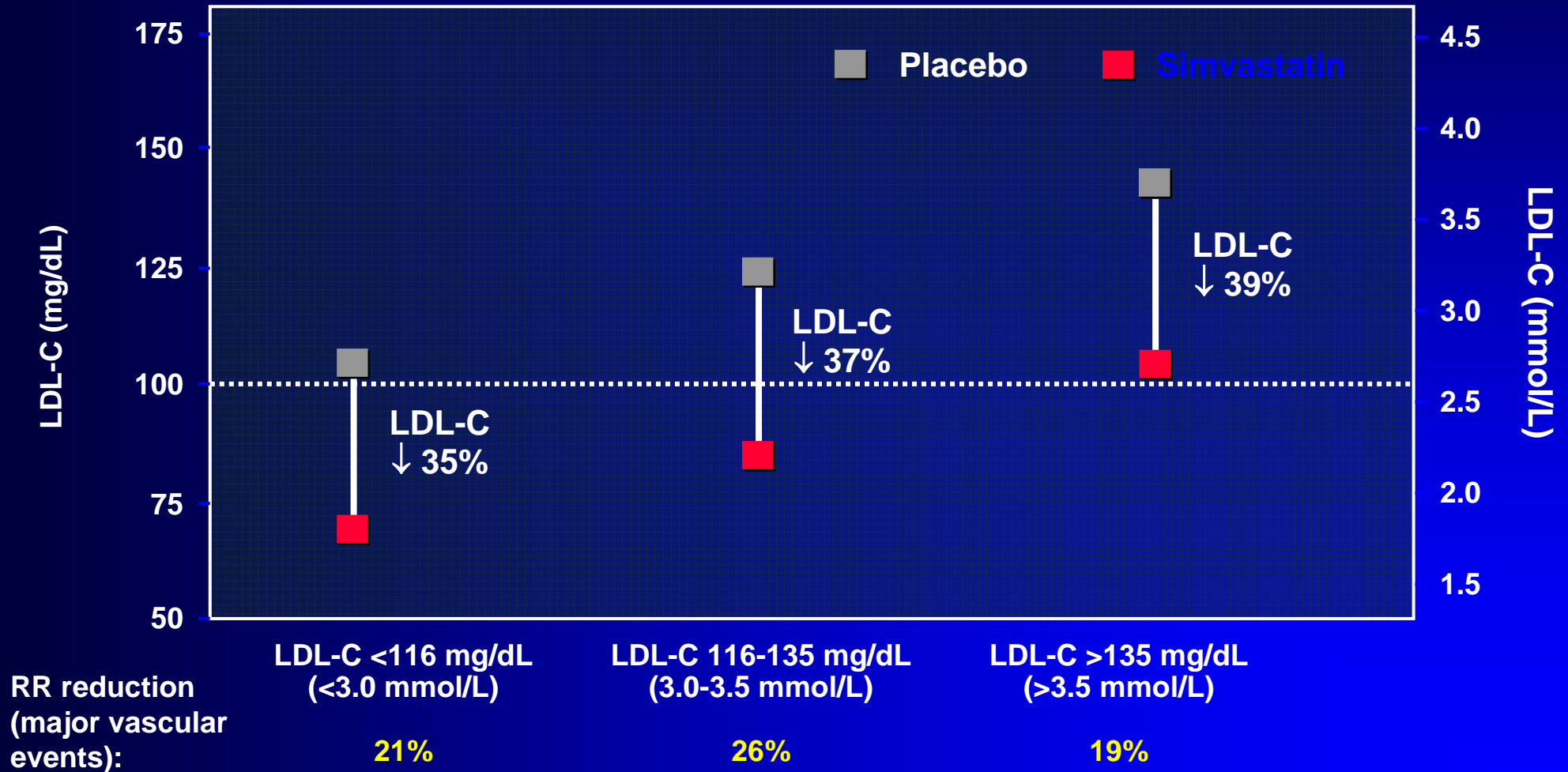
* $P \leq .001$ vs moderate therapy group

4S: Lower Cardiac Event Rates With Lower On-Treatment LDL-C



HPS: Decrease in Major Vascular Events Regardless of Baseline Cholesterol

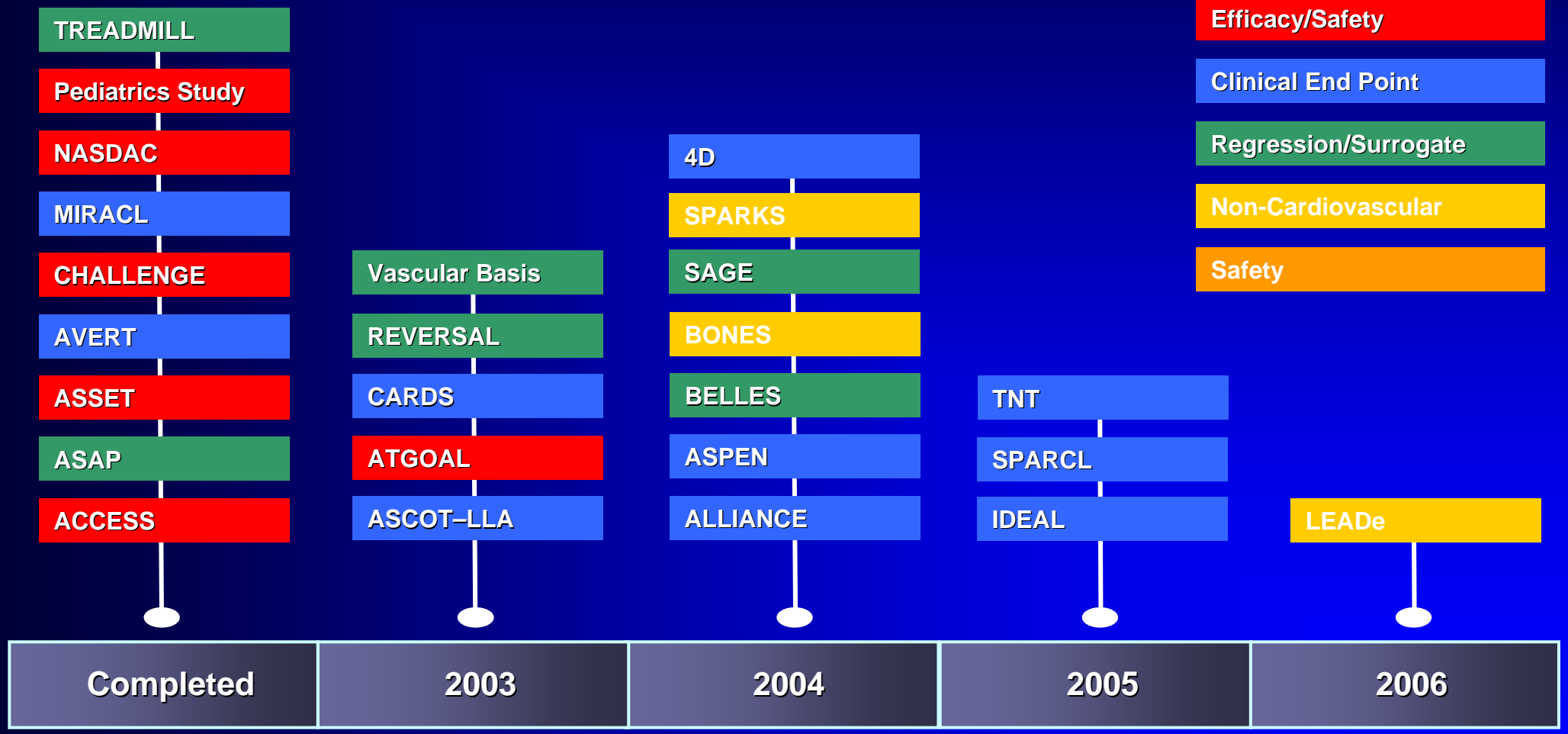
HPS LDL-C Subgroup Analysis



Prove the lower is the better
:Atorvastatin landmark studies

Key to Clinical Sections:

- Efficacy/Safety
- Clinical End Point
- Regression/Surrogate
- Non-Cardiovascular
- Safety



Intensive Lipid lowering : Consistent Clinical Benefits at On-Treatment LDL-C <100 with Atorvastatin

Study	Patient population	Follow-up LDL-C, mg/dL (mmol/L)		1 ^o end point reduction (%)	P-value
		Atorvastatin	Comparator		
2^o prevention					
PROVE-IT	ACS	62 (1.6)	95 (2.5) pravastatin	16*	.005
MIRACL	ACS	72 (1.9)	135 (3.5) placebo	16*	.048
ALLIANCE	CHD	95 (2.5)	110 (2.8) usual care	17 [†]	.02
AVERT	CHD	77 (2.0)	119 (3.1) angioplasty	36 [§]	.048
1^o prevention					
ASCOT	Hypertension	87 (2.3)	133 (3.5) placebo	36 [‡]	.0005
CARDS	Diabetes	68 (1.8)	119 (3.1) placebo	37 [†]	.001

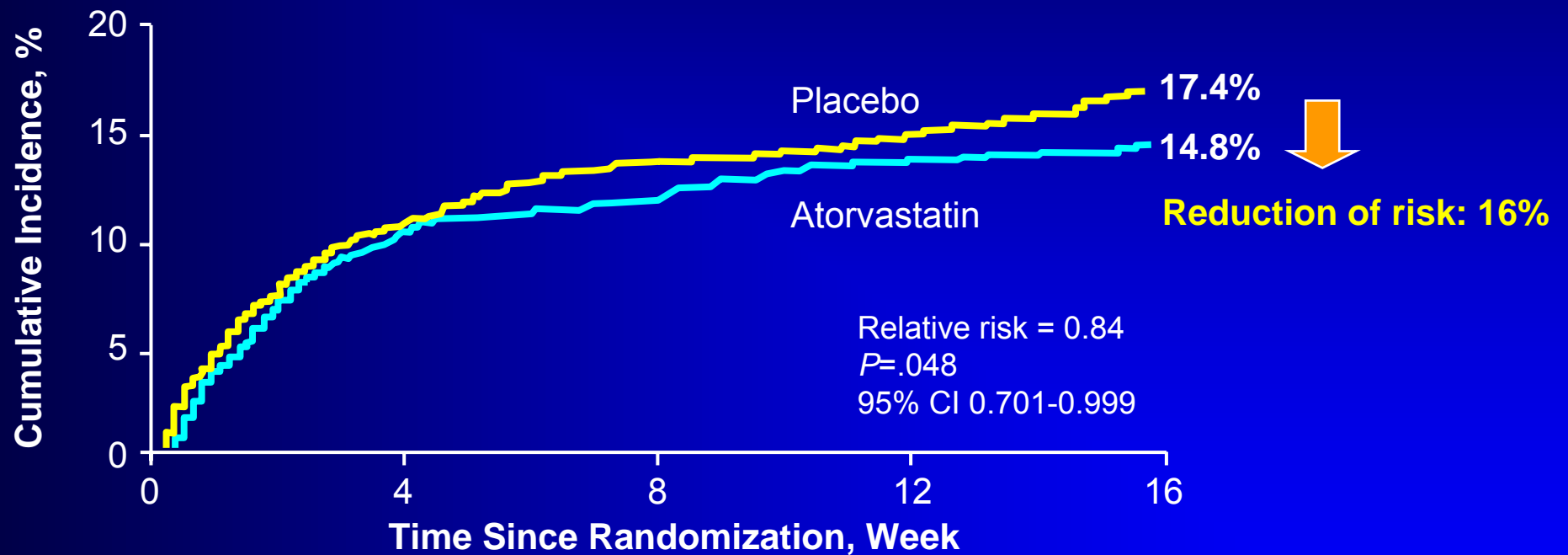
LDL-C values for PROVE-IT are medians; all other LDL-C values are means

* All-cause mortality + major CV event; † Major CV event; ‡ Nonfatal MI + fatal CHD; § Ischemic event

PROVE-IT: Cannon CP, et al. *N Engl J Med.* 2004;350:1495-1504; **MIRACL:** Schwartz GG, et al. *JAMA.* 2001;285:1711-1718; **ALLIANCE:** Koren MJ, et al. *J Am Coll Cardiol.* 2004;44:1772-1779; **AVERT:** Pitt B, et al. *N Engl J Med.* 1999;341:70-76; **ASCOT:** Sever PS, et al. *Lancet.* 2003;361:1149-1158; **CARDS:** Colhoun HM, et al. *Lancet.* 2004;364:685-696.

MIRACL: Myocardial Ischemia Reduction With Aggressive Cholesterol Lowering

Treatment With Atorvastatin 80 mg/dL Reduces Recurrent Ischemia Events in First 16 Weeks



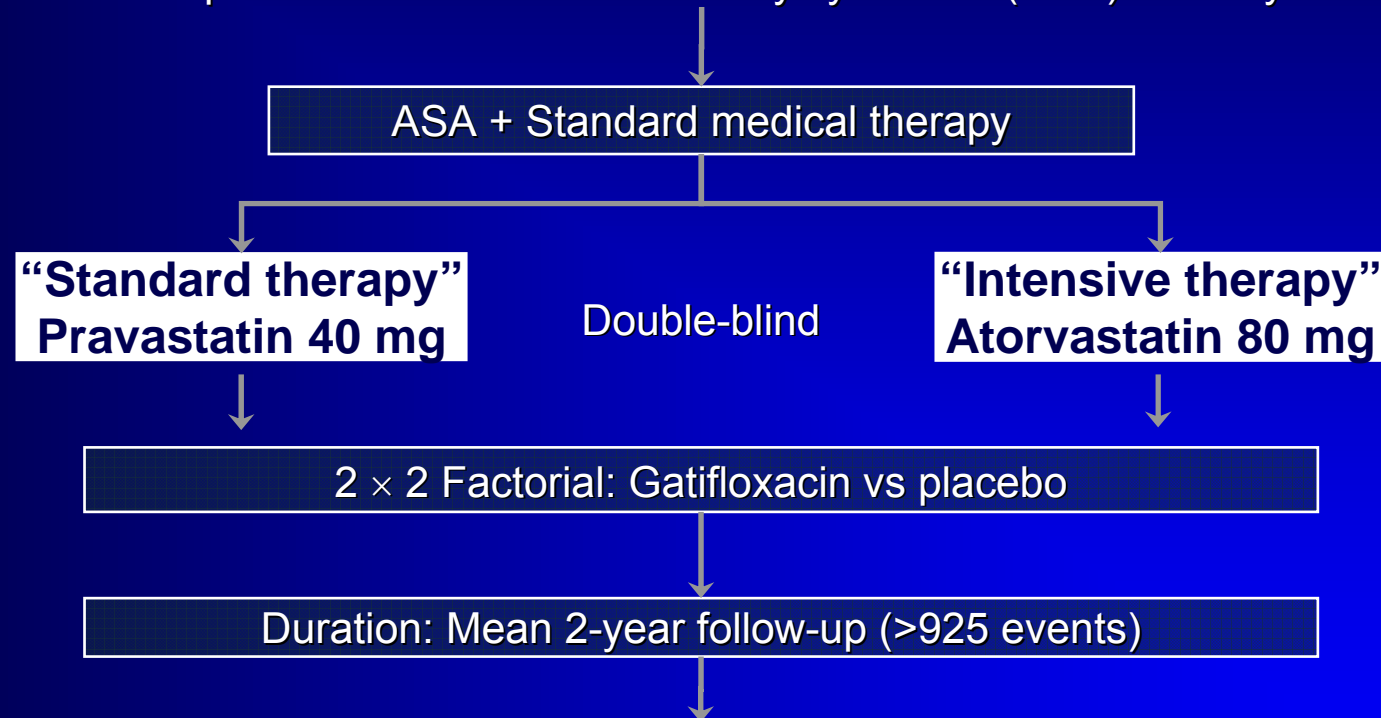
Number at Risk

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

PROVE-IT: Intensive Therapy Vs Standard Lipid-Lowering Therapy

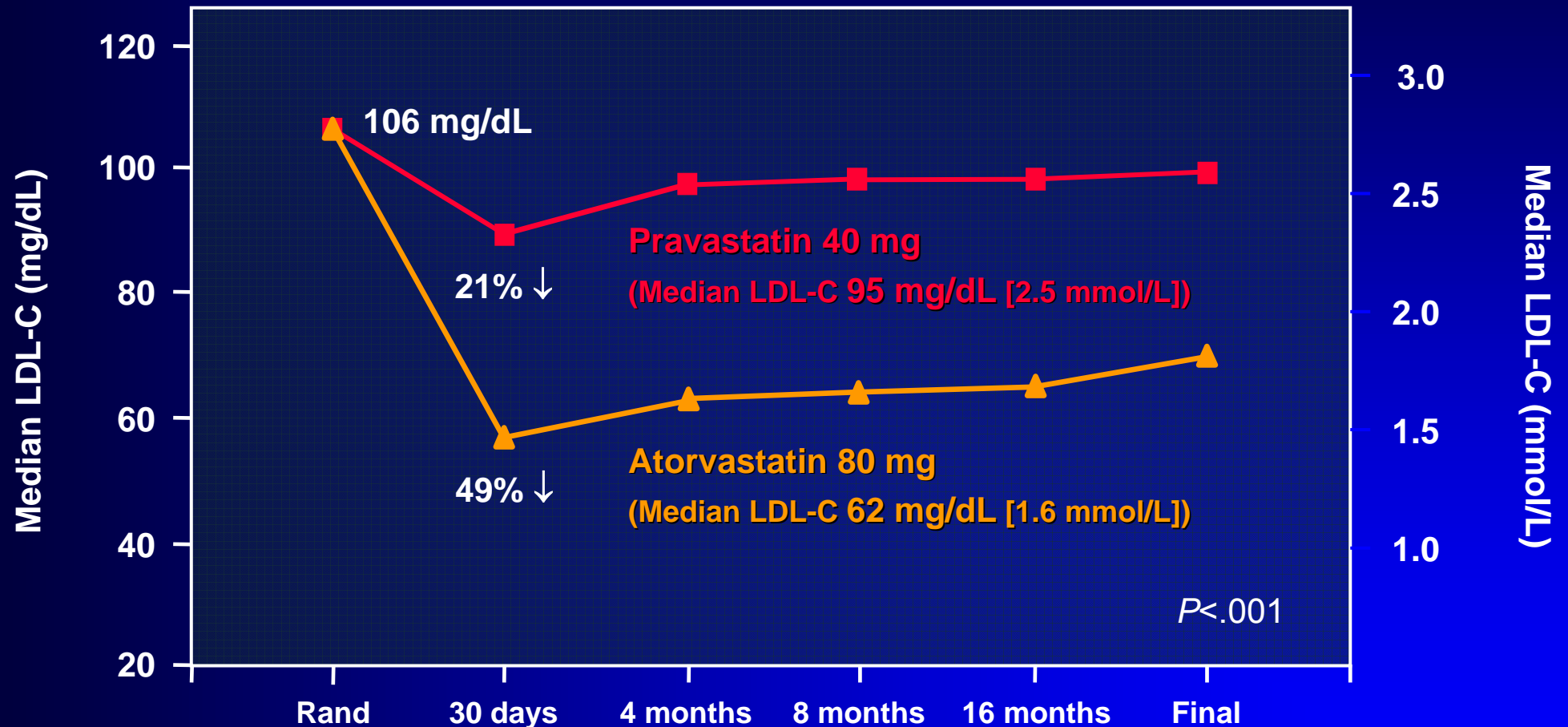
Study Design

4162 patients with an acute coronary syndrome (ACS) <10 days



Primary end point: Composite of death, MI, documented unstable angina requiring hospitalization, revascularization (>30 days after randomization), or stroke

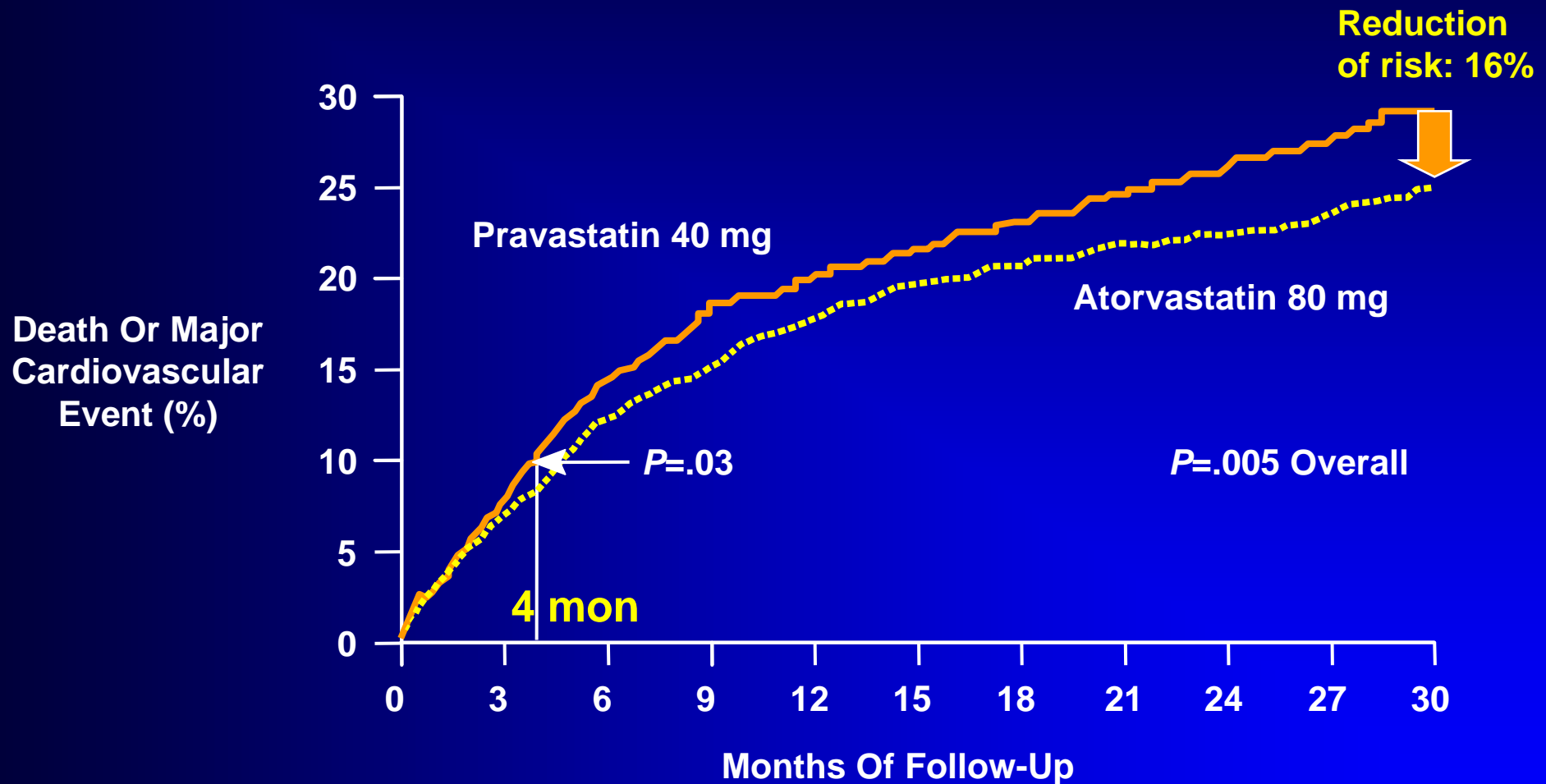
PROVE-IT: Changes From Baseline LDL-C



Note: Median changes in LDL-C may differ from prior trials:

- 25% of patients on statins prior to acute coronary syndrome event
- Acute coronary syndrome response lowers LDL-C from true baseline

PROVE IT: A Major Cardiovascular Event Or Death From Any Cause Primary End Point



Adapted from Cannon et al. *N Engl J Med.* 2004;350:1495, with permission.

Ray and Cannon. *Am J Cardiol.* 2005;96(suppl):54F.

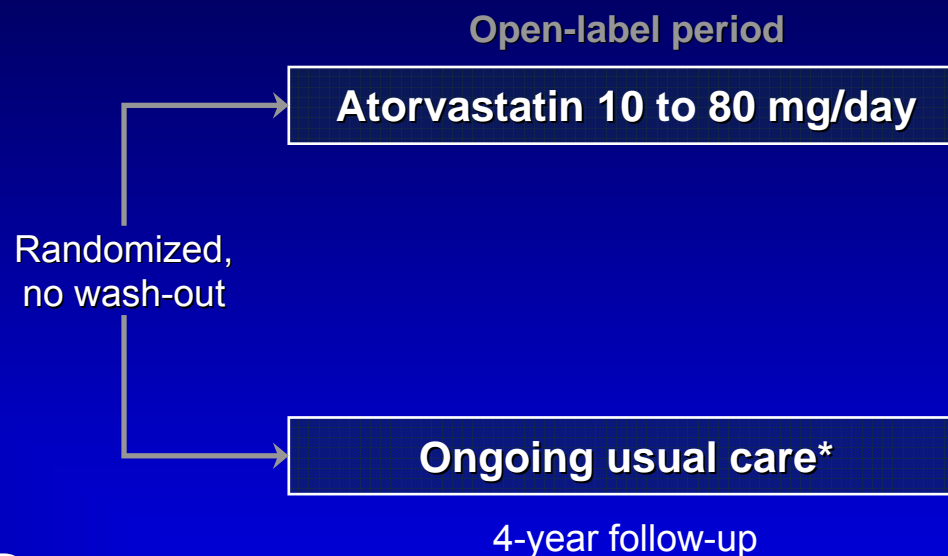
ALLIANCE: Aggressive Lipid Lowering Vs Usual Care

Study Design

- 2442 patients enrolled in 16 MCOs or VAs in the US
- History of CHD
- LDL-C:
 - 130 to 250 mg/dL (3.4 to 6.5 mmol/L) not on lipid-lowering therapy
 - 110 to 200 mg/dL (2.8 to 5.2 mmol/L) receiving lipid-lowering therapy

Primary end point:

- Time to occurrence of composite end point:
 - cardiac death
 - nonfatal MI
 - resuscitated cardiac arrest
 - cardiac revascularization
 - unstable angina requiring hospitalization

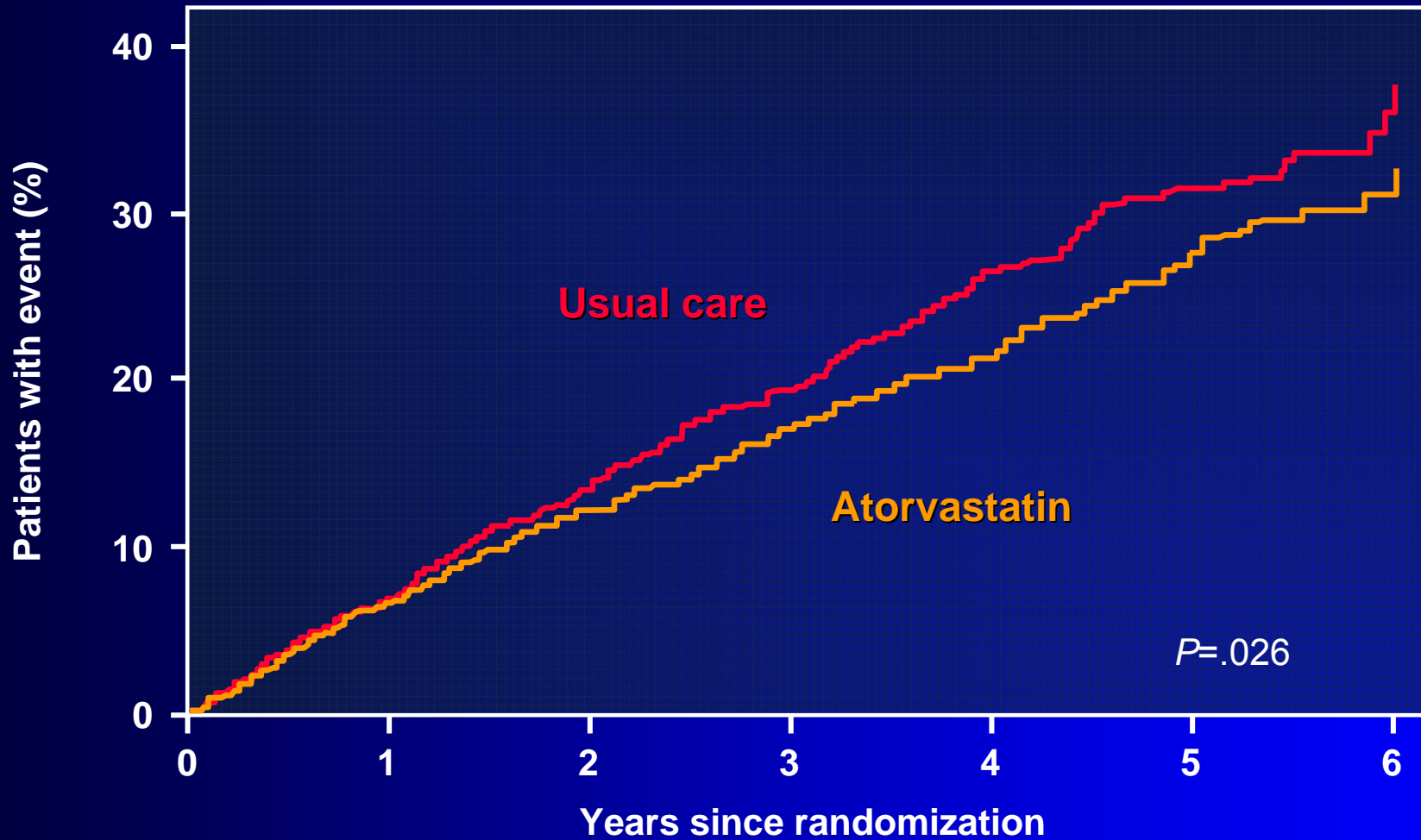


*Usual care is the lipid treatment program prescribed by the patient's primary physician and could include diet, behavior modification, and antihyperlipidemic medication (including atorvastatin after 1997)

MCOs = managed health care organization;
VA = Veterans Administration.

Koren MJ, et al. *J Am Coll Cardiol.* 2004;44:1772-1779.

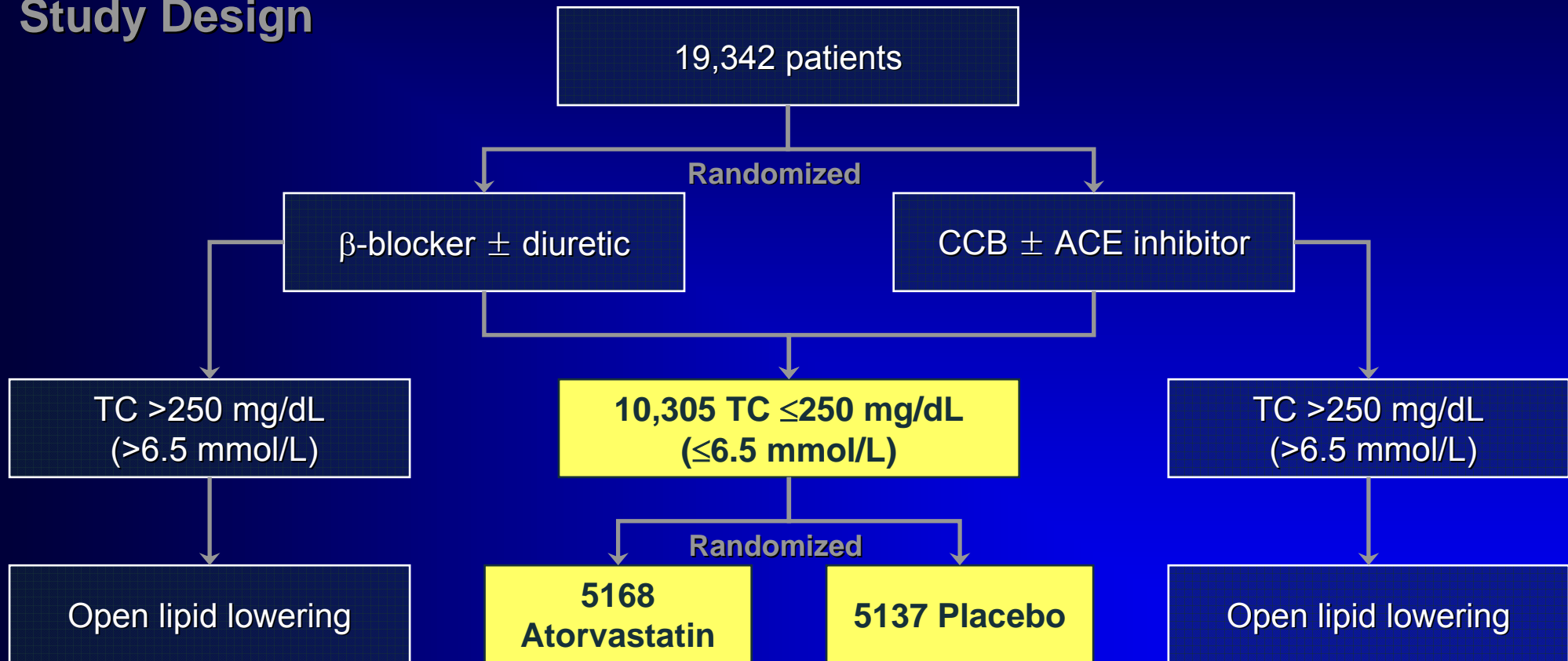
ALLIANCE: Time to Primary Cardiovascular Outcome



Relative risk
reduction
= 17%

ASCOT: Primary Prevention in Patients at Modest Risk of CHD

Study Design



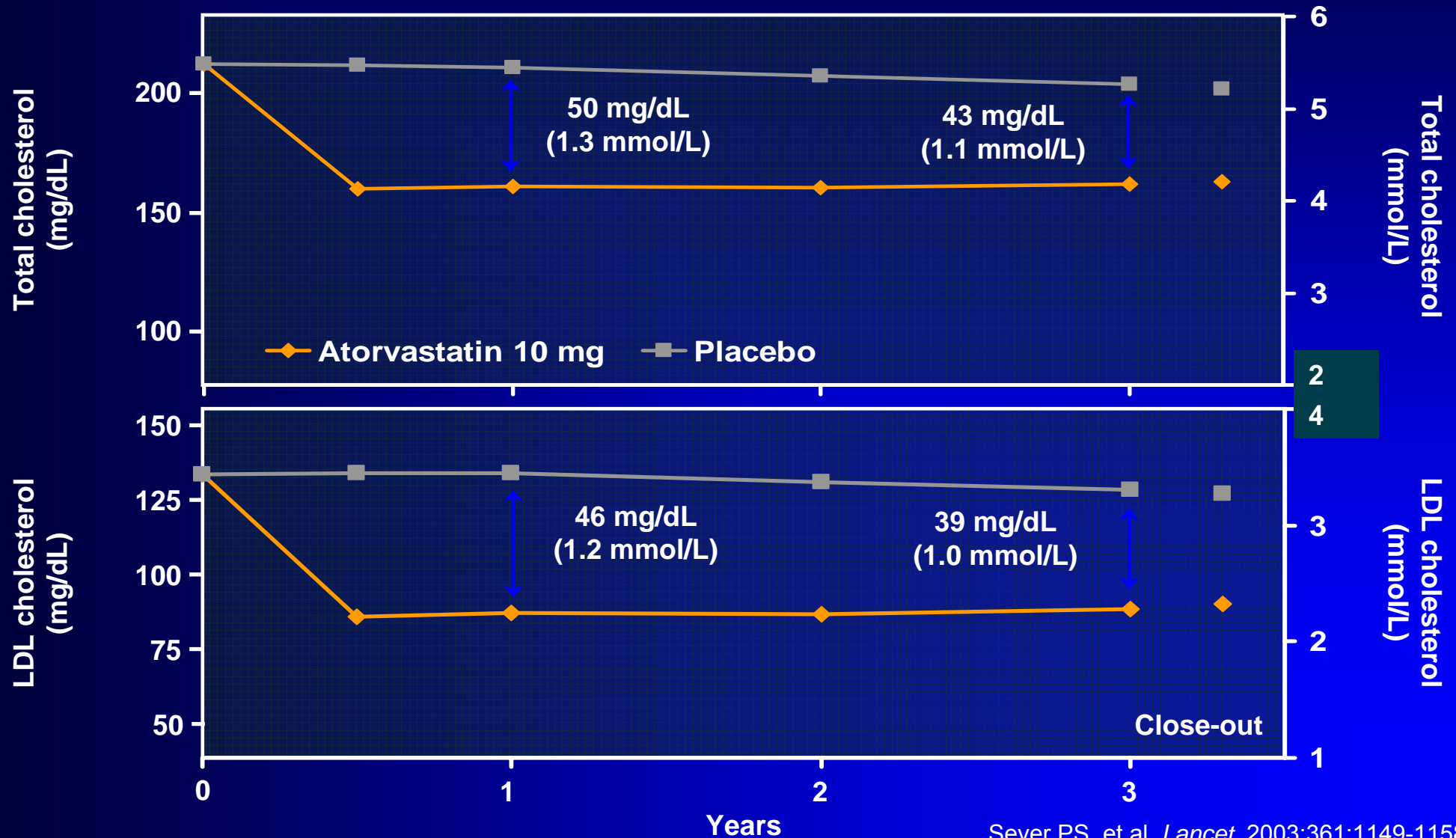
Primary end point: Composite of fatal CHD and nonfatal MI

Highlighted boxes indicate patients enrolled in lipid-lowering arm

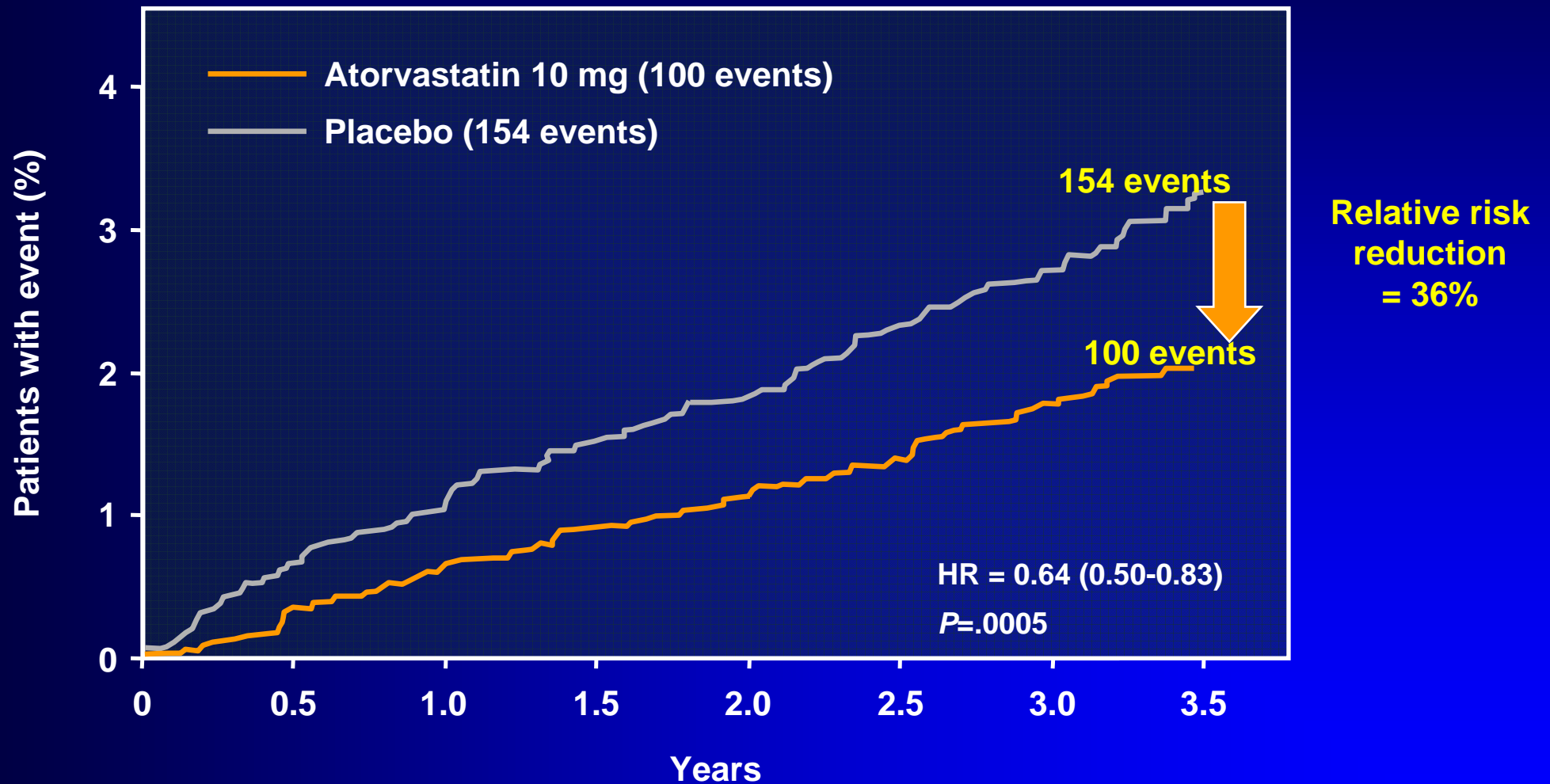
CCB = calcium channel blockers;
ACE = angiotensin converting enzyme.

Sever PS, et al. *J Hypertens*. 2001;19:1139-1147.
Sever PS, et al. *Lancet*. 2003;361:1149-1158.

ASCOT: Reductions in Total and LDL Cholesterol



ASCOT: Incidence of Nonfatal MI and Fatal CHD



REVERSAL and ARBITER: Vascular Benefits With Atorvastatin at On-Treatment LDL-C <100 mg/dL

Study	Mean follow-up LDL-C, mg/dL (mmol/L)		Atherosclerosis change	P-value
	Atorvastatin	Comparator		
REVERSAL	79 (2.0)	110 (2.8) pravastatin	Percent change in TAV -0.4% vs 2.7%	.02
ARBITER	76 (2.0)	110 (2.8) pravastatin	Change in mean carotid IMT -0.034 mm vs 0.025 mm	.03

TAV = total atheroma volume; IMT = intima media thickness.

REVERSAL: Nissen SE, et al. *JAMA*. 2004;291:1071-1080.
ARBITER: Taylor AJ, et al. *Circulation*. 2002;106:2055-2060.

REVERSAL: Reversing Atherosclerosis With Aggressive Lipid Lowering

Study Design

Patient population:

- Patients requiring diagnostic coronary angiography for a clinical indication
- Age 30-75 years
- LDL-C 125-210 mg/dL (3.2-5.4 mmol/L)
- Triglycerides <600 mg/dL (<6.8 mmol/L)

2-week placebo run-in

Randomization
654 patients

Double-blind period

Atorvastatin 80 mg/day

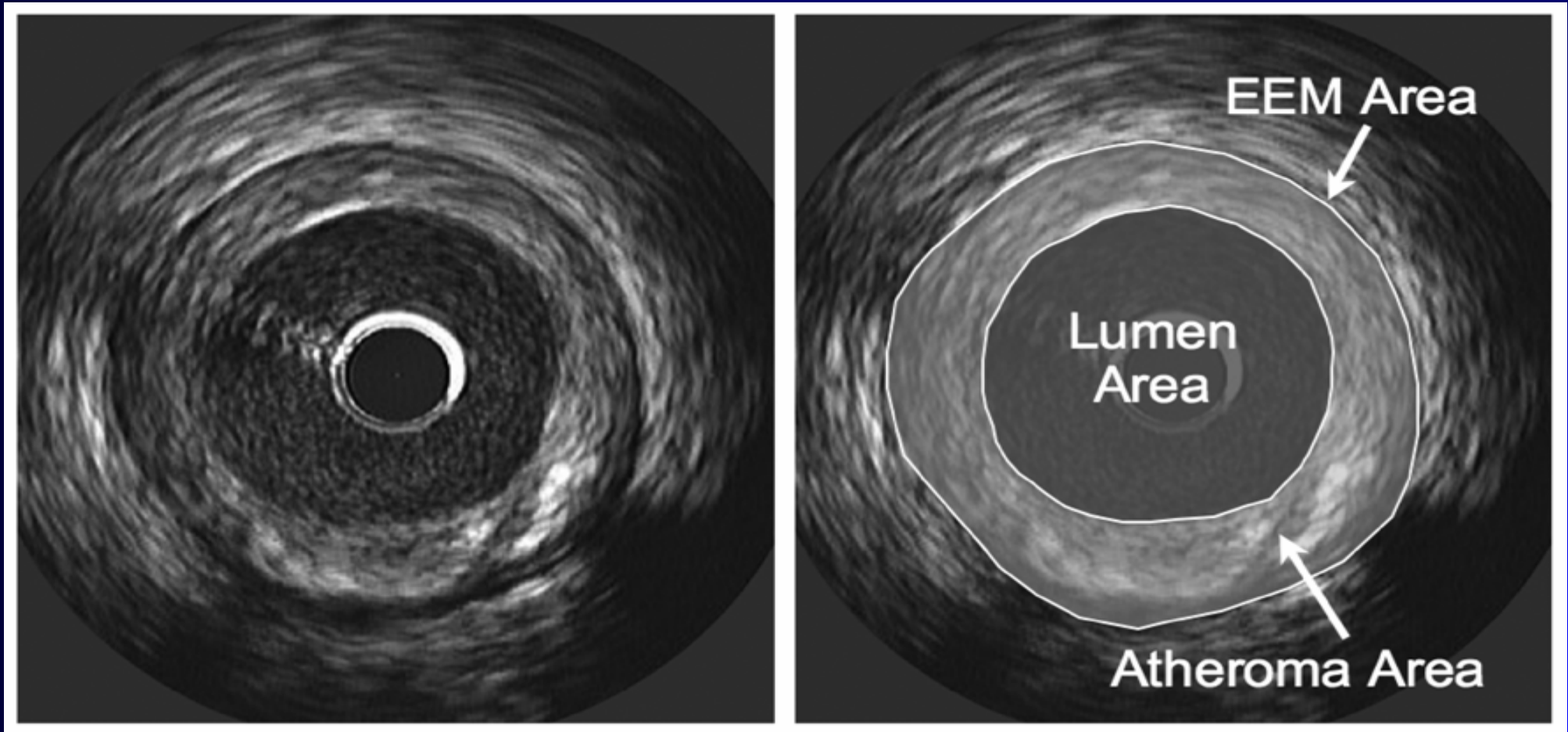
Pravastatin 40 mg/day

18-month follow-up

Primary end point:

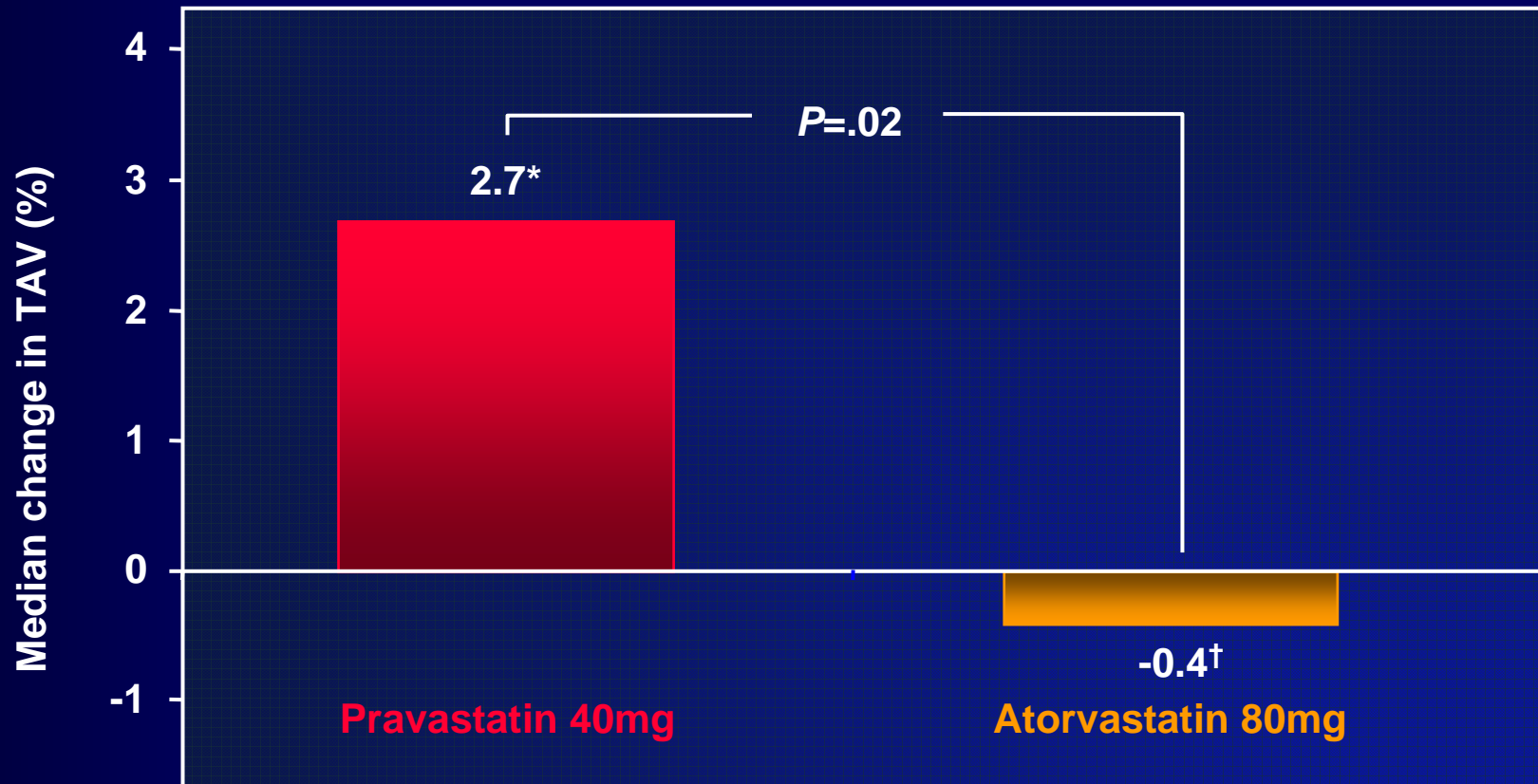
- Percent change from baseline in total atheroma volume of the target coronary artery as measured by IVUS

REVERSAL: Method For Measurement Of Intravascular Ultrasound Images



Reproduced from Nissen et al. *Am J Cardiol.* 2005;96(suppl):61F, with permission.

REVERSAL: Percent Change in Total Atheroma Volume



Significant atherosclerotic progression from baseline

No significant change from baseline; atherosclerotic progression was stopped

*Progression vs baseline ($P=.001$)

†No change vs baseline ($P=.98$)

TAV = total atheroma volume.

Nissen SE, et al. *JAMA*. 2004;291:1071-1080.

NCEP ATP III (Updated) and ADA: Treatment Thresholds and Goals in Patients with Diabetes

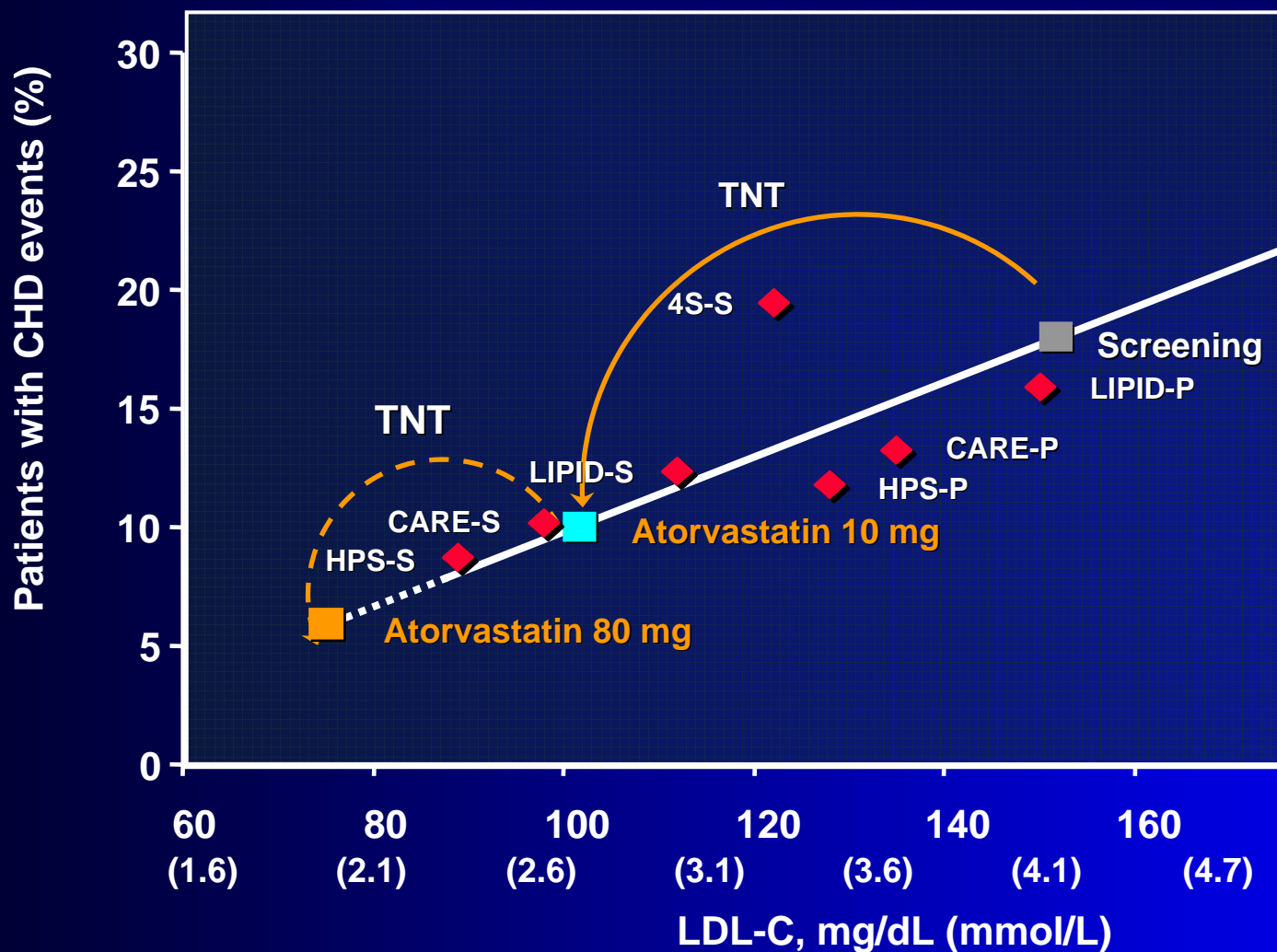
	Drug Therapy	LDL-C Goal (mg/dL)
NCEP ATP III		
CHD or CHD risk equivalent (<i>High risk</i>)	≥100*	<100 (Optional: <70*)
ADA		
With overt CVD	All patients with diabetes	30-40% reduction <100 <70 an option
Without overt CVD	>40 y 30% to 40% LDL-C reduction, regardless of baseline level	<100
	<40 y + CVD risk factors or long duration of diabetes	<100

*Updated guidelines, per NCEP ATP III White Paper (Grundy et al)

American Diabetes Association. *Diabetes Care*. 2005;28(suppl 1):S4-S36. Grundy SM, et al. *Circulation*. 2004;110:227-239.

**More evidences for benefit of
treating to “new target”**

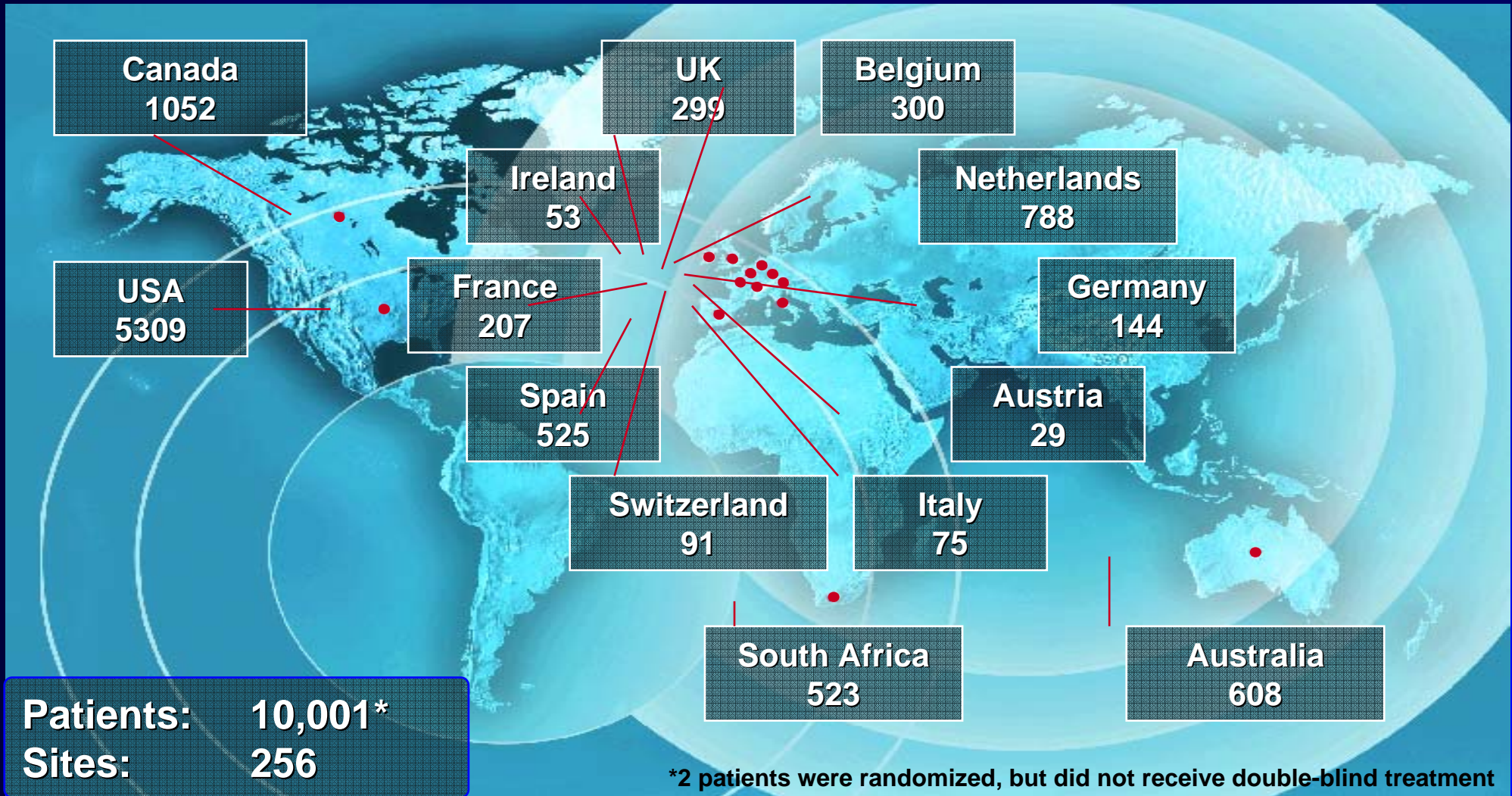
The Treating to New Targets (TNT) : Rationale



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

Patients and Sites

A total of 10,001 patients from 256 sites in 14 countries worldwide were randomized



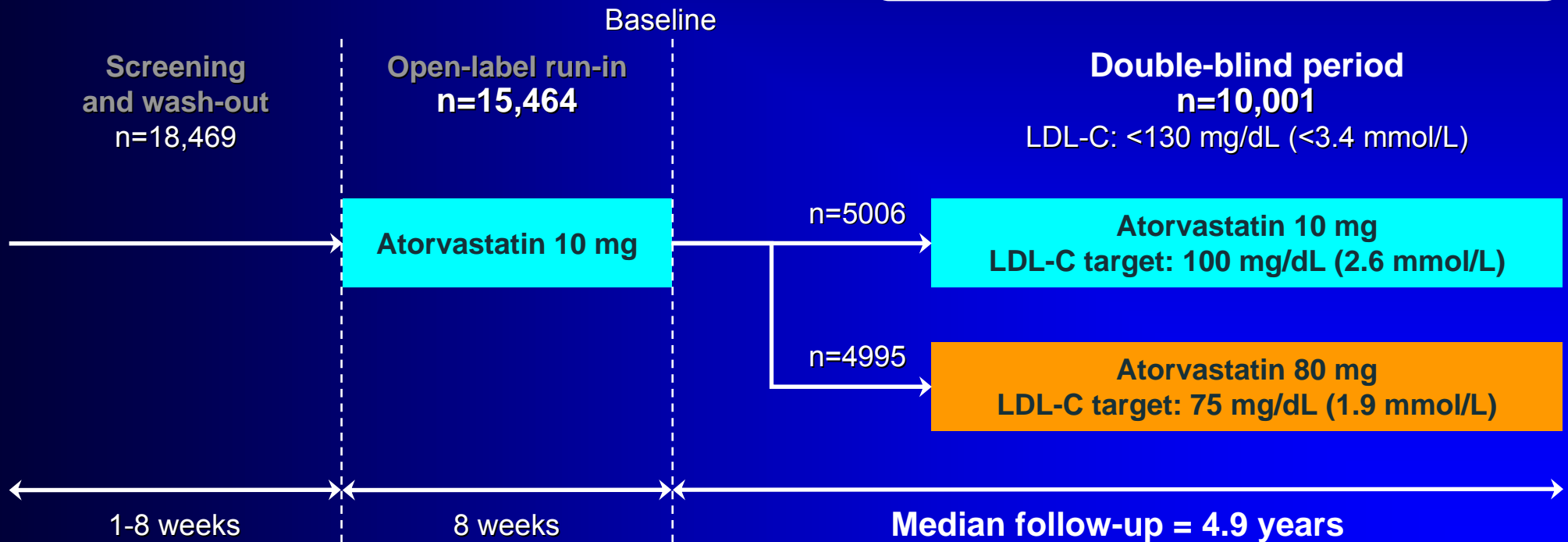
Study Design

Patient population:

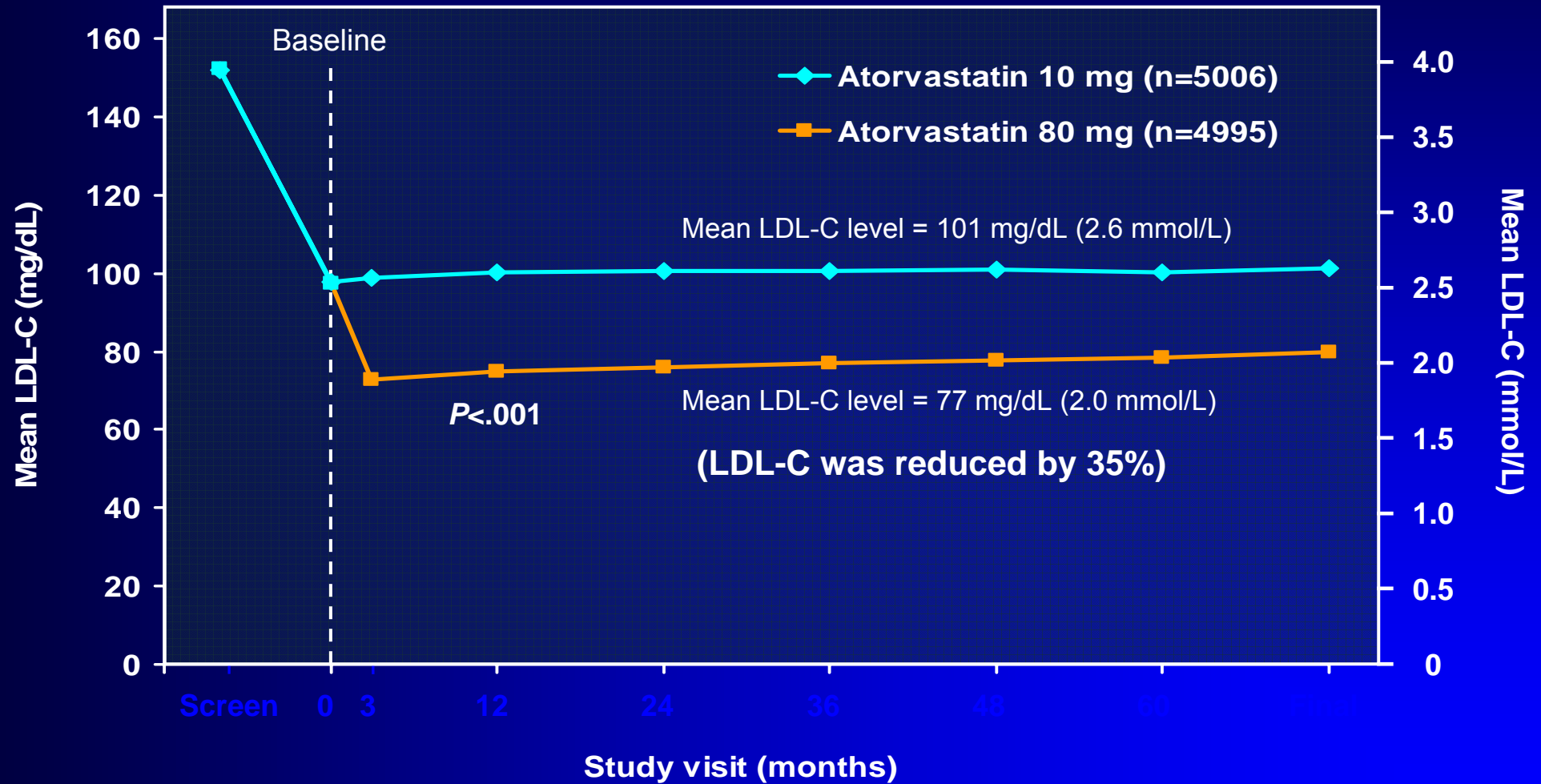
- CHD
- LDL-C: 130-250 mg/dL (3.4-6.5 mmol/L)
- Triglycerides \leq 600 mg/dL (\leq 6.8 mmol/L)

Primary efficacy outcome measure:

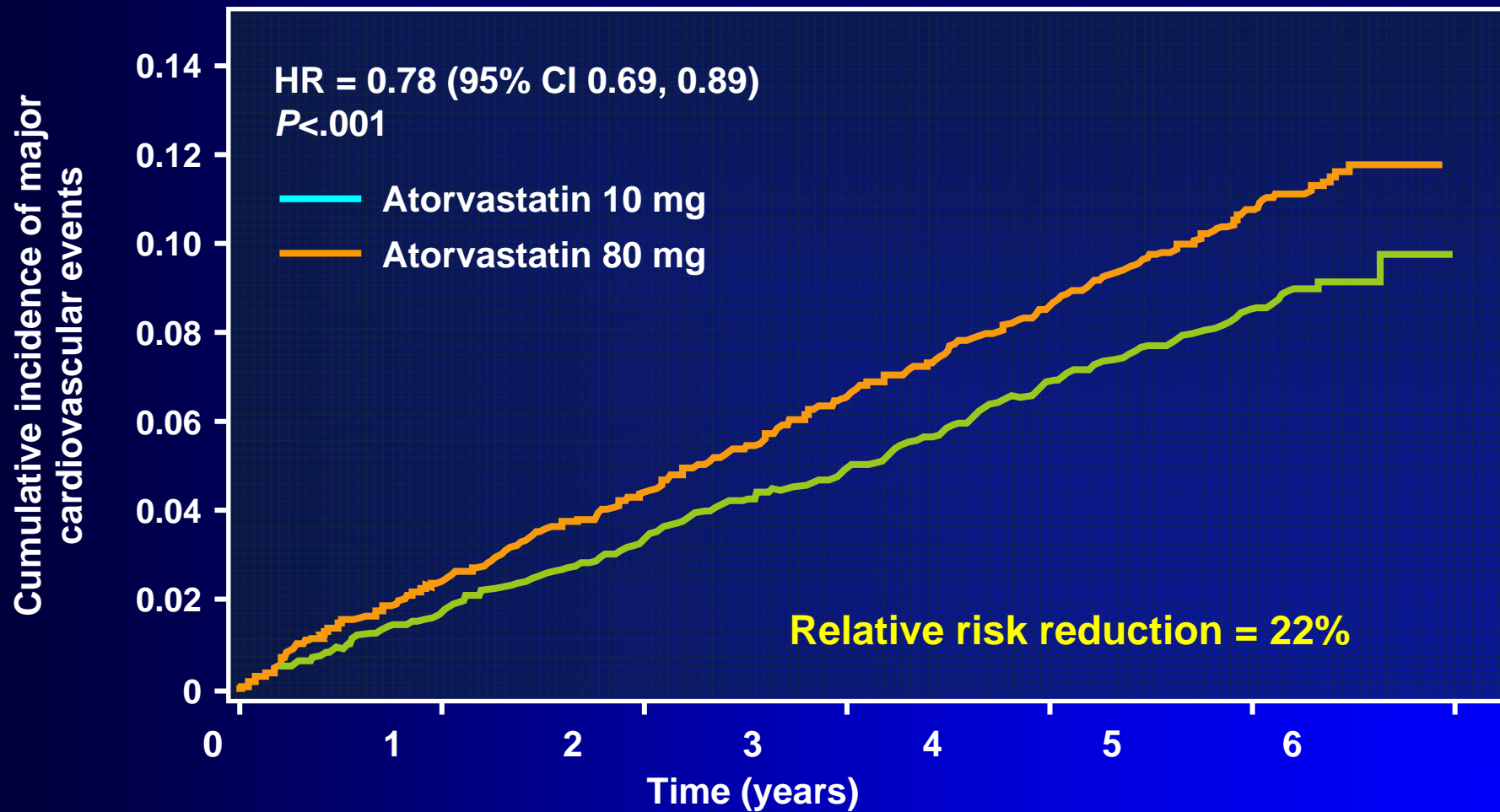
- Time to occurrence of a major CV event:
 - CHD death
 - Nonfatal, non-procedure-related MI
 - Resuscitated cardiac arrest
 - Fatal or nonfatal stroke



Changes in LDL-C By Treatment Group



Primary Efficacy Outcome Measure: Major Cardiovascular Events*

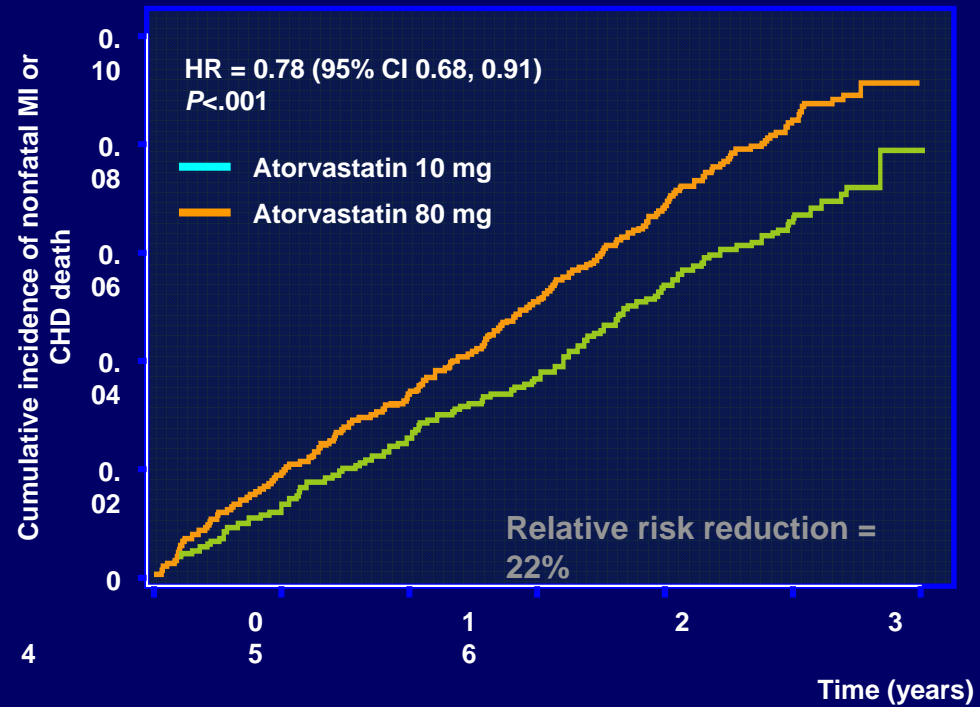
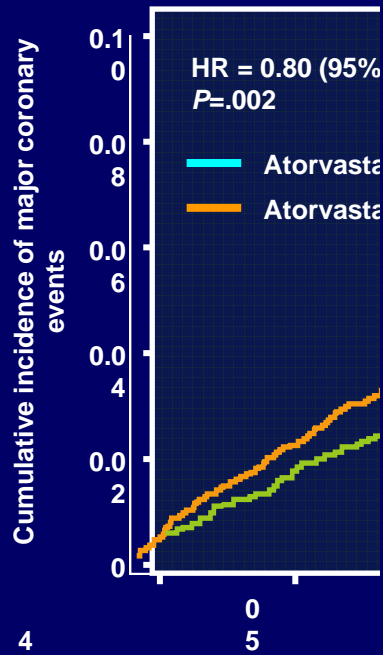
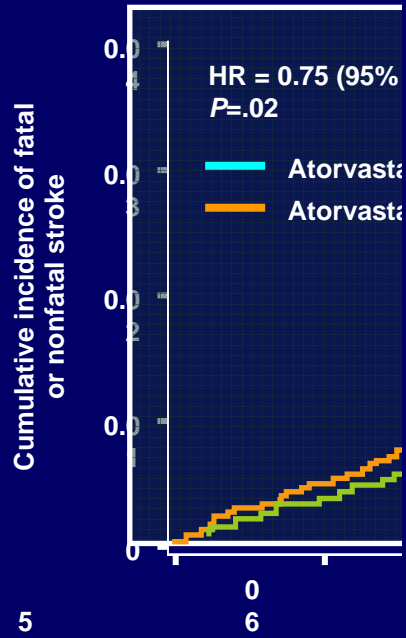


*CHD death, nonfatal non-procedure-related MI, resuscitated cardiac arrest, fatal or nonfatal stroke

Stroke (Fatal or Nonfatal)

Secondary Efficacy Outcome Measure

Nonfatal MI or CHD Death



Primary and Secondary Efficacy Outcome Measures: Hazard Ratios

Primary Efficacy Measure

Major CV event

- CHD death
- Nonfatal, non-PR MI
- Resuscitated cardiac arrest
- Fatal/nonfatal stroke

HR P-value

0.78 <0.001
 0.80 0.09
 0.78 0.004
 0.96 0.89
 0.75 0.02

Secondary Efficacy Measures

Any cardiovascular event

- Major coronary event*
- Any coronary event
- Cerebrovascular event
- Hospitalization for CHF
- Peripheral arterial disease

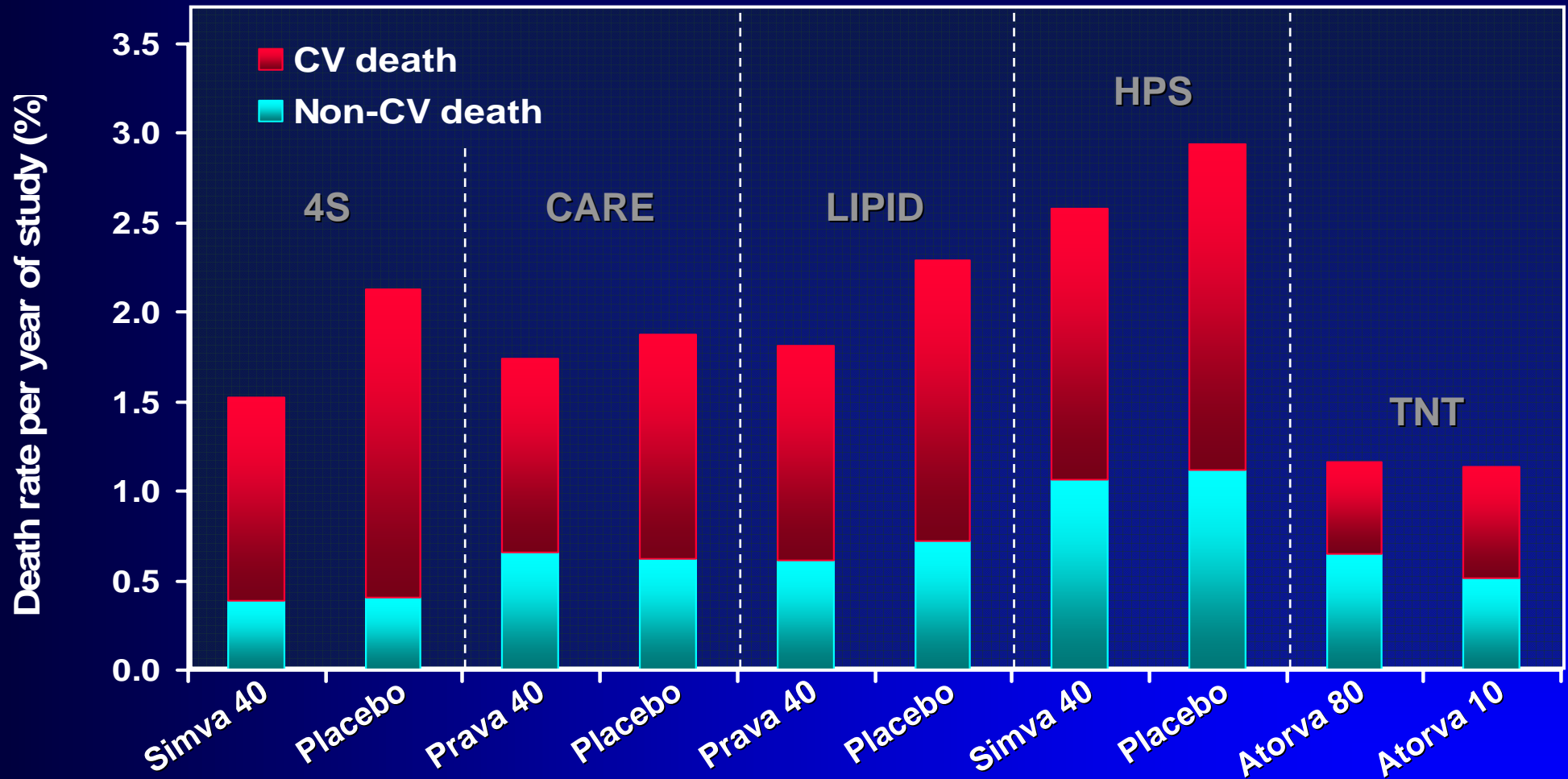
0.81 <0.001
 0.80 0.002
 0.79 <0.001
 0.77 0.007
 0.74 0.01
 0.97 0.76
 1.01 0.92

All-cause mortality



*CHD death, nonfatal non-procedure-related MI resuscitated cardiac arrest.

All-Cause, Non-CV, and CV Mortality in Secondary Prevention Studies



4S: Scandinavian Simvastatin Survival Study Group. *Lancet*. 1994;344:1383-1389; CARE: Sacks FM, et al. *N Engl J Med*. 1996;335:1001-1009; LIPID: The LIPID Study Group. *N Engl J Med*. 1998;339:1349-1357; HPS: HPS Collaborative Group. *Lancet*. 2002;360:7-22; TNT: LaRosa JC, et al. *N Engl J Med*. 2005;352:1425-1435.

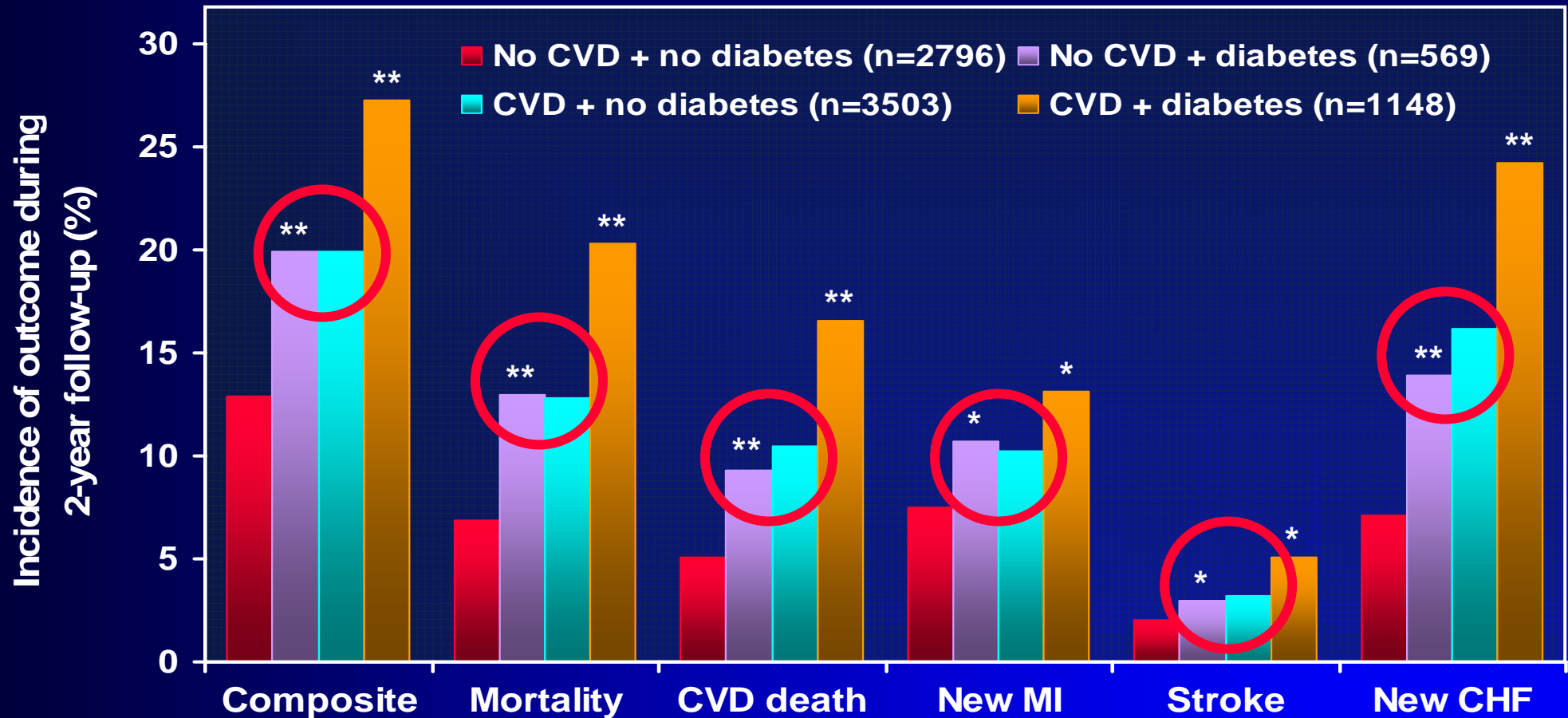
Conclusions of TNT

- ❑ Treatment with atorvastatin 80 mg to an **LDL-C of 77 mg/dL** provided significant clinical benefit to patients with stable CHD currently perceived to be well controlled at levels around 100 mg/dL (2.6 mmol/L)
- ❑ Benefits observed with atorvastatin 80 mg included highly significant reductions in the risk of **coronary events and stroke**
- ❑ This improved clinical outcome was achieved **without significant additional safety risk**

Subgroup Analysis in Patients With Diabetes



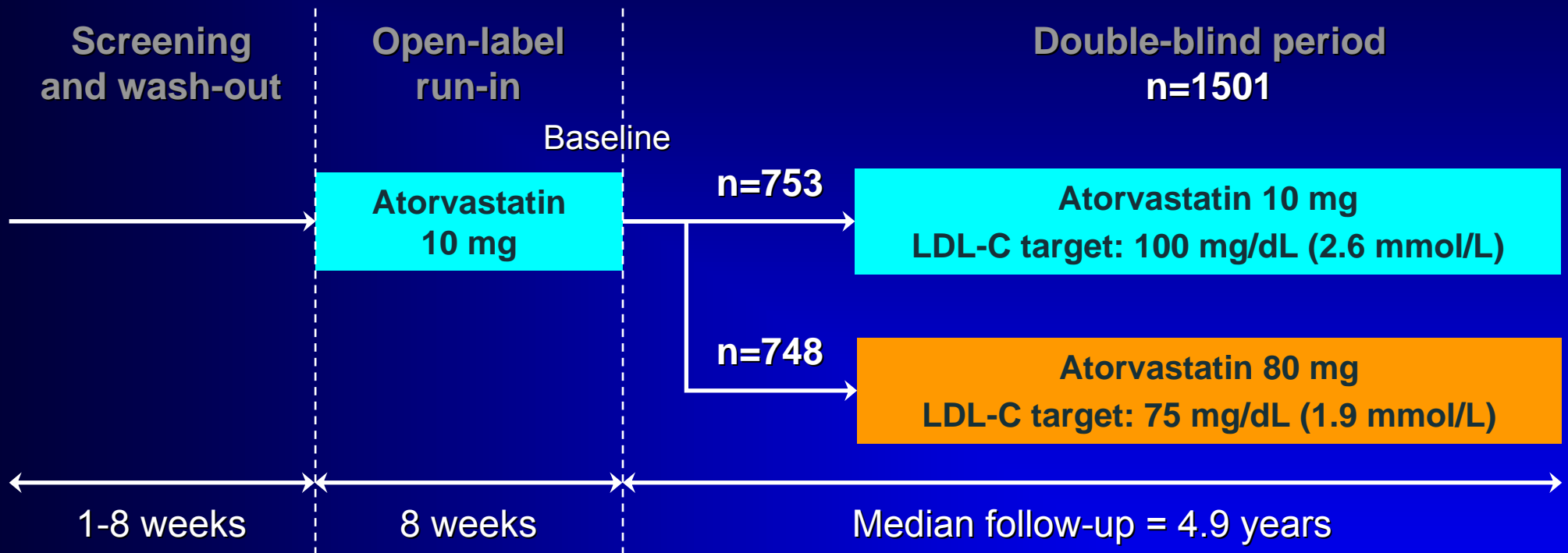
Diabetes and CVD: What We Knew



OASIS registry: Prospectively collected from patients hospitalized with unstable angina or non-Q-wave MI

* $P < .01$, ** $P < .001$ vs patients without diabetes

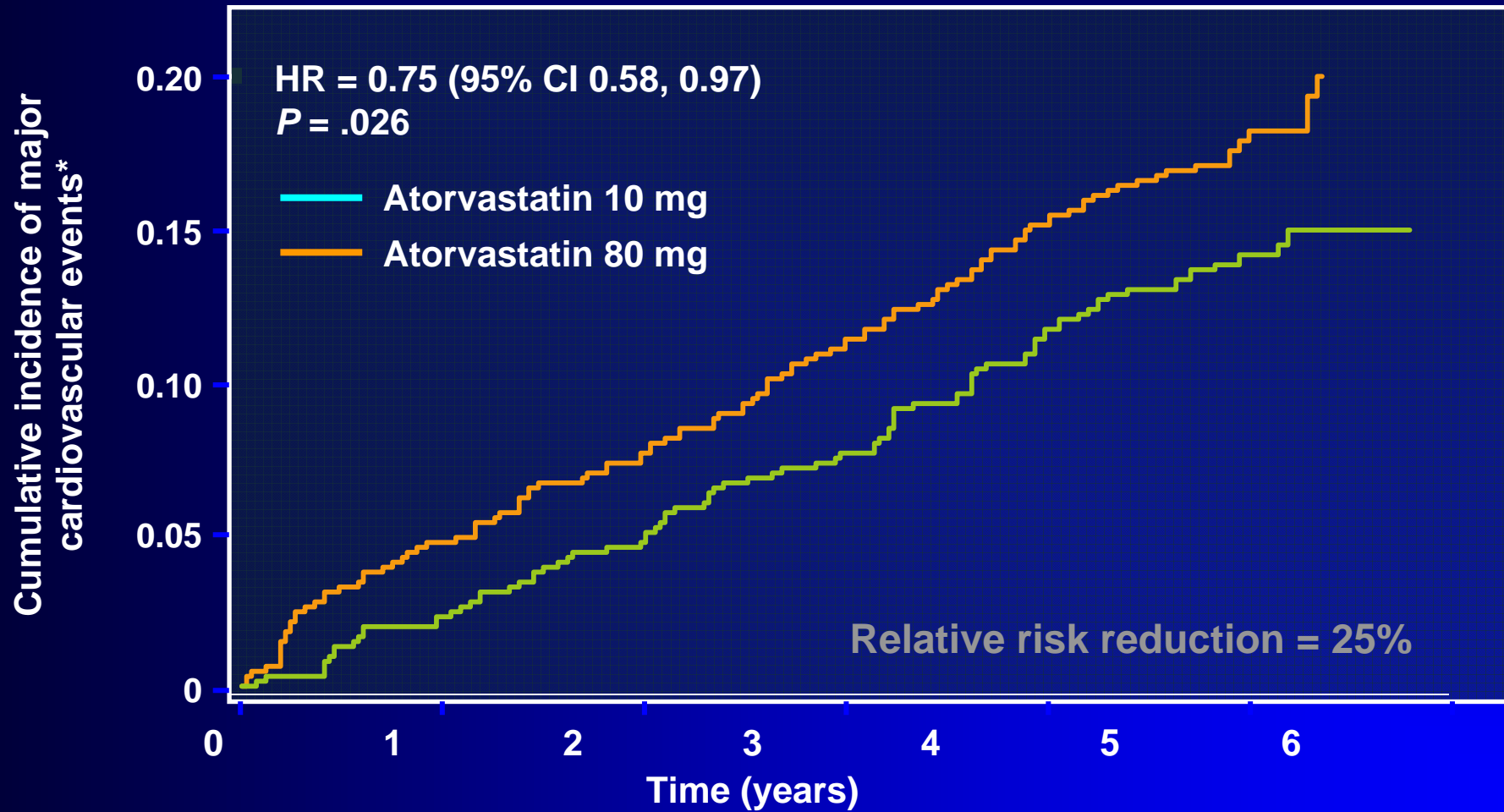
TNT Study Design: Post-hoc Analysis of Patients With Diabetes



Diabetes criteria:

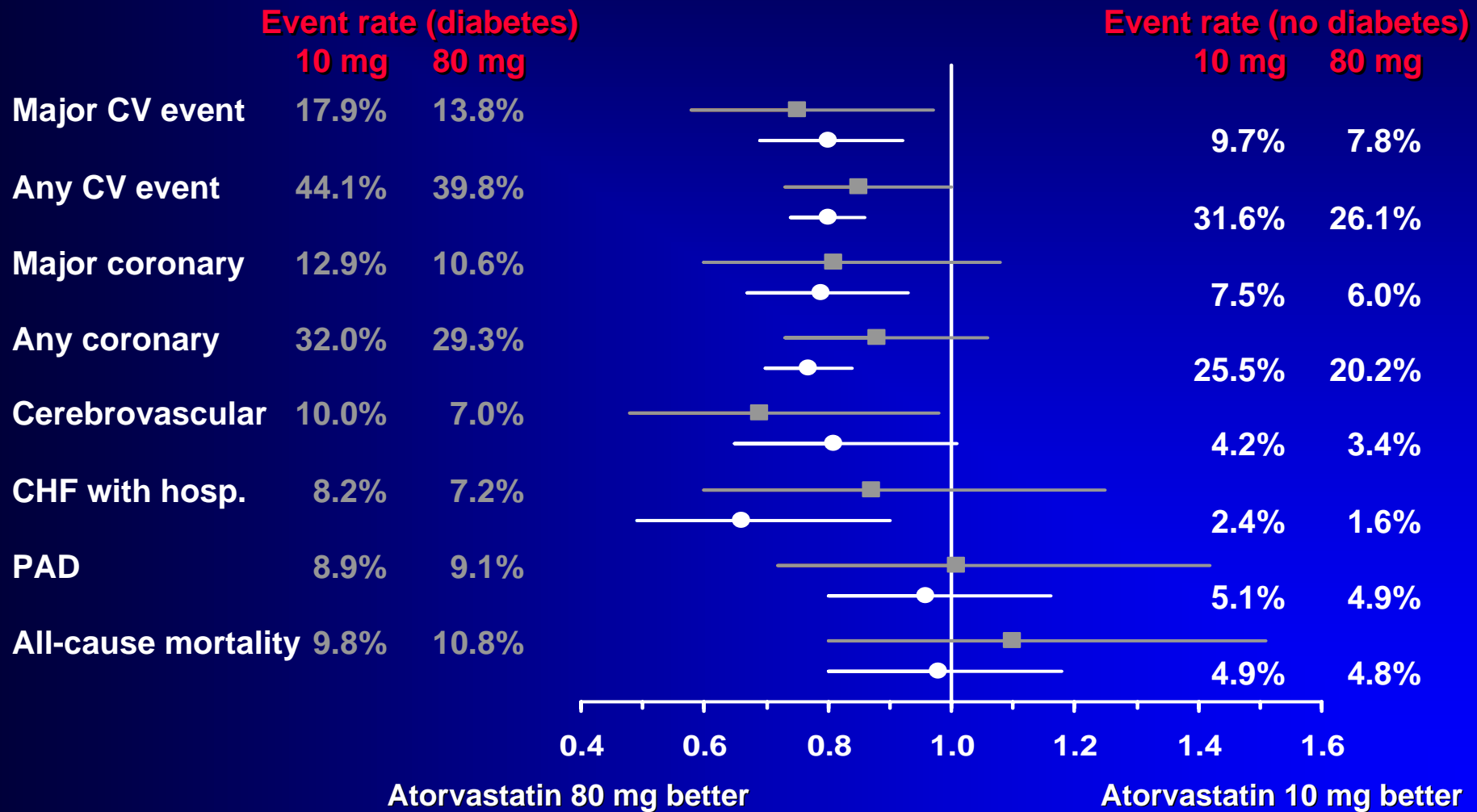
- Cohort includes patients with previous history of diabetes at screening

Time to First Major Cardiovascular Event in Patients With Diabetes

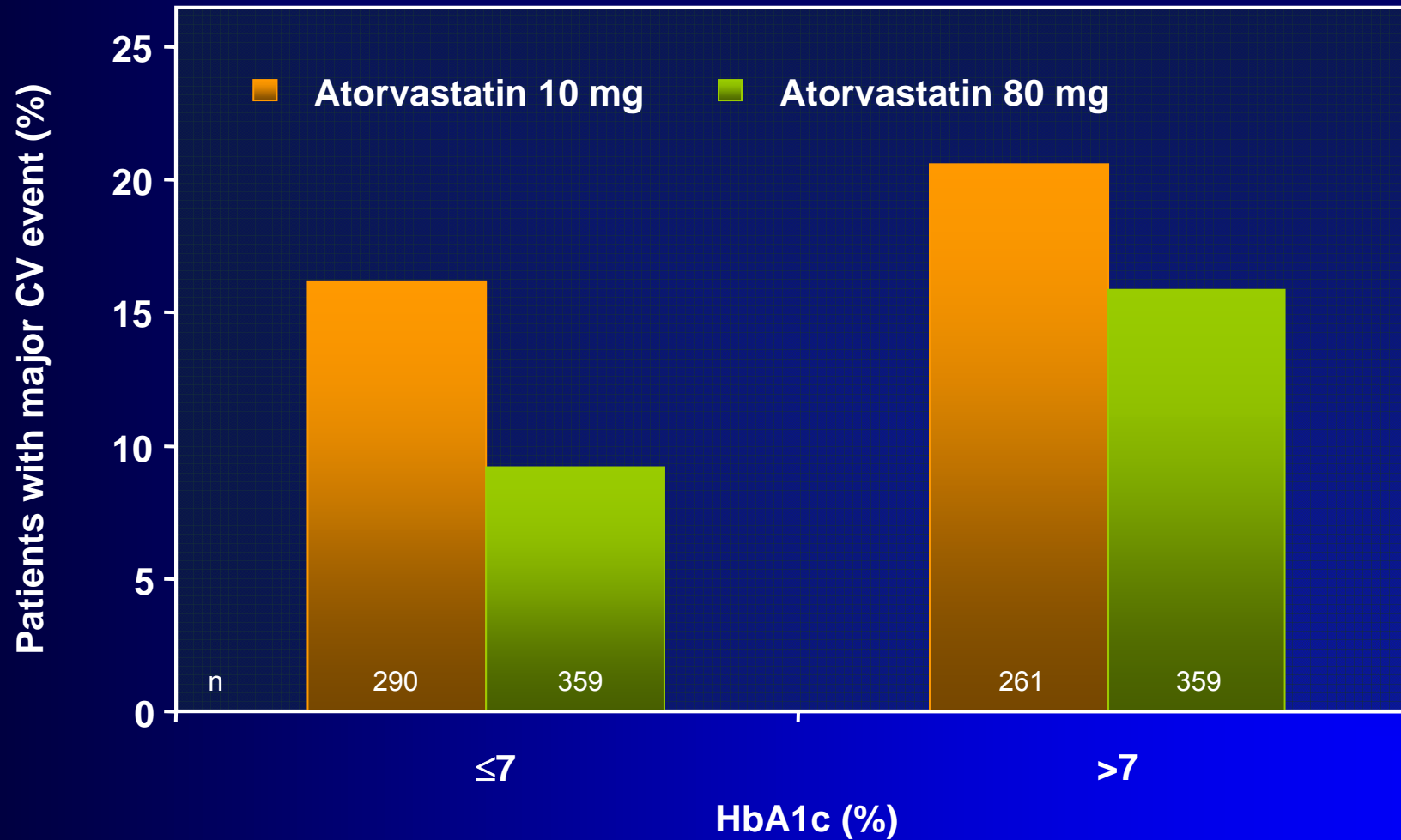


*CHD death, nonfatal non-procedure-related MI, resuscitated cardiac arrest, fatal or nonfatal stroke

Hazard Ratios in Patients With and Without Diabetes: Secondary Efficacy Outcomes



Major Cardiovascular Event Rate in Patients With Diabetes by Glycemic Control



* $P = .30$ for heterogeneity.

HbA1c = glycosylated hemoglobin.

Shepherd J, et al. *Diabetes Care*. 2006;29:1220-1226.

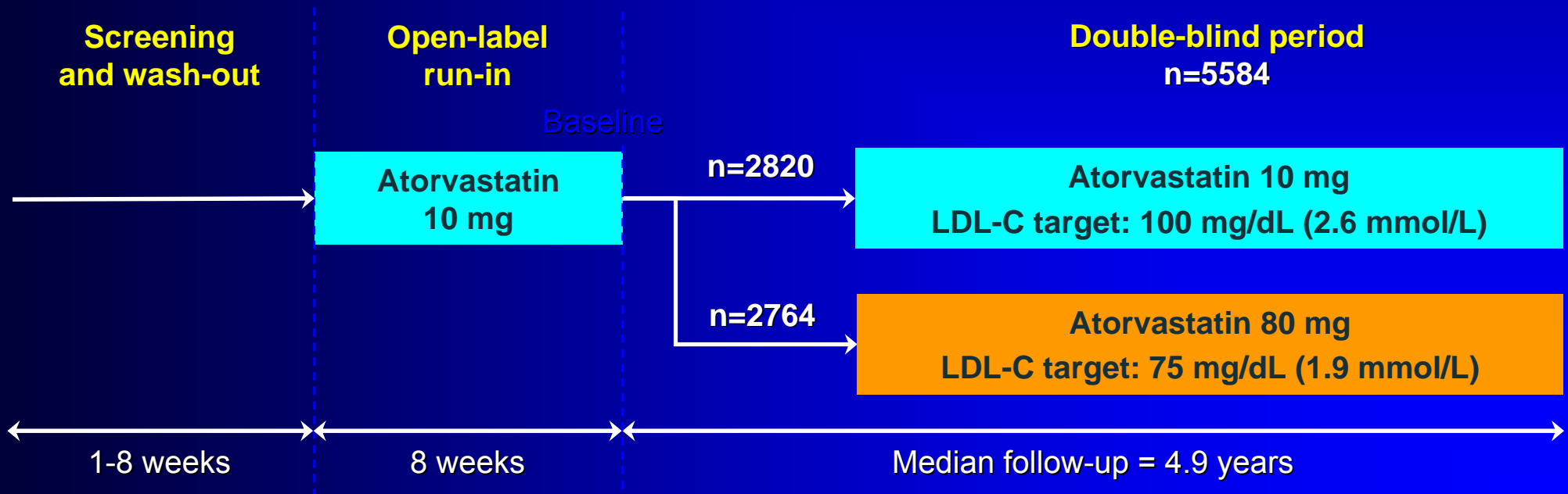
Subgroup Analysis in Patients With Metabolic Syndrome



TNT Study Design: Post-hoc Analysis of Patients With Metabolic Syndrome

Metabolic syndrome was based on the updated NCEP ATP III definition,¹ and was defined as ≥ 3 of the following prior to open-label run-in:

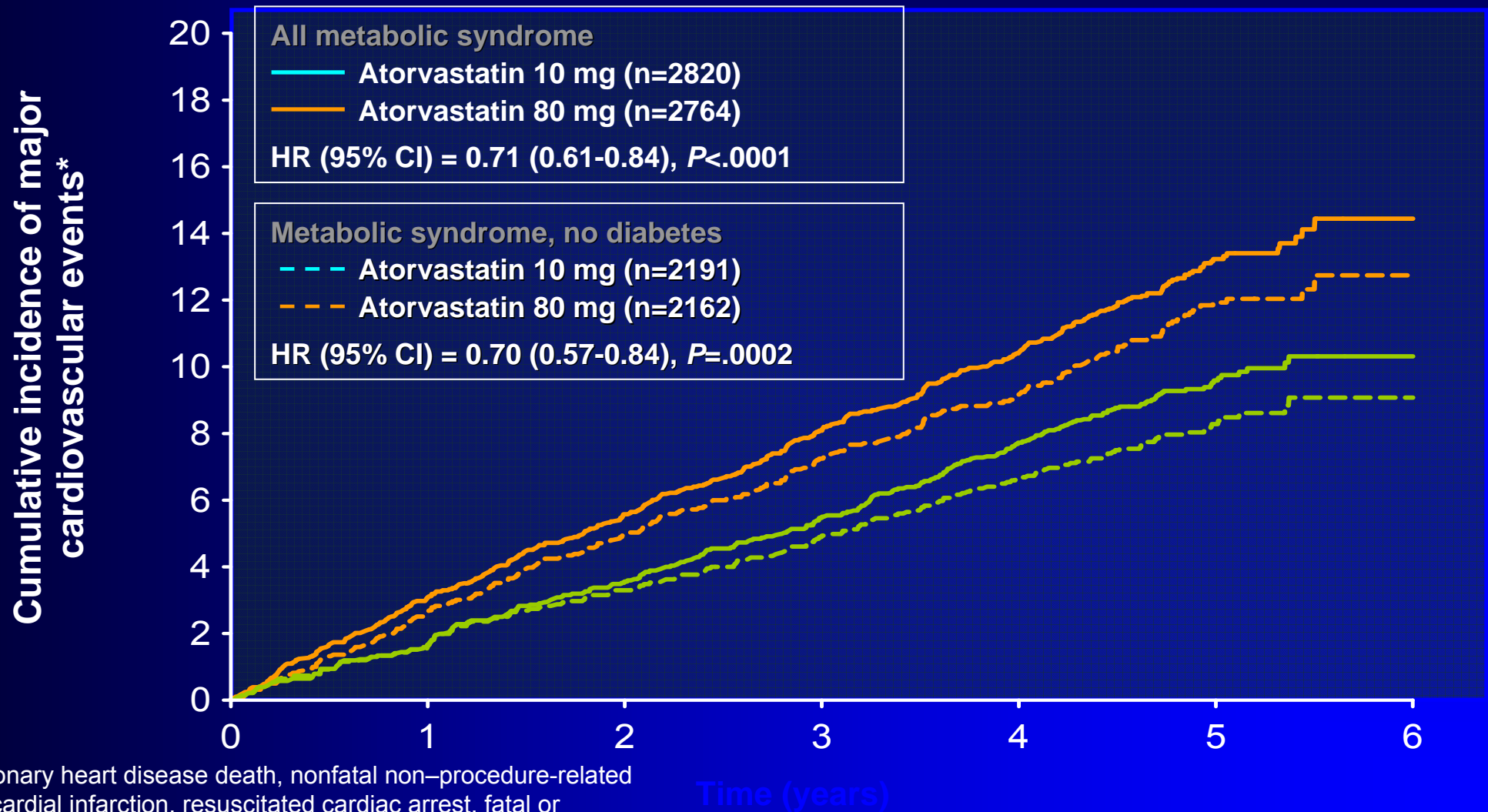
- Waist circumference: Men ≥ 40 inches (102 cm); Women ≥ 35 inches (88 cm)*
- Triglycerides ≥ 150 mg/dL (≥ 1.7 mmol/L)
- HDL-C: Men < 40 mg/dL (< 1.0 mmol/L); Women < 50 mg/dL (< 1.3 mmol/L)
- Blood pressure $\geq 130/\geq 85$ mm Hg
- Fasting glucose ≥ 100 mg/dL (≥ 5.6 mmol/L)



*BMI ≥ 28 substituted for waist circumference

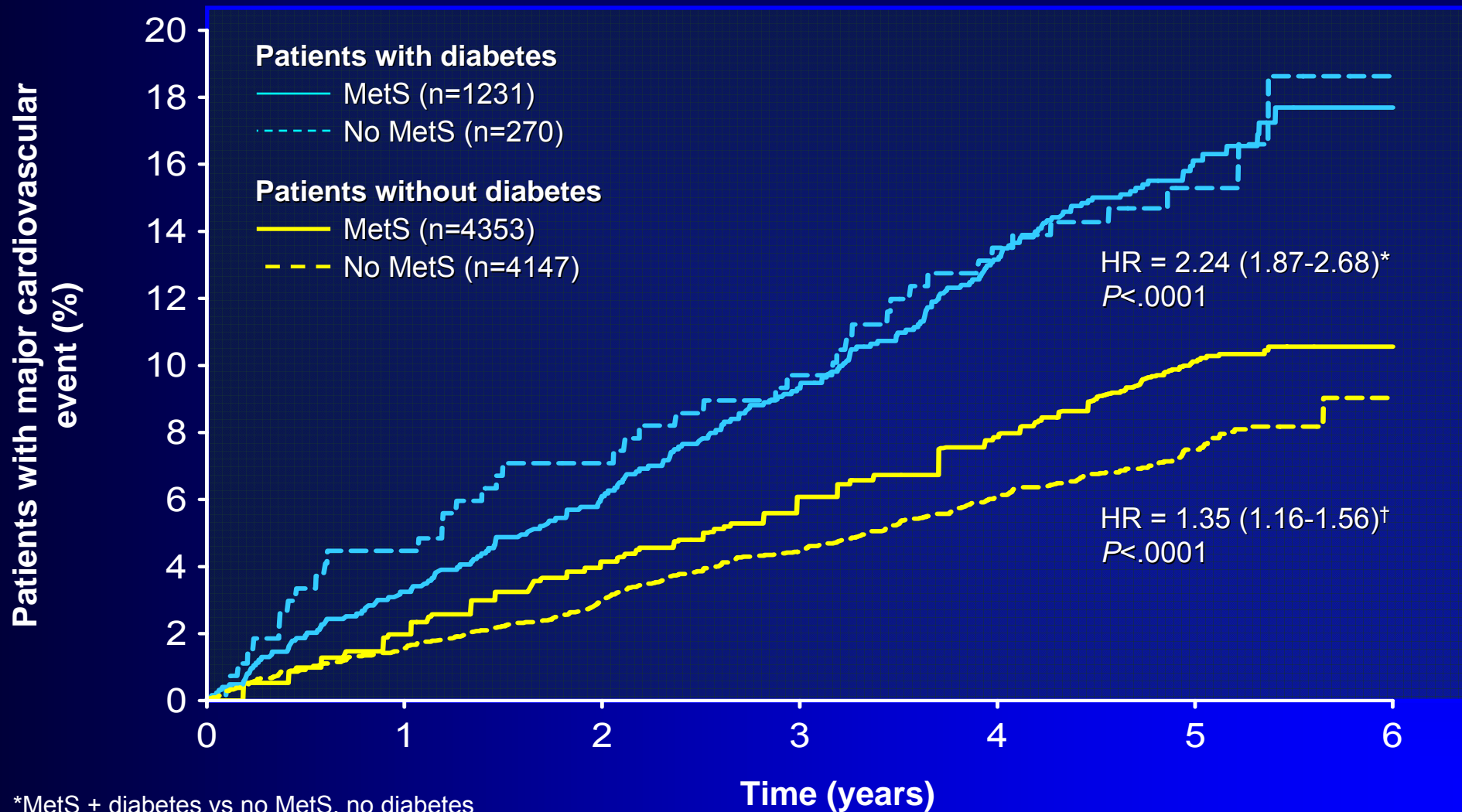
¹Grundy SM, et al. *Circulation*. 2005;112:2735-2752.

Time to First Major Cardiovascular Event in Patients with Metabolic Syndrome (MetS)



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

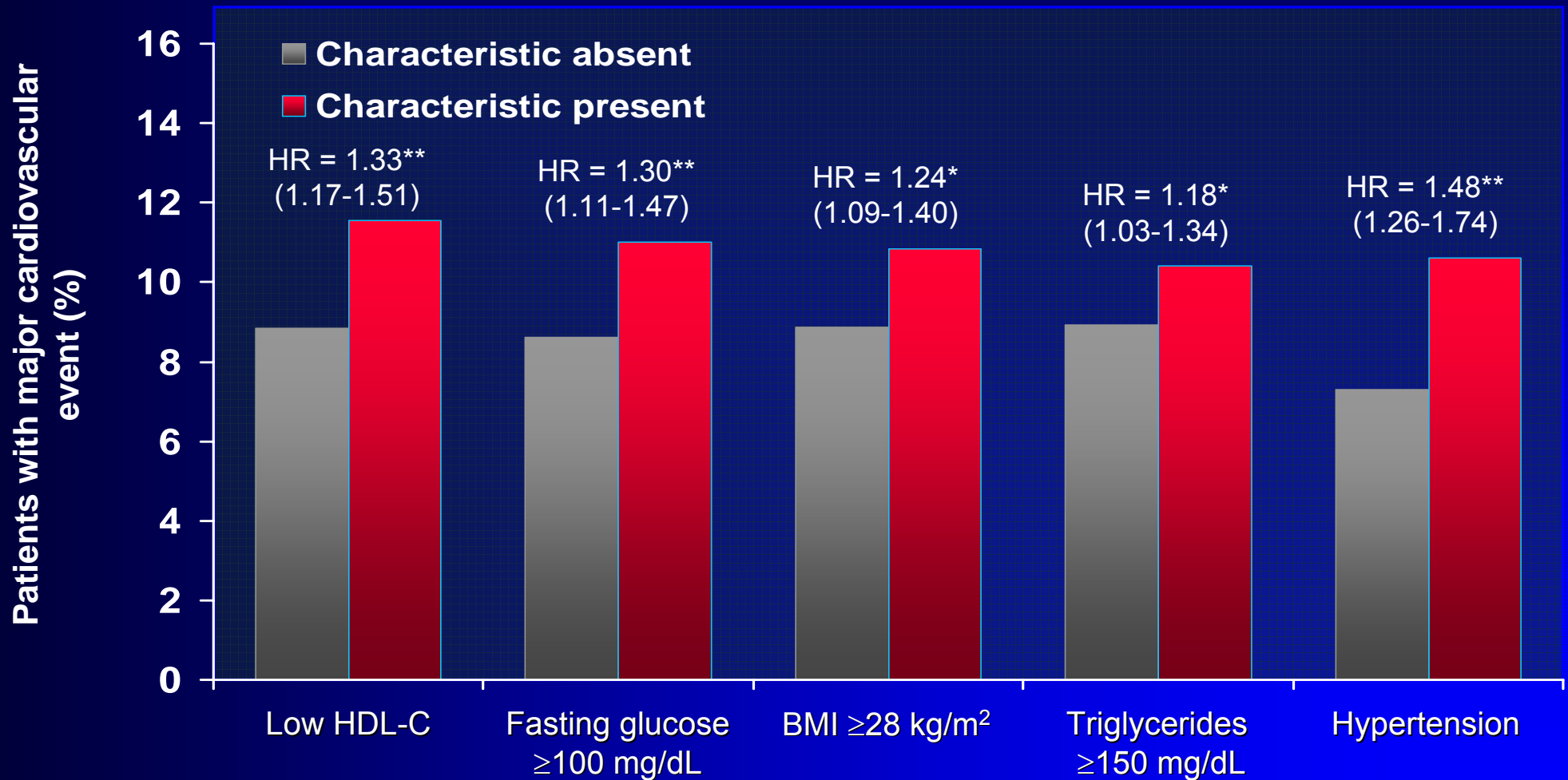
Time to First Major Cardiovascular Event By Metabolic Syndrome Status



*MetS + diabetes vs no MetS, no diabetes

†MetS, no diabetes vs no MetS, no diabetes

Univariate Effects of Individual Characteristics of MetS on Risk of Major Cardiovascular Events



Total n=10,001

* $P < .05$, ** $P < .0001$

MetS = metabolic syndrome.

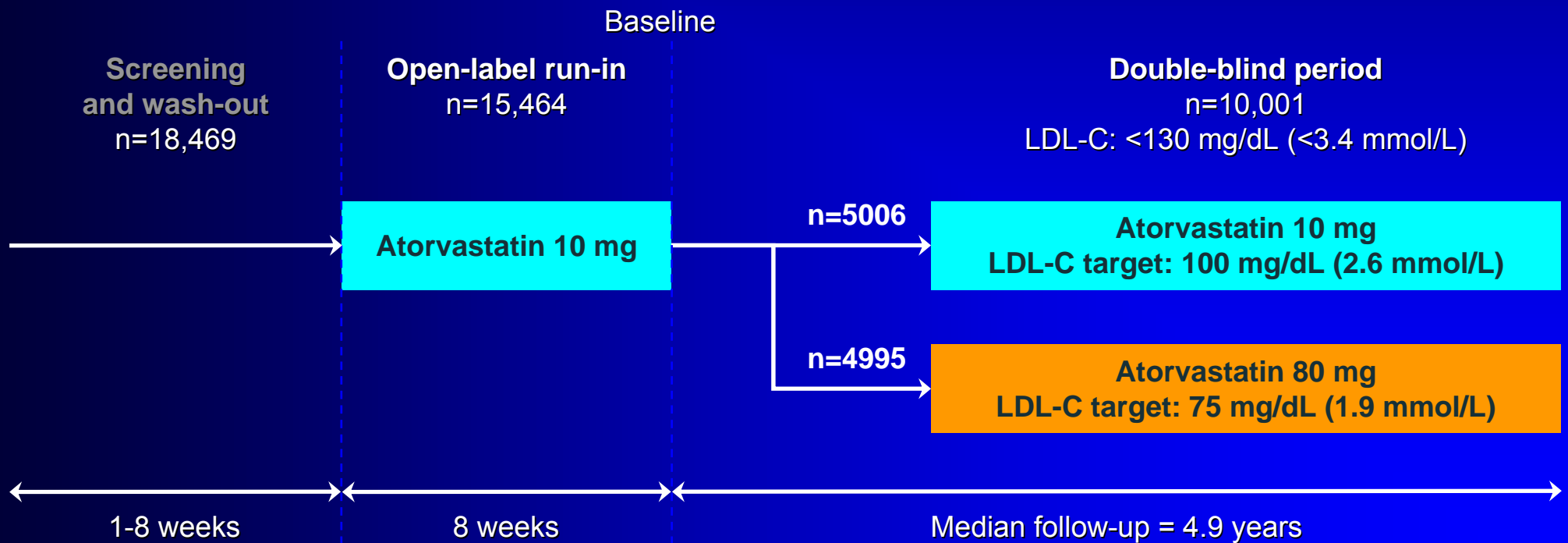
Analysis of Effects on Cerebrovascular Events



TNT Study Design: Analysis of Cerebrovascular Events

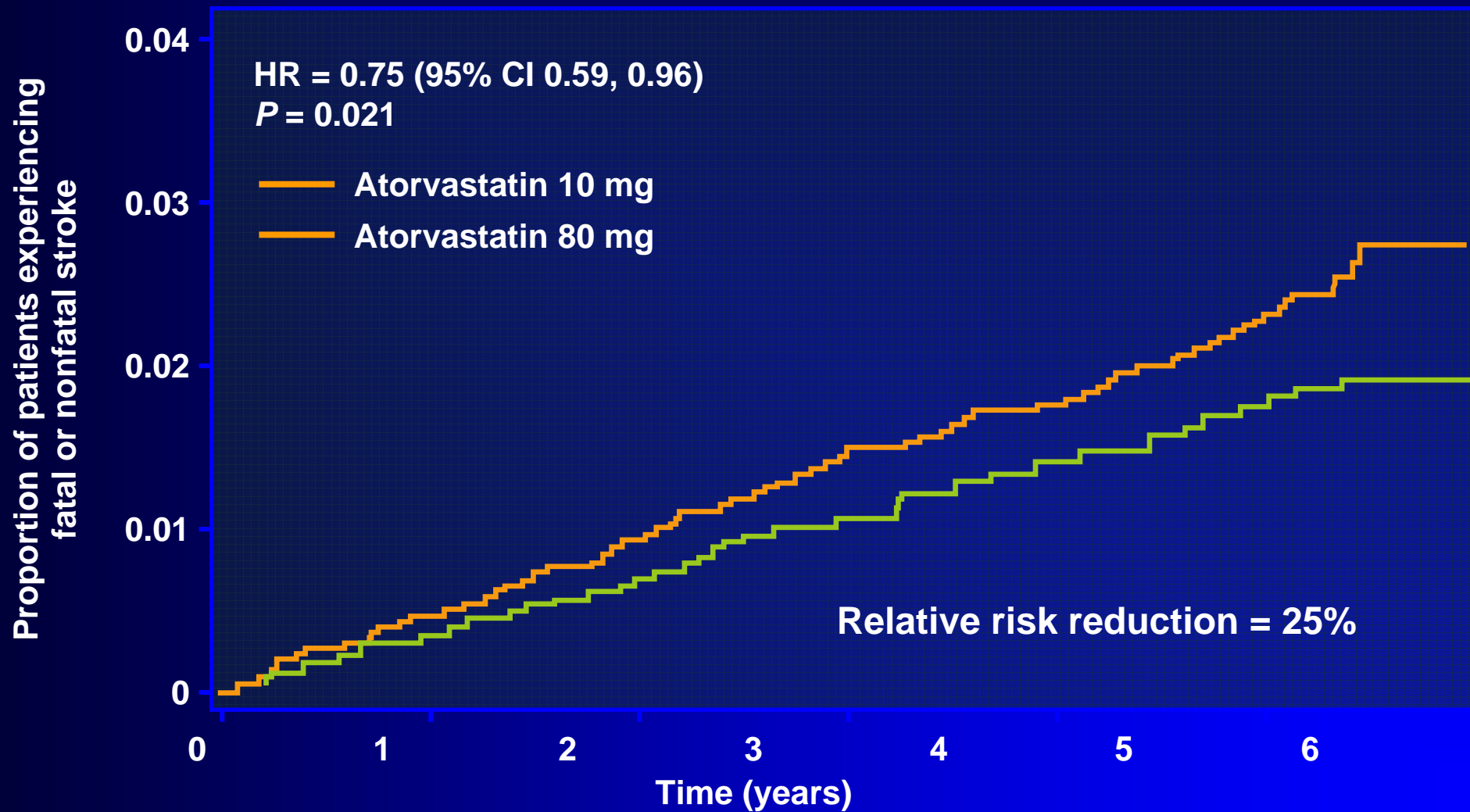
Predefined secondary end point:

- Time to occurrence of a cerebrovascular event, defined as fatal or nonfatal stroke, or transient ischemic attack (TIA)
 - Strokes were classified as ischemic, hemorrhagic, embolic, or unknown*



*Using Systolic Hypertension in the Elderly Program criteria.

Time to First Stroke (Fatal or Nonfatal)



Current guidelines HF

- ✓ 54,960 Medicare hospitalized pt
- ✓ discharge Dx of HF with age >65
- ✓ ischemic: 58%, EF < 40%: 48%,
- ✓ Use of **statin: 17 %**

By Follow the ATP-III guideline in HF patients

- ◆ Wait for the results of ongoing trials



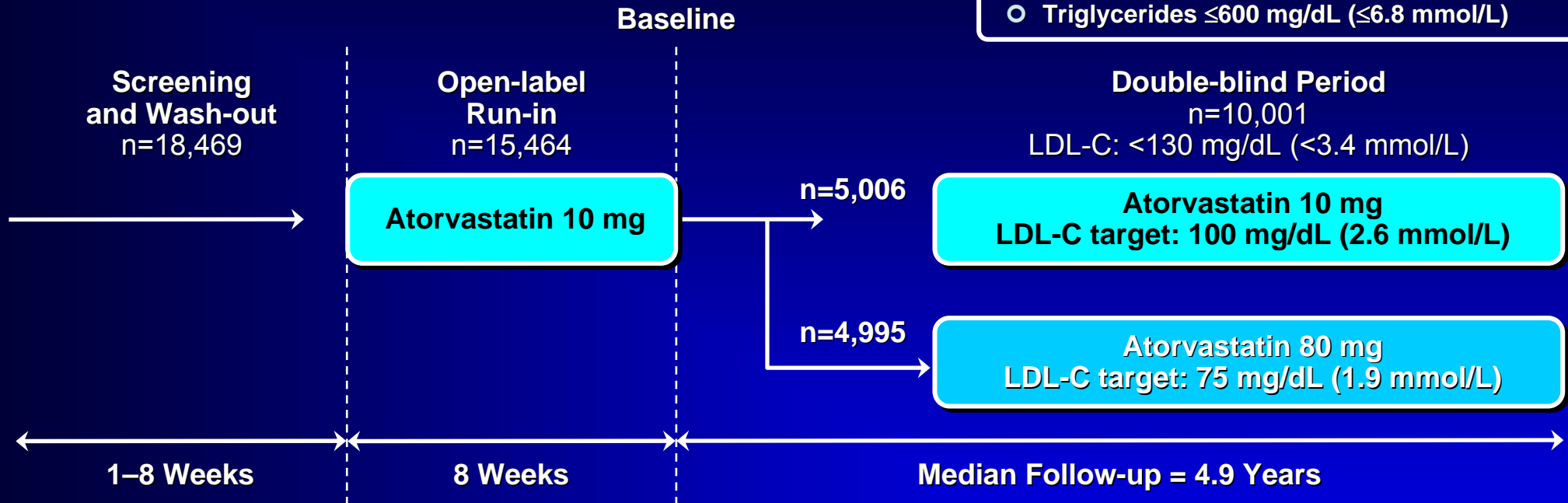
Effect of High-Dose Atorvastatin on Hospitalization for HF

Subgroup Analysis of the Treating to New Targets (TNT) Study

TNT: 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

Secondary Efficacy Outcome Measure

- Any cardiovascular event:
 - Major coronary event*
 - Any coronary event
 - Cerebrovascular event
 - **Hospitalization for CHF**
 - Peripheral arterial disease
- All cause mortality

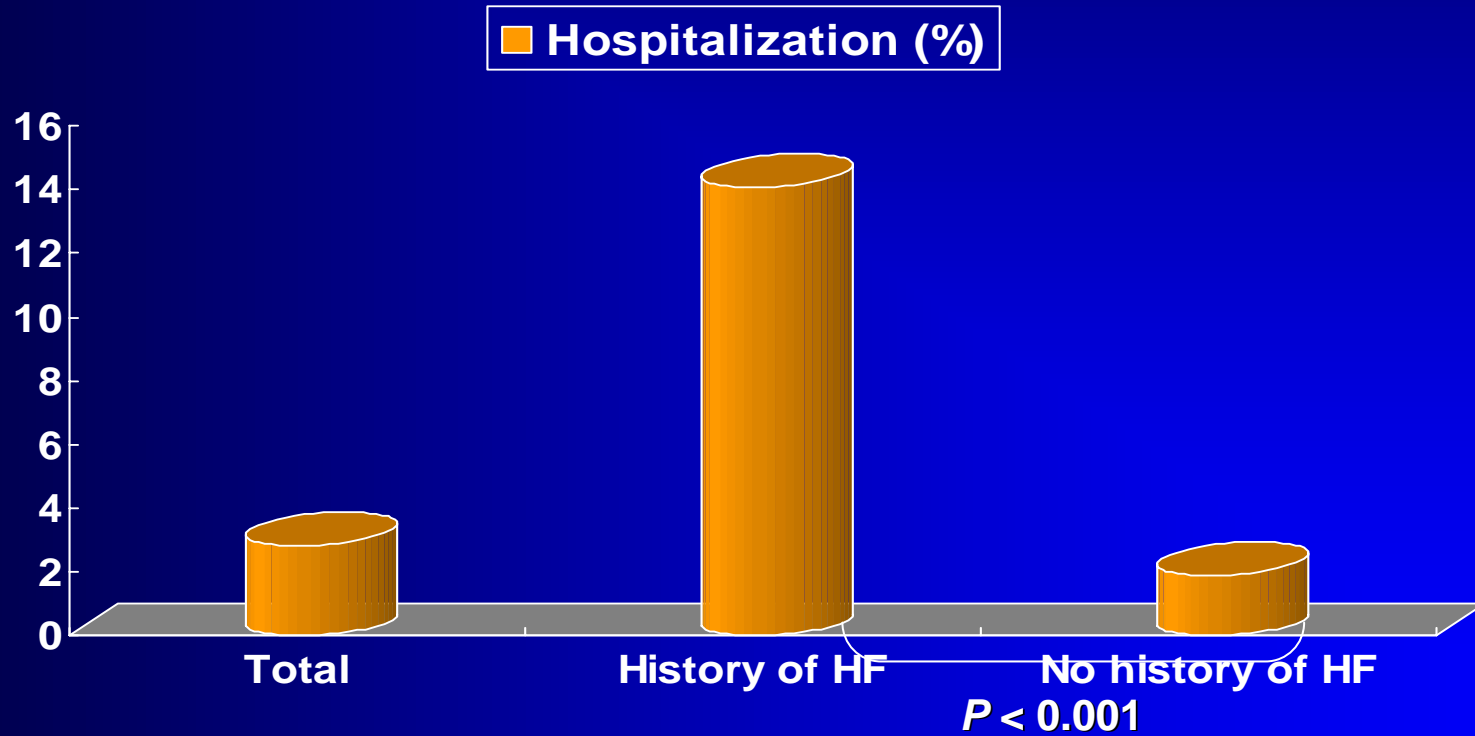
*CHD death, nonfatal non-procedure-related MI, resuscitated cardiac arrest

Baseline Patient Characteristics (2)

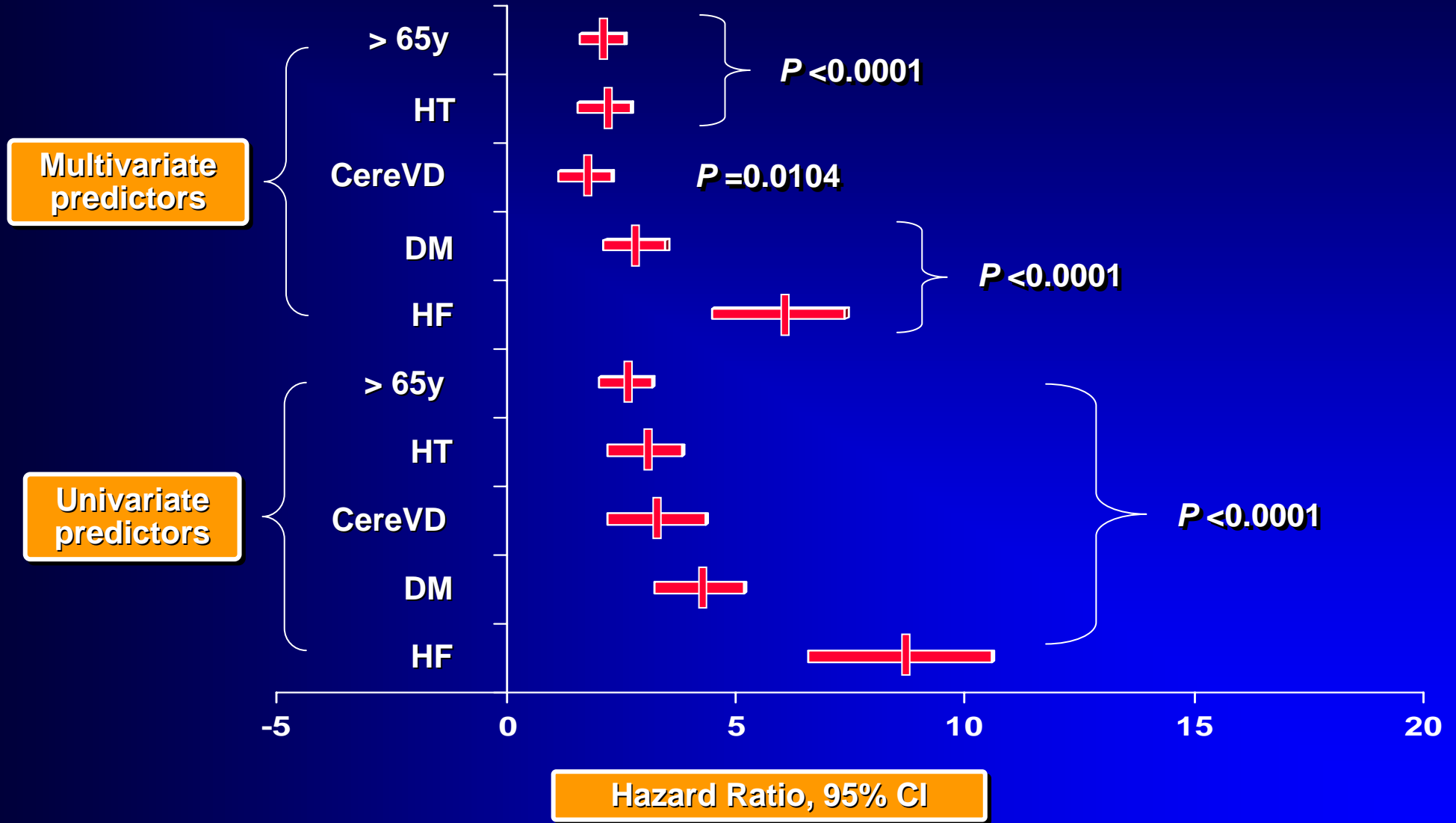
	History of HF (n=781)	No history of HF (n=9,220)	P value
Comorbidities (%)			
▪ Hypertension	67	53	<0.0001
▪ Diabetes Mellitus	27	14	<0.0001
▪ Peripheral arterial disease	24	11	<0.0001
▪ Prior MI	74	57	<0.0001
▪ Stroke	11	5	<0.0001
Medications (%)			
▪ ACE-I	61	26	<0.0001
▪ ARB	10	5	<0.0001
▪ Diuretics	54	12	<0.0001

Hospitalization for HF

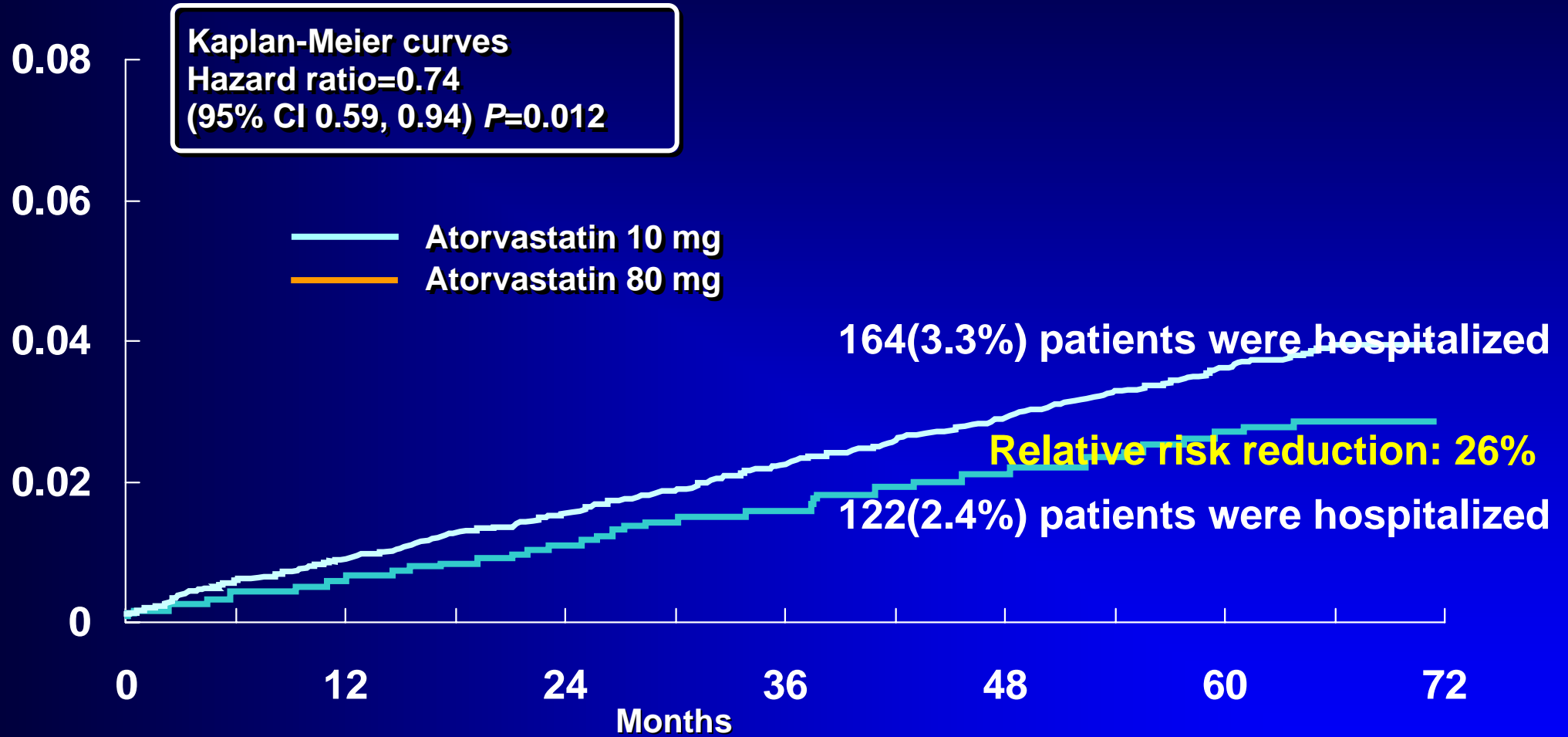
	Total	Pt with history of HF	Pt without history of HF
n	10,001	781	9,220
Hospitalization (%)	2.86	14.1	1.9



Predictors of Hospitalization for HF

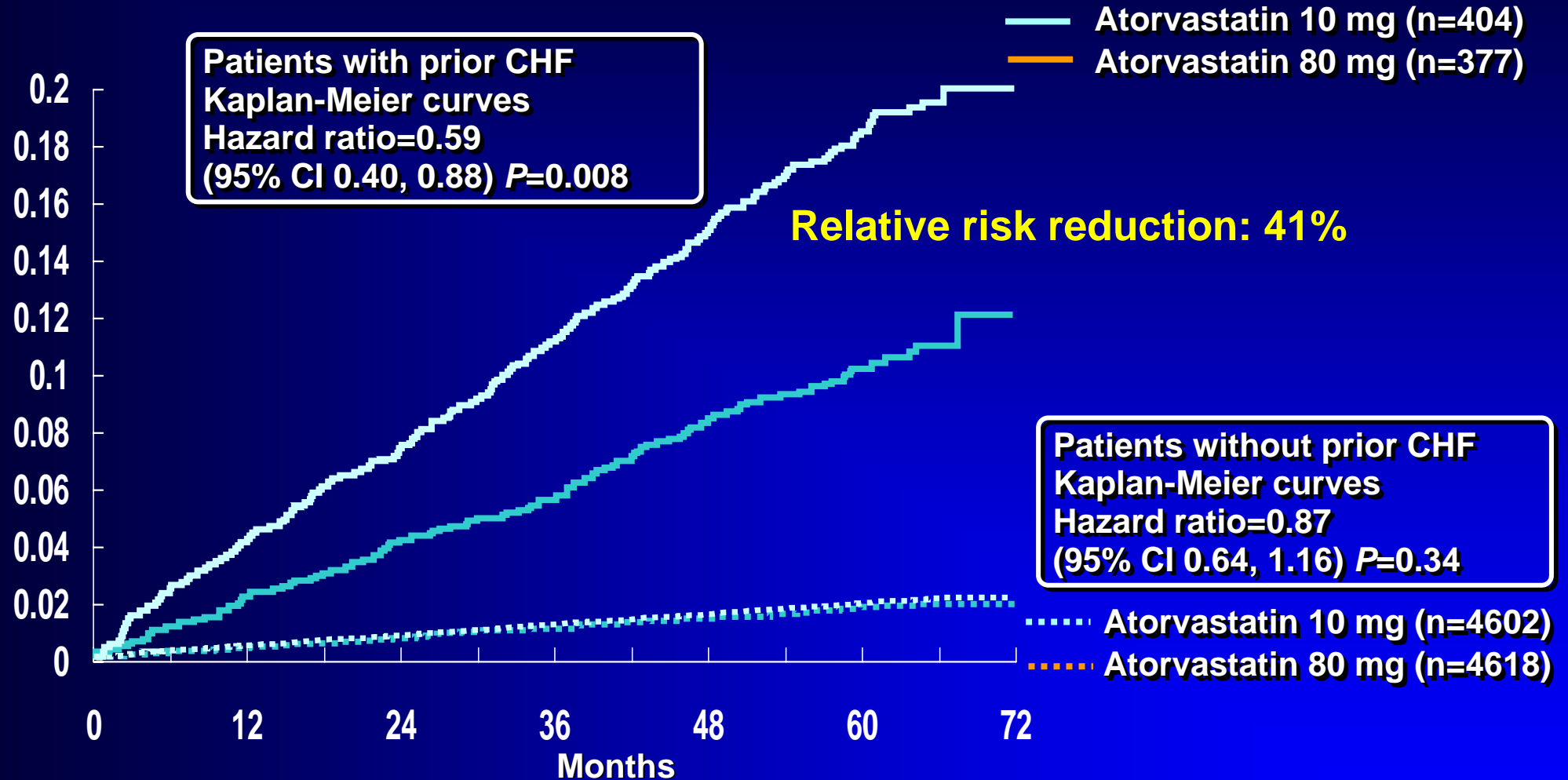


Effect of study treatment on HF hospitalization



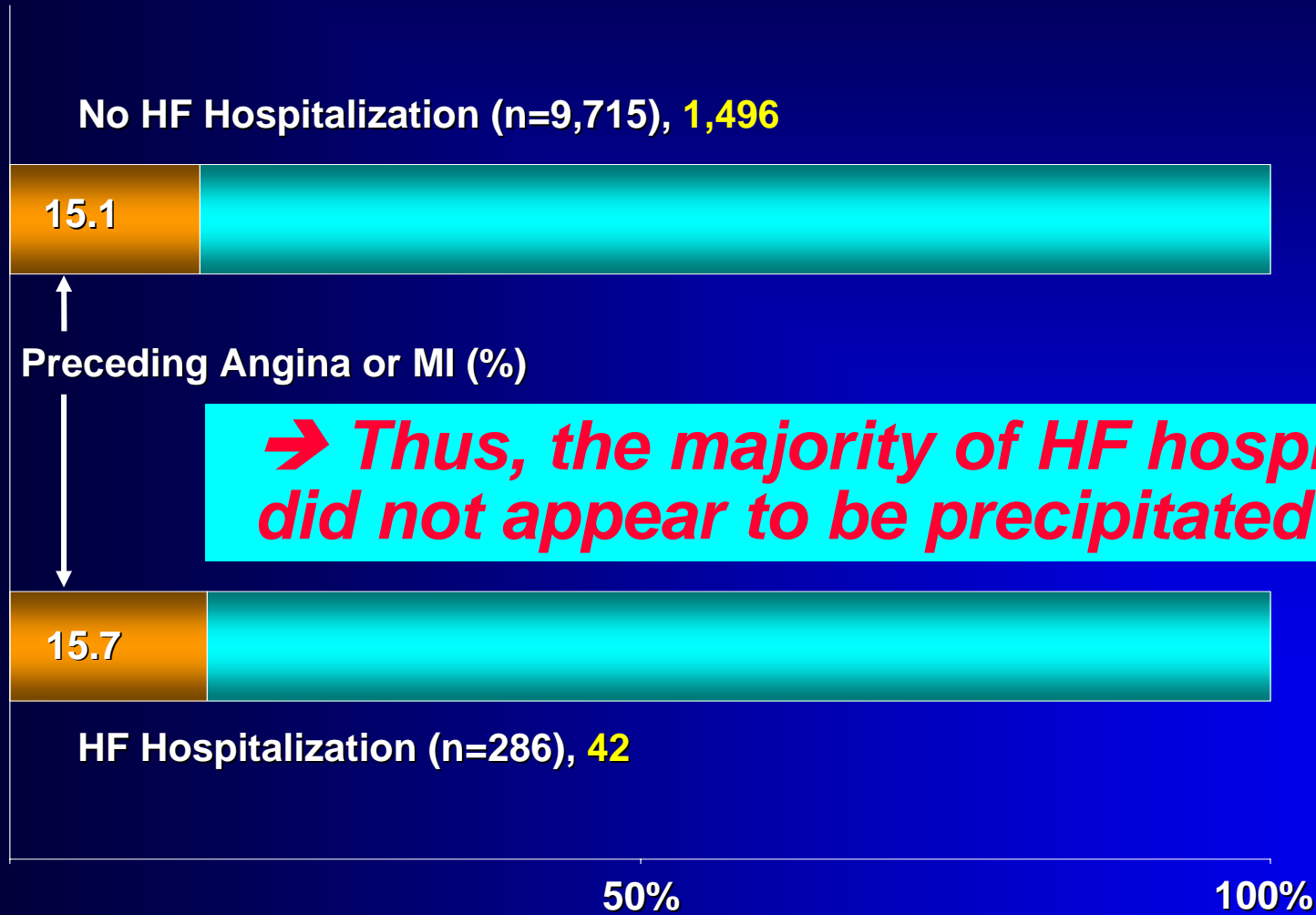
Proportion of patients in the 10- and 80-mg arms of TNT hospitalized with HF during follow-up

Effect of study treatment on HF hospitalization



Proportion of patients with and without a history of HF in the 10- and 80-mg arms of TNT experiencing hospitalization for HF during follow-up

Relationship between HF hospitalization and preceding ischemic coronary event



→ Thus, the majority of HF hospitalizations did not appear to be precipitated by angina or MI.

Summary of TNT substudy

- ❑ Patients with stable CHD and **diabetes** experienced a **25%** reduction in risk of major CV events with **atorvastatin 80 mg** vs atorvastatin 10 mg
- ❑ **A similar reduction** in risk was observed in **metabolic syndrome patients** without diabetes, with atorvastatin 80 mg yielding a significant 30% relative risk reduction vs atorvastatin 10 mg
- ❑ Intensive lipid lowering with atorvastatin 80 mg/day reduced the incidence of both **first stroke and first cerebrovascular event** by an additional 20-25% compared with the 10 mg/day dose.
- ❑ In the TNT trial, treatment with atorvastatin 80 mg/day significantly reduced the risk of **hospitalization due to HF** compared with 10 mg in patients with stable CHD

ARMYDA-ACS trial

Randomized Trial of Atorvastatin for Reduction of Myocardial Damage During Coronary Intervention

Results From the ARMYDA (Atorvastatin for Reduction of MYocardial Damage during Angioplasty) Study

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Background—Small myocardial infarctions after percutaneous coronary intervention have been associated with higher risk of cardiac events during follow-up. Observational studies have suggested that statins may lower the risk of procedural myocardial injury. The aim of our study was to confirm this hypothesis in a randomized study.

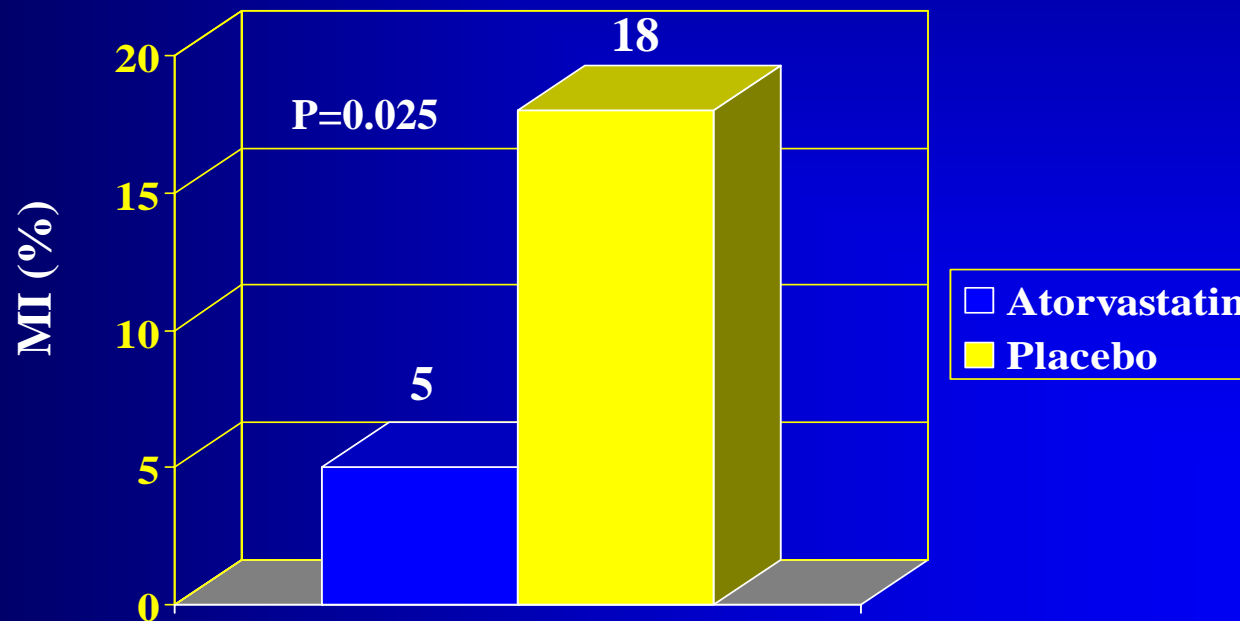
Methods and Results—One hundred fifty-three patients with chronic stable angina without previous statin treatment were enrolled in the study. Patients scheduled for elective coronary intervention were randomized to atorvastatin (40 mg/d, n=76) or placebo (n=77) 7 days before the procedure. Creatine kinase-MB, troponin I, and myoglobin levels were measured at baseline and at 8 and 24 hours after the procedure. Detection of markers of myocardial injury above the upper normal limit was significantly lower in the statin group versus the placebo group: 12% versus 35% for creatine kinase-MB ($P=0.001$), 20% versus 48% for troponin I ($P=0.0004$), and 22% versus 51% for myoglobin ($P=0.0005$). Myocardial infarction by creatine kinase-MB determination was detected after coronary intervention in 5% of patients in the statin group and in 18% of those in the placebo group ($P=0.025$). Postprocedural peak levels of creatine kinase-MB (2.9 ± 3 versus 7.5 ± 18 ng/mL, $P=0.007$), troponin I (0.09 ± 0.2 versus 0.47 ± 1.3 ng/mL, $P=0.0008$), and myoglobin (58 ± 36 versus 81 ± 49 ng/mL, $P=0.0002$) were also significantly lower in the statin than in the placebo group.

Conclusions—Pretreatment with atorvastatin 40 mg/d for 7 days significantly reduces procedural myocardial injury in elective coronary intervention. These results may influence practice patterns with regard to adjuvant pharmacological therapy before percutaneous revascularization. (*Circulation*. 2004;110:674-678.)

BACKGROUND

❖ The original ARMYDA trial demonstrated that 7-day pretreatment with atorvastatin (40 mg/day) confers 81% risk reduction of peri-procedural MI in patients with Stable Angina undergoing elective PCI

Primary end point: Incidence of MI



ARMYDA-ACS trial

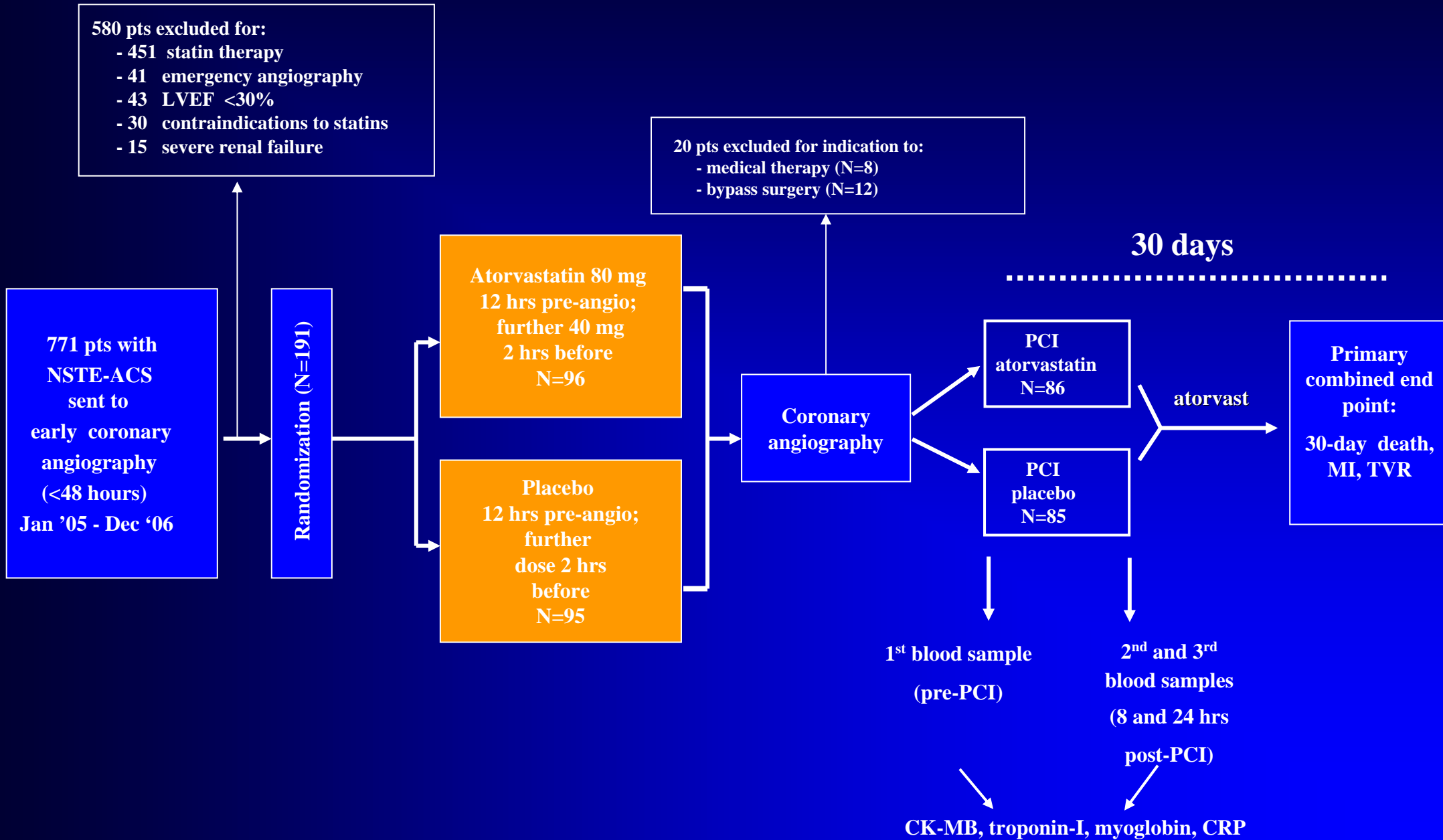
Inclusion criteria:

- ✓ NSTEMI-ACS undergoing early angiography (<48 hrs)

Exclusion criteria:

- ✓ STEMI
- ✓ ACS with high risk features warranting emergency angiography
- ✓ Previous or current statin therapy
- ✓ LVEF <30%
- ✓ Contraindications to statins (liver or muscle disease)
- ✓ Severe renal failure (creatinine >3 mg/dl)

ARMYDA-ACS trial: Study design



ARMYDA-ACS trial: Study end points

Primary end point:

Incidence of major adverse cardiac events (MACE: death, MI, TVR) from the procedure up to 30 days

MI definition:

- If normal baseline levels of CK-MB: post-procedural increase of CK-MB >2 times above UNL, according to the consensus statement of the Joint ESC/ACC Committee for the Redefinition of Myocardial Infarction for clinical trials on coronary intervention.

- If elevated baseline levels of CK-MB: subsequent rise of >2 times in CK-MB from baseline value

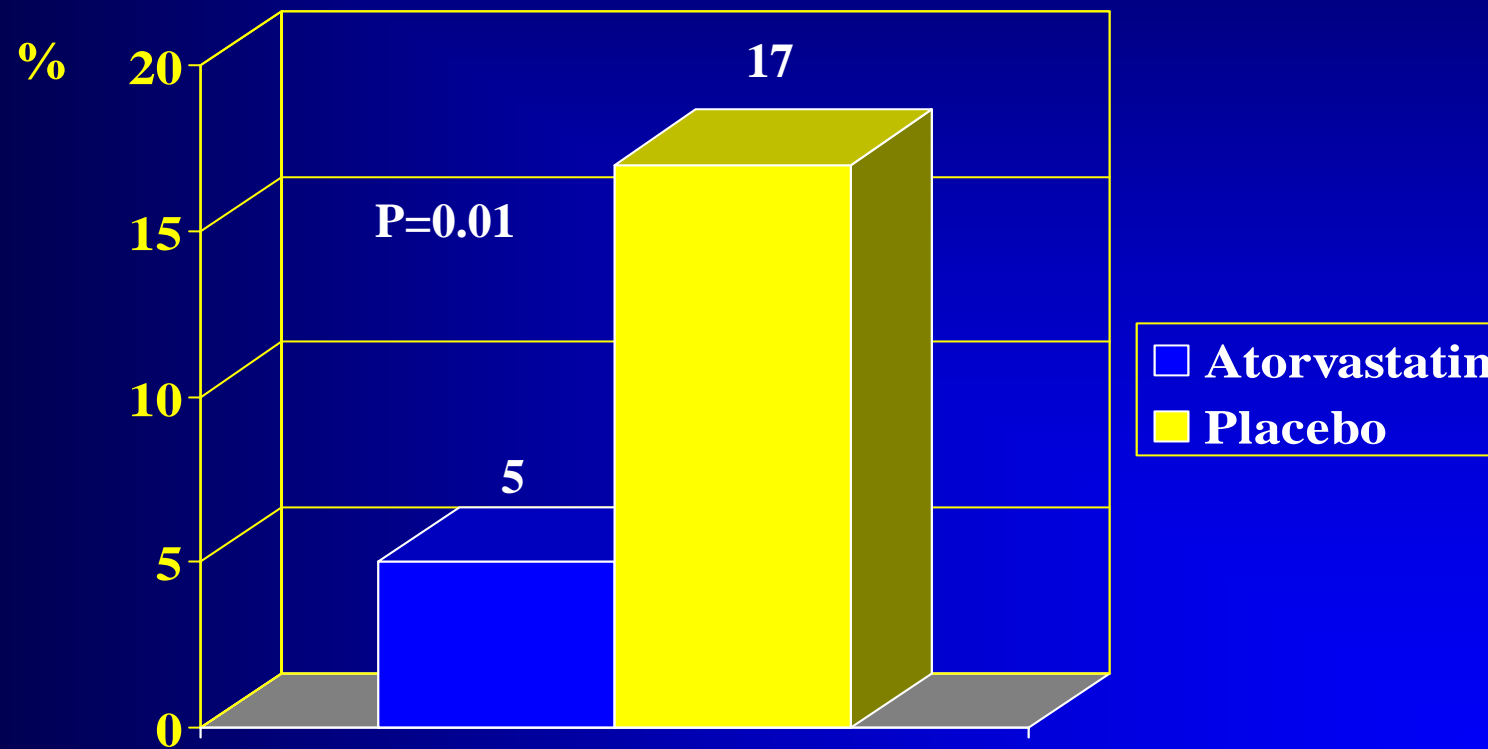
Secondary end points:

✓ Any post-procedural increase of markers of myocardial injury above UNL (CK-MB, troponin-I, myoglobin)

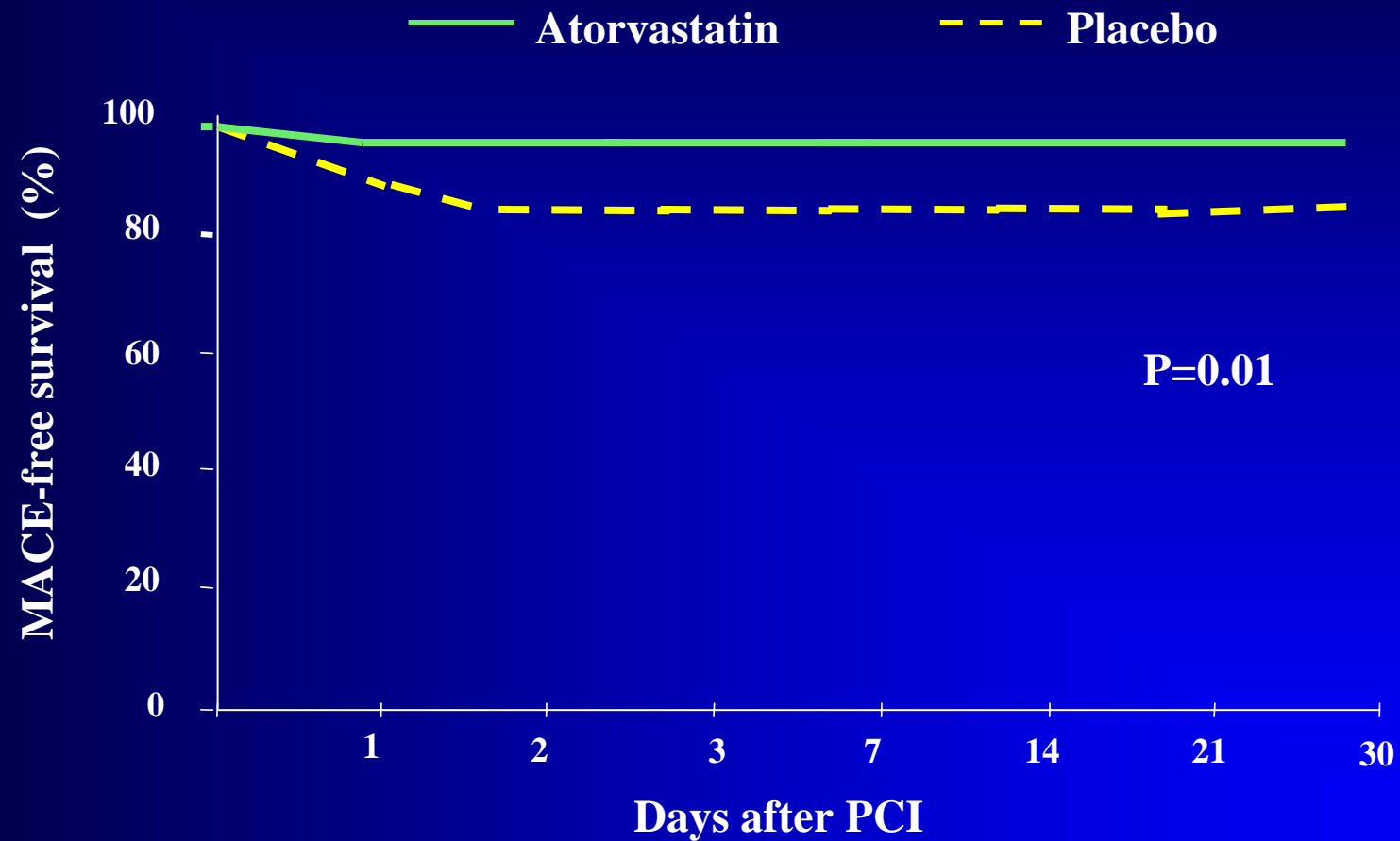
✓ Post-PCI variations from baseline of CRP levels in the 2 arms

ARMYDA-ACS trial

Composite primary end-point (30-day death, MI, TVR)

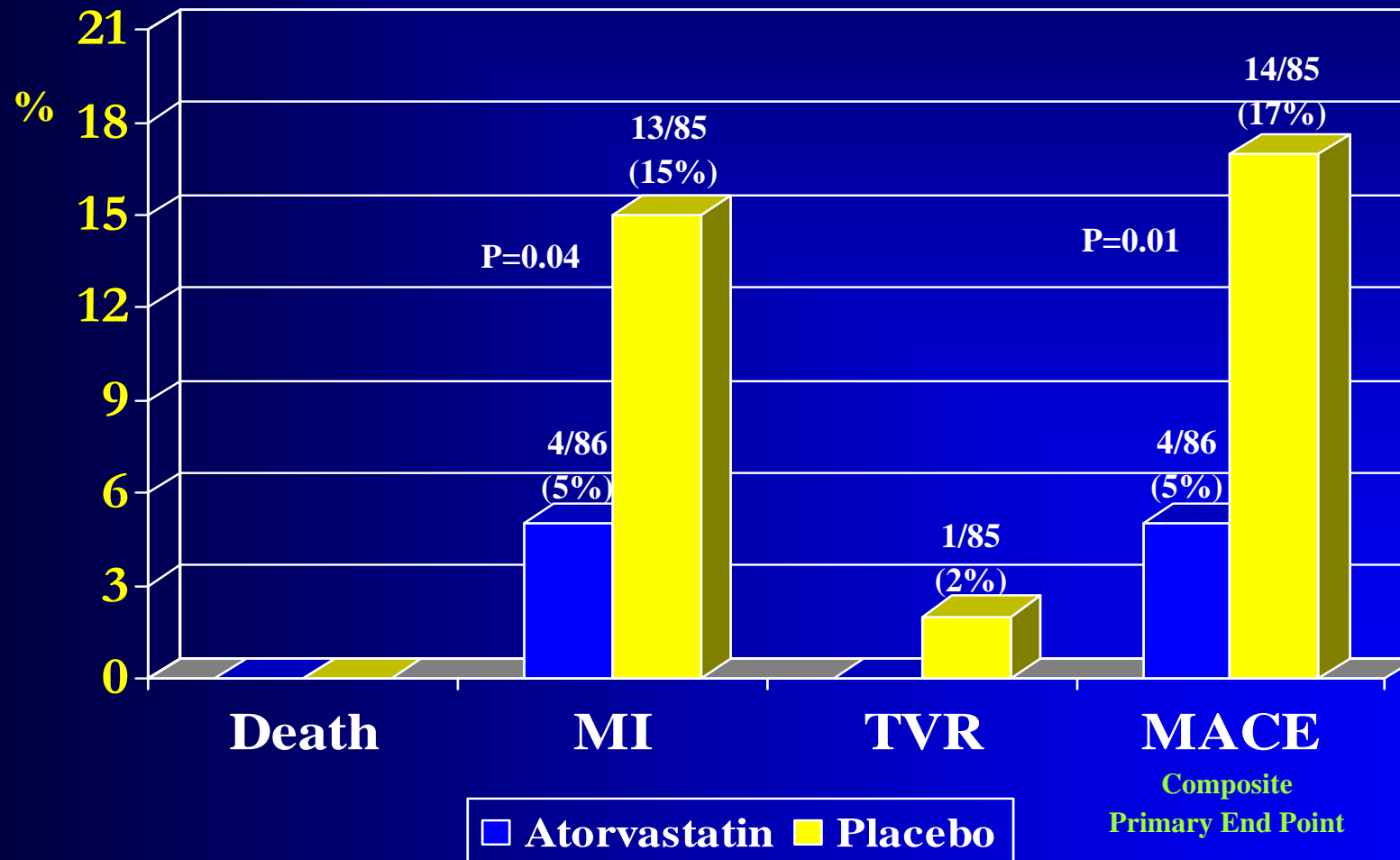


ARMYDA-ACS: Actuarial Survival curves



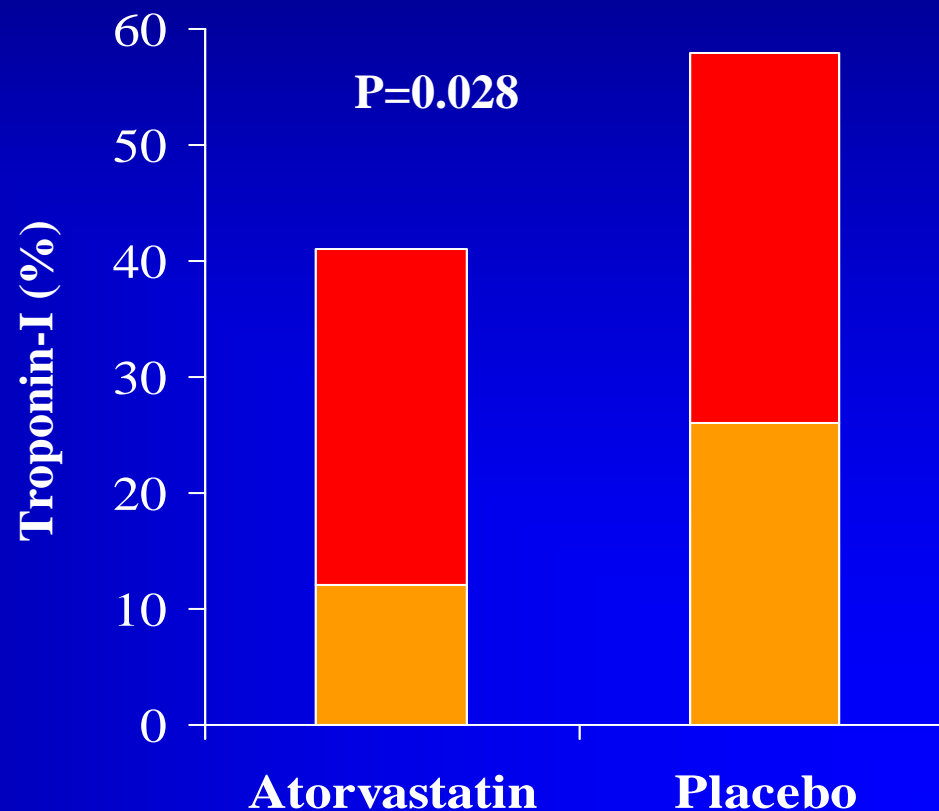
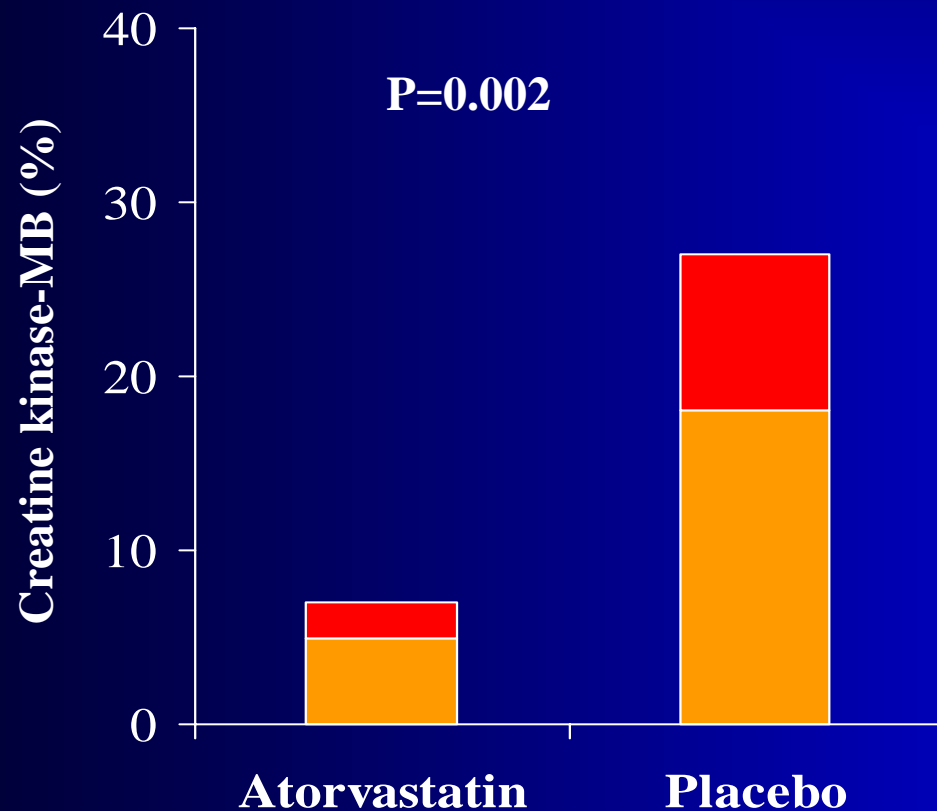
ARMYDA-ACS

Individual and Combined Outcome Measures of the Primary End Point at 30 days

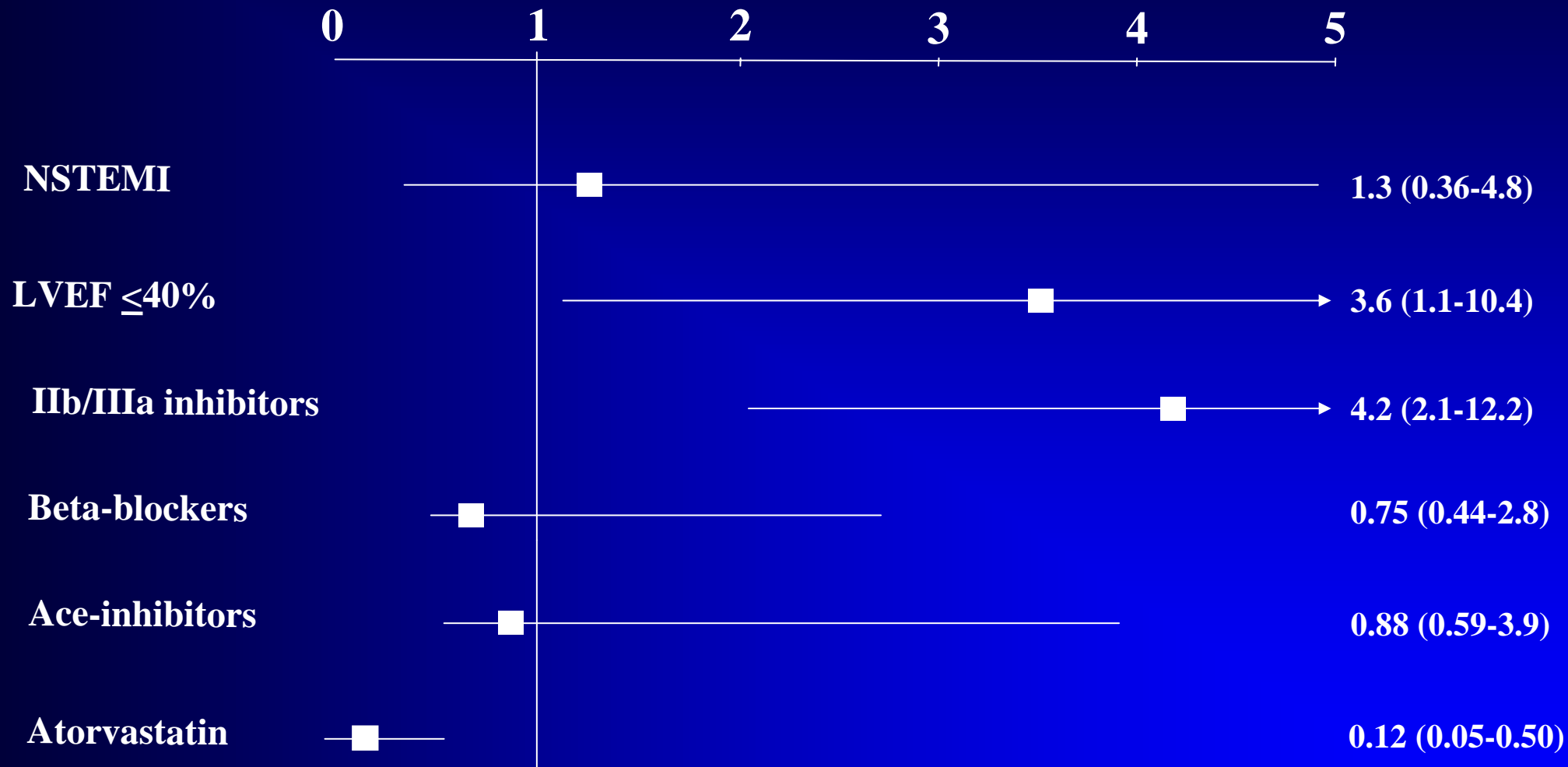


ARMYDA-ACS: Secondary end point Cardiac markers elevations

1-3 times >3 times



ARMYDA-ACS: Odds Ratio for 30-day MACE



Summary of ARMYD-ACS

- The ARMYDA-ACS trial indicates that even short-term pretreatment with atorvastatin may improve outcomes in patients with ACS undergoing early invasive strategy.

Conclusions

- ❑ The clinical trials provide substantial support for the institution of **high-dose statin therapy** in various clinical settings in the primary and secondary prevention of cardiovascular disease.
- ❑ In an analysis of high-dose statin therapy in the setting of **ACS, diabetes mellitus, metabolic syndrome, cerebrovascular disease and heart failure** demonstrated reduction in mortality and morbidity.
- ❑ Use of high-dose statins **before intervention** in patients with ACS may be beneficial.