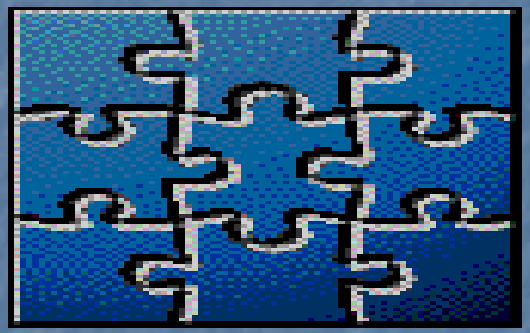
The TNT Trial Is It Time to Shift Our Goals in Clinical



Angioplasty Summit Luncheon Symposium Korea

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29 April 2005

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ATP III: Treatment Cutpoints

Risk Category	LDL -C Goal	Non-HDL-C Goal	Apo B Goal
Very High Risk	<100mg/dL (optional: <70mg/dL)	<130mg/dL (optional: <100mg/dL)	<90mg/dl
High Risk	<130 mg/dL (optional: <100mg/dL)	<160mg/dL (optional: <130mg/dL)	<105mg/dL (optional: <90mg/dL)
Moderate Risk	<130mg/dL	<160mg/dL	<105mg/dL
Lower Risk	<160mg/dL	<190 mg/dL	<120mg/dL

NCEP (ATP III) Circ 2002;106:3143-3421
NCEP (ATP III) Optional Targets Circ 2004;110:227-239

Risk Stratification for Major CHD Results from LIPID Trial

- n = 9,014 post ACS (3mths - 3 years)
- 5 year Risk for Major CHD
- Risk Score calculated on presence of Risk Factors
  - revascularization since event (-4)

Risk Level	Score	Event Rate	
		placebo	pravachol
Low	<4	5.8%	4.6%
High	7-9	13.5%	10.7%
Very High	≥10	20.2%	16.1%

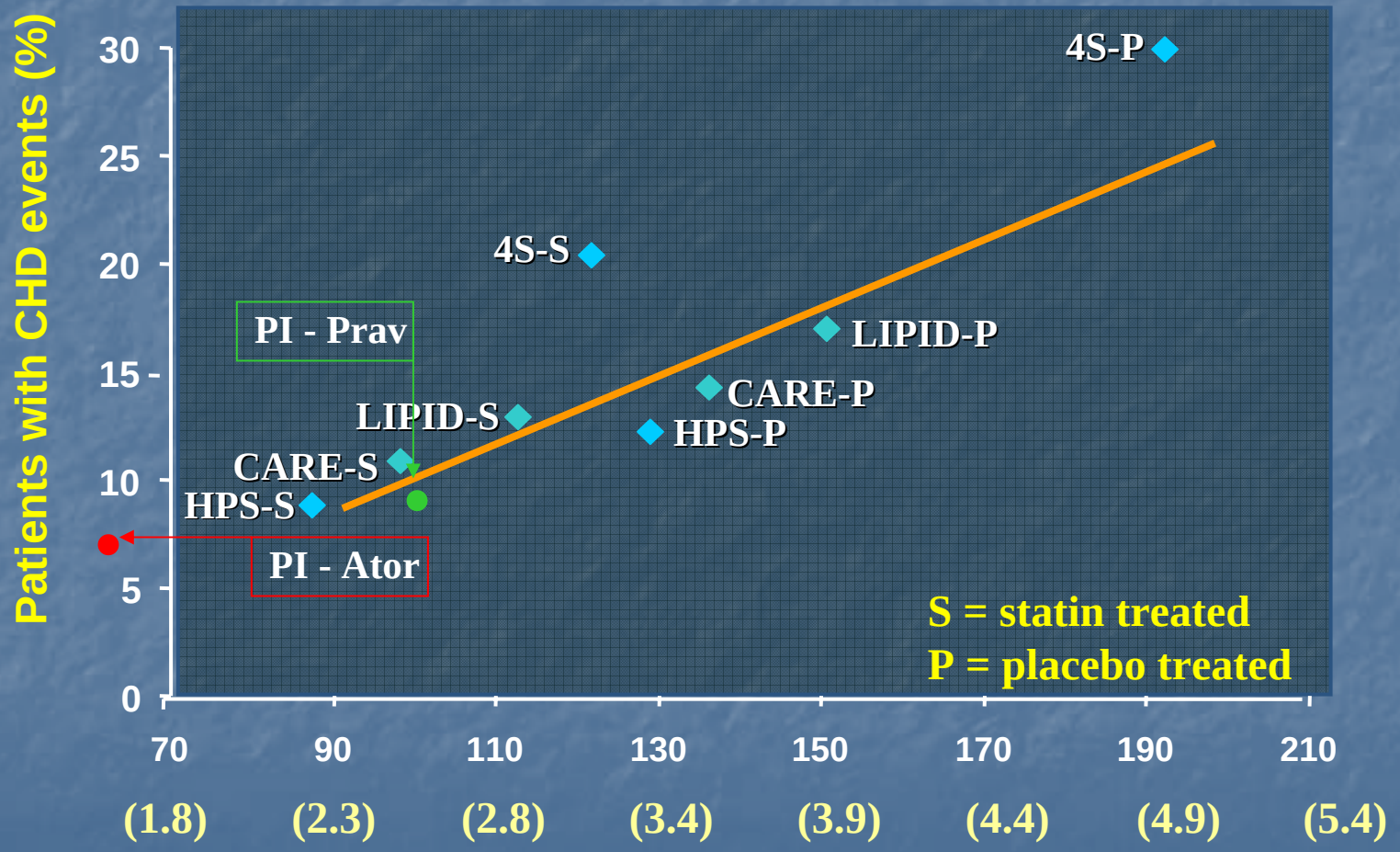
Marschner IC, Colquhoun DM, Simes JR et al. JACC 2001;38:56-63

Intensive Lipid Lowering with Atorvastatin in Patients With Stable Coronary Disease

TNT Steering Committee* and Investigators

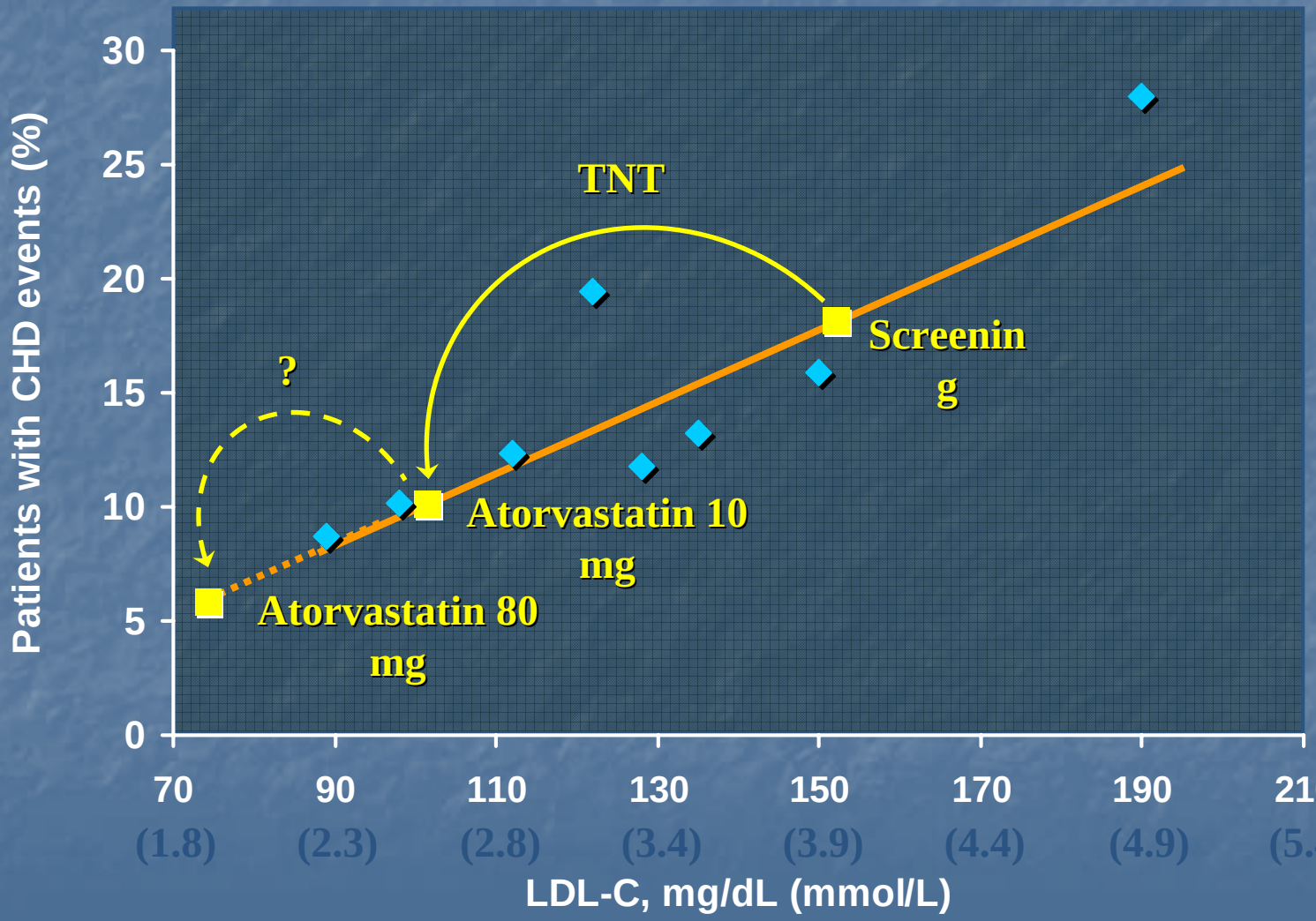
*TNT Steering Committee: J LaRosa (Chairman), USA; P Barter, Australia; J-C Fruchart, France; A Gotto, USA; H Greten, Germany; S Grundy, USA; J Kastelein, The Netherlands; J Shepherd, UK; D Waters, USA; N Wenger, USA

On Treatment LDL-C and CHD Events (Results from Landmark Statin Trials)



Modified from Kastelein JJP. *Atherosclerosis.* 1999;143(suppl 1):S17-S21

TNT Study: Rationale

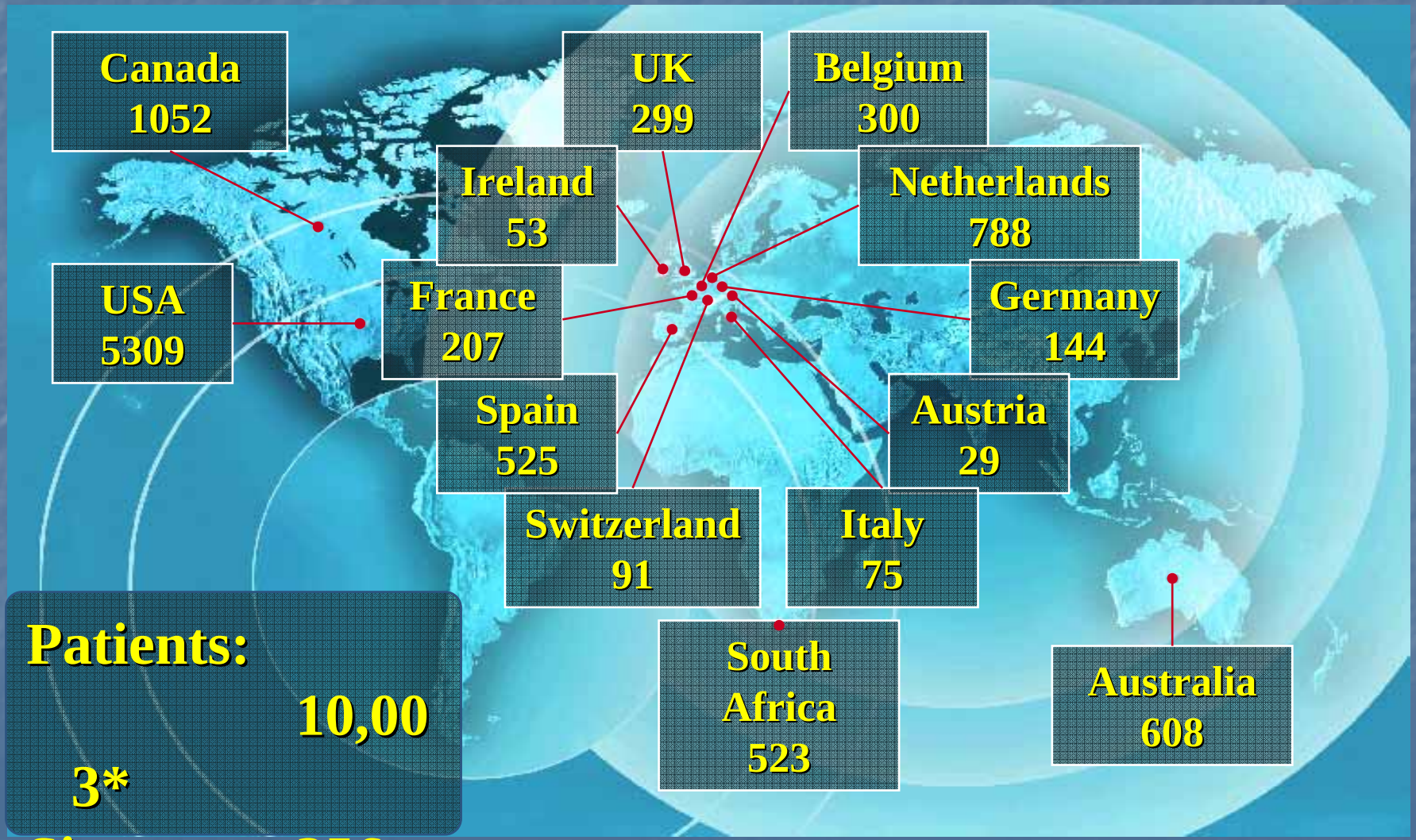


Modified from Kastelein JJP. *Atherosclerosis.* 1999;143(suppl 1):S17-

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 (2.6 mmol/L)

Patients and Sites



Patients: 10,00

3*

Sites: *256

*2 patients were randomized, but did not receive double-blind treatment

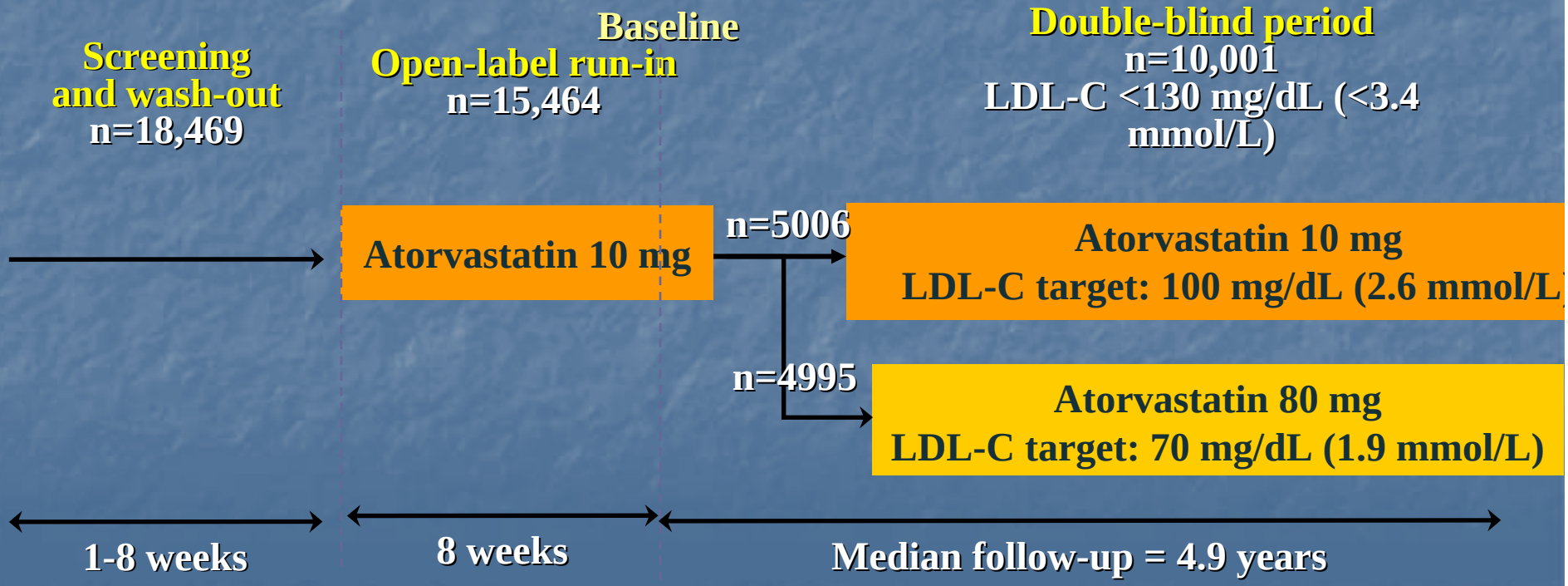
Study Design

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



Patient Inclusion Criteria

- Men and women aged 35-75 years with clinically evident CHD
  - Previous MI
  - Previous/current angina with objective evidence of atherosclerotic CHD
  - Coronary revascularization
- LDL-C 130-250 mg/dL (3.4-6.5 mmol/L) and triglycerides ≤600 mg/dL (≤6.8 mmol/L) at the beginning of open-label run-in period
- LDL-C <130 mg/dL (<3.4 mmol/L) at the end of open-label run-in period

Waters DD, *et al. Am J Cardiol.* 2004;93:154-8

Patient Exclusion Criteria

- Statin hypersensitivity
- Current liver disease, nephrosis, pregnancy, or uncontrolled CHD risk factors (eg, diabetes, hypertension)
- MI, coronary revascularization procedure, or severe/unstable angina within 1 month of screening
- Congestive heart failure
- Unexplained CPK levels >6 × ULN
- Life-threatening malignancy
- Immunosuppressive or lipid-lowering drug treatment

Waters DD, *et al. Am J Cardiol.* 2004;93:154-8

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

Waters DD, *et al. Am J Cardiol.* 2004;93:154-8

Secondary Efficacy Outcome Measures

- Major coronary event
  - CHD death, nonfatal non-procedure-related MI, resuscitated cardiac arrest
- Any coronary event
  - Major coronary event, revascularization procedure, procedure-related MI, documented angina
- Cerebrovascular event
  - Fatal or nonfatal stroke, transient ischemic attack
- Peripheral arterial disease (PAD)
  - New diagnosis of PAD, admission related to its treatment, any incidental discovery of plaques or stenosis
- Hospitalization with primary diagnosis of CHF
- Any CV event
- All-cause mortality

Waters DD, *et al. Am J Cardiol.* 2004;93:154-8

Baseline Patient Characteristics

	Atorvastatin 10mg (n=5006)	Atorvastatin 80mg (n=4995)
Age (mean ± SD), years	61 ± 8.8	61 ± 8.8
Men (%)	81	81
White (%)	94	94
Cardiovascular risk factors (%)		
Current smoker	13	13
Hypertension	54	54
Diabetes mellitus	15	15
Cardiovascular history (%)		
Angina	81	82
Myocardial infarction	58	59
Coronary angioplasty	54	54
Coronary bypass	47	47
Cerebrovascular accident	5	5

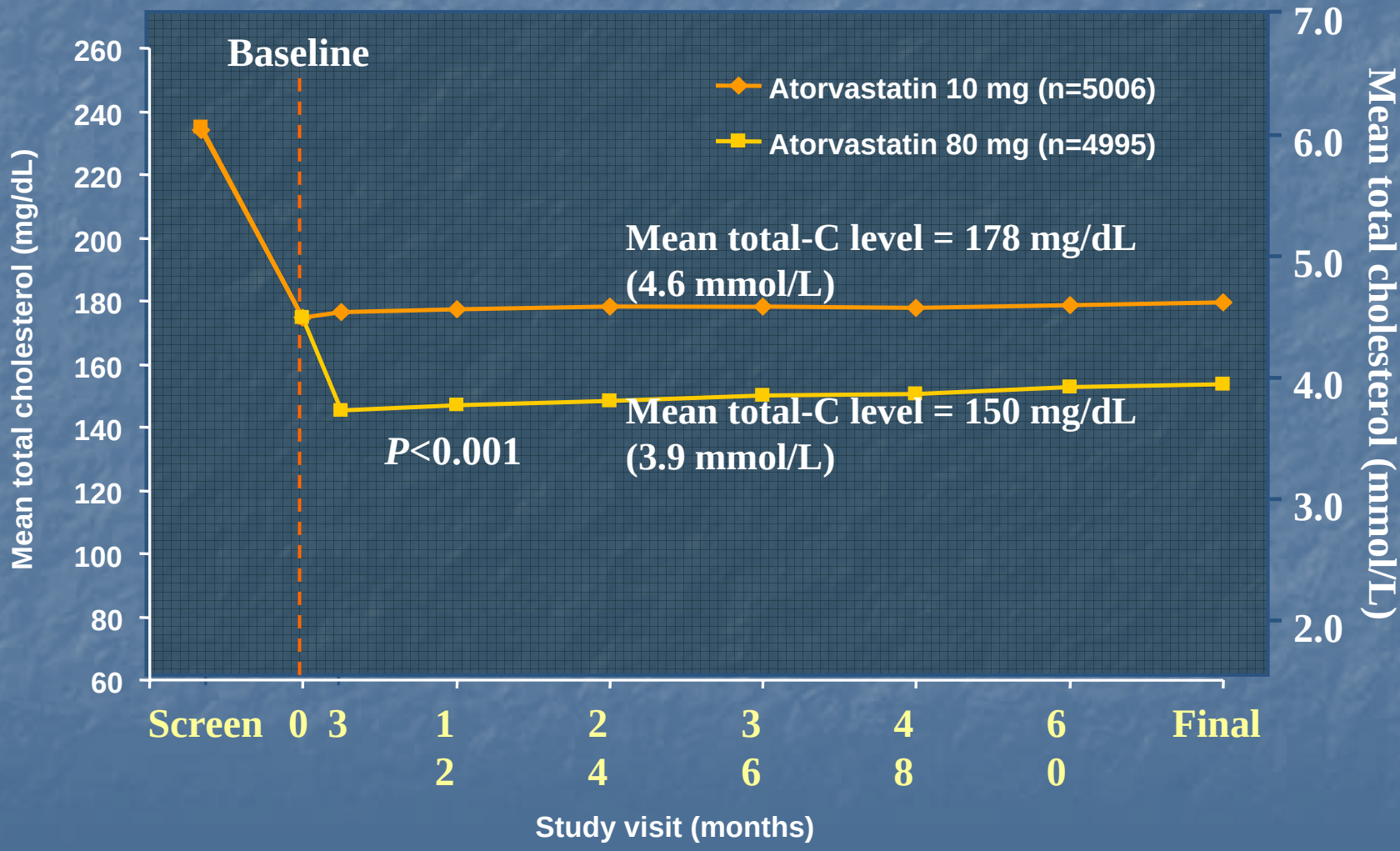
LaRosa JC, *et al. N Eng J Med.* 2005;352

Baseline Patient Characteristics: Fasting Serum Lipids

Lipid parameter	Mean ± SD, mg/dL (mmol/L)	
	Atorvastatin 10 mg (n=5006)	Atorvastatin 80 mg (n=4995)
LDL cholesterol	98 ± 18 (2.5 ± 0.5)	97 ± 18 (2.5 ± 0.5)
Total cholesterol	175 ± 24 (4.5 ± 0.6)	175 ± 24 (4.5 ± 0.6)
Triglycerides	151 ± 72 (1.7 ± 0.8)	151 ± 70 (1.7 ± 0.8)
HDL cholesterol	47 ± 11 (1.2 ± 0.3)	47 ± 11 (1.2 ± 0.3)

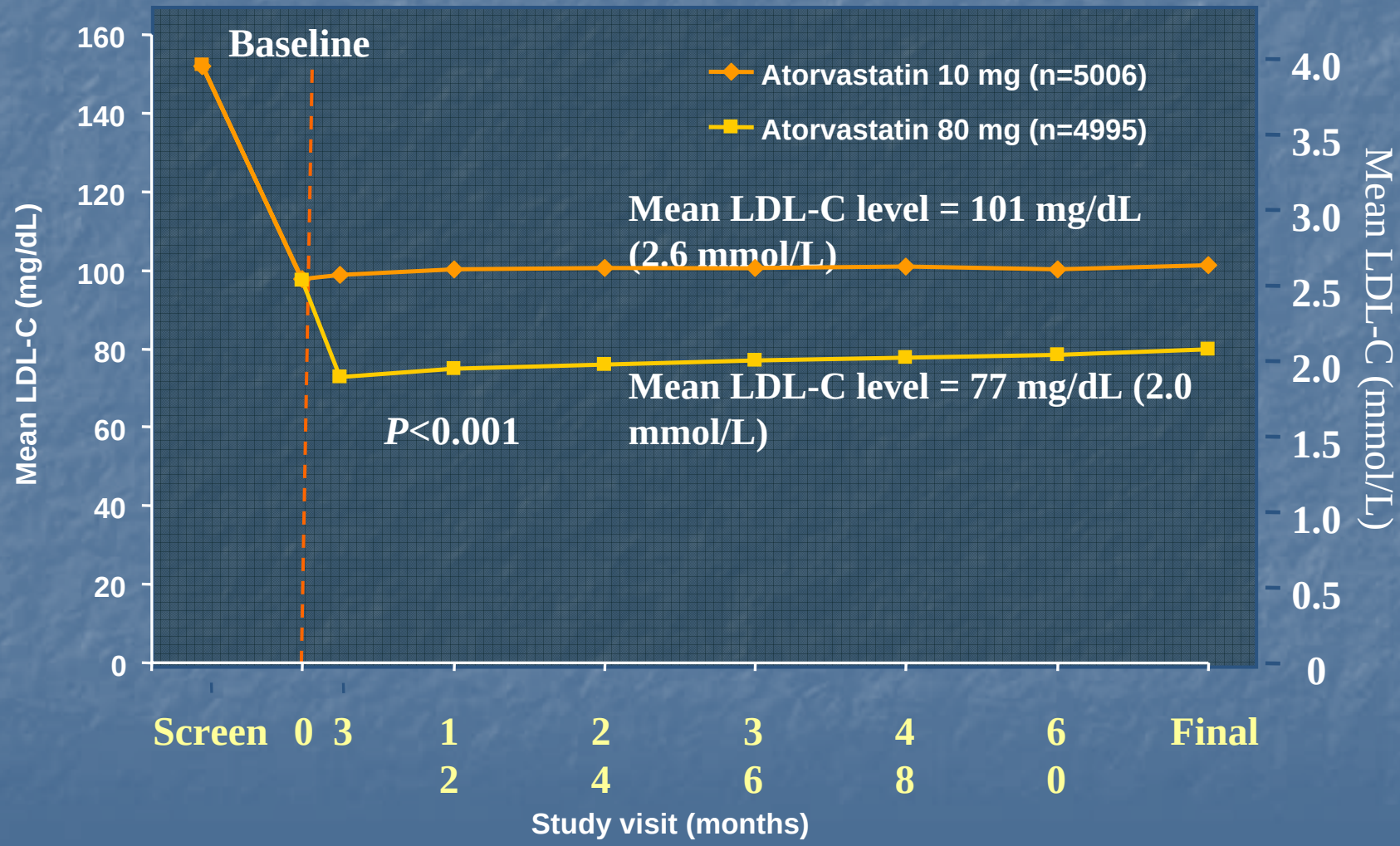
LaRosa JC, et al. N Eng J Med. 2005;352

Changes in Total Cholesterol By Treatment Group



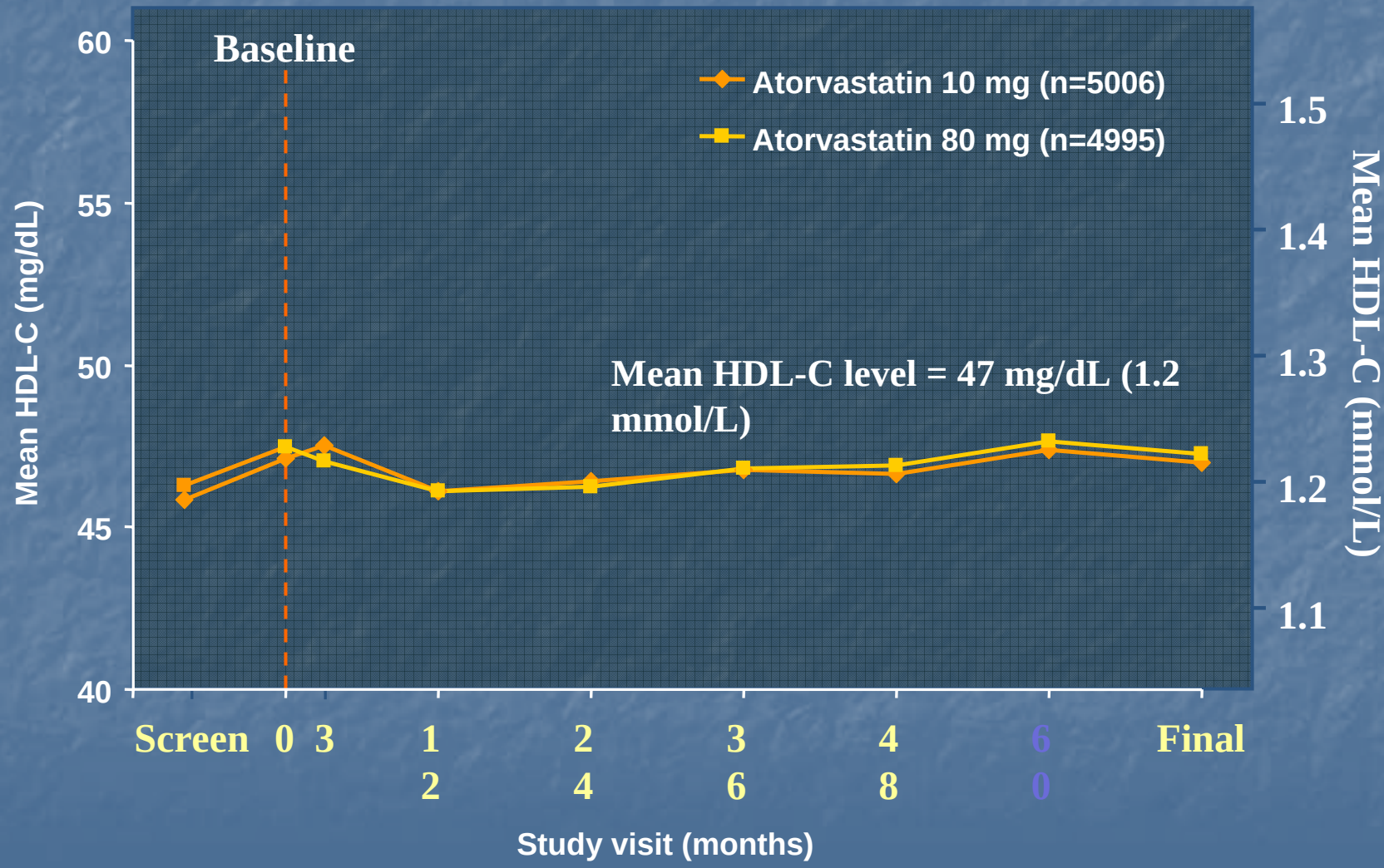
LaRosa JC, *et al. N Eng J Med.* 2005;352

Changes in LDL-C By Treatment Group



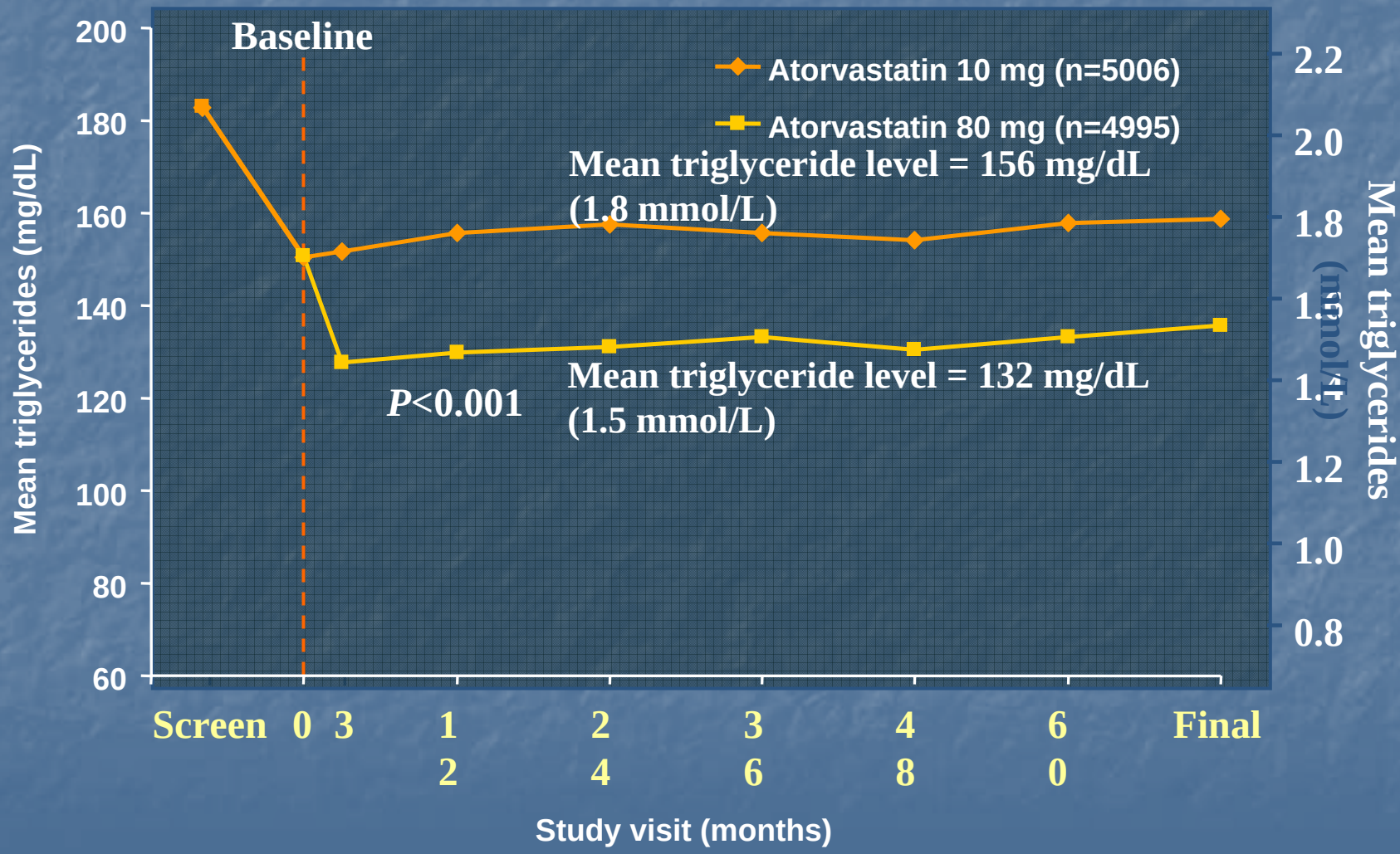
LaRosa JC, *et al. N Eng J Med.* 2005;352

Changes in HDL-C By Treatment Group



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

Changes in Triglycerides By Treatment Group



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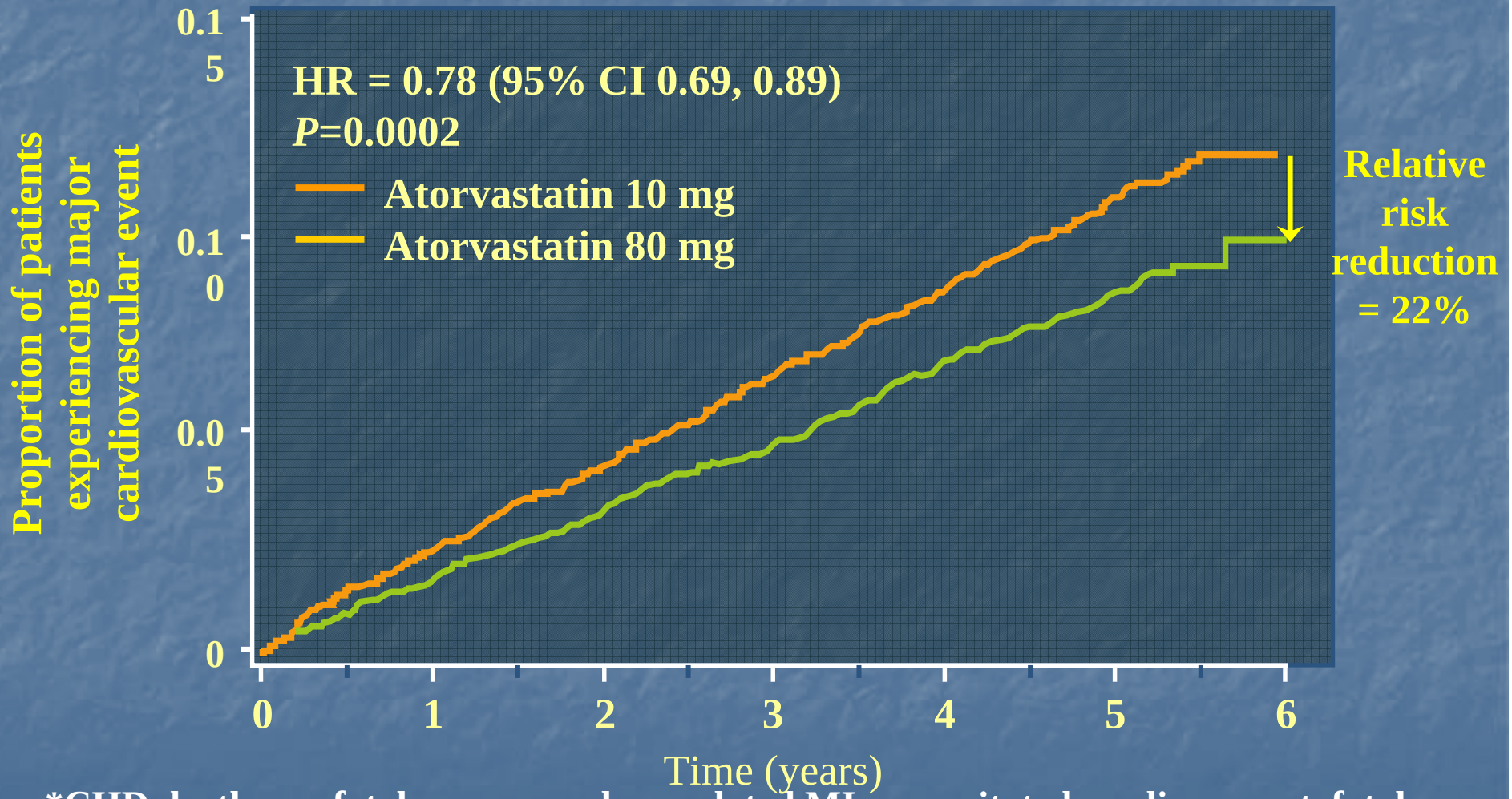
Major Cardiovascular Events



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

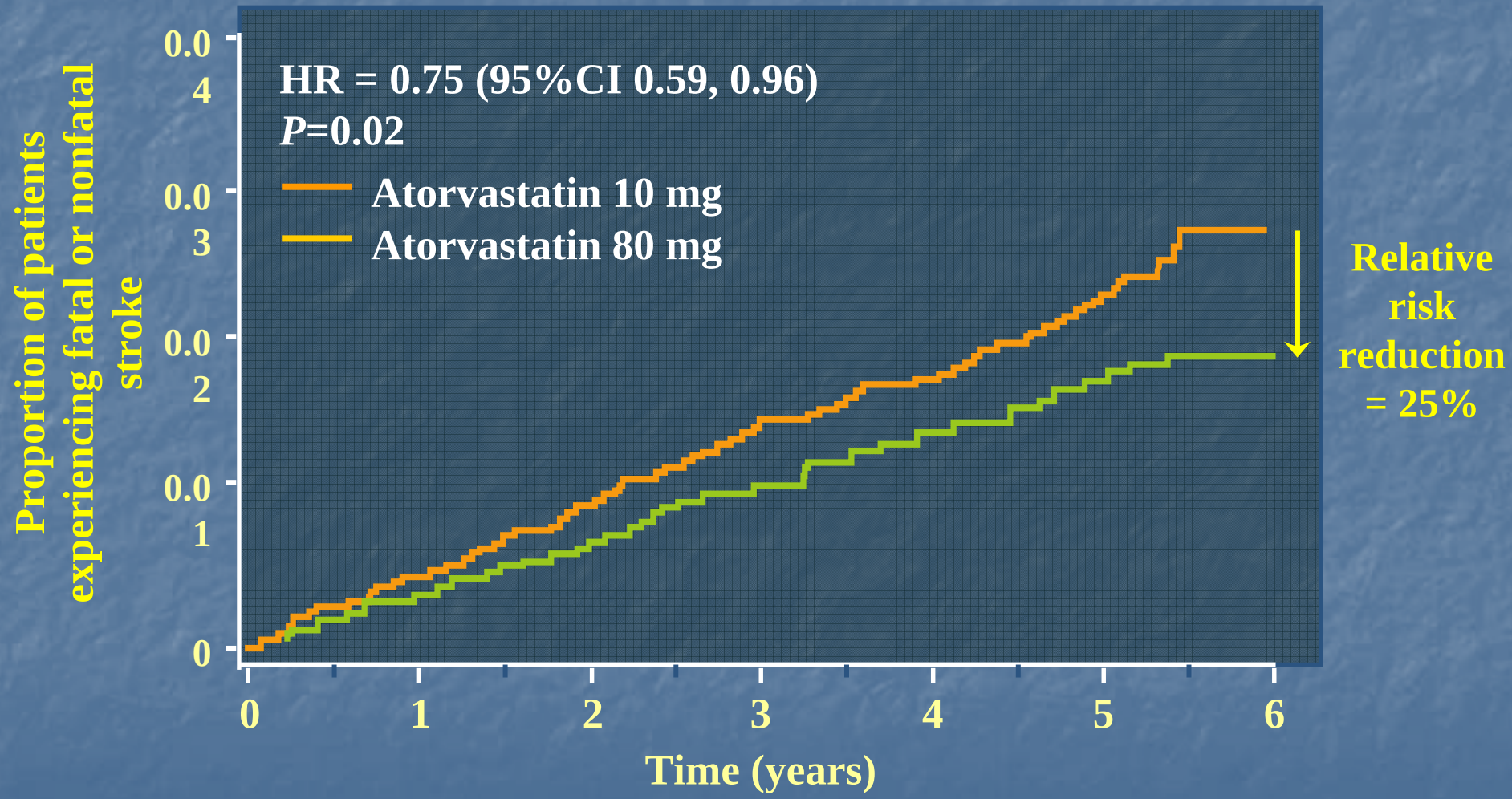
LaRosa JC, *et al. N Eng J Med.* 2005;352

Primary Efficacy Outcome Measure: Summary

End point	No. of patients (%)		HR	*P*-value
	Atorvastatin 10 mg (n=5006)	Atorvastatin 80 mg (n=4995)		
Major CV event	**548 (10.9)**	**434 (8.7)**	**0.78**	**0.0002**
CHD death	127 (2.5)	101 (2.0)	0.80	0.09
Nonfatal non-PR MI	308 (6.2)	243 (4.9)	0.78	0.004
Resuscitated cardiac arrest	26 (0.5)	25 (0.5)	0.96	0.89
Fatal/Nonfatal stroke	155 (3.1)	117 (2.3)	0.75	0.02

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

Stroke (Fatal or Nonfatal)



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

Secondary Efficacy Outcome Measures: Summary

End point	No. of patients (%)		HR	*P*-value
	Atorvastatin 10 mg (n=5006)	Atorvastatin 80 mg (n=4995)		
Any CV event	1677 (33.5)	1405 (28.1)	0.81	<0.001
Major coronary event	418 (8.3)	334 (6.7)	0.80	0.002
Any coronary event	1326 (26.5)	1078 (21.6)	0.79	<0.001
Cerebrovascular event	250 (5.0)	196 (3.9)	0.77	0.007
Hospitalization for CHF	164 (3.3)	122 (2.4)	0.74	0.01
PAD	282 (5.6)	285 (5.7)	0.97	0.76
All-cause mortality	282 (5.6)	284 (5.7)	1.01	0.92

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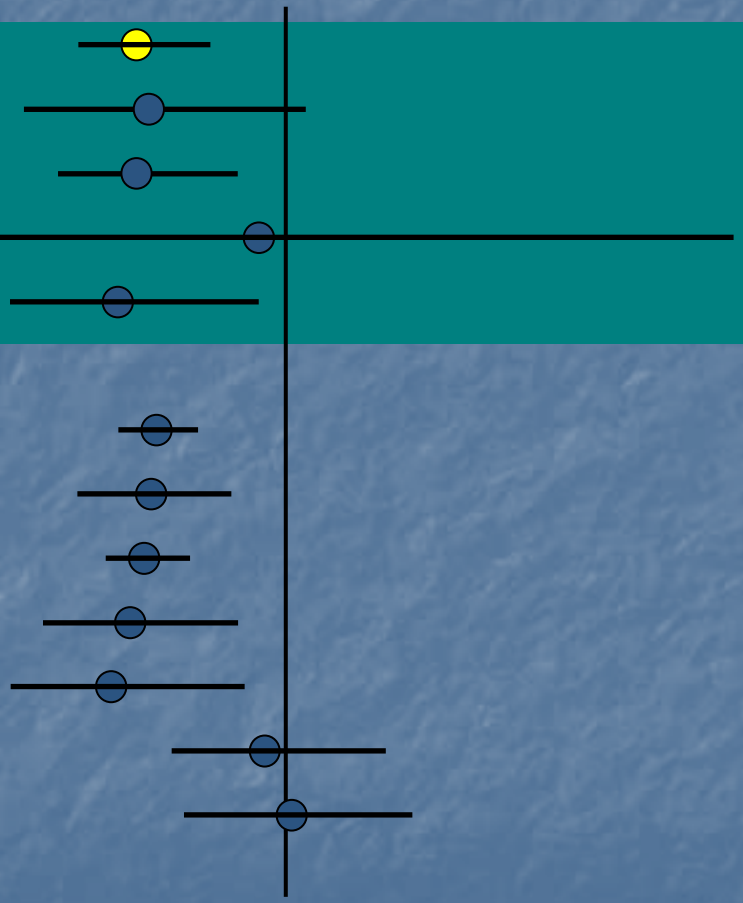
Primary and Secondary Efficacy Outcome Measures: Hazard Ratios



Primary Efficacy Measure	HR	*P*-value
Major CV event	**0.78**	**0.0002**
– CHD death	0.80	0.09
– Nonfatal, non-PR MI	0.78	0.004
– Resuscitated cardiac arrest	0.96	0.89
– Fatal/nonfatal stroke	0.75	0.02
Secondary Efficacy Measures		
Any cardiovascular event	0.81	<0.001
– Major coronary event*	0.80	0.002
– Any coronary event	0.79	<0.001
– Cerebrovascular event	0.77	0.007
– Hospitalization for CHF	0.74	0.01
– Peripheral arterial disease	0.97	0.76
All cause mortality	1.01	0.92

Atorvastatin 80 mg better **Atorvastatin 10 mg better**

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

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)

- No single cause of death (by body system, or pathological process) and no single cancer type drove the non-significant difference in all-cause mortality between groups
- No statistically significant differences were observed between treatment groups for any cause of death

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

Safety[1]

	No. of patients (%)	
	Atorvastatin 10 mg (n=5006)	Atorvastatin 80 mg (n=4995)
Treatment-related AEs	289 (5.8)	406 (8.1)
Treatment-related myalgia	234 (4.7)	241 (4.8)
Rhabdomyolysis*	3 (0.06)	2 (0.04)
AST/ALT elevation >3 × ULN	9 (0.2)	60 (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

1. LaRosa JC, *et al*. N Eng J Med. 2005;352
2. Pasternak RC *et al*. *Circulation*. 2002;106:1024-1028

TNT confirms and extends results of -

Prove-It

Ascot - LLA

Reversal

HPS

A to Z

that lowering LDL-C considerably below 100mg/dL provides further clinical benefit

Summary – 1

- TNT study first randomized trial designed to demonstrate the benefits of lowering LDL-C below 100 mg/dL in stable CHD
- Significant (>20%) declines in CHD and CVD atorvastatin 80 mg vs atorvastatin 10 mg
- 25% lower stroke atorvastatin 80 mg vs atorvastatin 10 mg

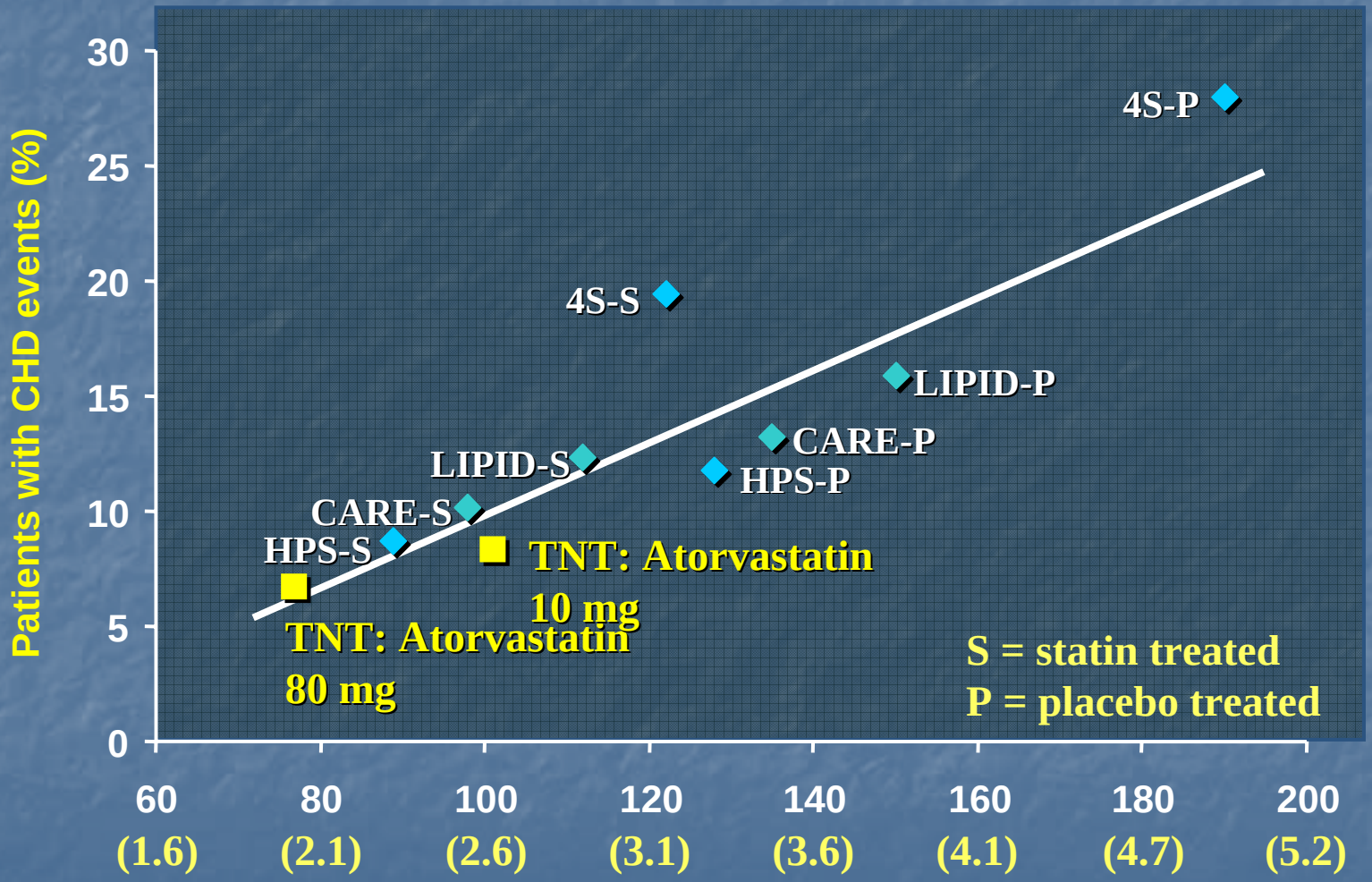
LaRosa JC, *et al. N Eng J Med.* 2005;352

Summary – 2

- No difference between doses of atorvastatin for all-cause, CHD, or non-cardiovascular mortality
- Even at high atorvastatin dose, there was a very low incidence of elevated LFTs (1.2%) or myalgias (4.8%)
- No treatment-related rhabdomyolysis

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

On Treatment LDL-C and CHD Events (TNT and Landmark Statin Trials)



Modified from Kastelein JJP. *Atherosclerosis.* 1999;143(suppl 1):S17-S21

Conclusions

- Treatment with atorvastatin 80 mg to an LDL-C of 77 mg/dL (2.0 mmol/L) provided significant additional clinical benefit compared to around 100 mg/dL (2.6 mmol/L)
- Less CHD events, less stroke
- No increased risk of side effects

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

Take Home Message

- New Target for high and very high risk <70mg/dL (1.9mmol/L) is validated and indicated
- New target of <70mg/dL (1.9mmol/L) optional for all CHD and asymptomatic high risk pts
- Benefits of vigorous LDL-lowering are proven and safe
- Don’t forget lifestyle measures and other risk factor control
- Don’t forget adherence