Aggressive Lipid Lowering Treatment

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Centre of Preventive Cardiology

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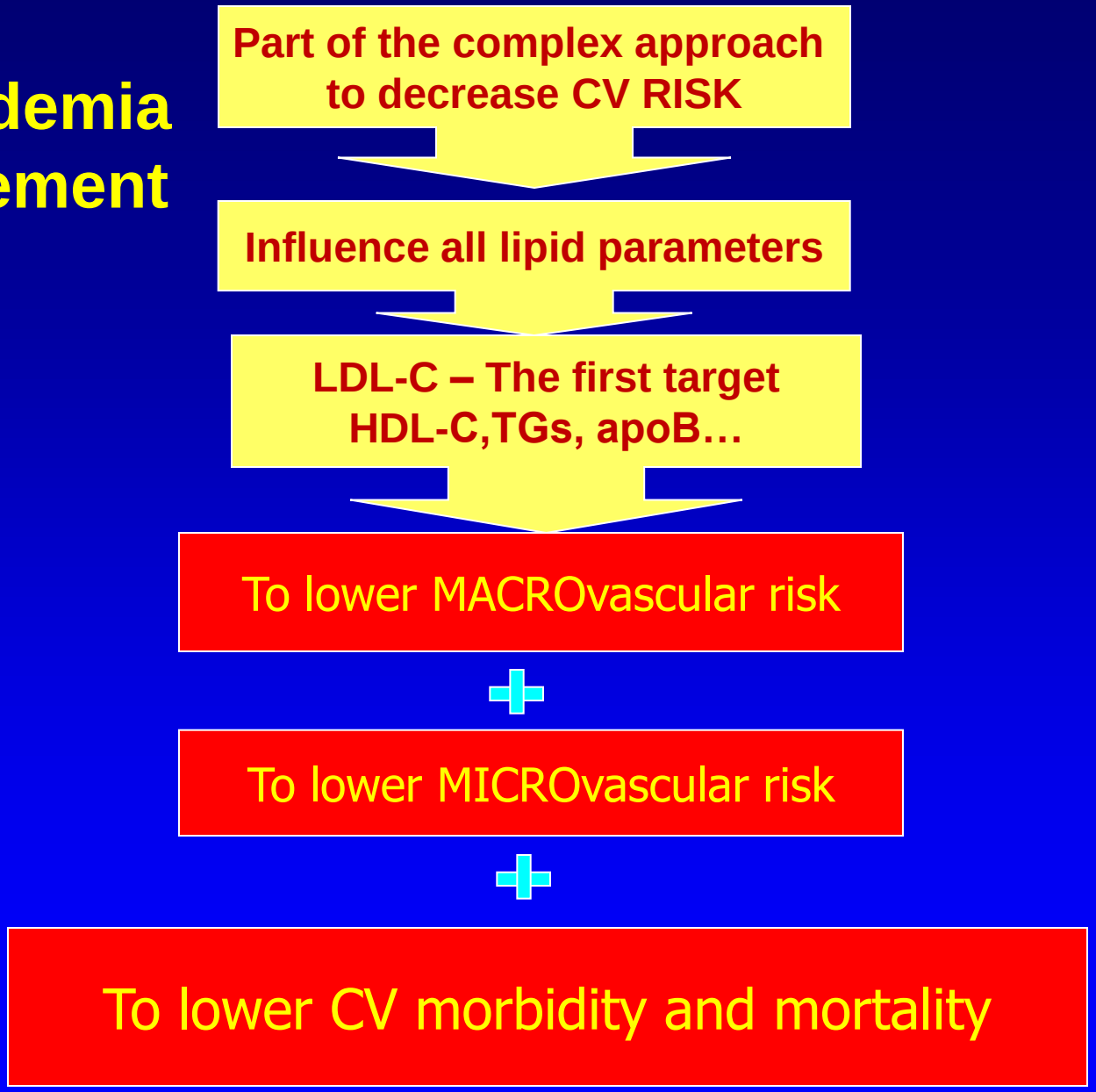
International Atherosclerosis Society

Chair: Federation for EUROPE

Dyslipidemia Management



What does it mean?
„Agressive Lipid Lowering“
.

1. **LDL-C**

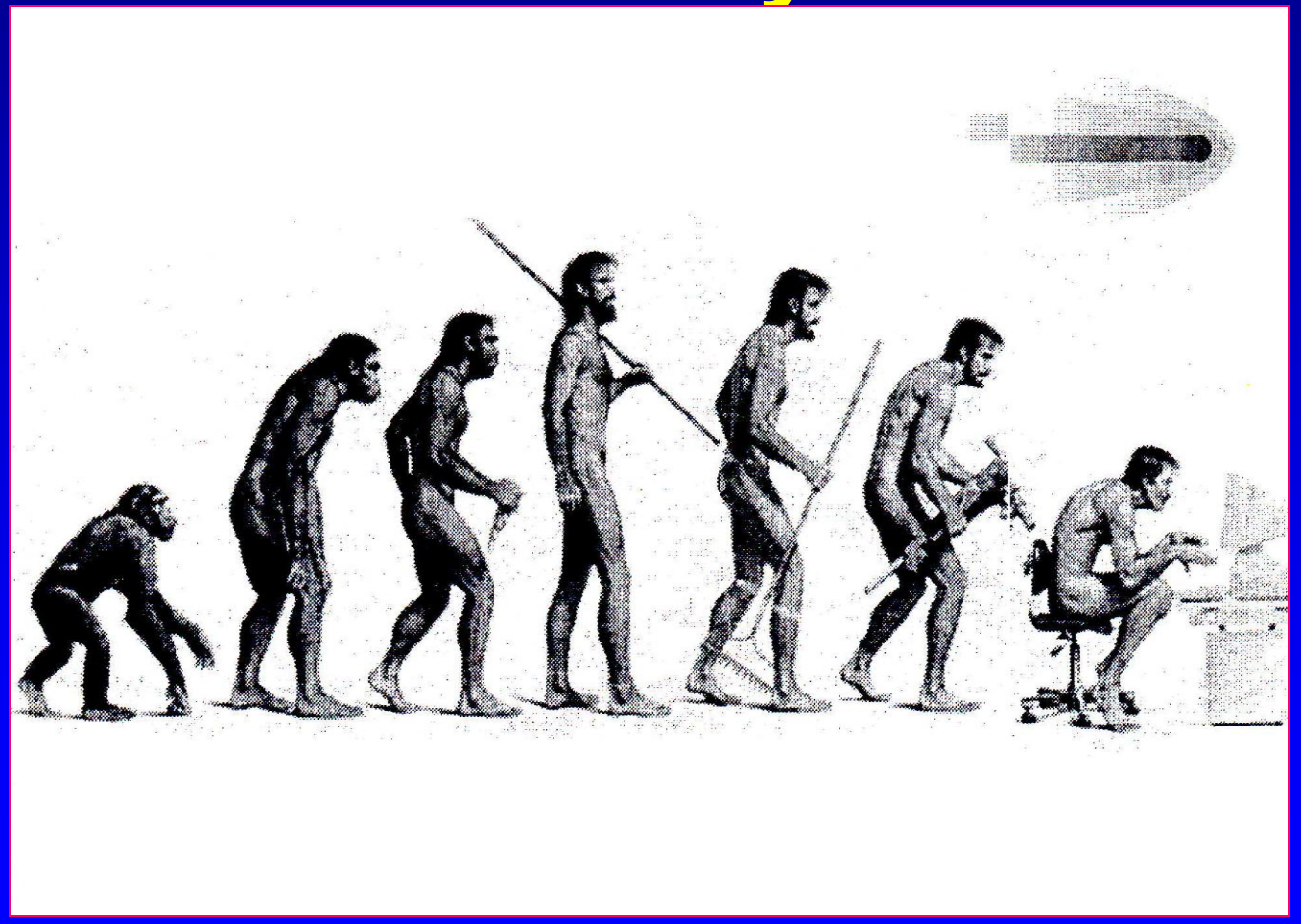
2. **Residual Risk (DLP risk)**

LDL-C

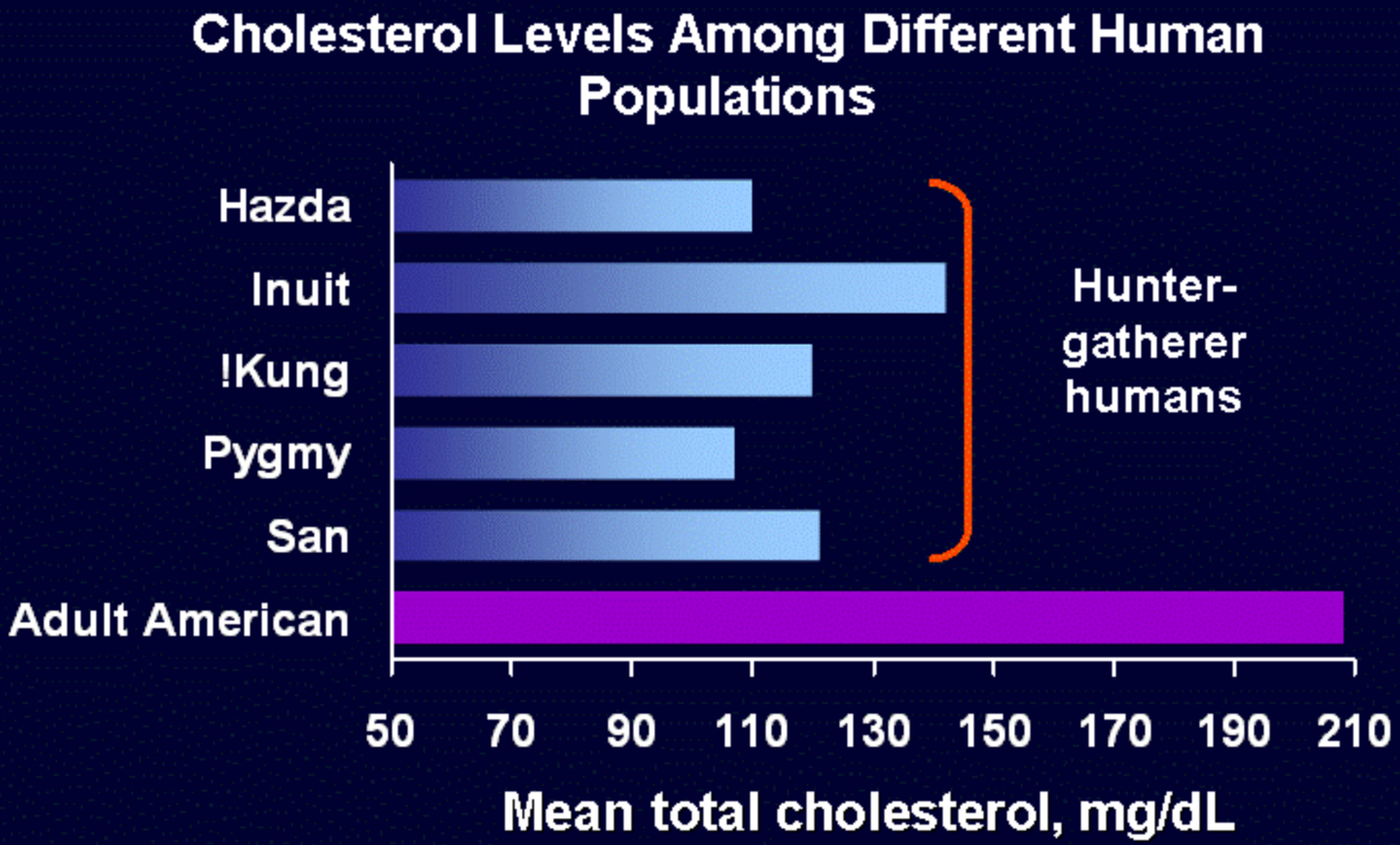
- **Killer No 1**
- **The most important risk factor for CVD**
- **The first target for lipid lowering treatment**

What is an appropriate therapeutic target for LDL-C?

The human evolution
What was the LDL-C of our ancestry?



What Is Desirable Cholesterol?



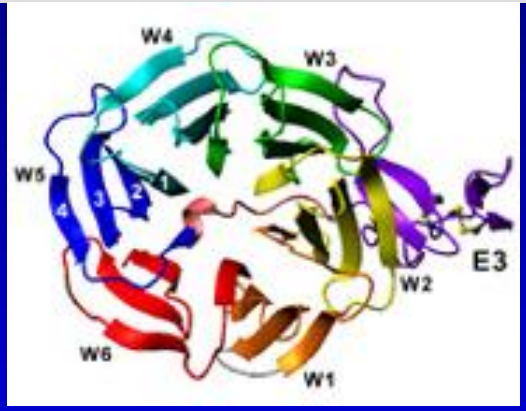
Adapted from O'Keefe JH Jr et al. *J Am Coll Cardiol*. 2004;43:2142–2146.

What is desirable LDL- C ?

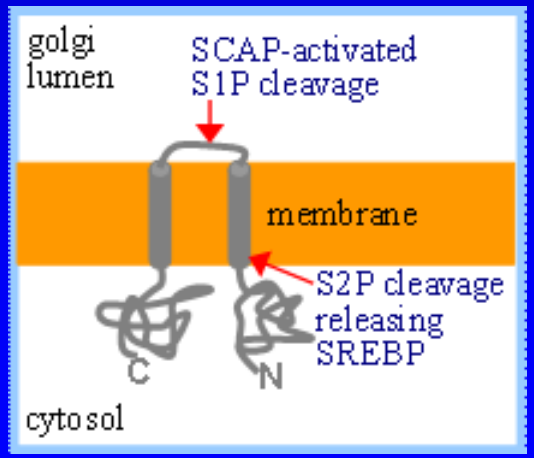
•Hunter-Gatherer humans	•1,3-1,9	50-75
•Newborn	•0,8-1,8	30-70
•Primates	•1,0-2,1	40-80
•Domestic animals	• > 2,1	>80
•Adult Euro/American	•1,3-1,8	50-70
•(probable physiologic level)	•Desirable	

LDL-Receptor Pathway
SREBP Pathway

Michael BROWN



LDL-receptor

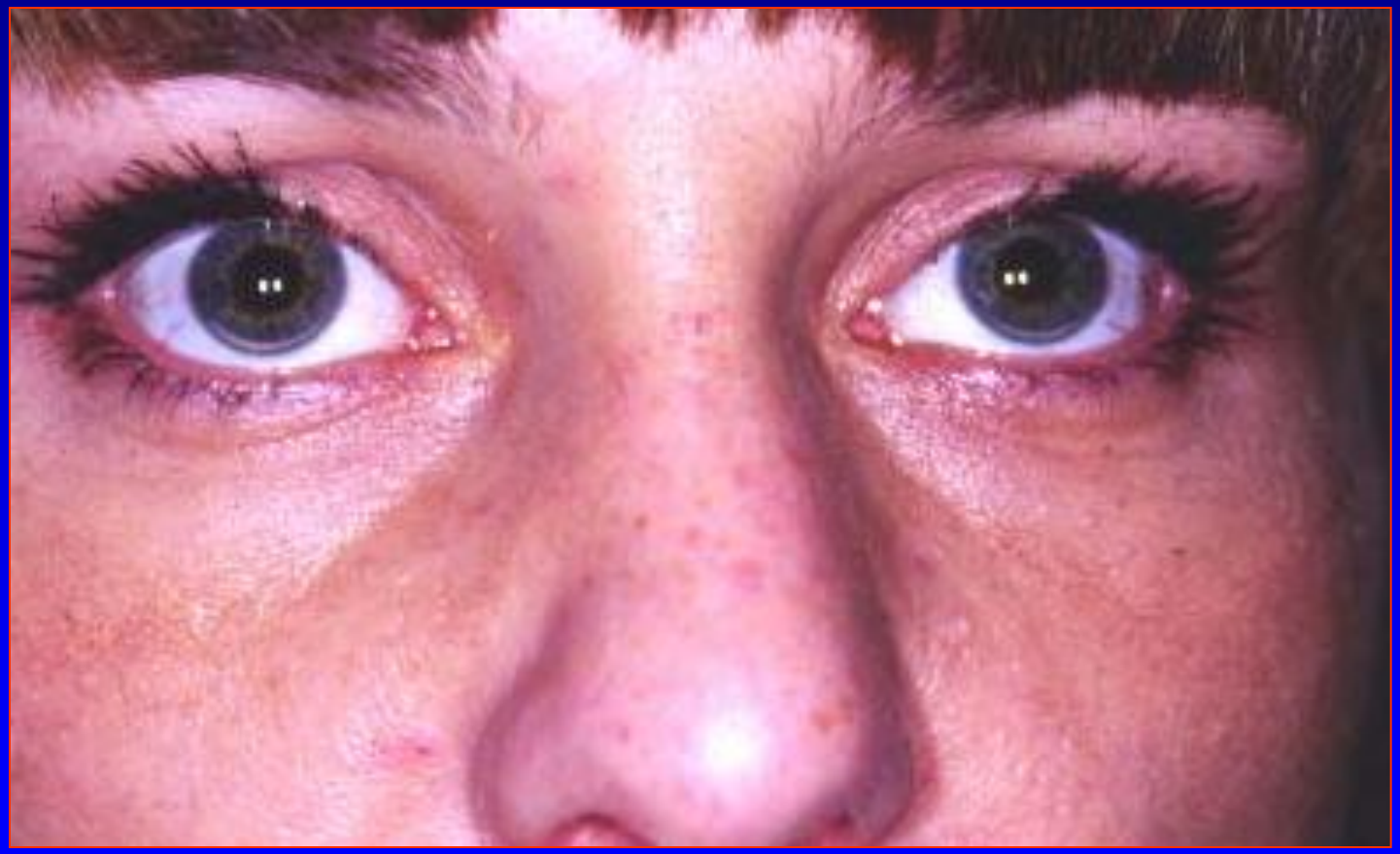


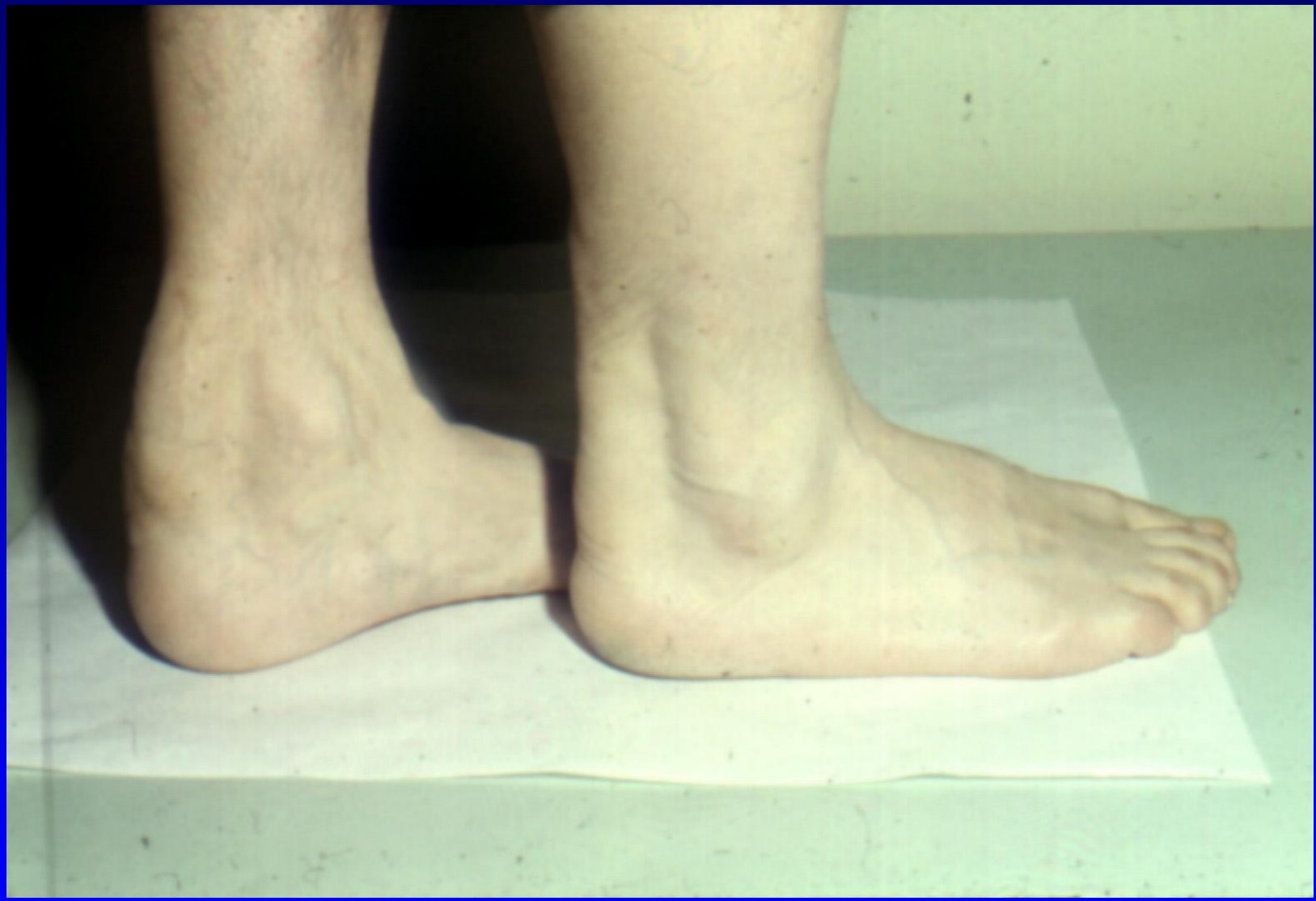
SREBP

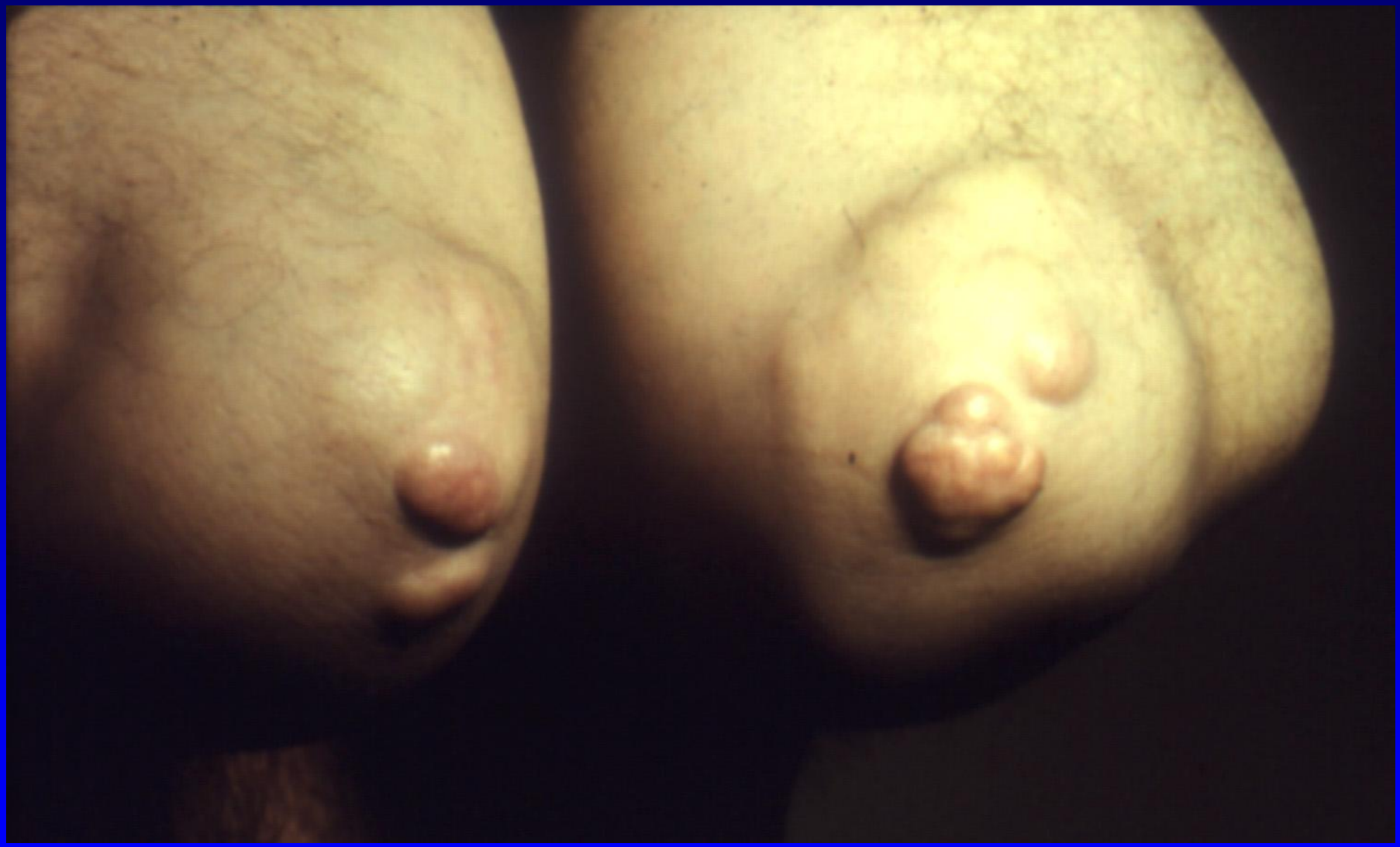
Joseph GOLDSTEIN

Nobel Prize 1985

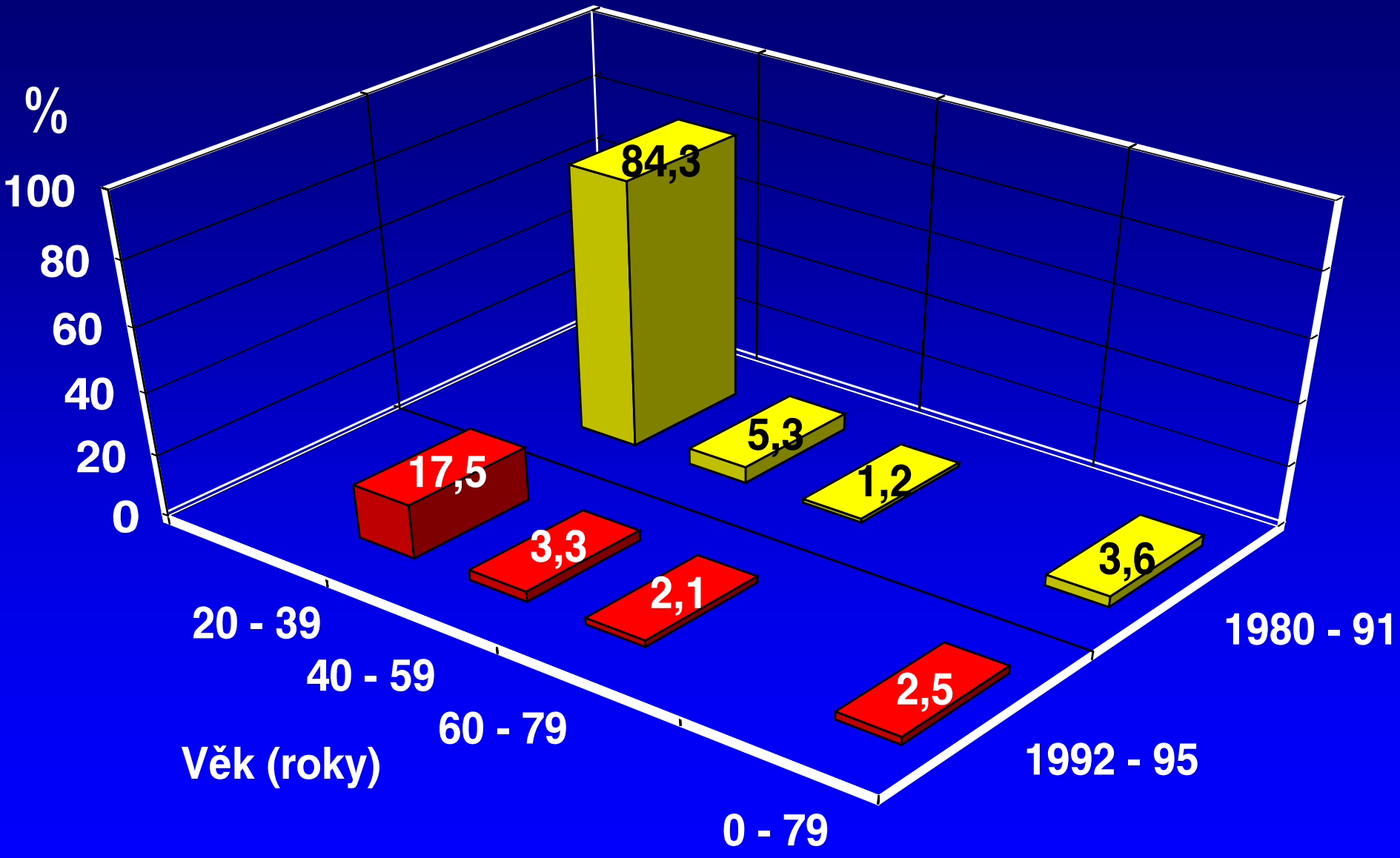
Familial hypercholesterolemia, positive family history, LDL-C 8,2mmol/l (W 27years)





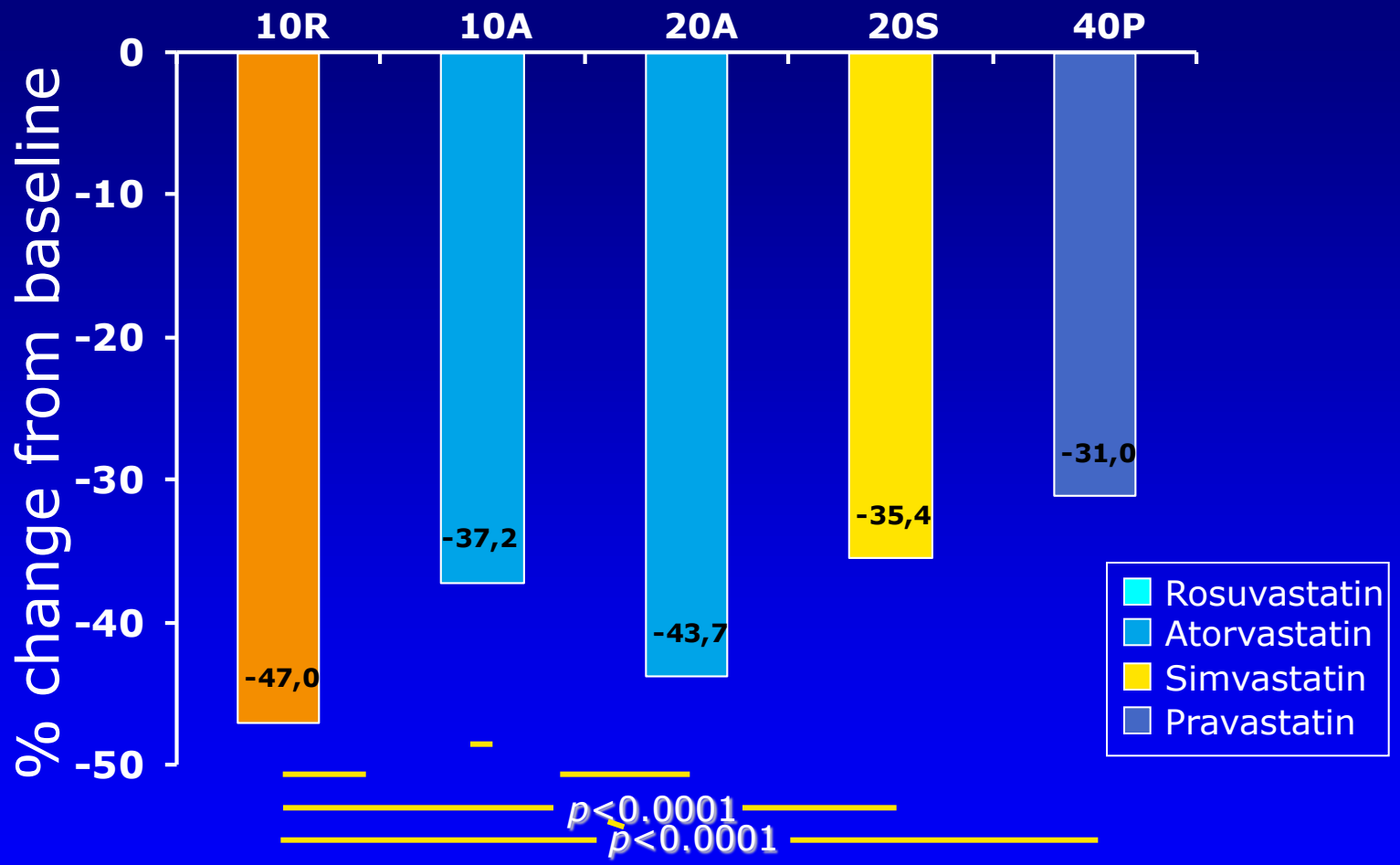


FH - CHD MORTALITA

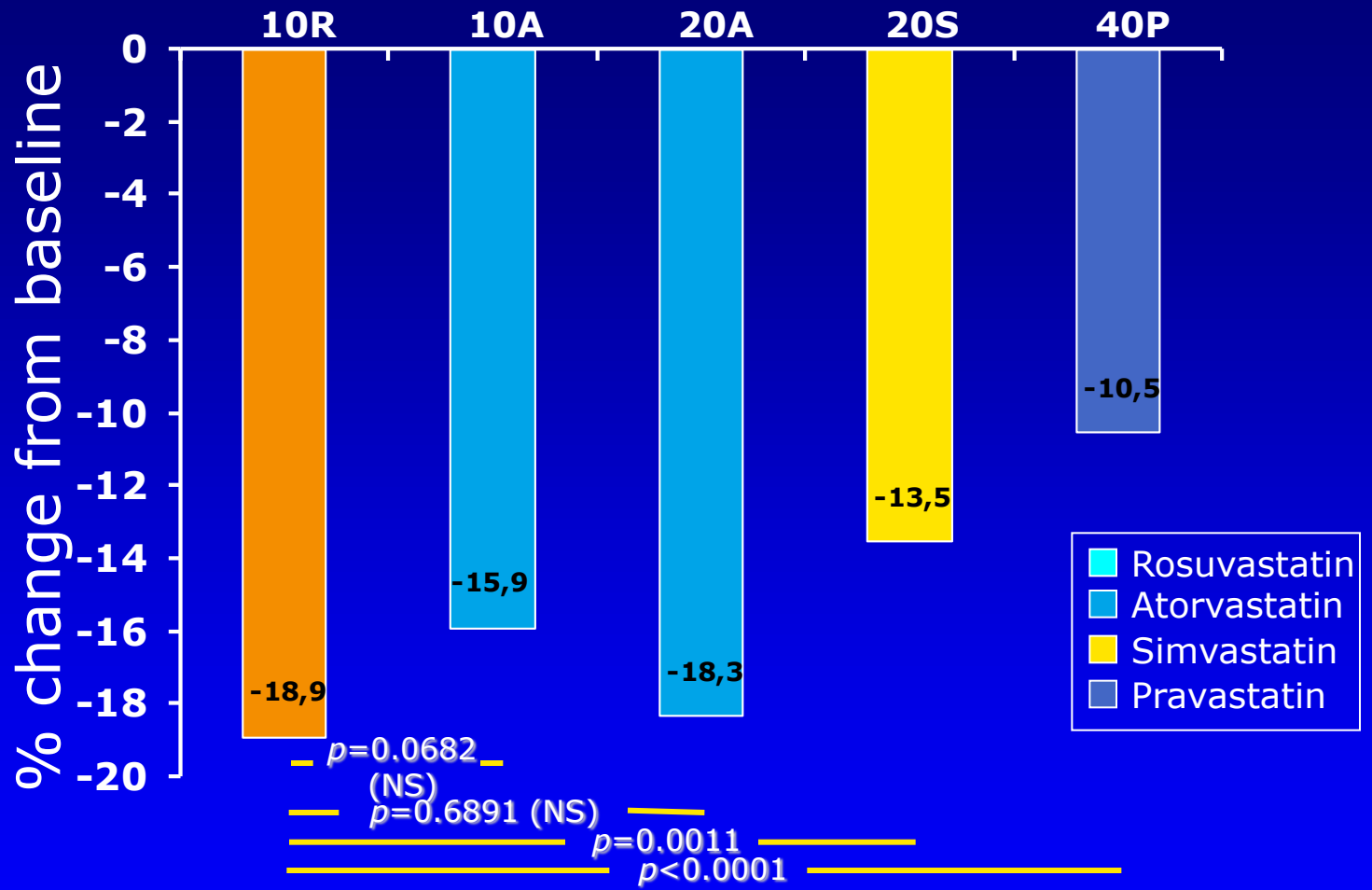


Atherosclerosis 142 (1999) 105 - 112

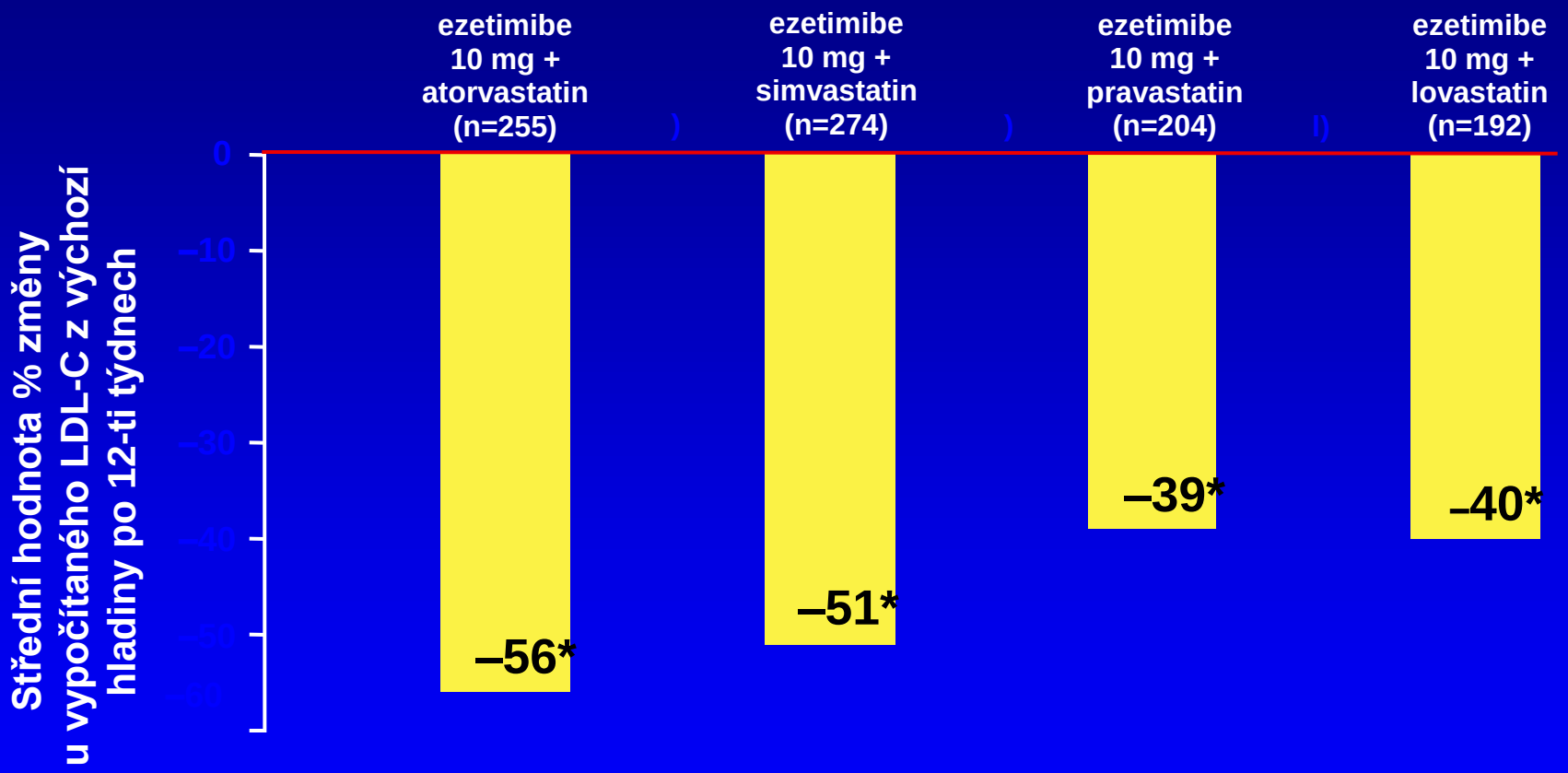
MERCURY: LDL-C



MERCURY: TG


10R
10A
20A
20S
40P
0
-2
-4
-6
-8
-10
-12
-14
-16
-18
-20
% change from baseline
-18,9
-15,9
-18,3
-13,5
-10,5
Rosuvastatin
Atorvastatin
Simvastatin
Pravastatin
p=0.0682 (NS)
p=0.6891 (NS)
p=0.0011
p<0.0001

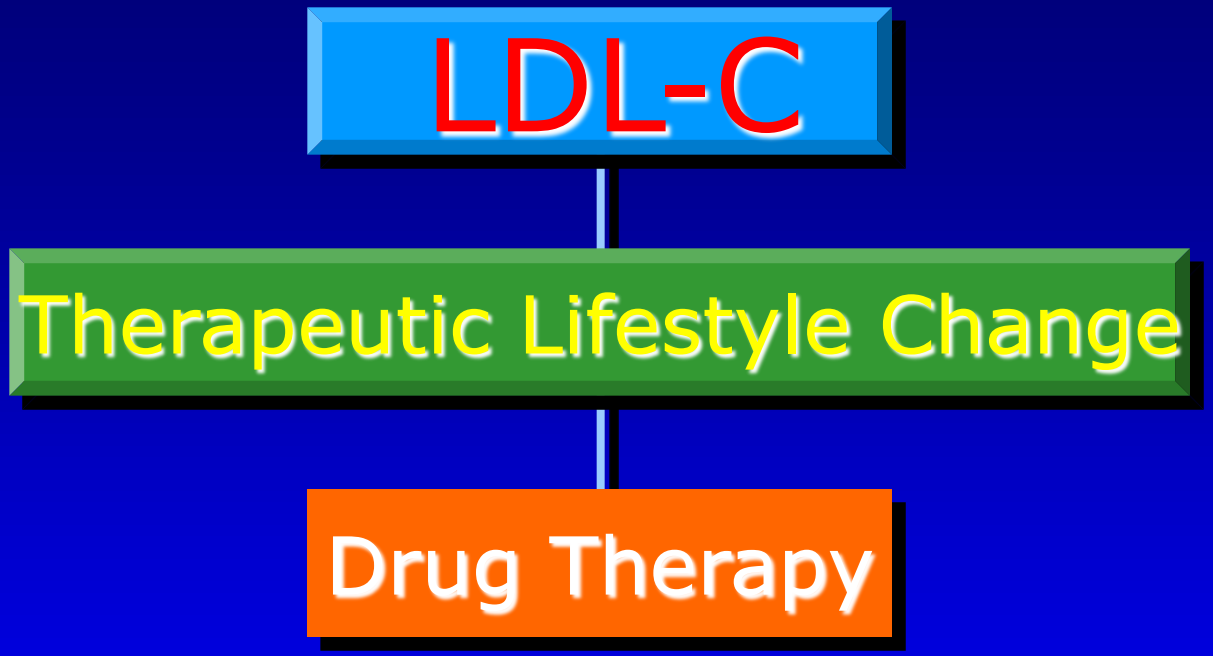
Ezetimibe + statins
LDL-C



*p<0,01 ezetimibe + sdružené dávky statinů vs. sdružené dávky statinů samotné

Ballantyne CM et al *Circulation* 2003;107:2409–2415; Davidson MH et al *J Am Coll Cardiol* 2002;40:2125–2134; Melani L et al *Eur Heart J* 2003;24:717–728,1381; Kerzner B et al *Am J Cardiol* 2003;91:418–424.

Treatment of Hyperlipidemia



Therapy of Choice: Statin

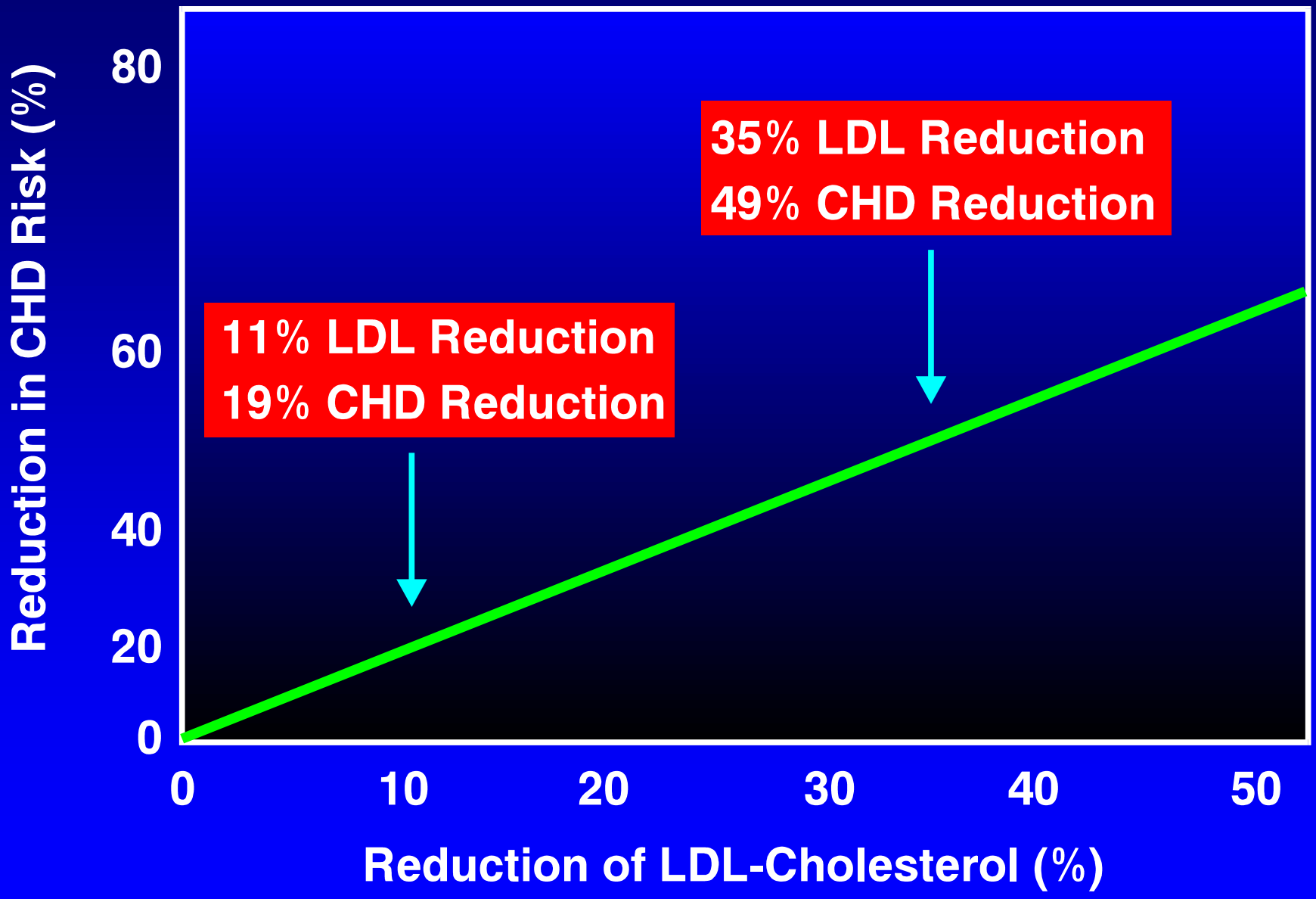
Alternative/combo: Ezetimibe, resin or niacin

Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. *JAMA* 2001;285:2486-2497.

The Lower = The Better

- *for LDL-C lowering*
- *For clinical outcomes reduction*

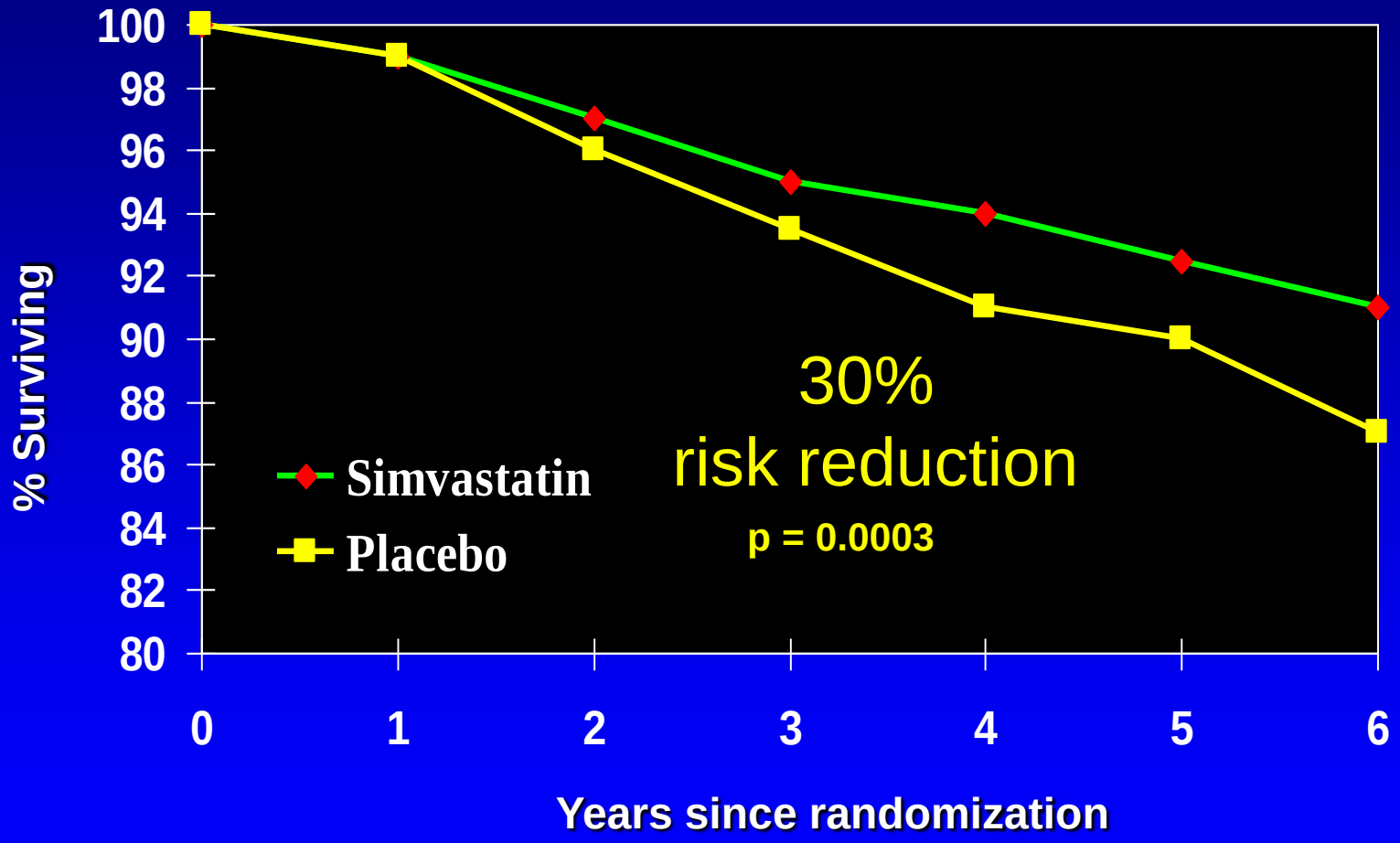
LRC - CPPT


Reduction in CHD Risk (%)
80
60
40
20
0
35% LDL Reduction
49% CHD Reduction
11% LDL Reduction
19% CHD Reduction
0
10
20
30
40
50
Reduction of LDL-Cholesterol (%)

Scandinavian Simvastatin Survival Study (4S)

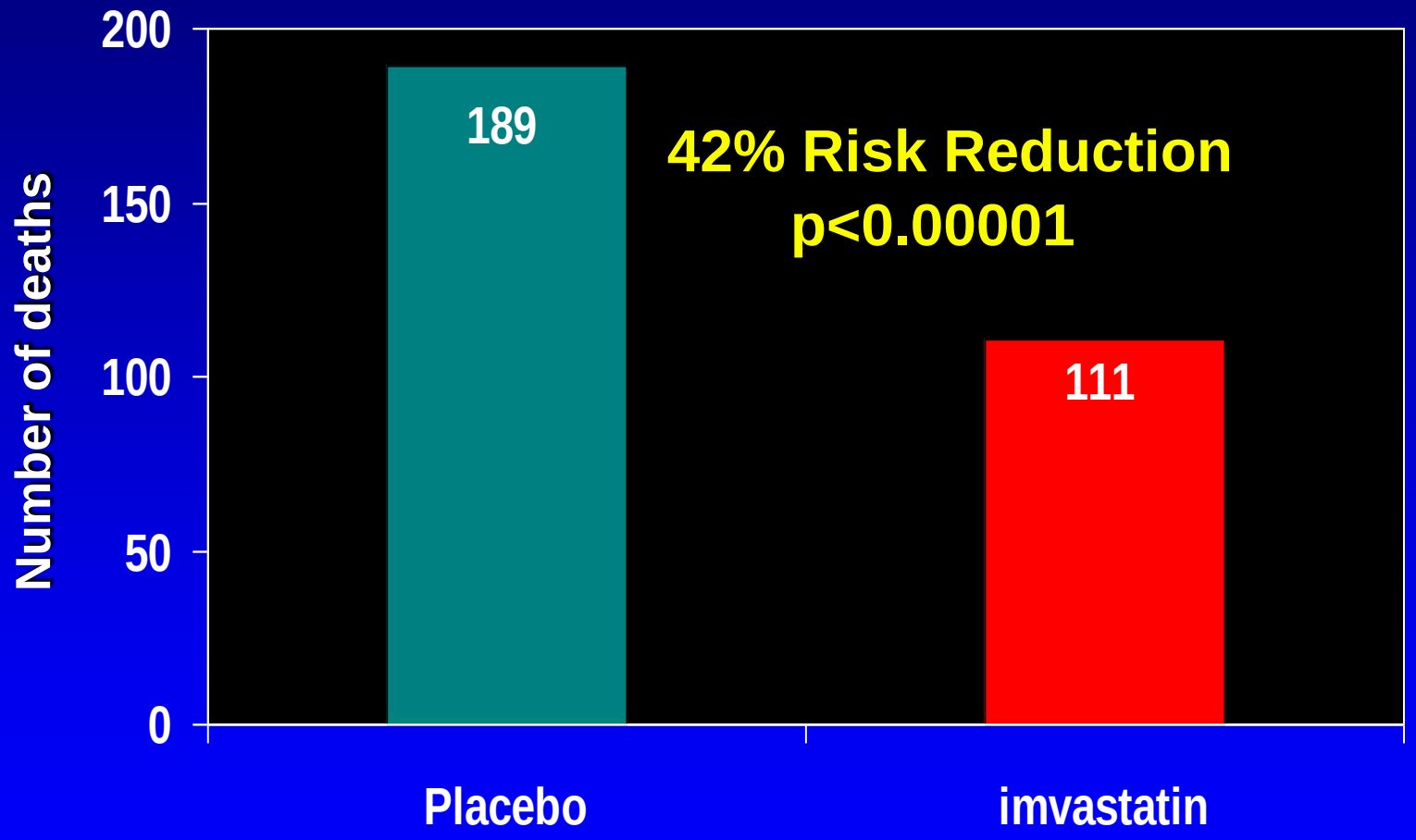
The Lancet, Vol 344, November 19, 1994

Primary Endpoint: Overall Survival



The Lancet, Vol 344, November 19, 1994

Coronary Mortality



The Lancet, Vol 344, November 19, 1994

TNT Trial

10,003 patients with stable coronary heart disease

Age 35-75 years, LDL between 130 and 250 mg/dL, triglyceride ≤ 600 mg/dL

19% female, mean age 60.3 years

All received atorvastatin 10 mg during 8 week open-label run-in period

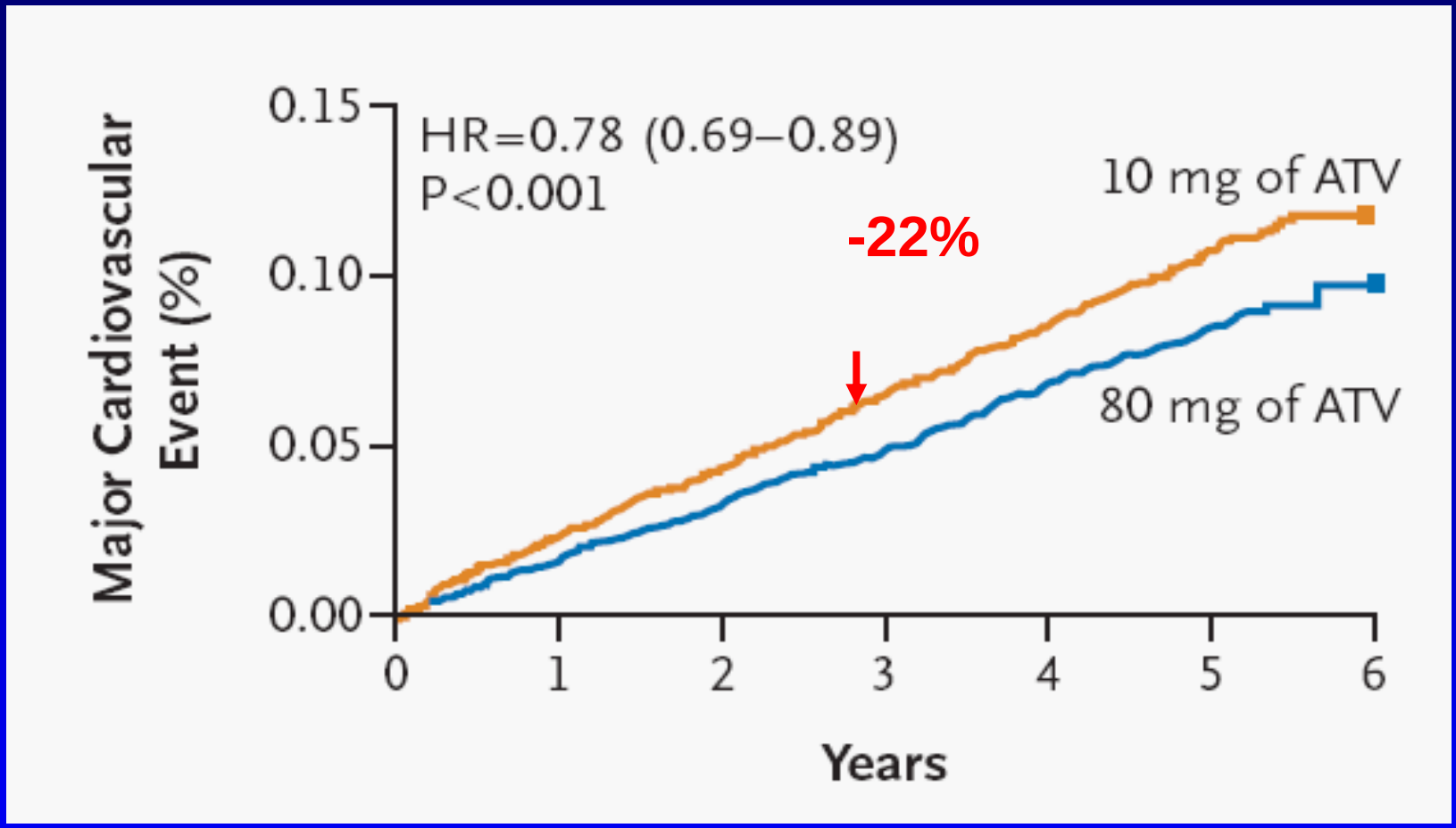
Atorvastatin 80 mg n=4,995	Atorvastatin 10 mg n=5,006

Primary Endpoint: Major cardiovascular event defined as coronary heart death (CHD) , nonfatal M, resuscitated cardiac arrest, and fatal or nonfatal stroke at a mean follow-up of 4.9 years.

Secondary Endpoint: Major coronary events, cerebrovascular events, hospitalization for congestive heart failure (CHF), all-cause mortality, peripheral artery disease, any cardiovascular event, any coronary event

Presented at ACC 2005

TNT: The Lower the Better

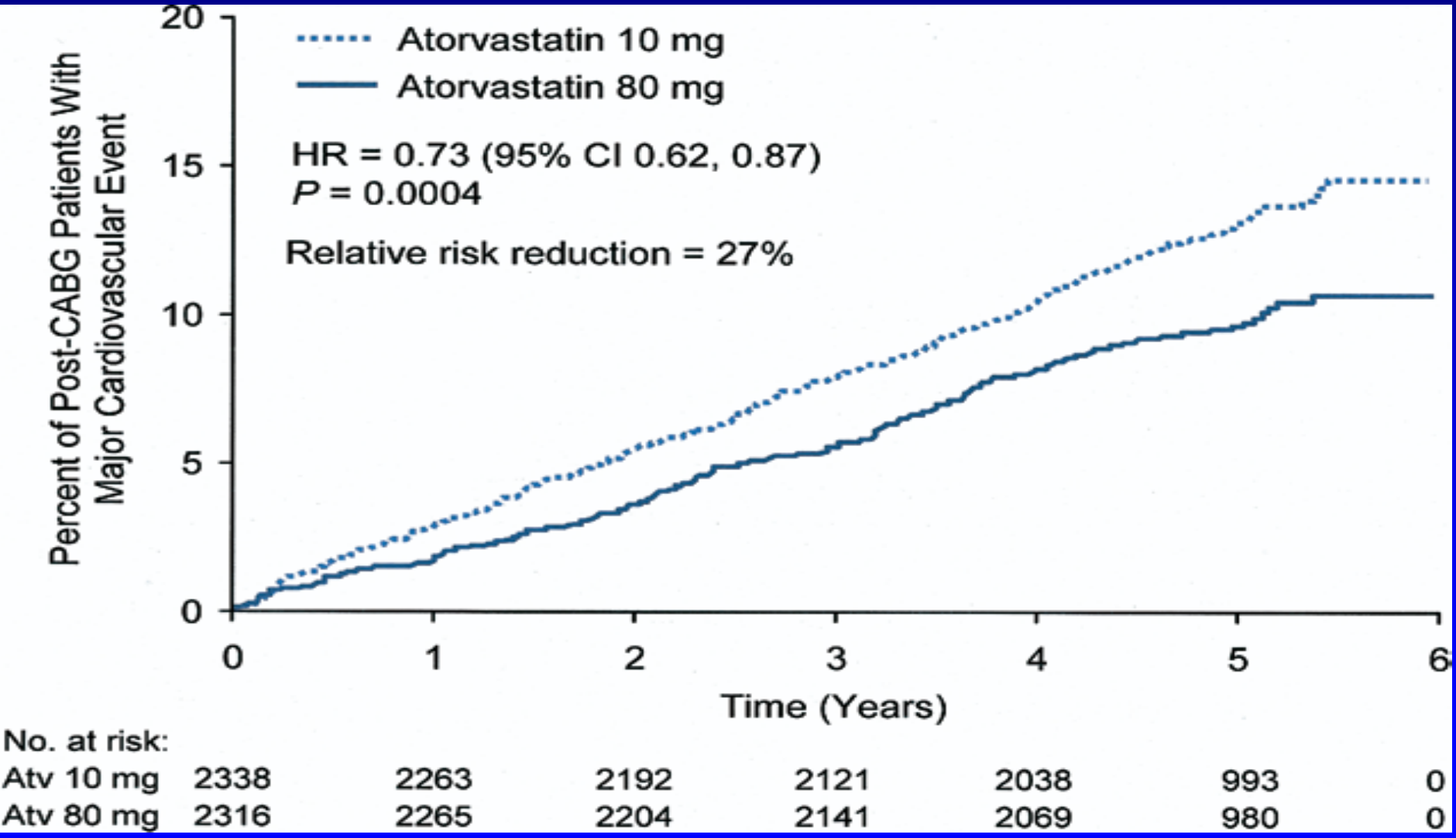


Intensive lipid-lowering therapy with atorvastatin 80 mg/day in patients with stable CHD provides significant clinical benefit beyond that provided by atorvastatin 10 mg/day

J. C. LaRosa et al. Intensive Lipid Lowering with Atorvastatin in Patients with Stable Coronary Disease. // N Engl J Med 2005;352:1425-35.

TNT pts after CABG n = 4,654

MACE -27%



IDEAL Trial: Study Design

8,888 patients ≤80 years with definite history of myocardial infarction and qualified for stain therapy at time of recruitment

Randomized

High-dose atorvastatin

80 mg/day

If LDL was <40 mg/dL at 24 wks dose could be reduced to 40 mg/day

n=4,439

Standard-dose simvastatin

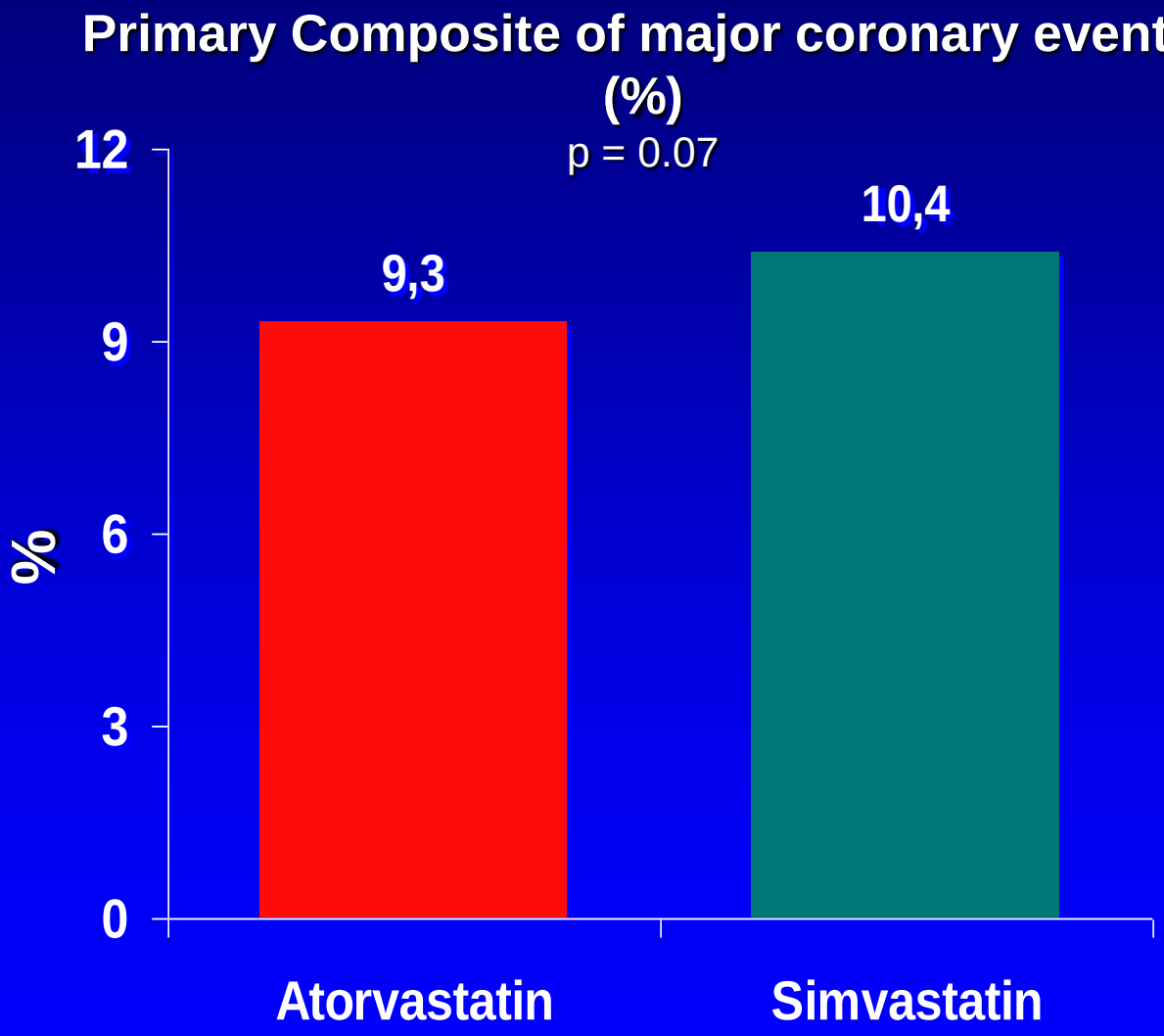
20 mg/day

If cholesterol >190 mg/dL at 24 wks dose could be increased to 40 mg/day

n=4,449

Presented at AHA 2005

IDEAL Trial: Primary Endpoint

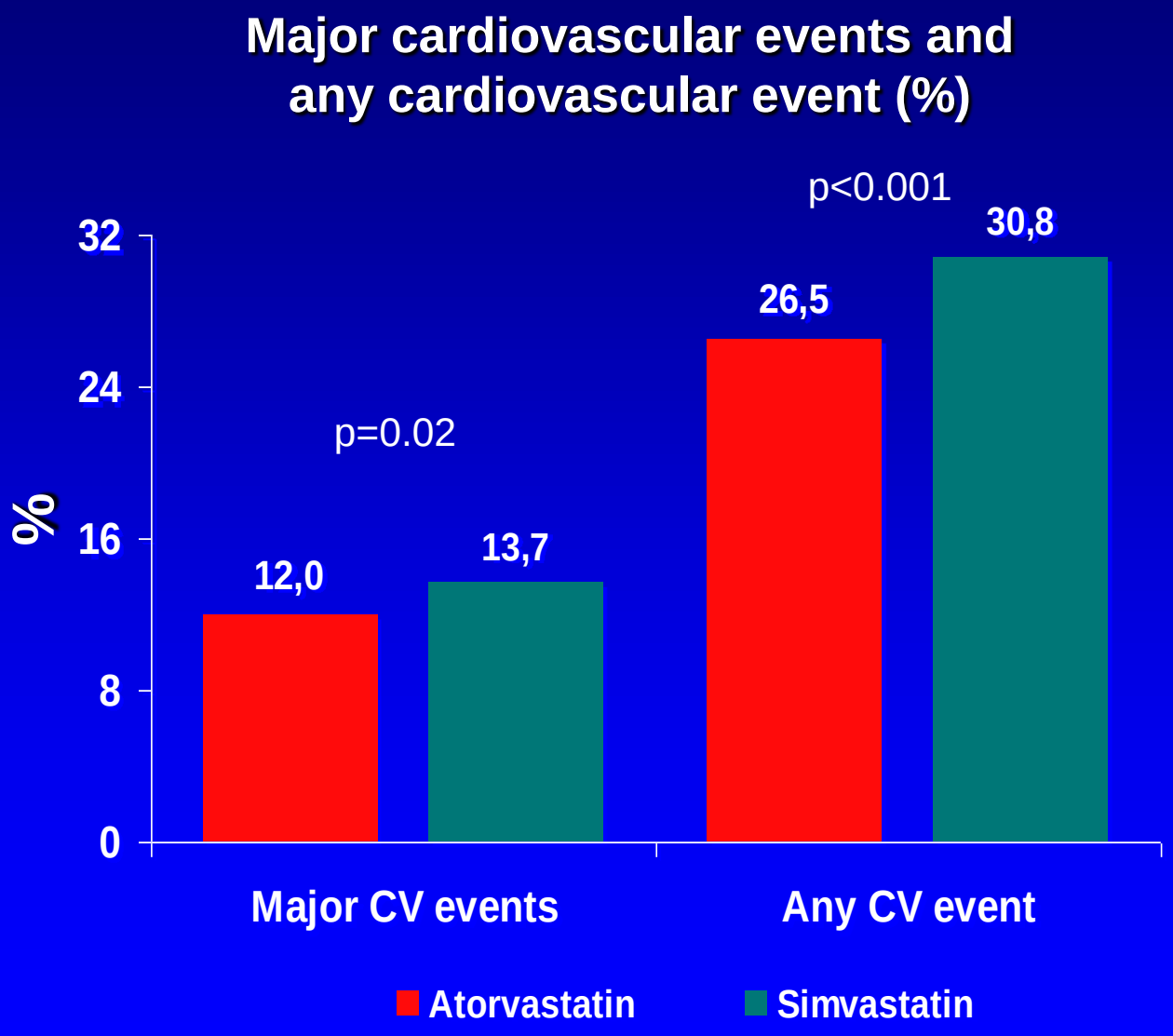


- **The primary composite endpoint of major coronary event occurred in 9.3% of the atorvastatin group and 10.4% of the simvastatin group.**

* Major coronary event defined as coronary death, hospitalization for non-fatal acute MI or resuscitated cardiac arrest.

Presented at AHA 2005

IDEAL Trial: Secondary Endpoints

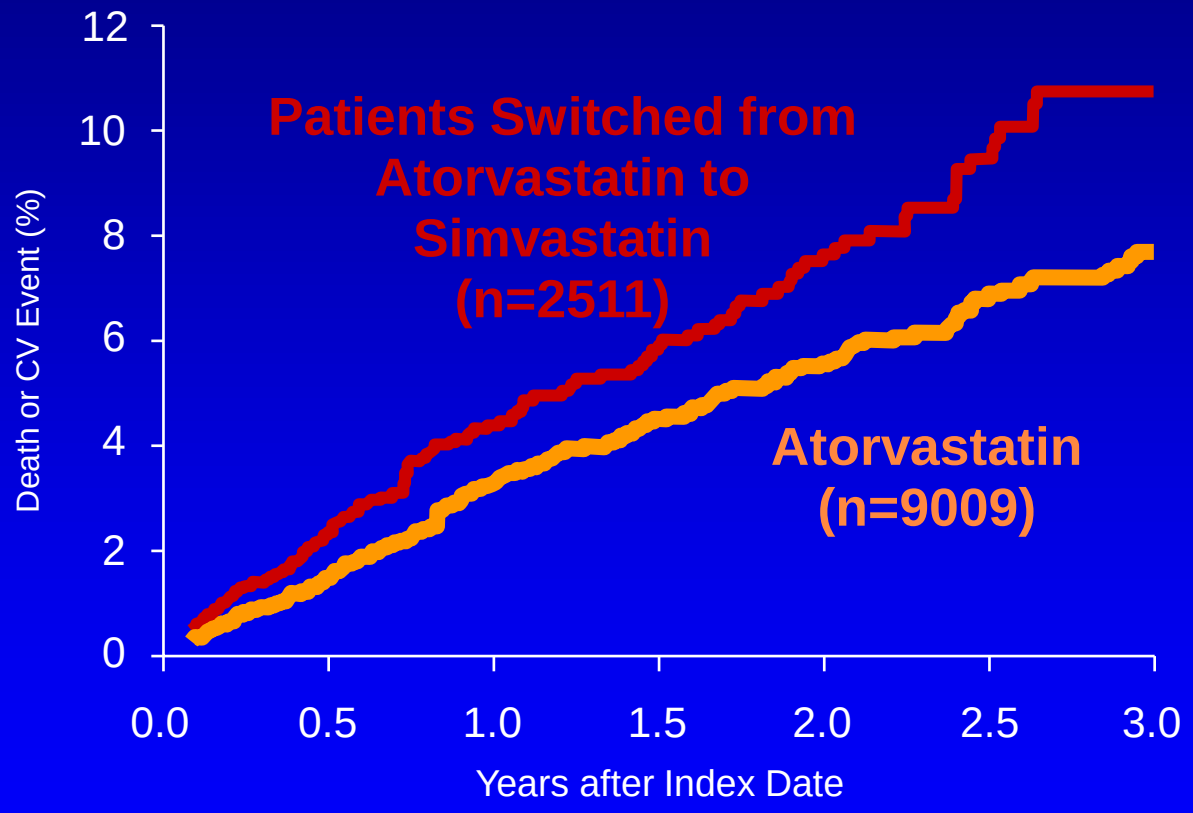


- **Major cardiovascular events, defined as any primary event plus stroke, occurred less often in the atorvastatin group.**

- **Any cardiovascular event, defined as major CV event plus hospitalization for CHF and peripheral artery disease, also occurred less often in the atorvastatin group.**

Presented at AHA 2005

UK Switching Study: Impact of Switching From Atorvastatin to Simvastatin



33%

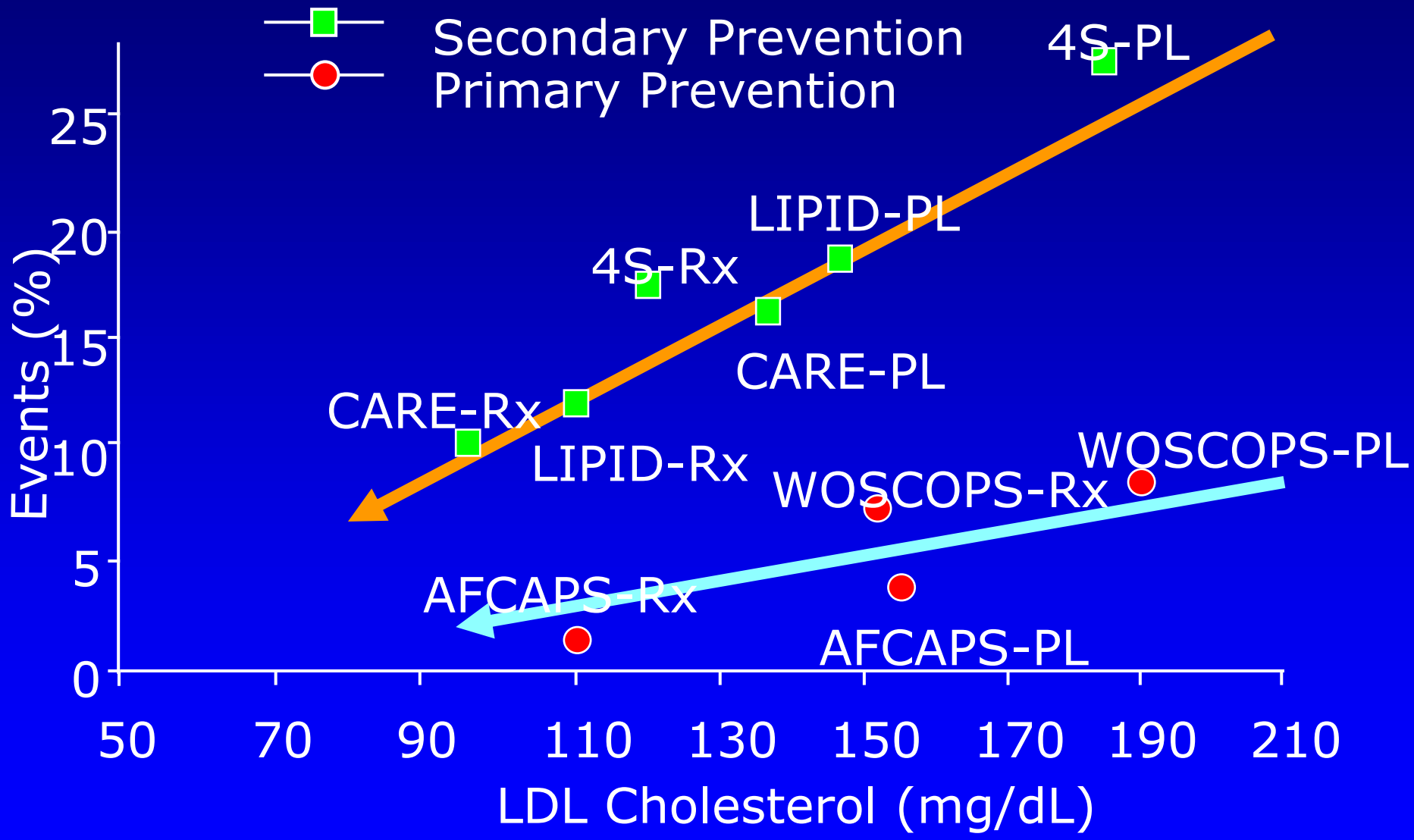
Increase in death or CV events with switch to Simvastatin

(P=0.007)

Primary end point: time to death or first major CV event (MI, stroke, and revascularization)

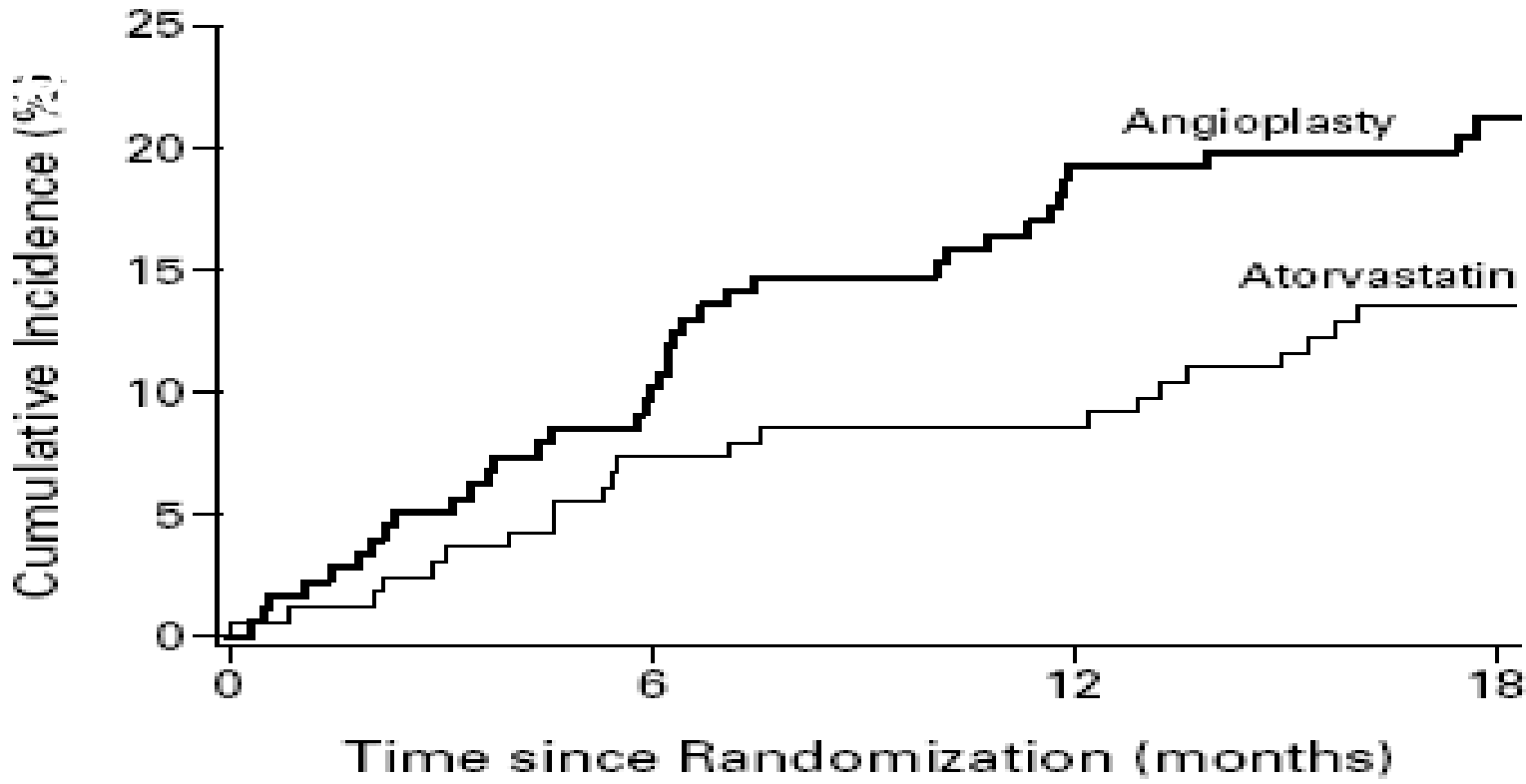
PHILLIPS B, et al. Poster accepted for presentation at the European Society of Cardiology Congress, Sep 1-5, 2007

LDL-C lowering with statins: reduced CHD events



The Lower The Better

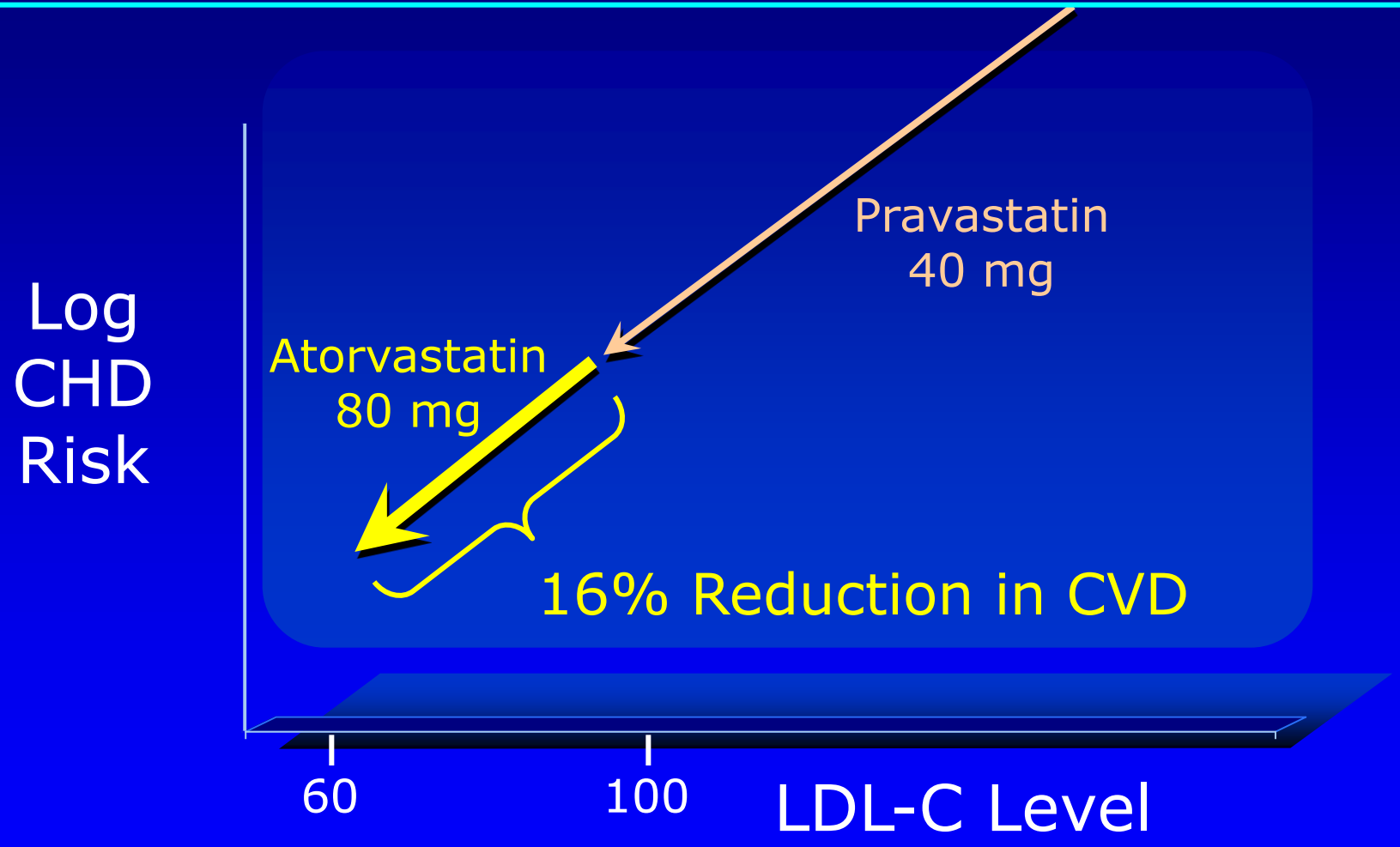
Aggressive lipid-lowering therapy is as effective as angioplasty



Treatment with atorvastatin, as compared with angioplasty, was associated with a significantly longer time to a first ischemic event and with a reduction in risk of ***36%***

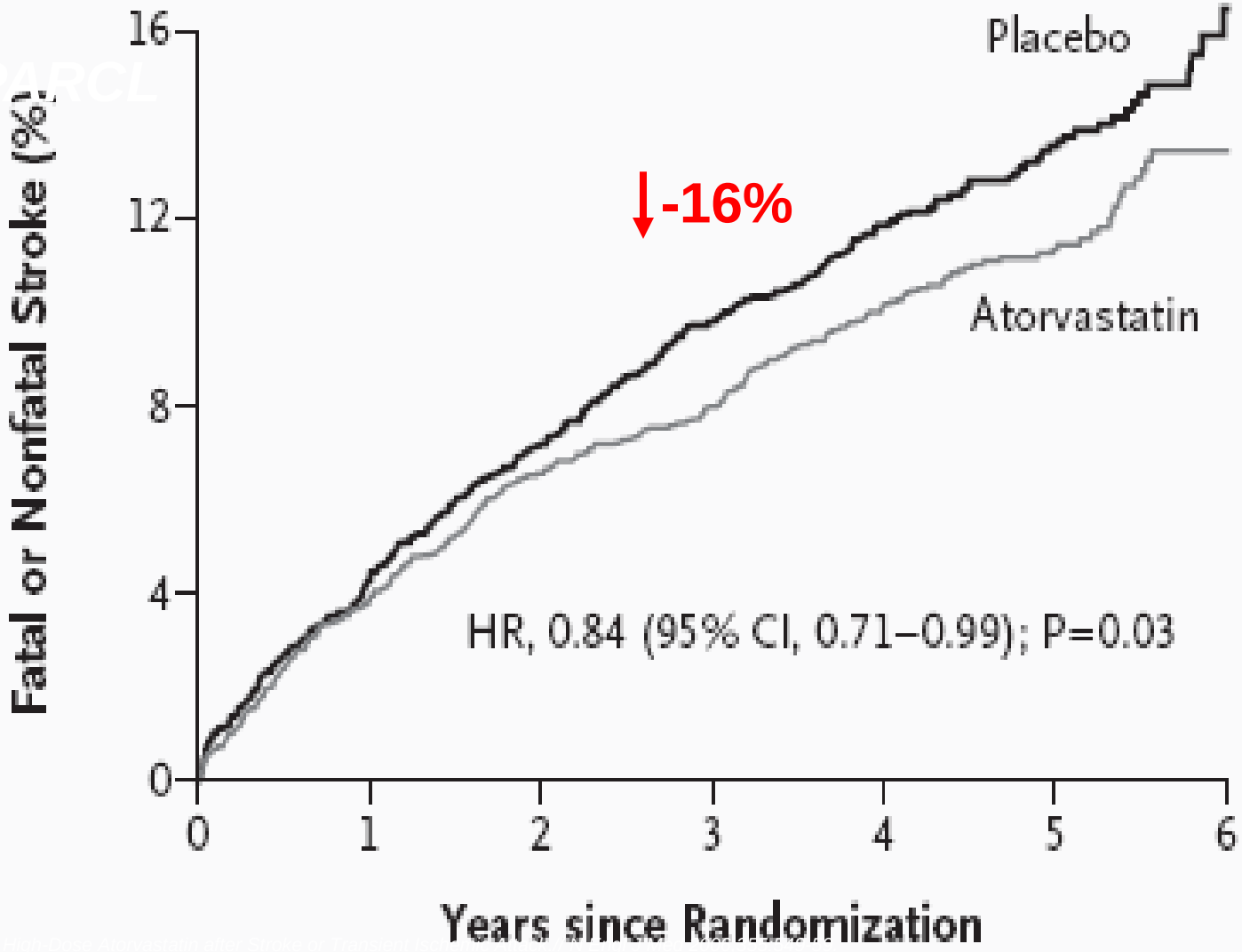
Pitt B.et al. AGGRESSIVE LIPID-LOWERING THERAPY COMPARED WITH ANGIOPLASTY IN STABLE CORONARY ARTERY DISEASE. // New Engl. J. Med. 1999;341:70-76.

PROVE IT–TIMI 22 (2-Year Trial)



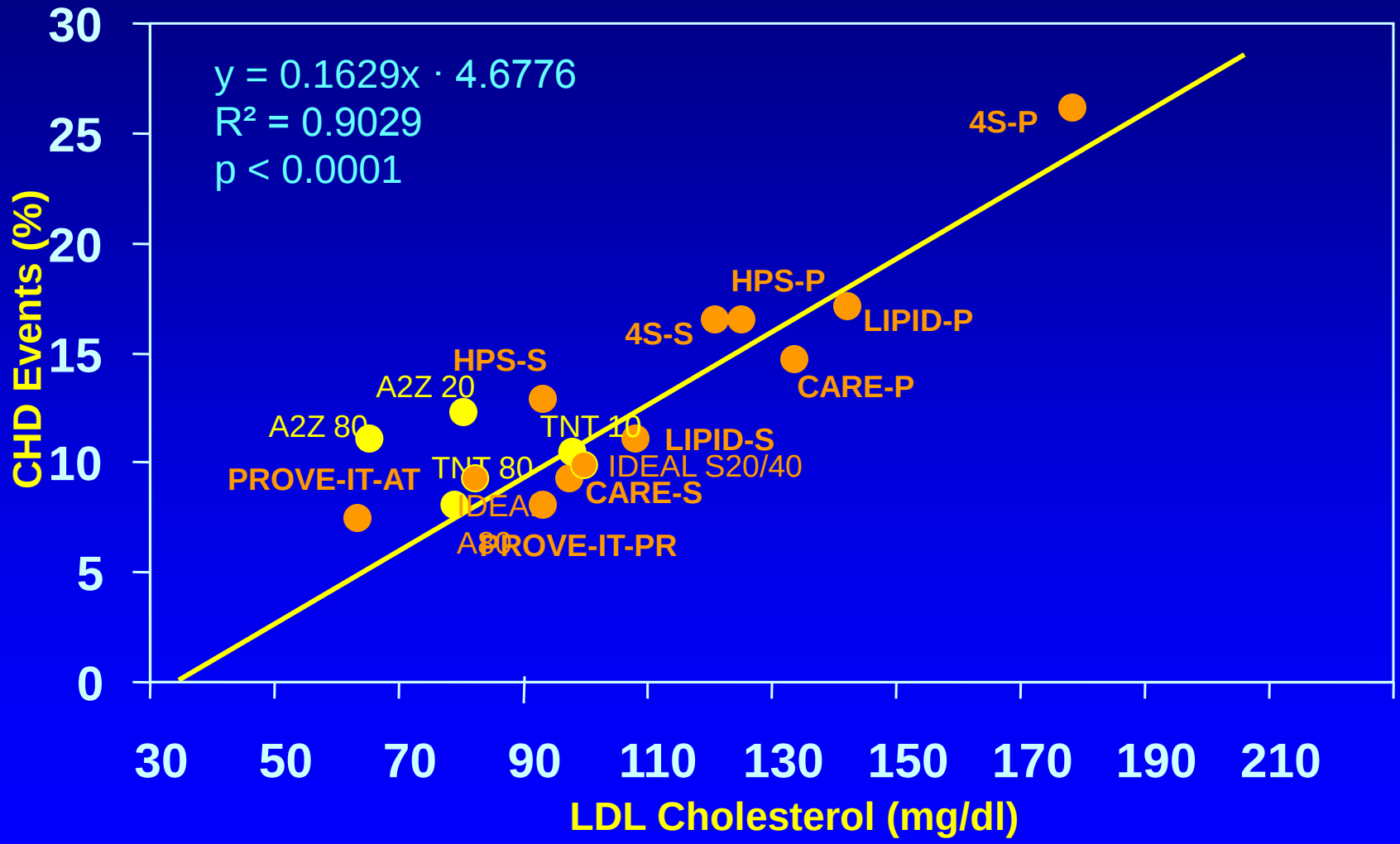
Cannon CP et al. *N Engl J Med* 2004;350:1495-1504.

High dose atorvastatin after stroke or trasient ischemic attack (SPARCL)



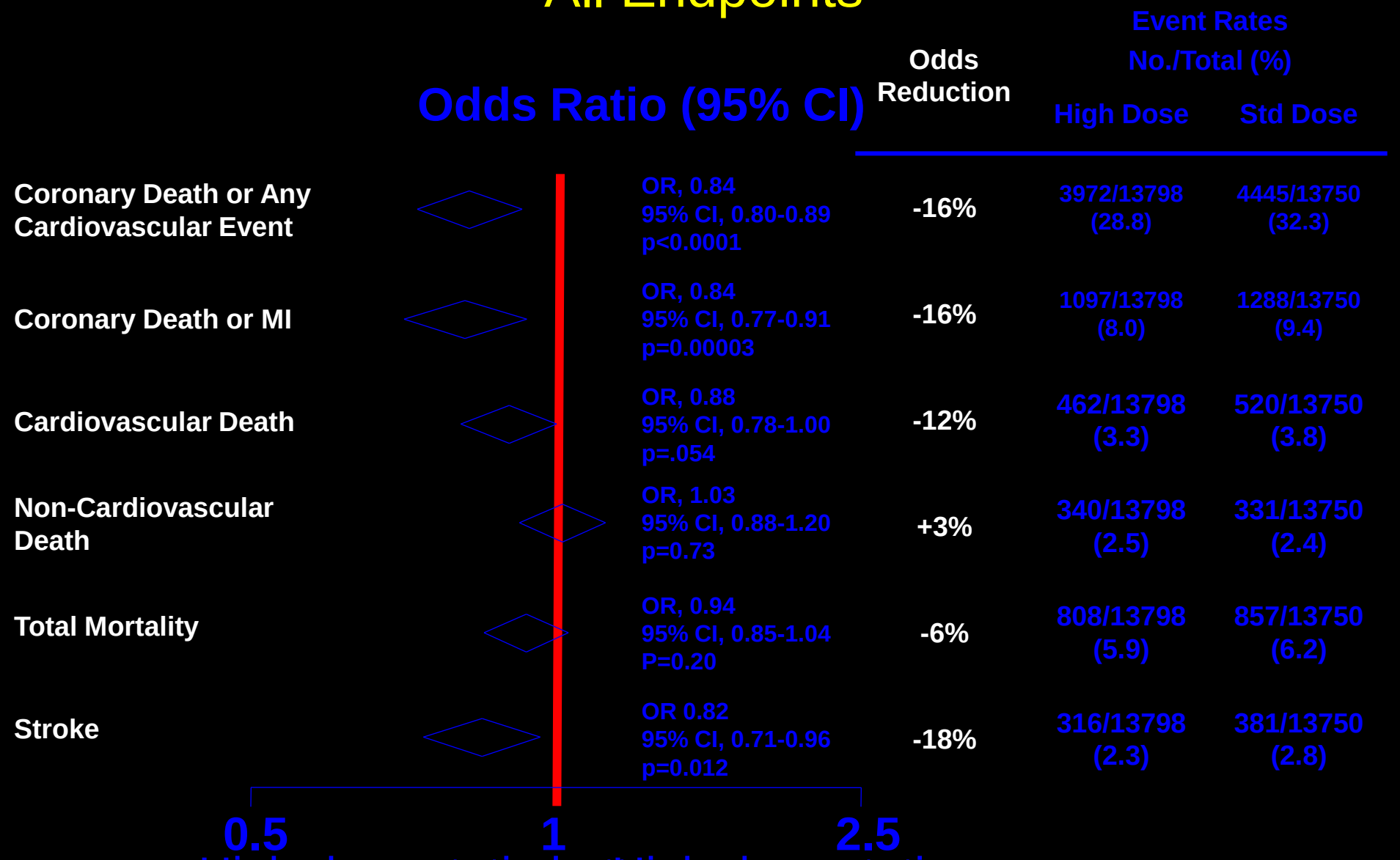
P. Amarenco et al. High Dose Atorvastatin after Stroke or Transient Isch

CHD Event Rates in Secondary Prevention and ACS Trials



Updated from - O'Keefe, J. et al., *J Am Coll*

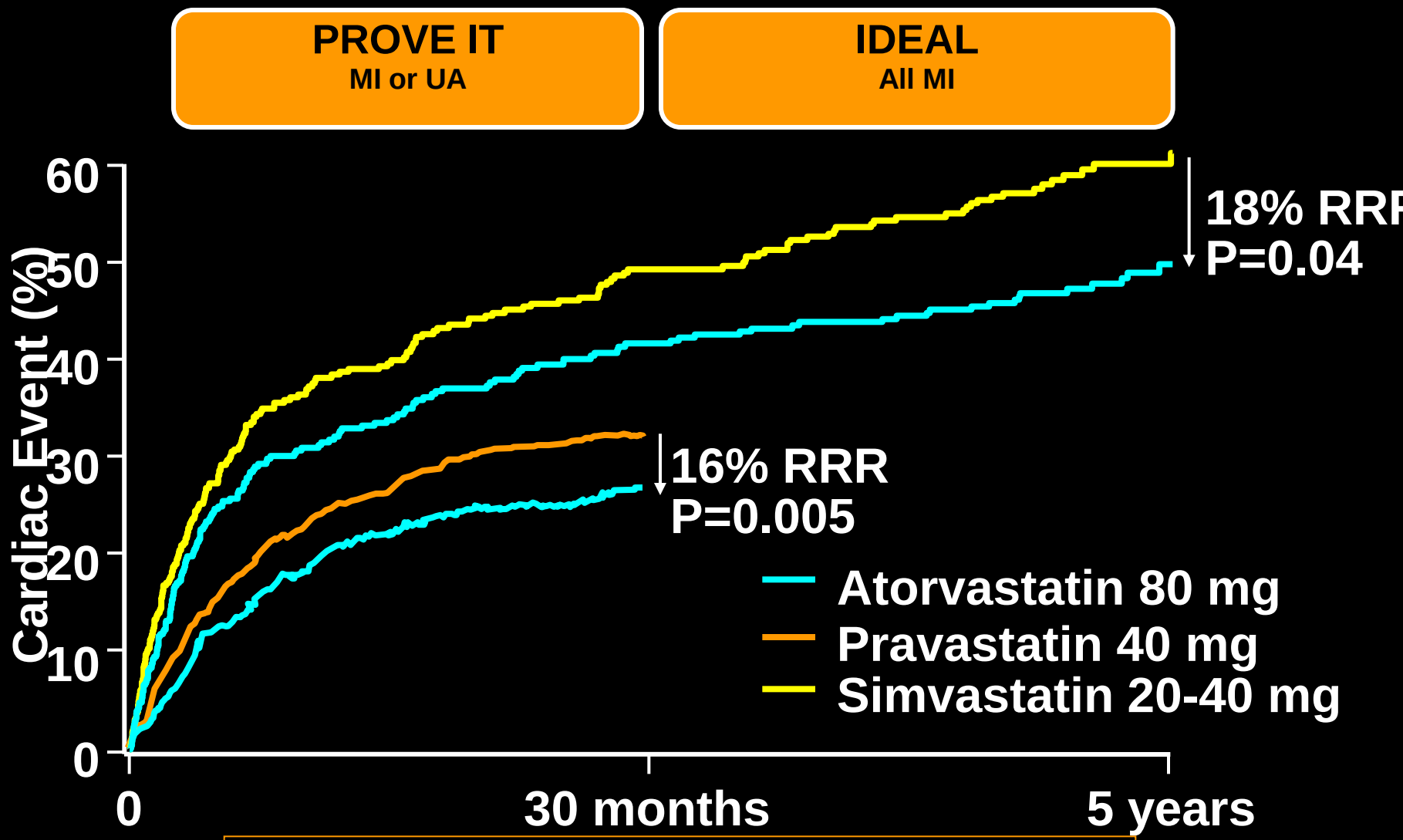
Meta-Analysis of Intensive Statin Therapy
All Endpoints



Cannon CP, et al.

Cannon CP, et al. JACC 2006; 48: 438 - 445.

Summary: 5 Years Of Follow-Up In IDEAL Is The Longest Period Of Follow-Up Of ACS Patients On Statin Therapy



Pedersen, Olsson, Cater et al. Presented at World Congress of Cardiology 2006

PCSK9 (proprotein convertase subtilisin/kexin type 9)

Enzyme - associated with plasma levels of LDL –C

(expressed in the liver, intestine and kidney)

Overexpression of gene for PCSK9 → **more PCSK9** enzyme → **LDL receptors reduction** (LDL-Receptor enable removal of LDL-C from the plasma) → **increase in circulating LDL-C**

High levels of PCSK9 = high LDL-C levels

Conversely, lacking *Pcsk9 leads to* increased levels of hepatic LDL receptors,and they remove LDL from the plasma at an accelerated rate)

Low levels of PCSK9 = low LDL- C levels

1.Brown, M.S.,Science, Vol 311, March 24, 2006

2. Cohen J.C. et al.,New England Journal of Medicine, Volume 354, 2006 Number 12

Cohens et al. study

The Longer The Better

- Studied patients with **lifelong low LDL-C levels**, due to loss of-function mutations in the gene encoding PCSK9 = they have **low level of PCSK9 = low level of LDL-C**

- **Severe mutation: LDL-C was reduced by 1 mmol/l (38 mg/dl)**

  → **prevalence of CHD declined by a remarkable 88%.**

- Less severe mut.:LDL-C was reduced by only 0,52 mmol/l (21 mg/dl)

  → **CHD incidence declined by 47%.**

Cohen et al., N Engl J Med 2006;354:1264-72.

Brown, M.S.,Science, Vol 311, March 24, 2006

The Longer The Better

Cohen et al. study

Why does lowering of LDL-C concentration by 40 mg/dl

by a PCSK9 mutation reduce CHD incidence by 88%,

whereas a 40-mg/dl lowering with a statin reduces CHD

prevalence by only 23% on average ???

Cohen et al., N Engl J Med 2006;354:1264-72.

Brown, M.S.,Science, Vol 311, March 24, 2006

Cohens et al. study

The Longer The Better

The most likely answer is

DURATION

Cohen et al., N Engl J Med 2006;354:1264-72.

Brown, M.S.,Science, Vol 311, March 24, 2006

The Longer The Better

Cohens et al. study

- People with mutations in PCSK9 likely have maintained relatively **low LDL levels throughout their lives.**

- **People in statin trials** have had their LDL levels lowered for **only 5 years.**

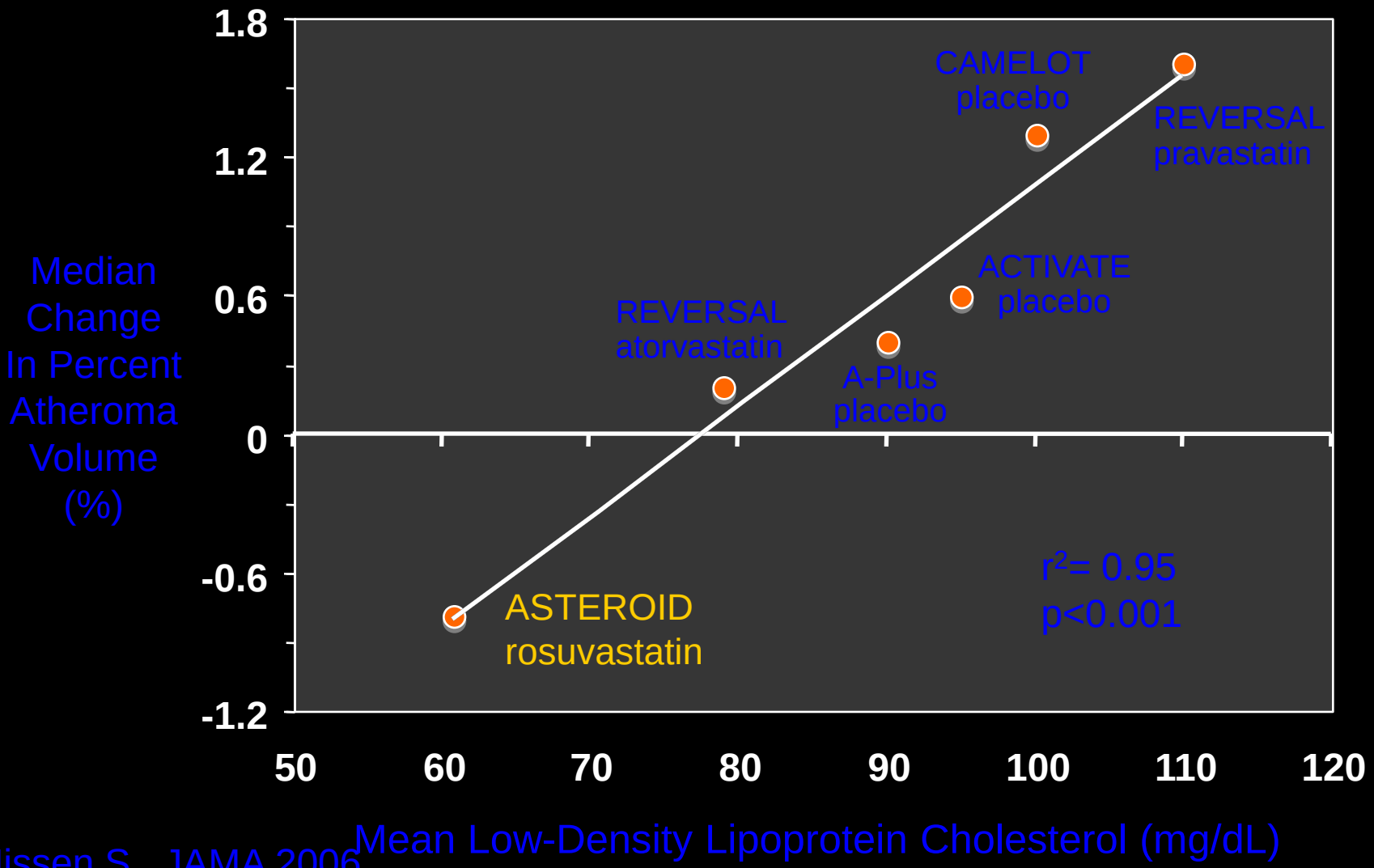
- **Atherosclerosis is a chronic disease that begins in the teenage years**

Cohen et al., N Engl J Med 2006;354:1264-72.

Brown, M.S.,Science, Vol 311, March 24, 2006

Relationship between LDL-C and Progression Rate

Recent Coronary IVUS Progression Trials



Nissen S. JAMA 2006

ASTEROID: study design

Patients

CAD, undergoing coronary angiography

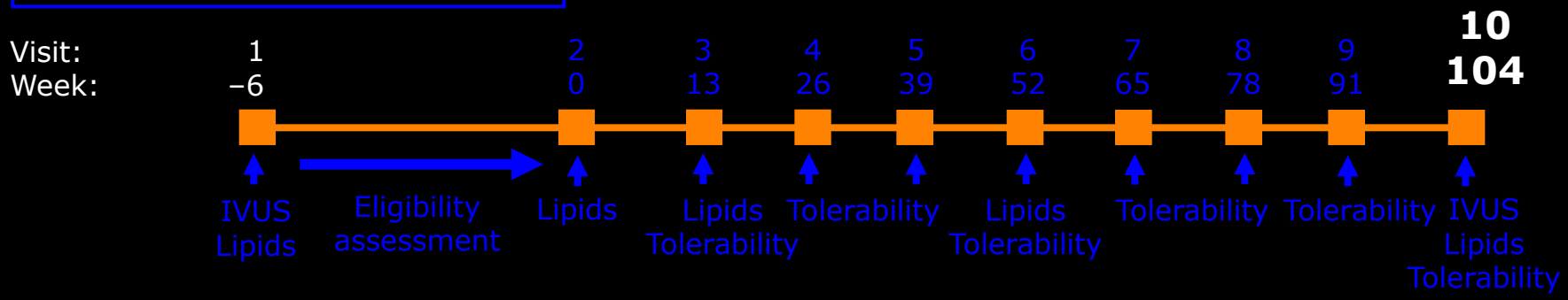
Target coronary artery: ≤50% reduction in lumen diameter of ≥40 mm segment

No cholesterol entry criteria

≥18 years

Rosuvastatin 40 mg

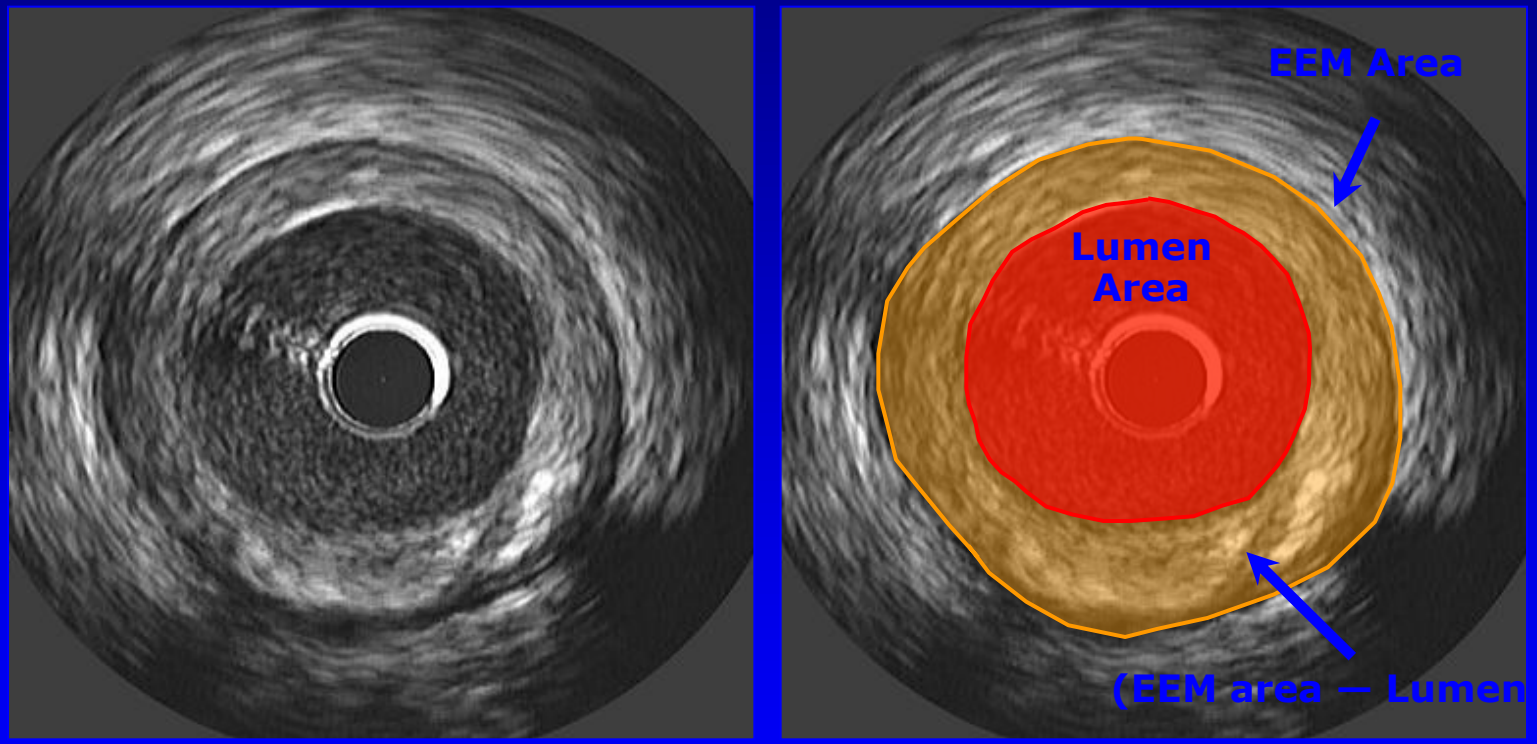
(n=349 evaluated serial IVUS examinations)



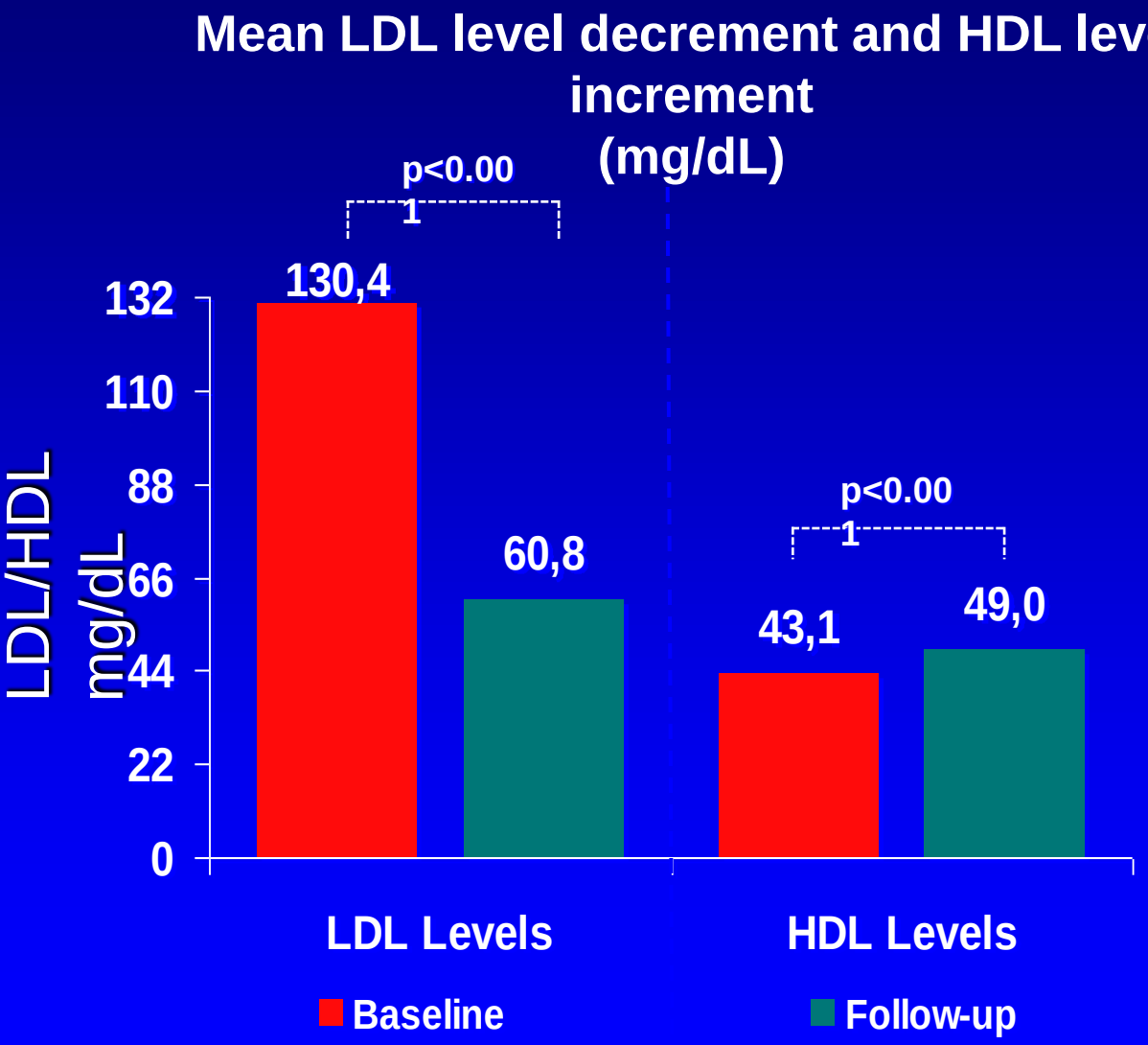
CAD=coronary artery disease; PCI=percutaneous coronary intervention; IVUS=intravascular ultrasound

IVUS Objem atero plátu

Precise Planimetry of EEM and Lumen Borders
allows calculation of Atheroma Cross-sectional Area



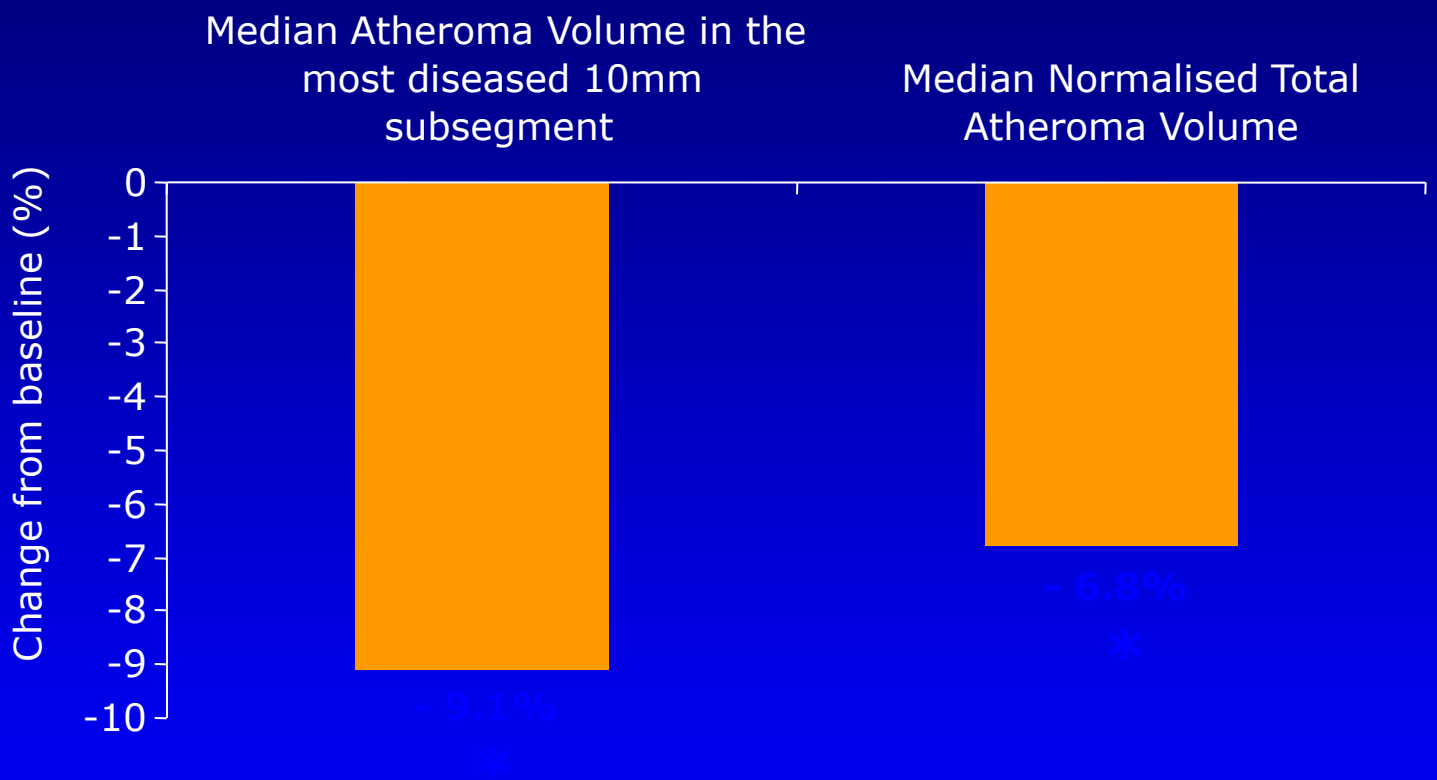
ASTEROID Trial: Principal Findings



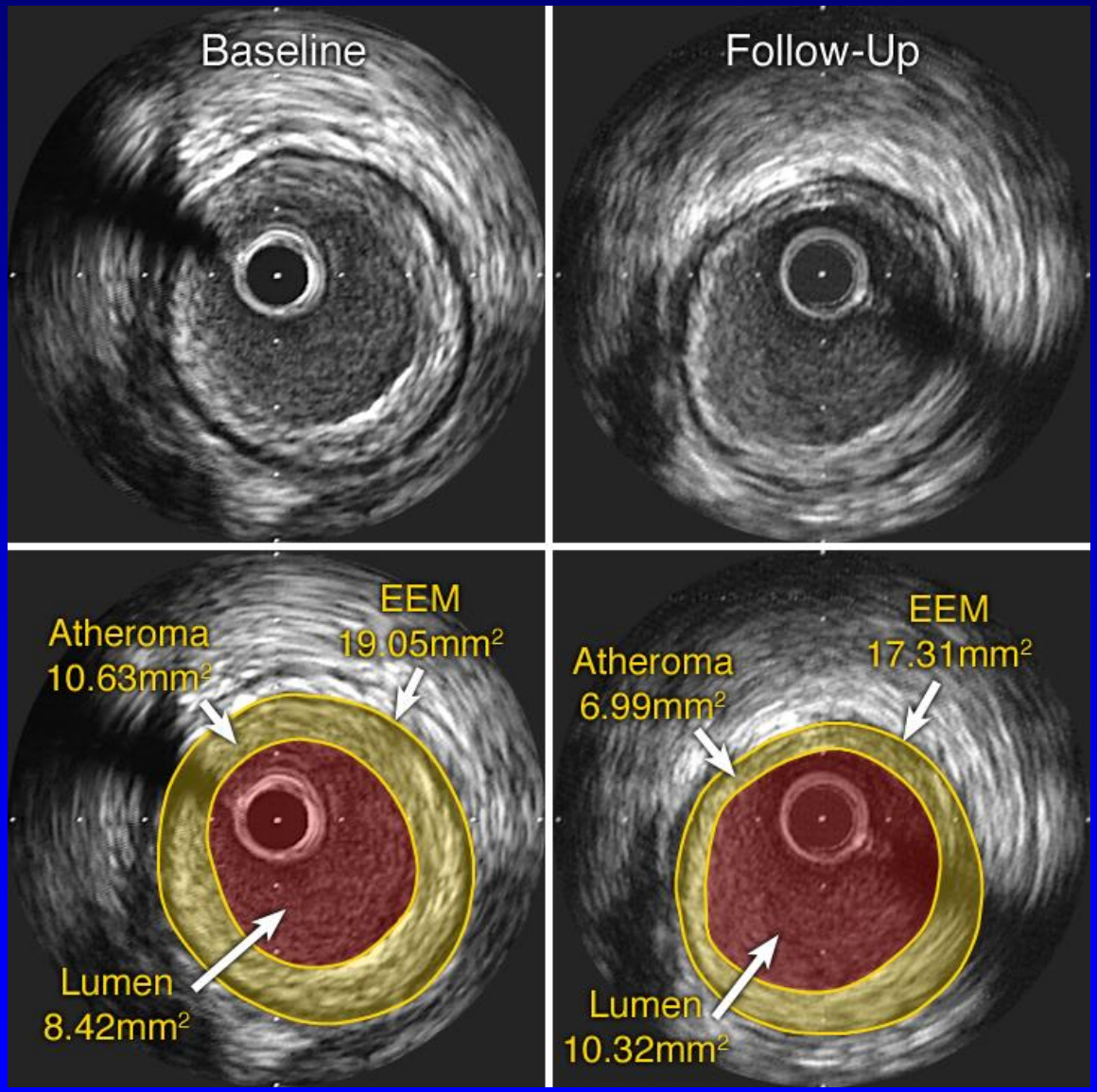
- LDL Levels were reduced from 130.4 mg/dL at baseline to a mean of 60.8 mg/dL at 2 year follow-up (p<0.001), with 75% of patients achieving an LDL <70 mg/dL.
- HDL levels were increased from 43.1 mg/dL at baseline to a mean of 49.0 mg/dL at follow-

Presented at ACC 2006

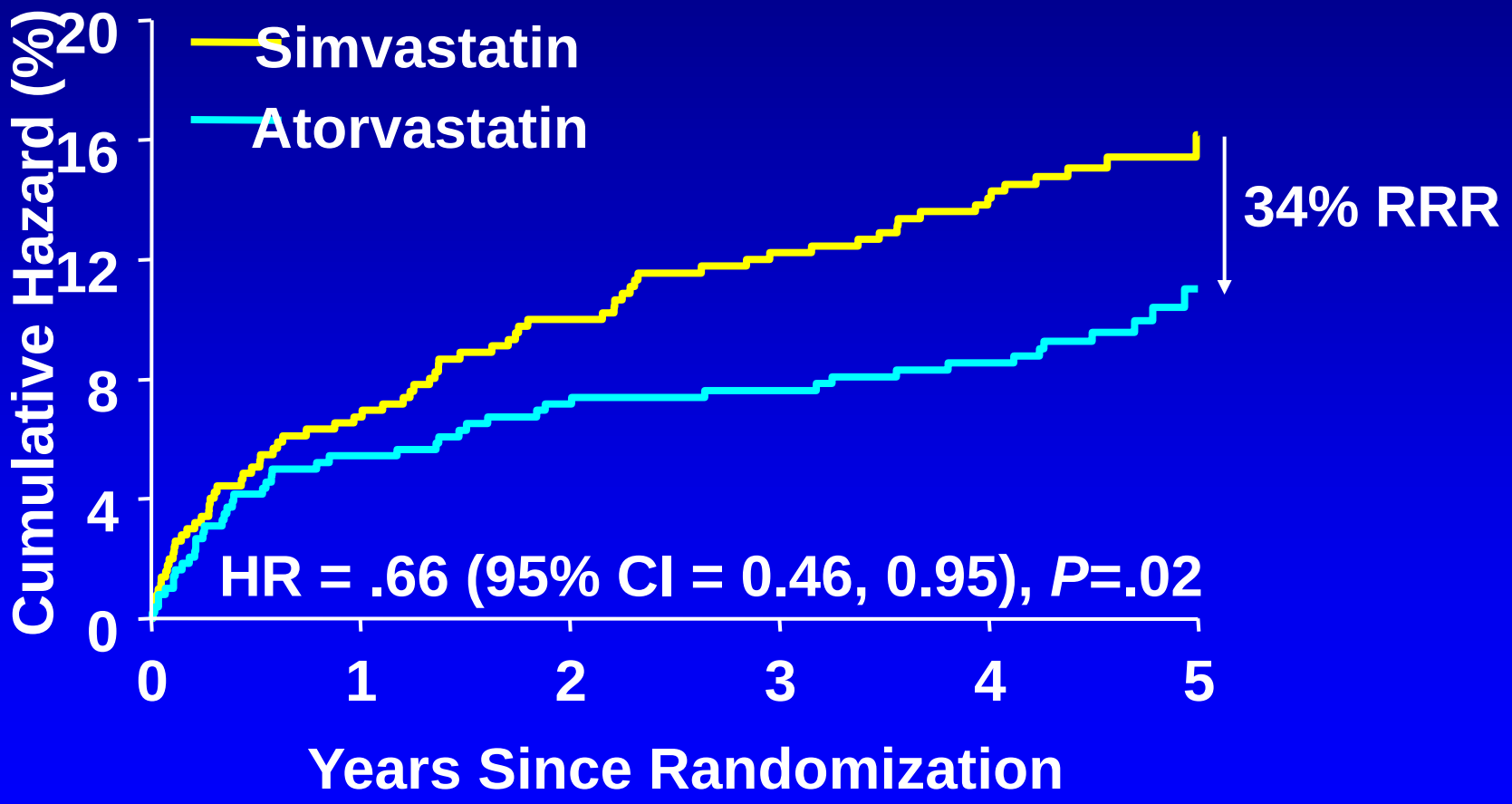
Endpoint analysis: Change in key IVUS parameters



Regression of atherosclerosis in ASTEROID

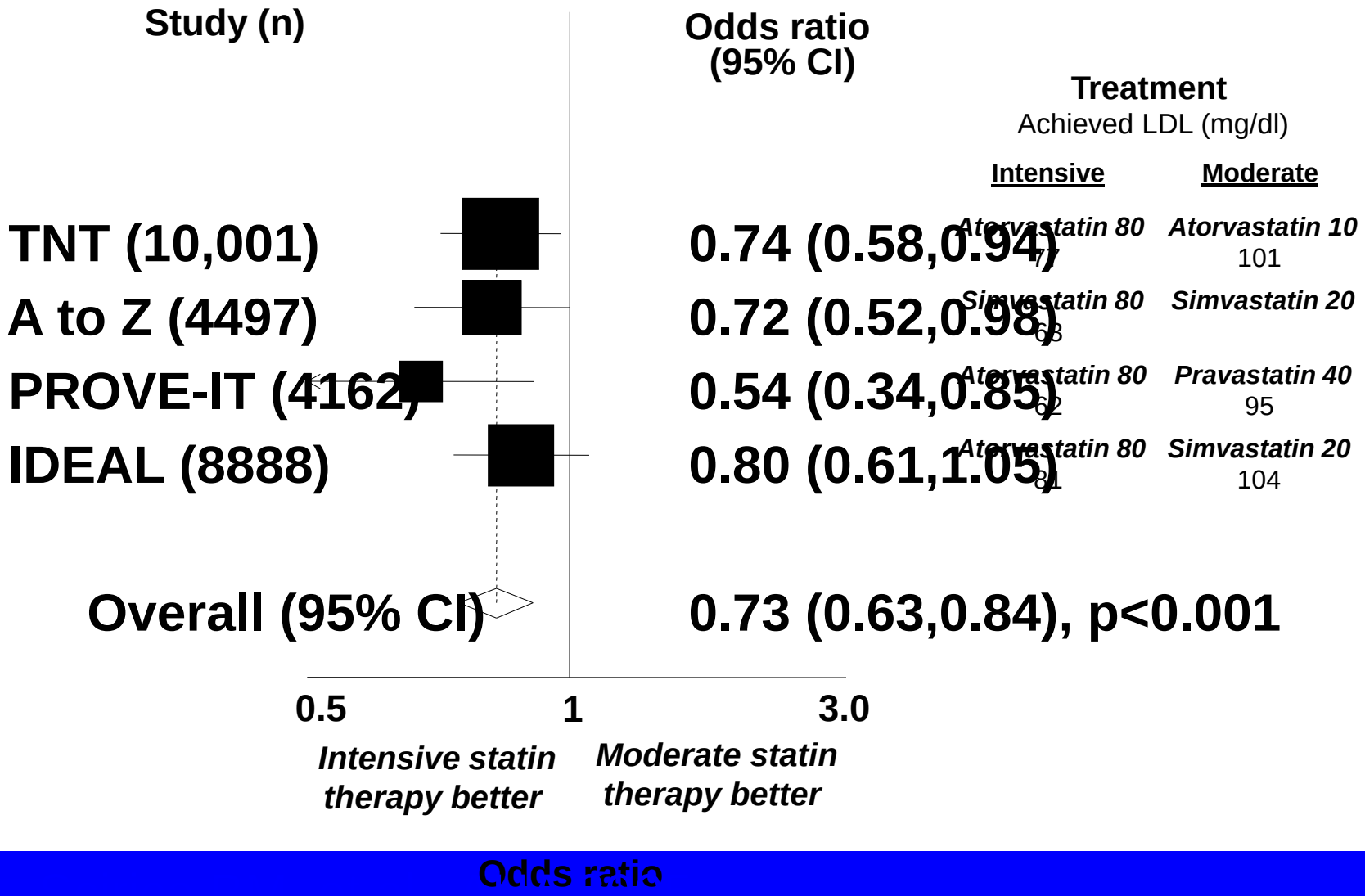


ACS Patients: Major Coronary Events MI + CHD Death + Resuscitated Cardiac Arrest

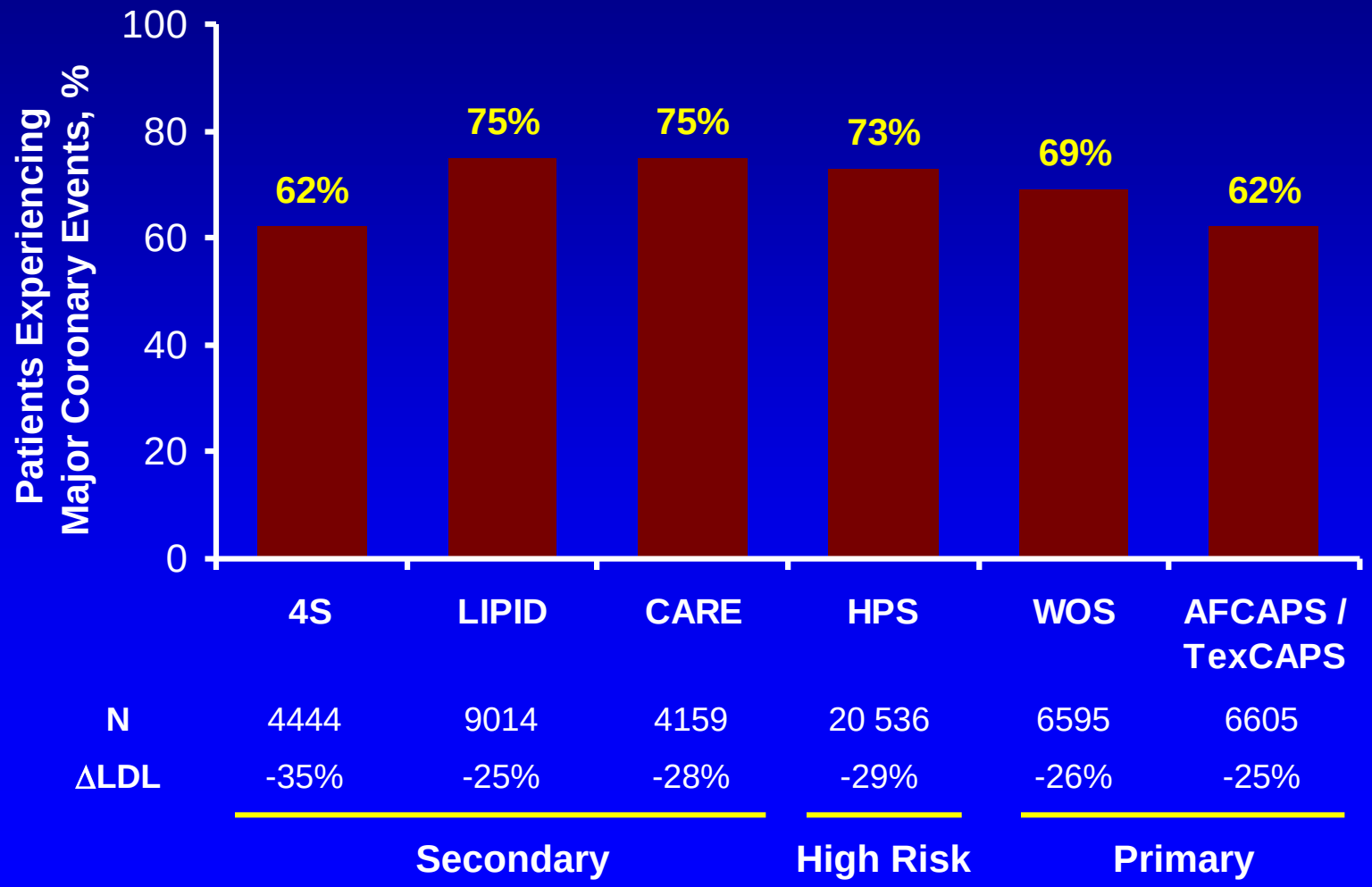


Pedersen, Olsson, Cater et al. Presented at World Congress of Cardiology 2006

Meta-Analysis of Intensive Statin Therapy CHF

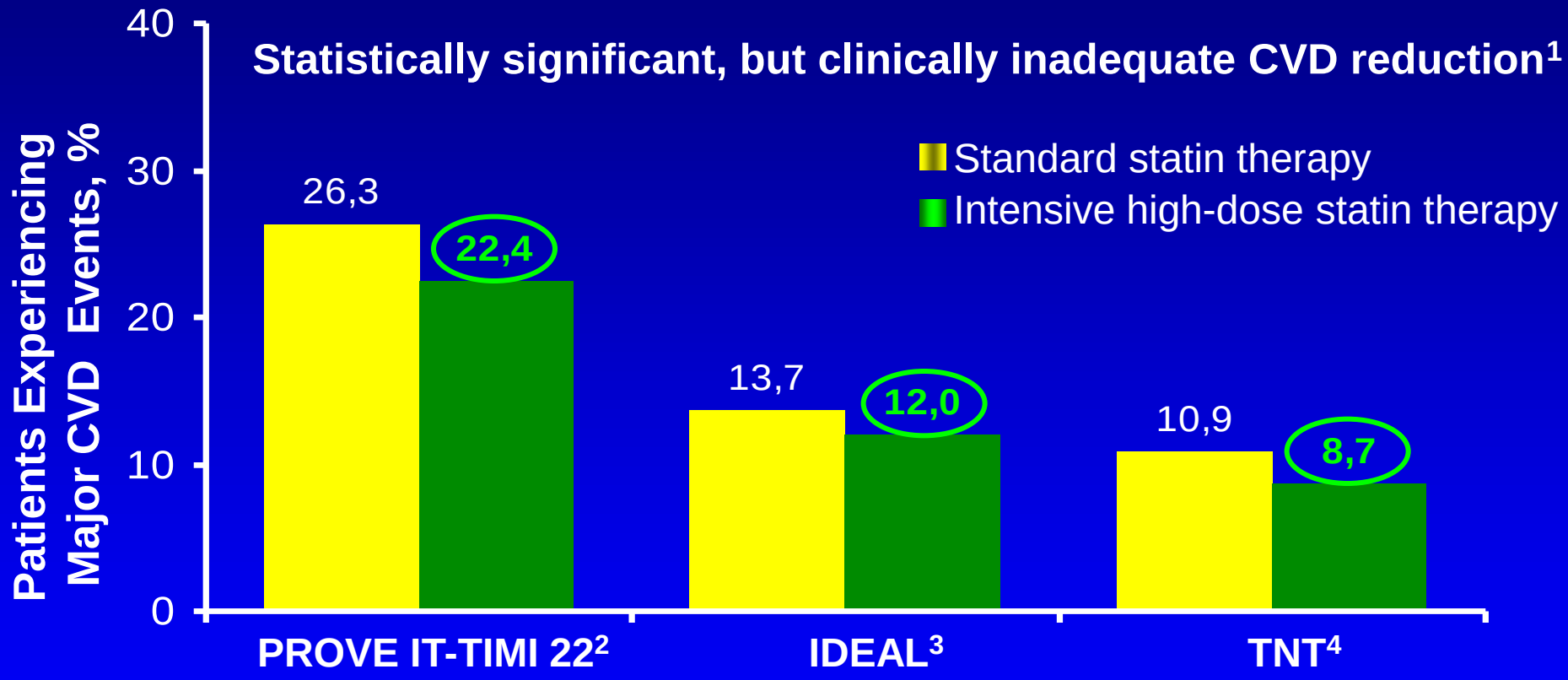


Residual Cardiovascular Risk in Major Statin Trials: Standard Doses



Adapted from Libby PJ, et al. *J Am Coll Cardiol*, 2005:46:1225-1228.

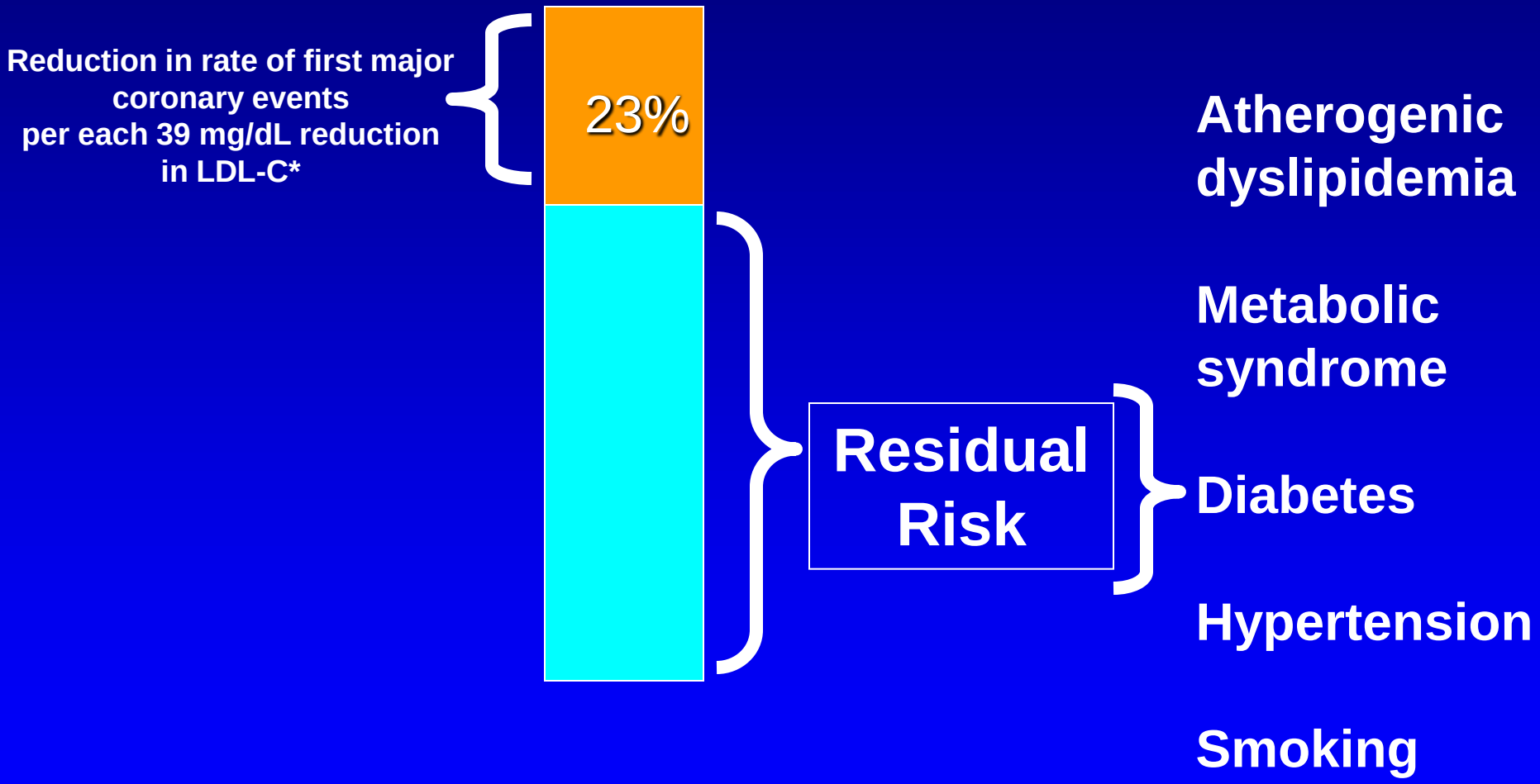
Residual CVD Risk in Patients Treated With Intensive Statin Therapy



[1]Superko HR. *Br J Cardiol.* 2006;13:131-136. [2]Cannon CP, et al. *N Engl J Med.* 2004;350:1495-1504.[3]Pedersen TR, et al. *JAMA.* 2005;294:2437-2445. [4]LaRosa JC, et al. *N Engl J Med.* 2005;352:1425-1435.

*Mean or median LDL-C after treatment

It is time to treat the Residual CVD Risk in Patients With Dyslipidemia

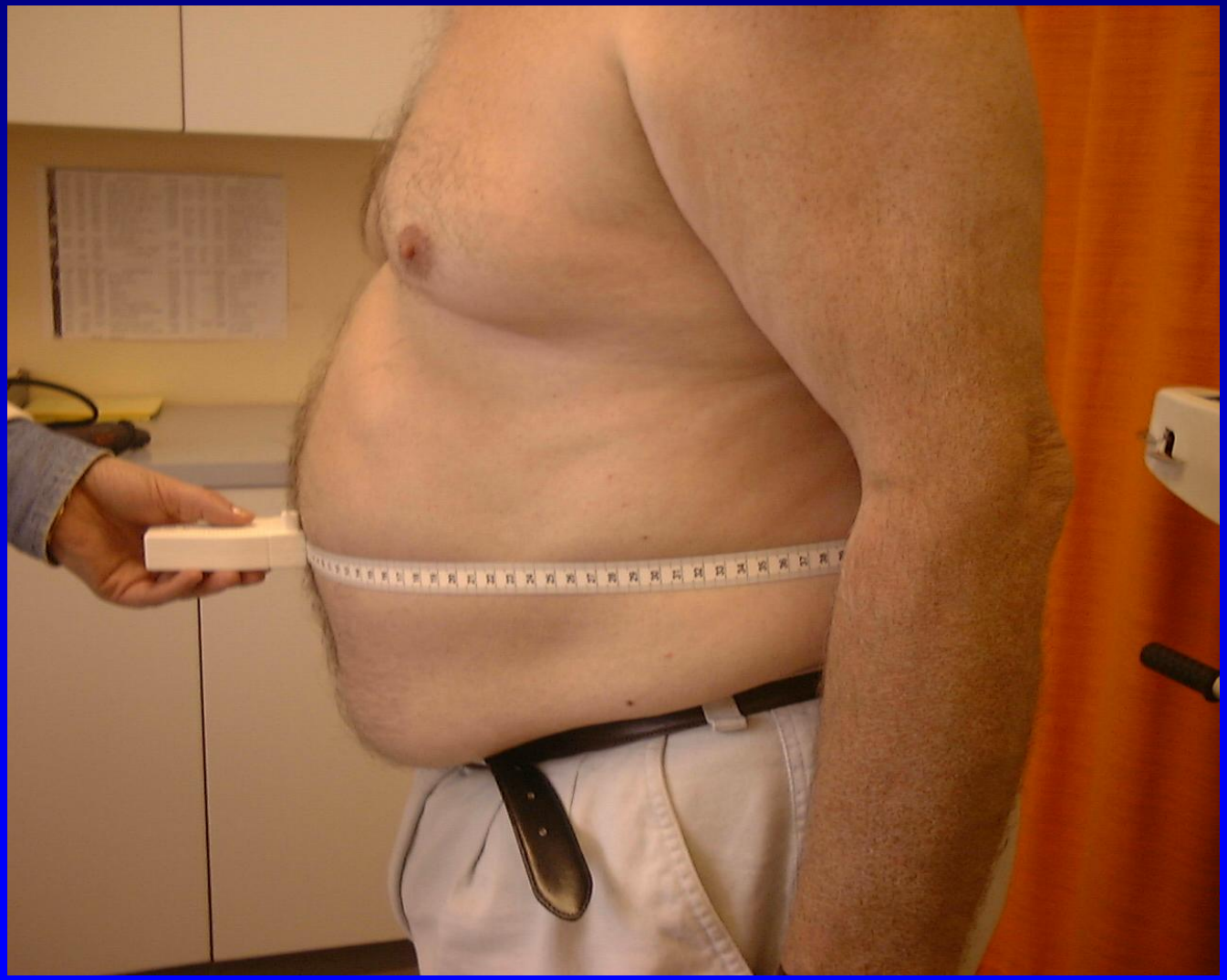


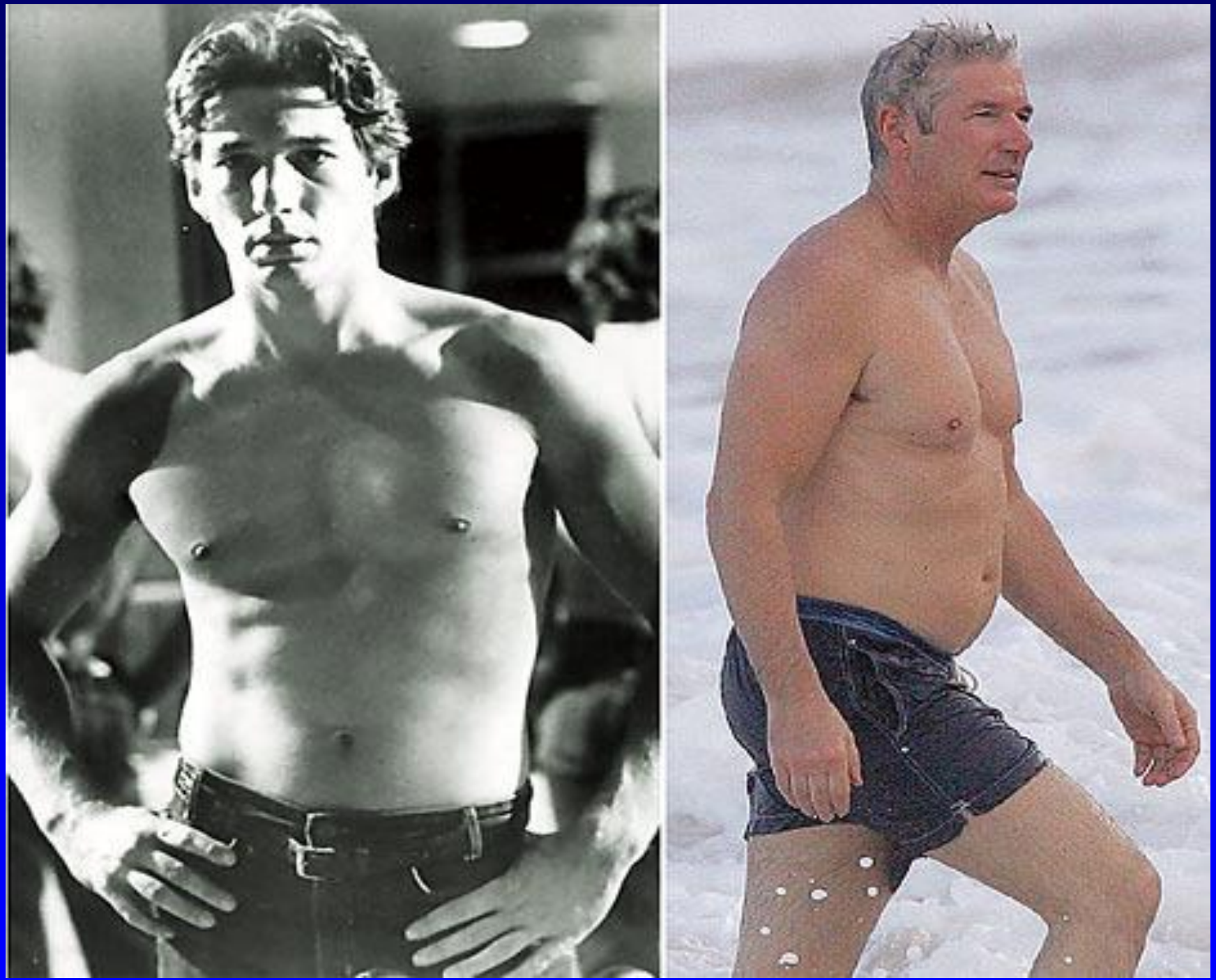
*Cholesterol Treatment Trialists' (CTT) Collaborators. Lancet. 2005;366:1267-1278.

Residual Risk: Definitions

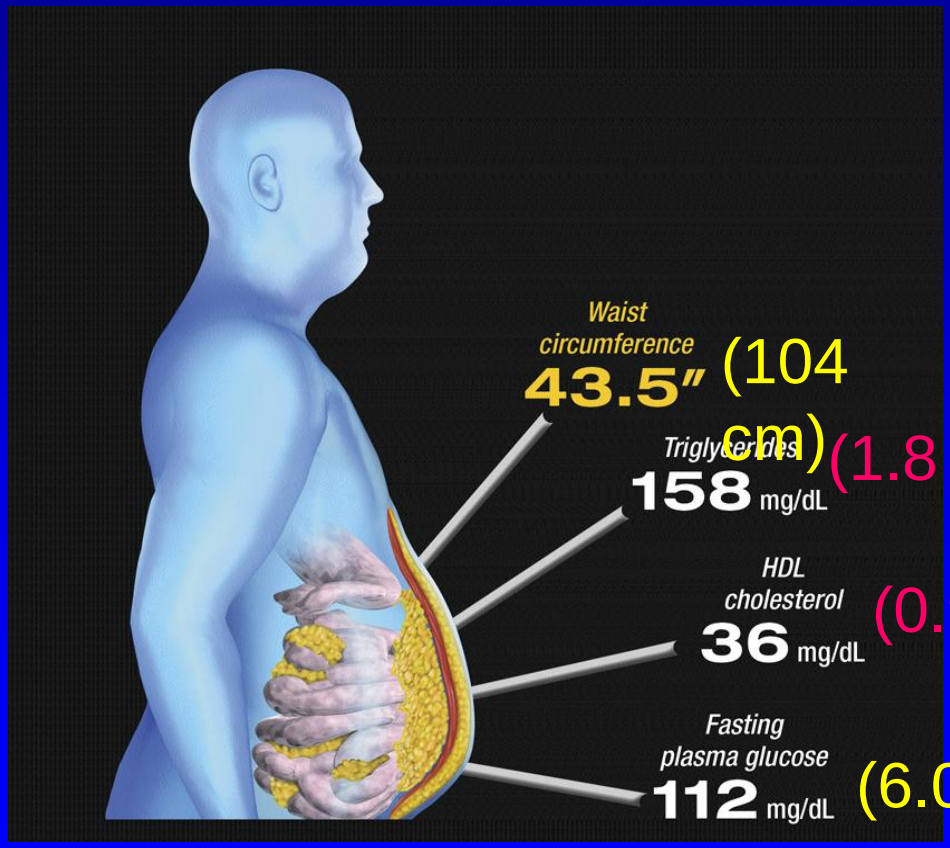
1. CVD incidence in patients on statin treatment
   - Standard dose, e.g. simvastatin 20-40 mg
   - Intensive dose, e.g. atorva 80, rosuva 40
2. CVD incidence in patients treated to LDL goal
3. CVD incidence in patients on optimal treatments to prevent CVD, including anti-hypertensive, anti-platelet, LDL, smoking, nutrition, lifestyle

30% of adults in CZ: Metabolic Syndrome





RFs in abdominal obesity



(104 cm)

(1.8 mmol/L)

(0.9 mmol/L)

(6.0 mmol/L)

Patients with abdominal obesity (high waist circumference) often present with one or more additional CV risk factors

Cardiometabolic risk in MS patient

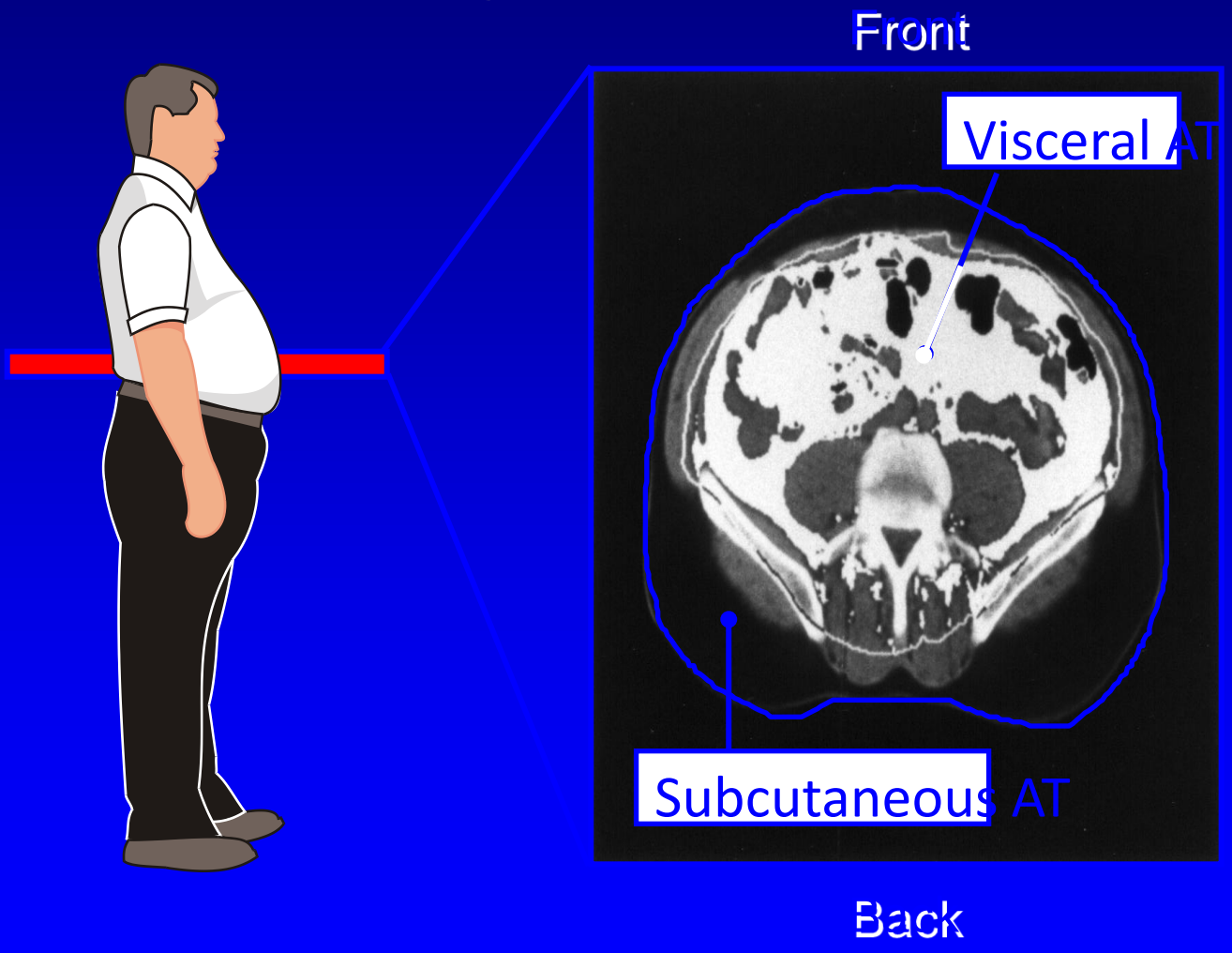
- Hypertriglyceridemia
- Low HDL-C
- Elevated apolipoprotein B
- Small, dense LDL particles
- Postprandial hyperlipidaemia

- Hyperinsulinemia
- Glucose intolerance
- Insulin resistance
- Impaired fibrinolysis
- Endothelial dysfunction

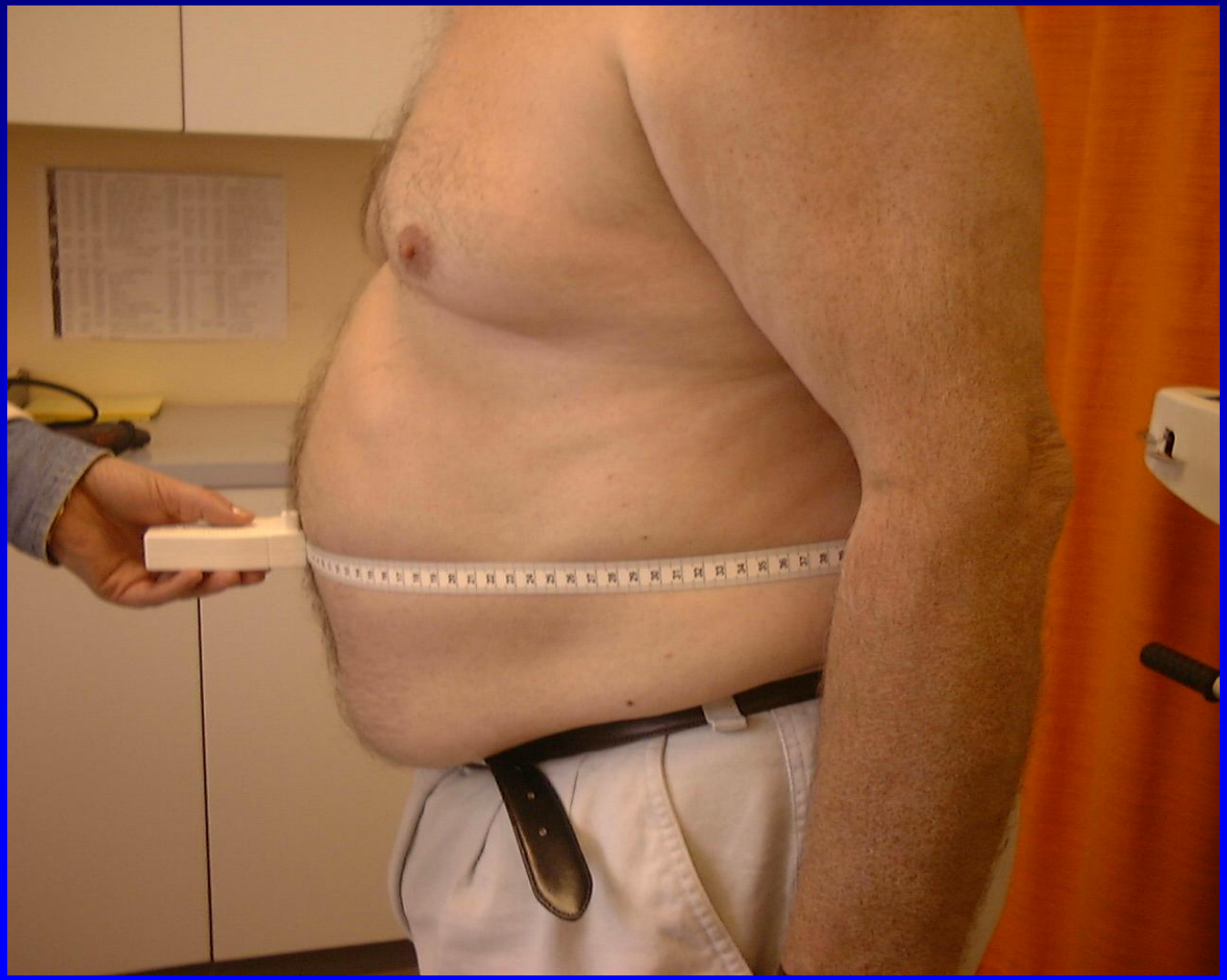
Hypertension
Central obesity
Smoking , Depression

Intra-abdominal (visceral) fat examination

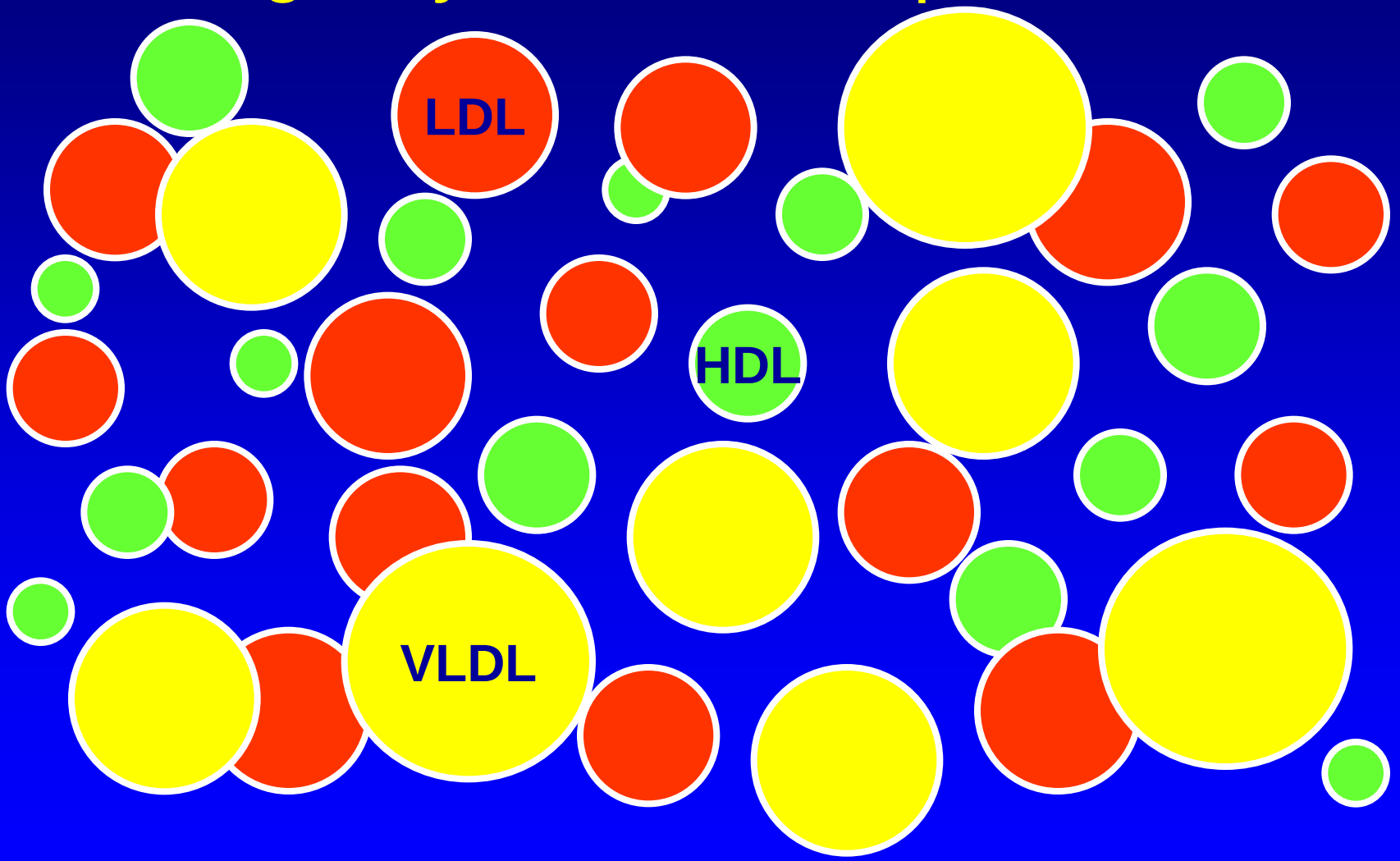
The dangerous inner fat!



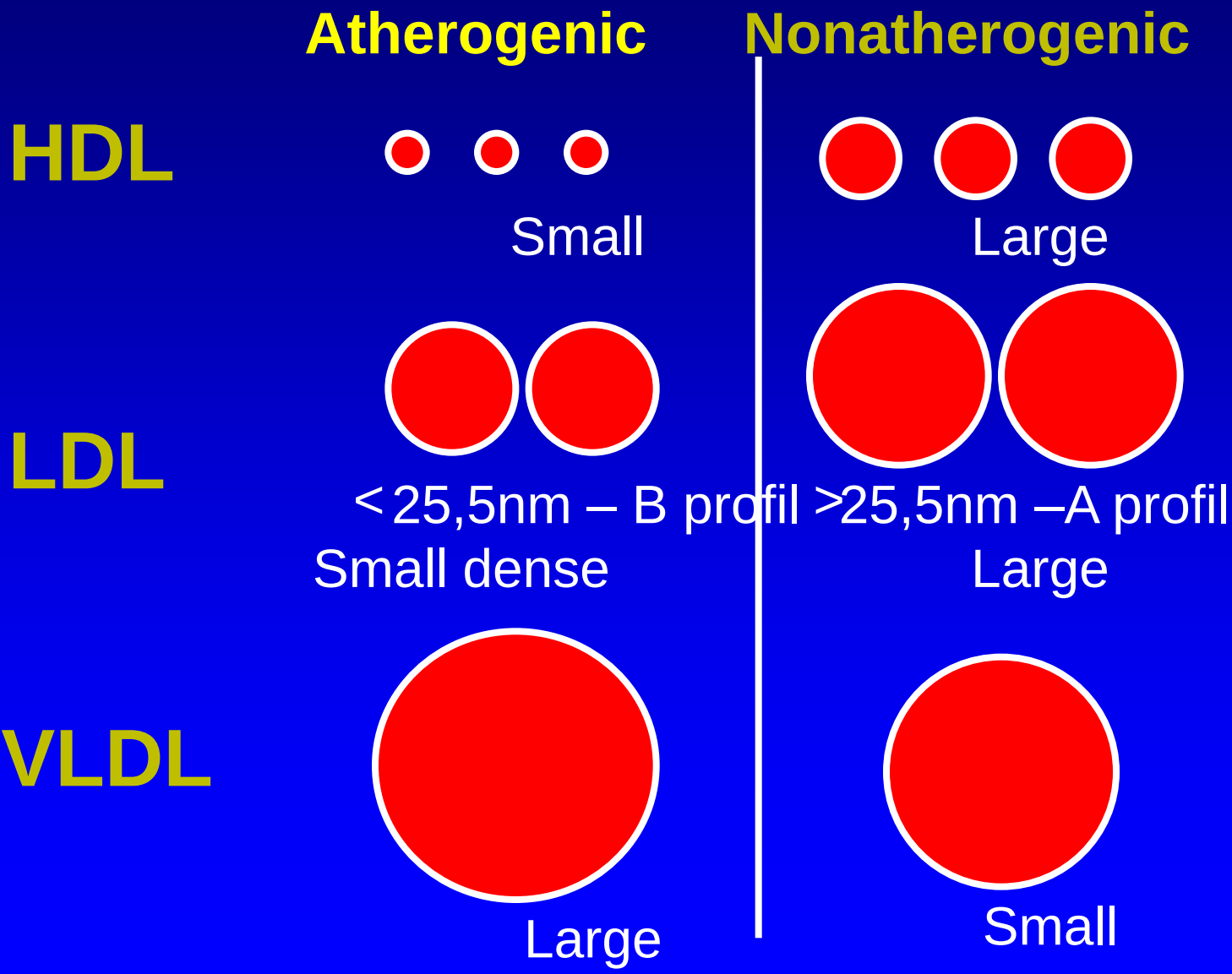
Intra-abdominal fat examination



Atherogenity: The role of particle size



Particle size and CV risk



How to decrease residual risk?

- **Treatment of HLP/ DLP**
- ***(part of the complex approach)***

Focused on:

HDL-C

TGs

TGs, (HDL-C)

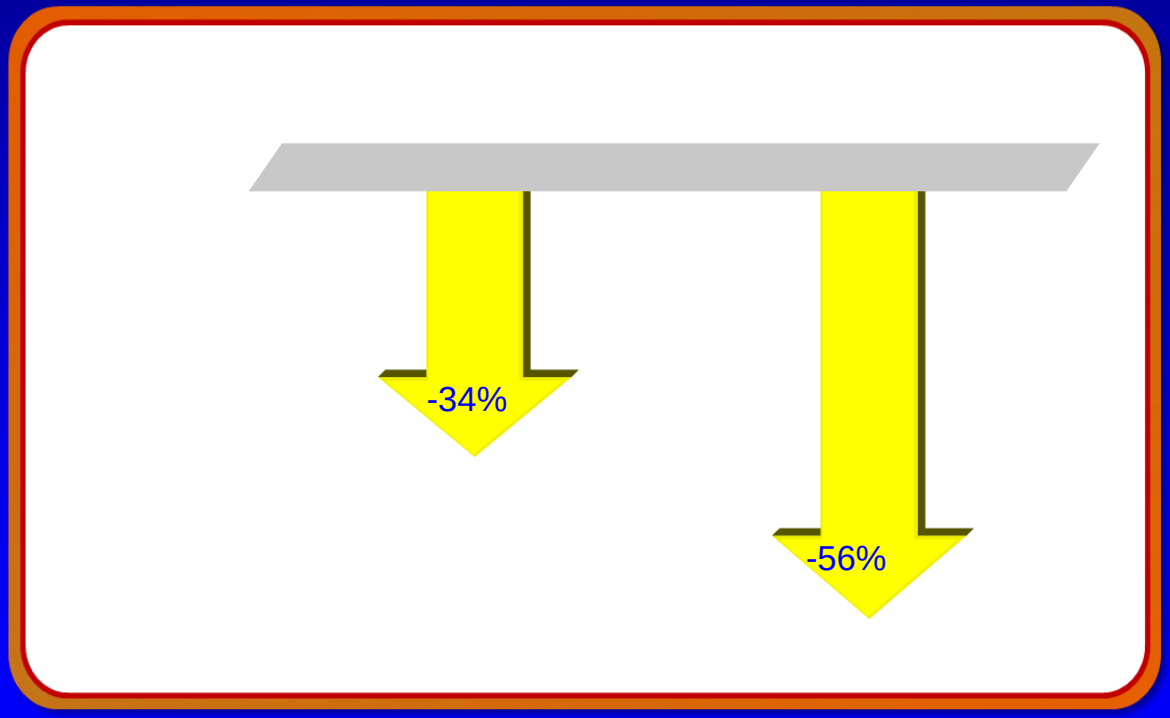
Fibrates

Statin + Fibrate

COMBO

Elevated TGs identify patients in whom fibrate therapy reduces CV risk (1)

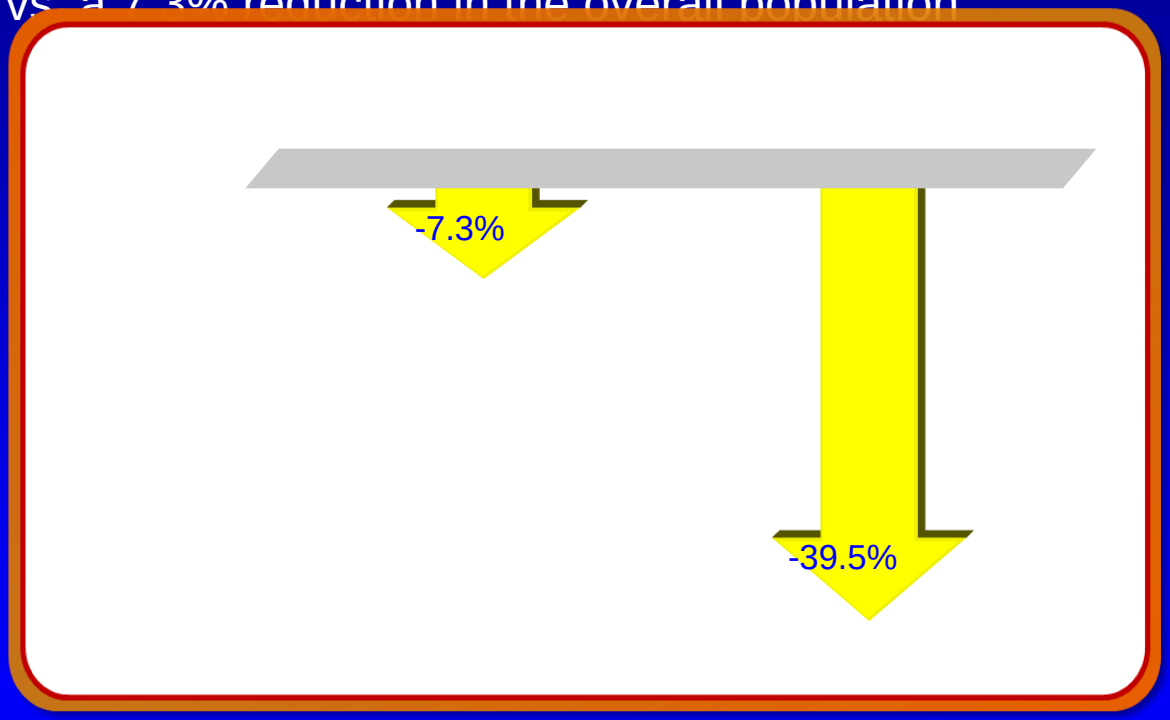
- **HHS**[1,2]: Fibrates reduced the incidence of CV events **by 56%** in patients with TG levels >2.3 mmol/L (200 mg/dL) compared with a 34% reduction in the overall population



[1] Frick MH *et al. N Engl J Med* 1987;317:1237-45.
[2] Barter PH, Rye KA. *Arterioscler Thromb Vasc Biol* 2008;28:39-46.

Elevated TGs identify patients in whom fibrate therapy reduces CV risk

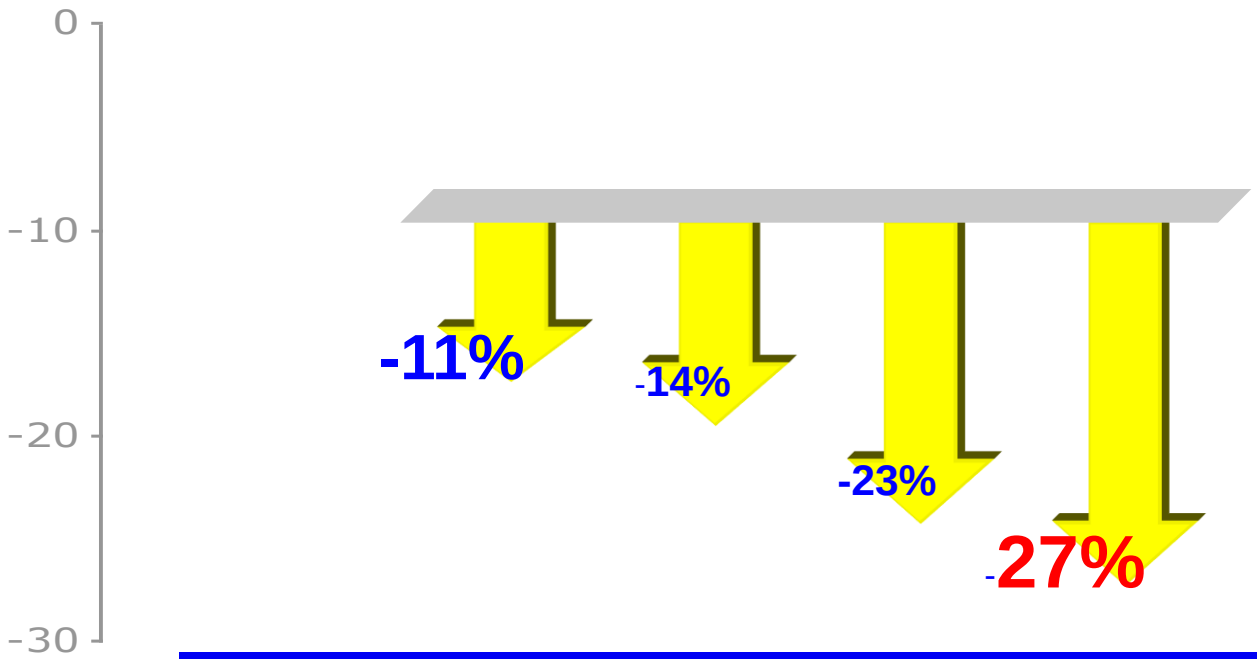
- **BIP**[1]: Fibrate treatment significantly reduced the risk of CV events **by 39.5%** in patients with TG ≥2.3 mmol/L (200 mg/dL) vs. a 7.3% reduction in the overall population



*CV events: fatal or nonfatal MI or sudden death (primary endpoint)

[1] The BIP Study Group. *Circulation* 2000;102:21-7.

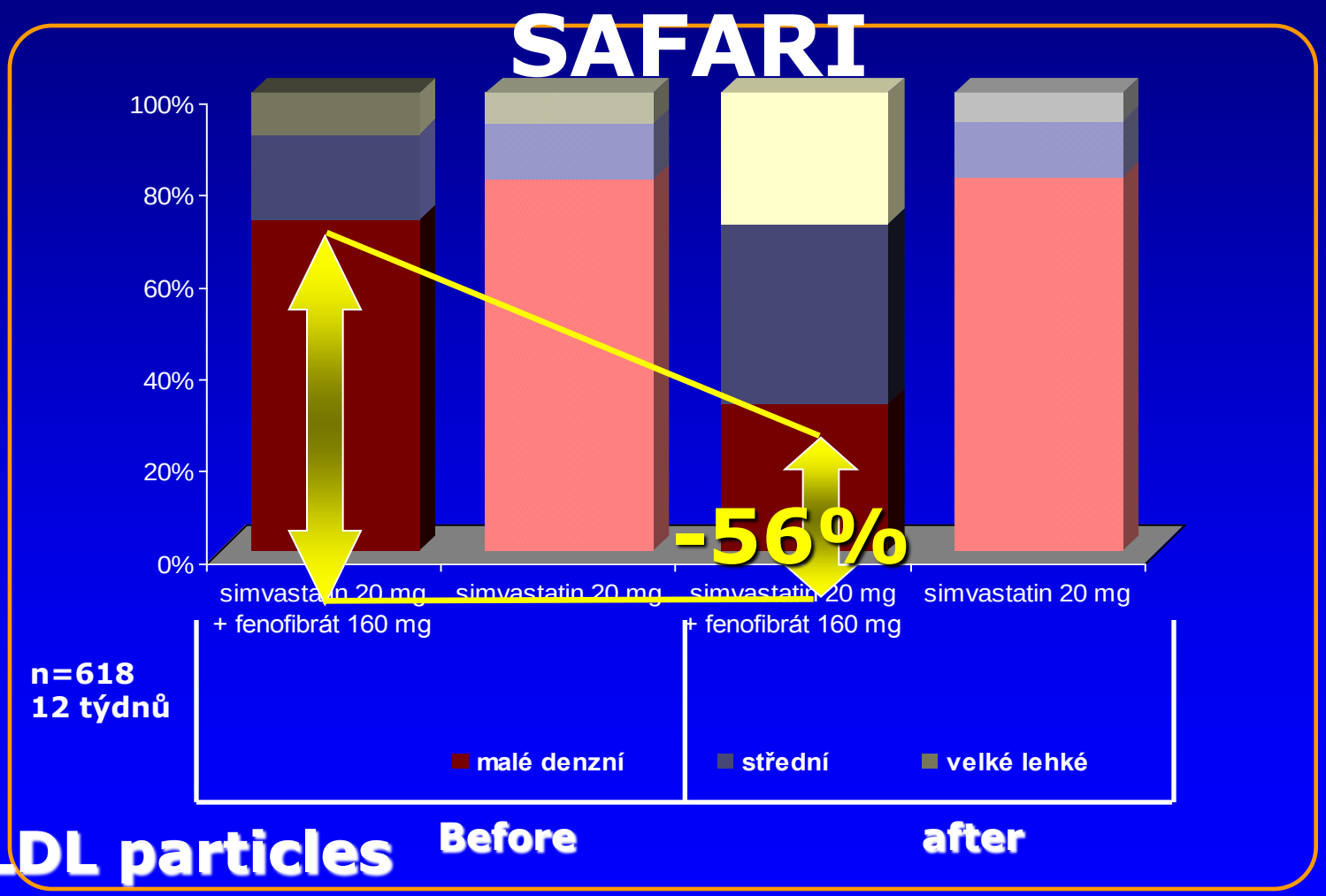
High TGs /low HDL-C identify patients in whom fibrate reduces CV risk



Low HDL-C (<1.03 mmol/L or 40 mg/dL for men and <1.29 mmol/L or 50 mg/dL for women) and elevated TG (≥2.3 mmol/L or 200 mg/dL) defined according to ATP III criteria

Small dense LDL reduction - 56%

after statin + fenofibrate combo



Grundy SM, Vega GL, Yuan Z, et al. Effectiveness and Tolerability of Simvastatin Plus Fenofibrate for Combined Hyperlipidemia (The SAFARI Trial) Am J Cardiol 2005;95:462–468

Studies with fibrates: Comparison of general population and subgroups ith lo HDL and high Tgs

Trial (Drug)	Primary Endpoint: Entire Cohort (P-value)	Lipid Subgroup Criterion	Primary Endpoint: Subgroup
HHS (Gemfibrozil)	-34%	TG > 200 mg/dl LDL-C/HDL-C > 5.0	**-71%**
BIP (Bezafibrate)	-7.3%	TG ≥ 200 mg/dl	**-39.5%**
FIELD (Fenofibrate)	-11%	TG ≥ 204 mg/dl HDL-C < 42 mg/dl	**-27%**
ACCORD (Fenofibrate)	-8%	TG ≥ 204 mg/dl HDL-C ≤ 34 mg/dl	**-31%**

HDL-C

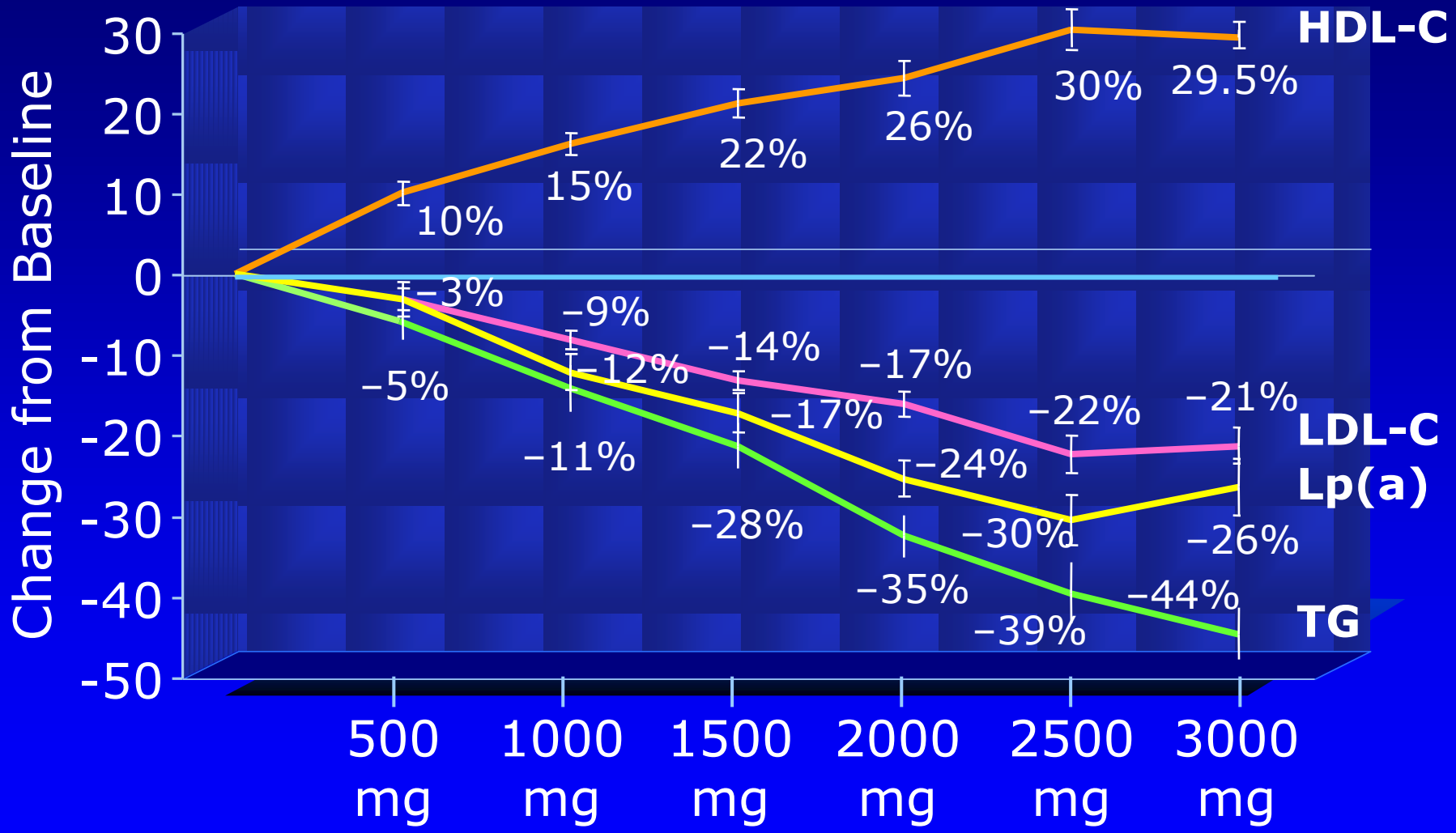
(LDL,TG)

Niacin

Statin + Niacin

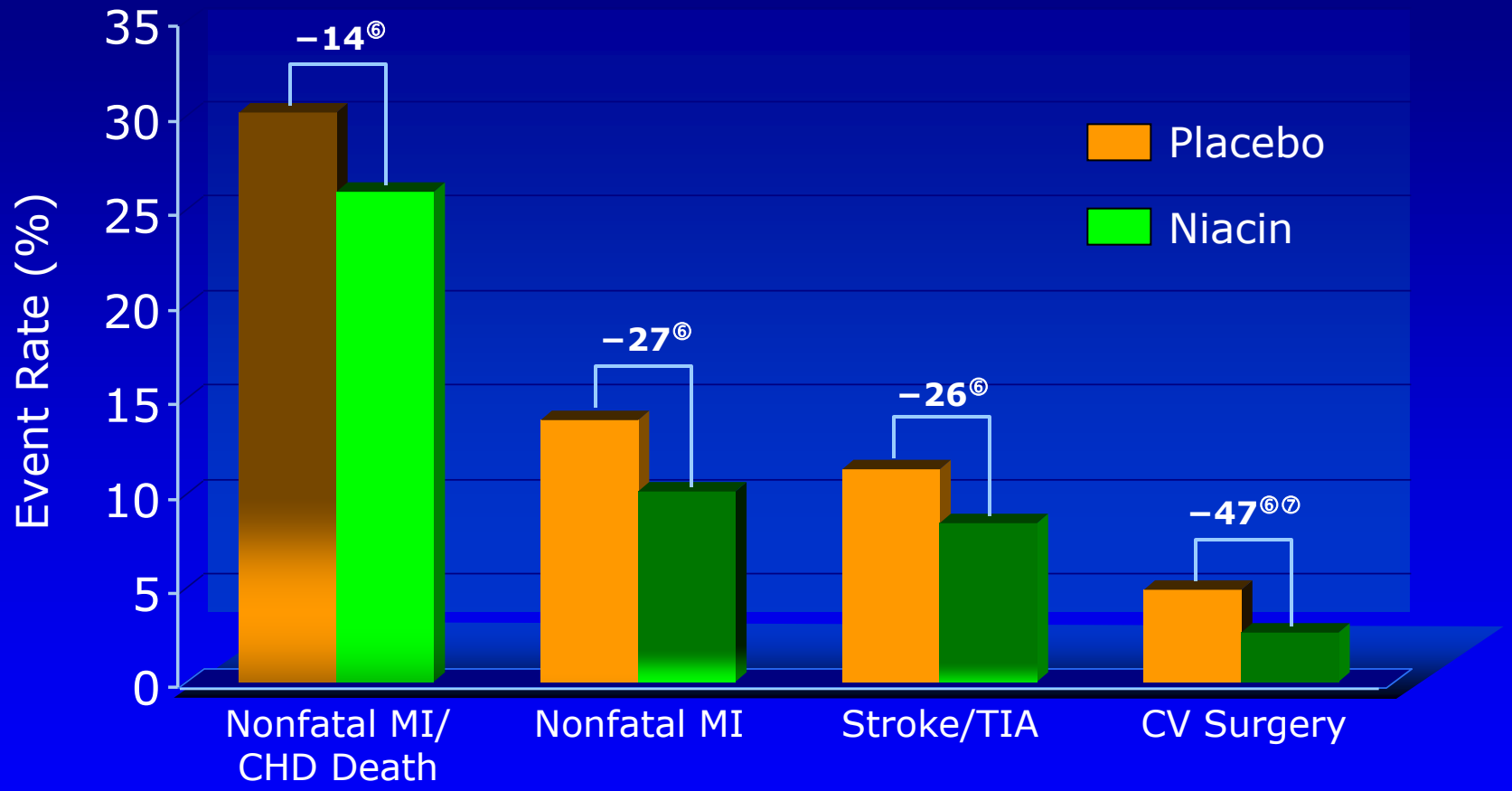
(laropiprant)

Efficacy of Extended-Release Niacin



Goldberg A et al. *Am J Cardiol* 2000;85:1100-1105.

Coronary Drug Project: *Clinical Outcomes**



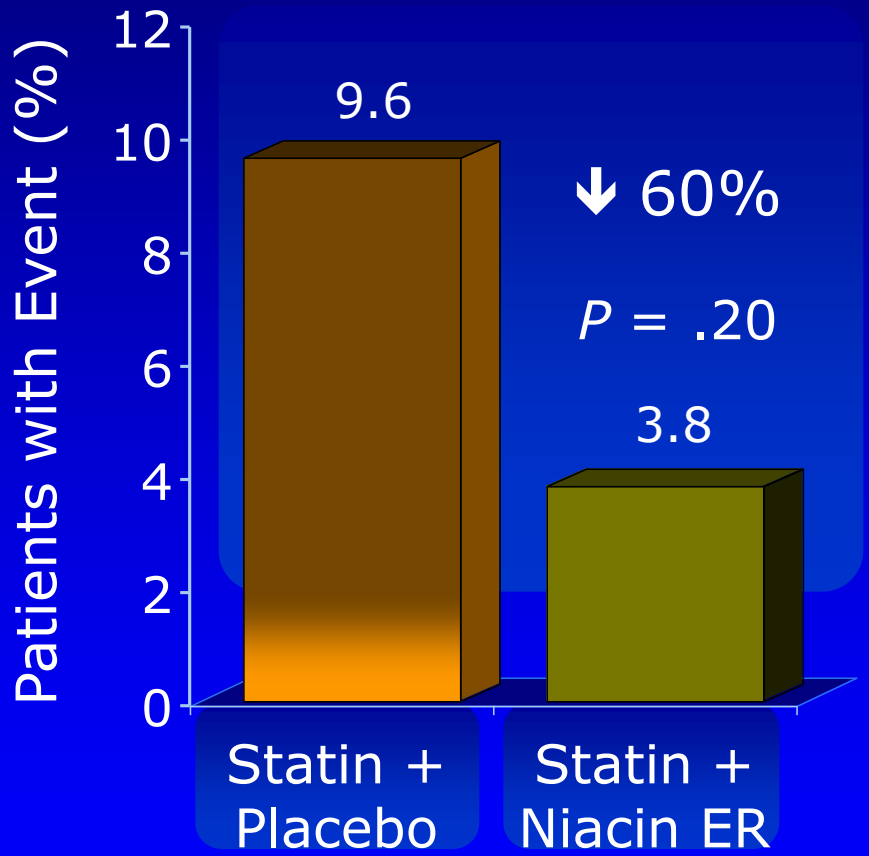
MI=myocardial infarction; CHD=coronary heart disease; TIA=transient ischemic attack; CV=cardiovascular

*Total follow-up, adjusted for baseline characteristics, ⑥p<0.05, ⑦5-year rate

Coronary Drug Project Research Group. *JAMA* 1975;231:360–381.

ARBITER 2: Secondary Efficacy Endpoint—Clinical Events

- Composite clinical event endpoint
  - Unstable angina/MI hospitalization
  - Stroke
  - Sudden cardiac death
  - Percutaneous coronary revascularization, CABG, or peripheral revascularization



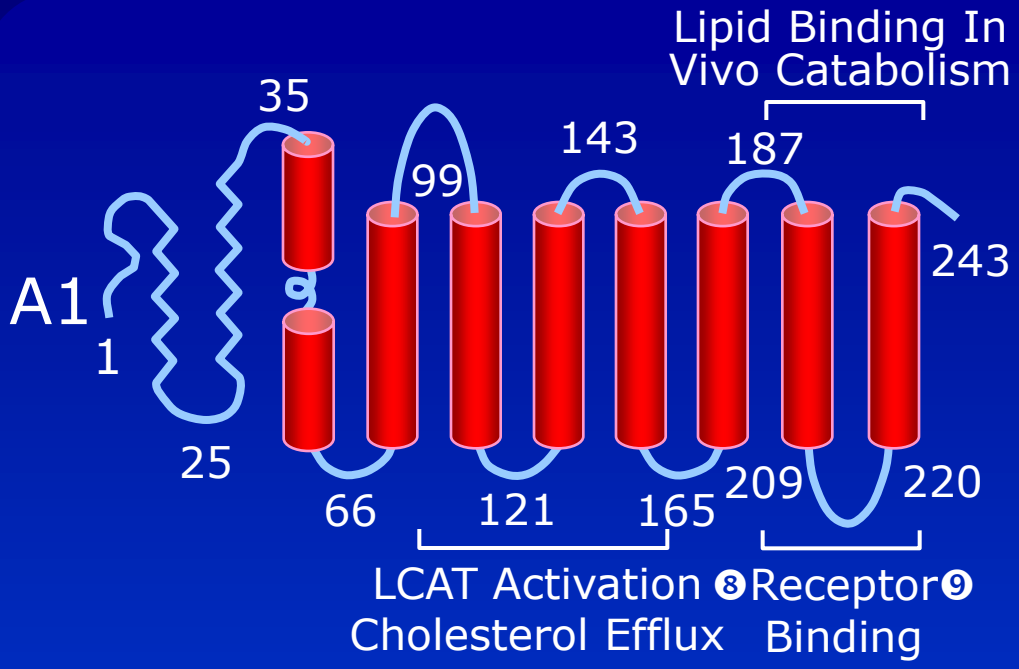
Taylor AJ et al. *Circulation* 2004;110:3512-3517.

HDL-C

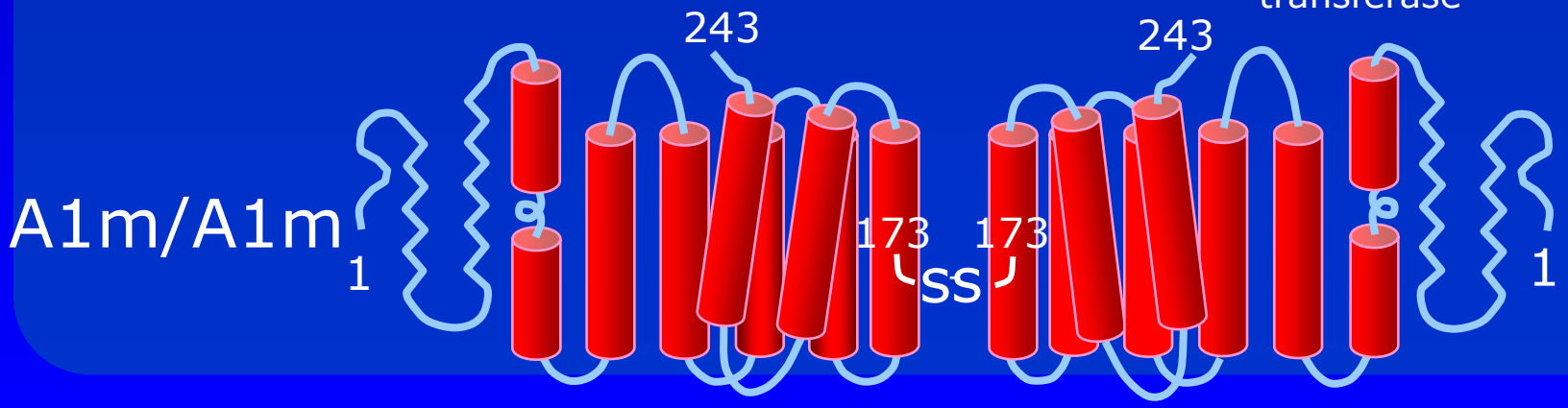
New experimental approach

ApoA-I Milano

Normal Apo A1 and Apo A1 Milano Dimer



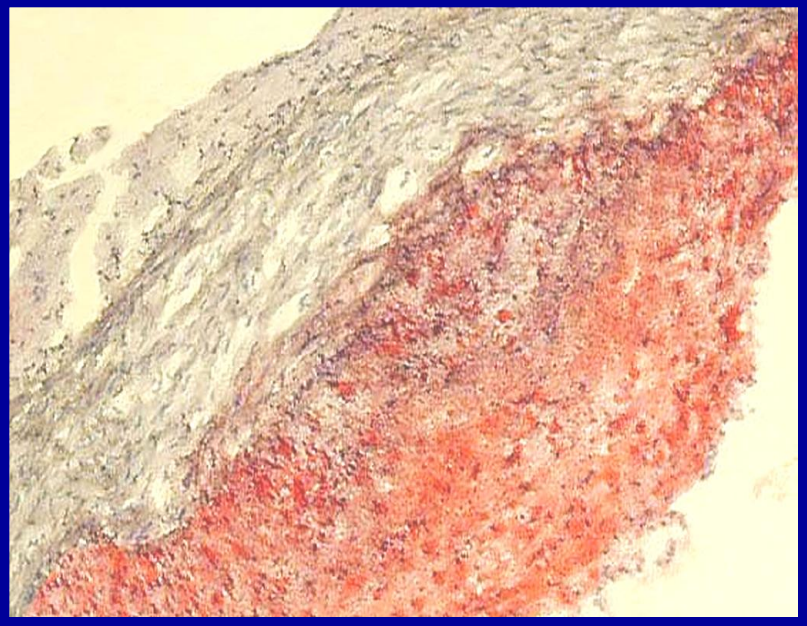
A1=apolipoprotein A1
A1m=apolipoprotein A1 Milano
LCAT=lecithin cholesterol acyl-transferase



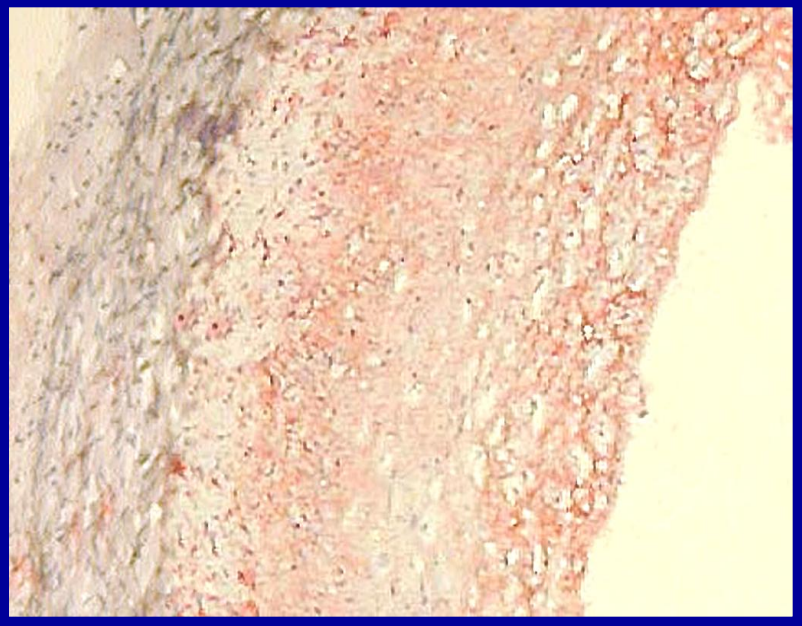
Franceschini G. *Eur J Clin Invest 1996;*26:733–746.

Evaluation of Plaque Changes in Rabbits by Apo A1 Milano Infusion: *Plaque Lipid Content*

Saline



Apo A1 Milano (1g)



Unpublished data from Chiesa G et al. *Circ Res* 2002;90:974–980.

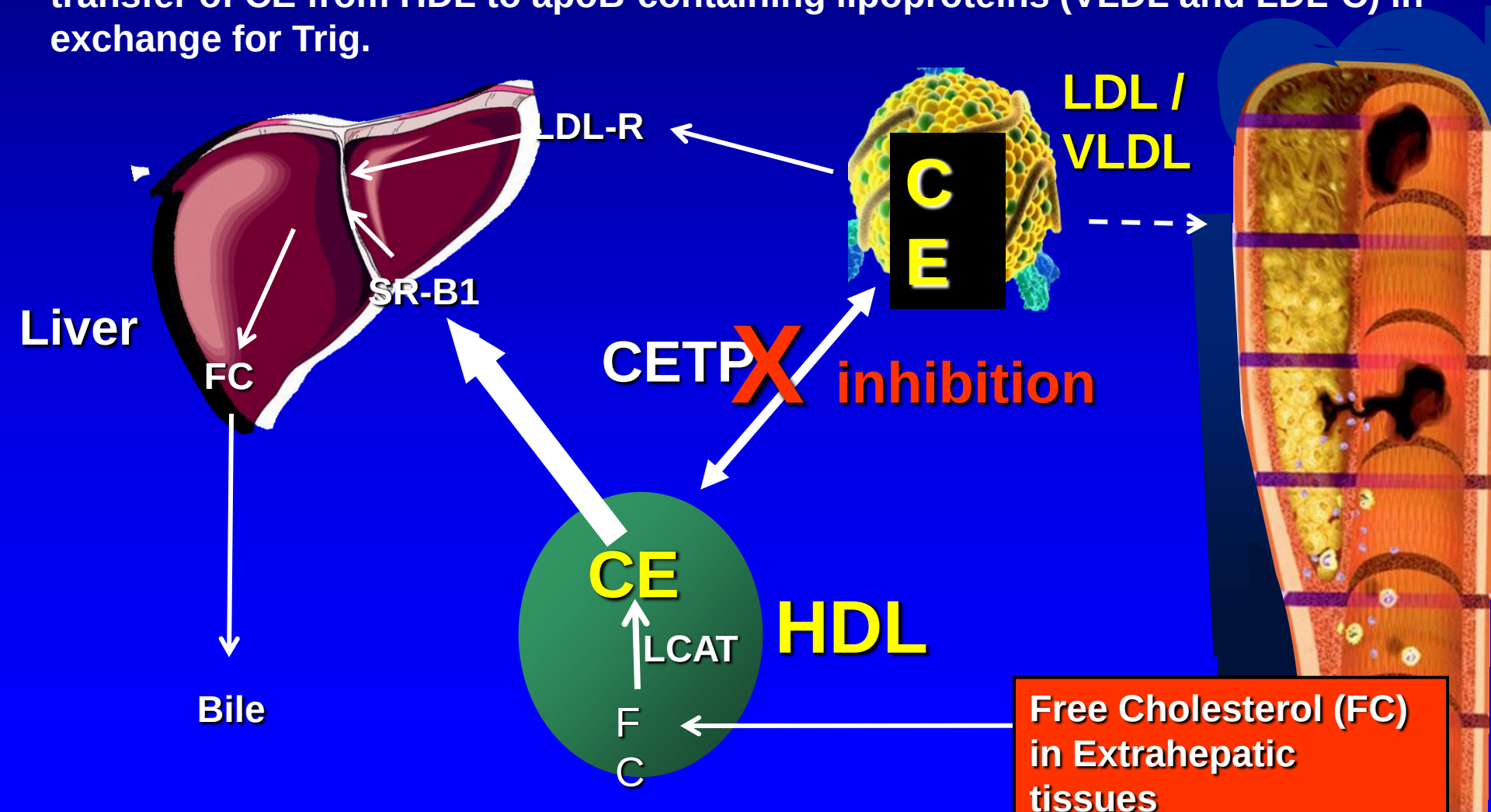
HDL-C

New experimental approach

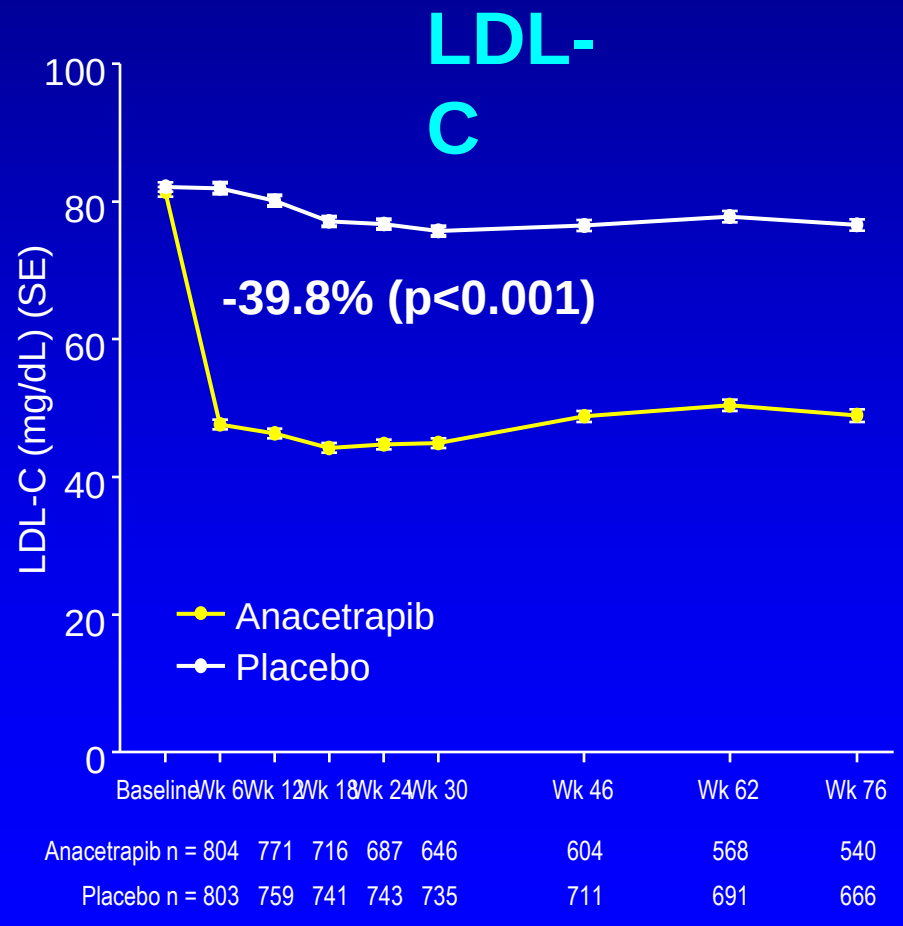
CETP inhibitors

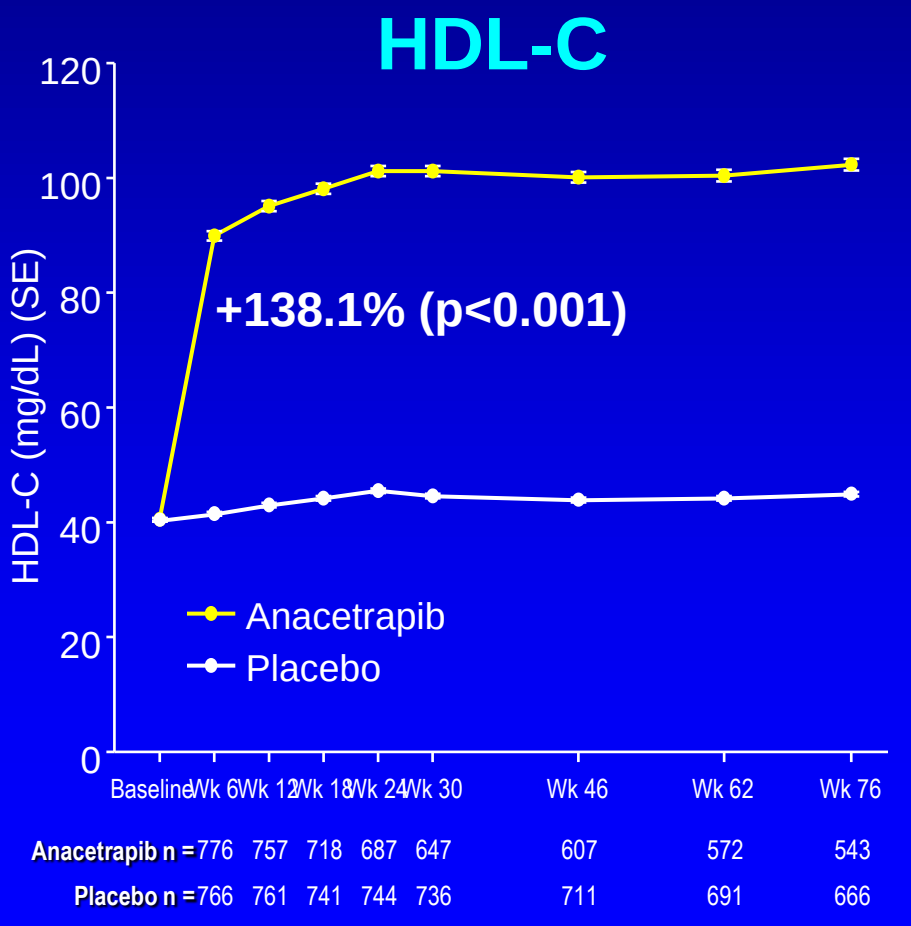
Background: CETP inhibition

Cholesteryl ester transfer protein (CETP) is a plasma protein that catalyzes the transfer of CE from HDL to apoB-containing lipoproteins (VLDL and LDL-C) in exchange for Trig.



Effects on LDL-C and HDL-C





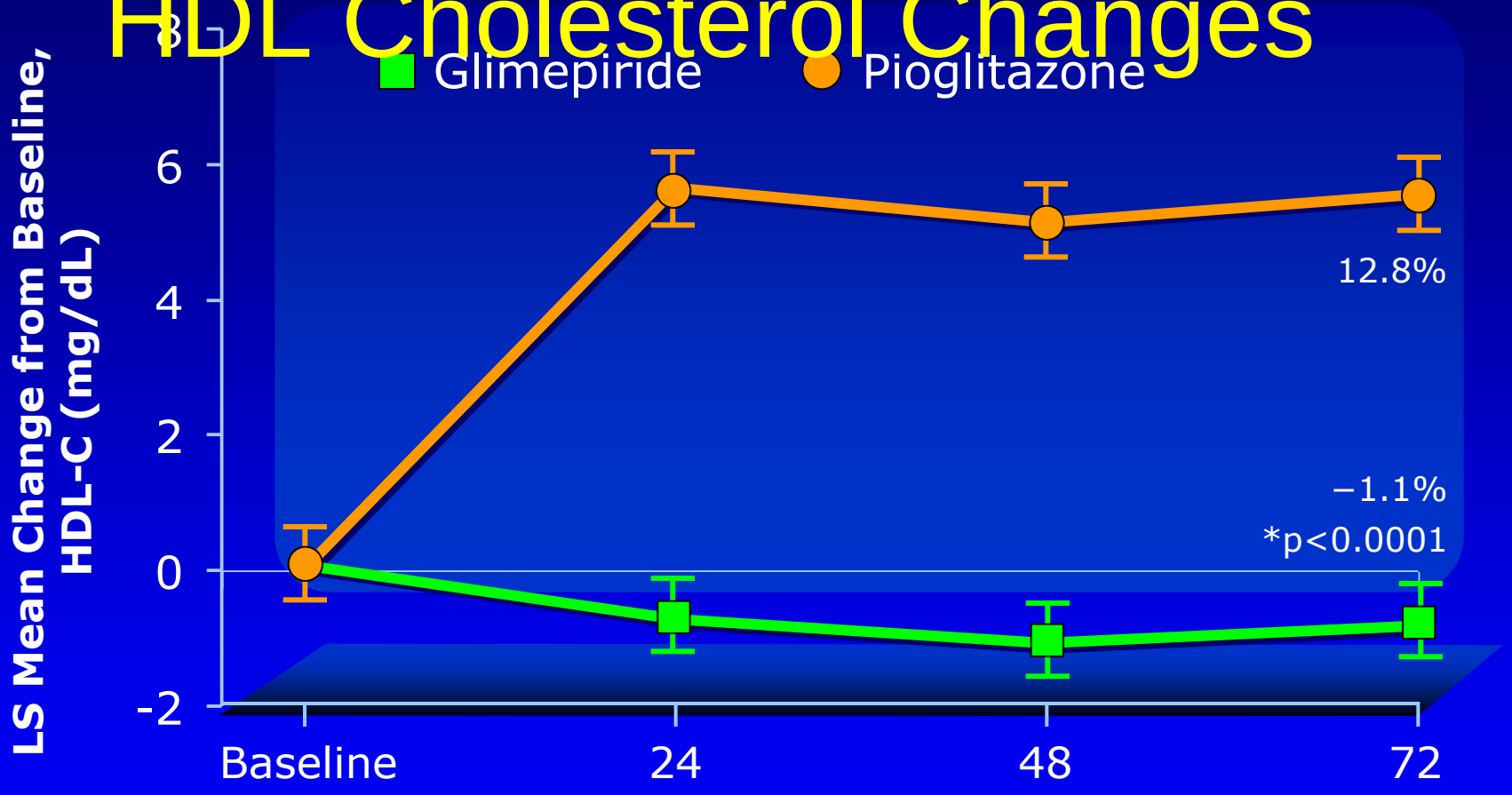
Lipid Parameters

Parameter	LS Mean Percent (95% CI) Placebo-Adjusted Change from Baseline	
	Week 24	Week 76
Non-HDL-C	-31.7* (-33.6, -29.8)	-29.4* (-31.6, -27.3)
Apo B	-21.0* (-22.7, -19.3)	-18.3* (-20.2, -16.4)
Apo A-1	44.7* (42.8, 46.5)	42.3* (40.5, 44.1)
TC	13.7* (12.0, 15.3)	15.6* (13.8, 17.3)
TG	-6.8 (-9.9, -3.9)	-5.3 (-8.9, -1.7)
Lp(a)	-36.4 (-40.7, -32.3)	-38.8 (-44.5, -33.9)
ApoE	29.2* (24.7, 33.7)	35.3* (30.6, 40.1)

*p<0.001; means for all variables except for triglycerides, lipoprotein(a), for which medians are shown

Pioglitazone

HDL Cholesterol Changes

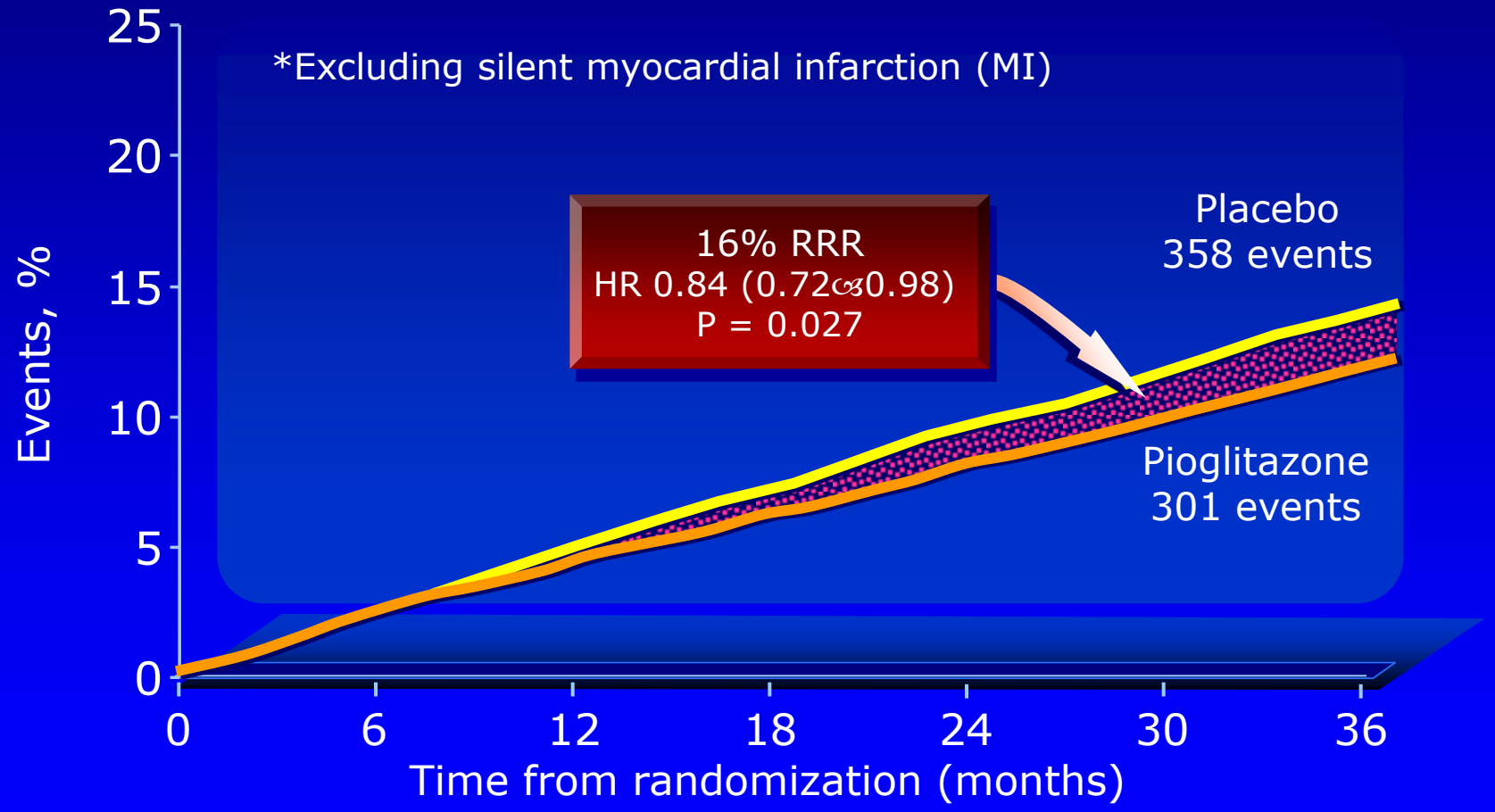


No. of Observations				
Glimepiride	206	203	206	206
Pioglitazone	201	198	201	201

Mazzone T et al. *JAMA* 2006;296:2572–2581.

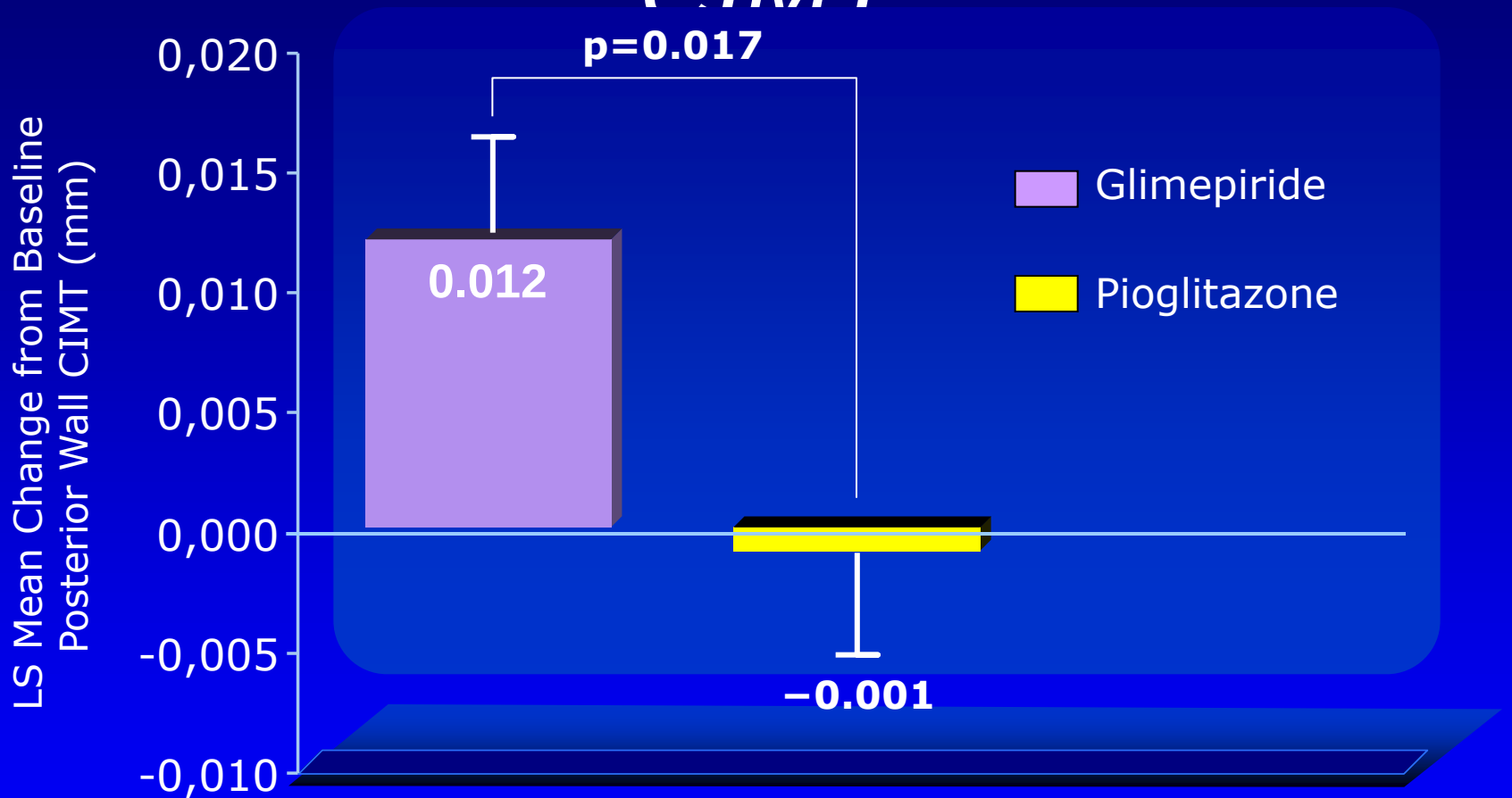
PROactive Trial: *Significant Reduction in Secondary Outcome*

All-cause mortality, nonfatal MI*, stroke



Dormandy JA et al. *Lancet* 2005;366:1279–1289.

CHICAGO: *Mean Change in CIMT*

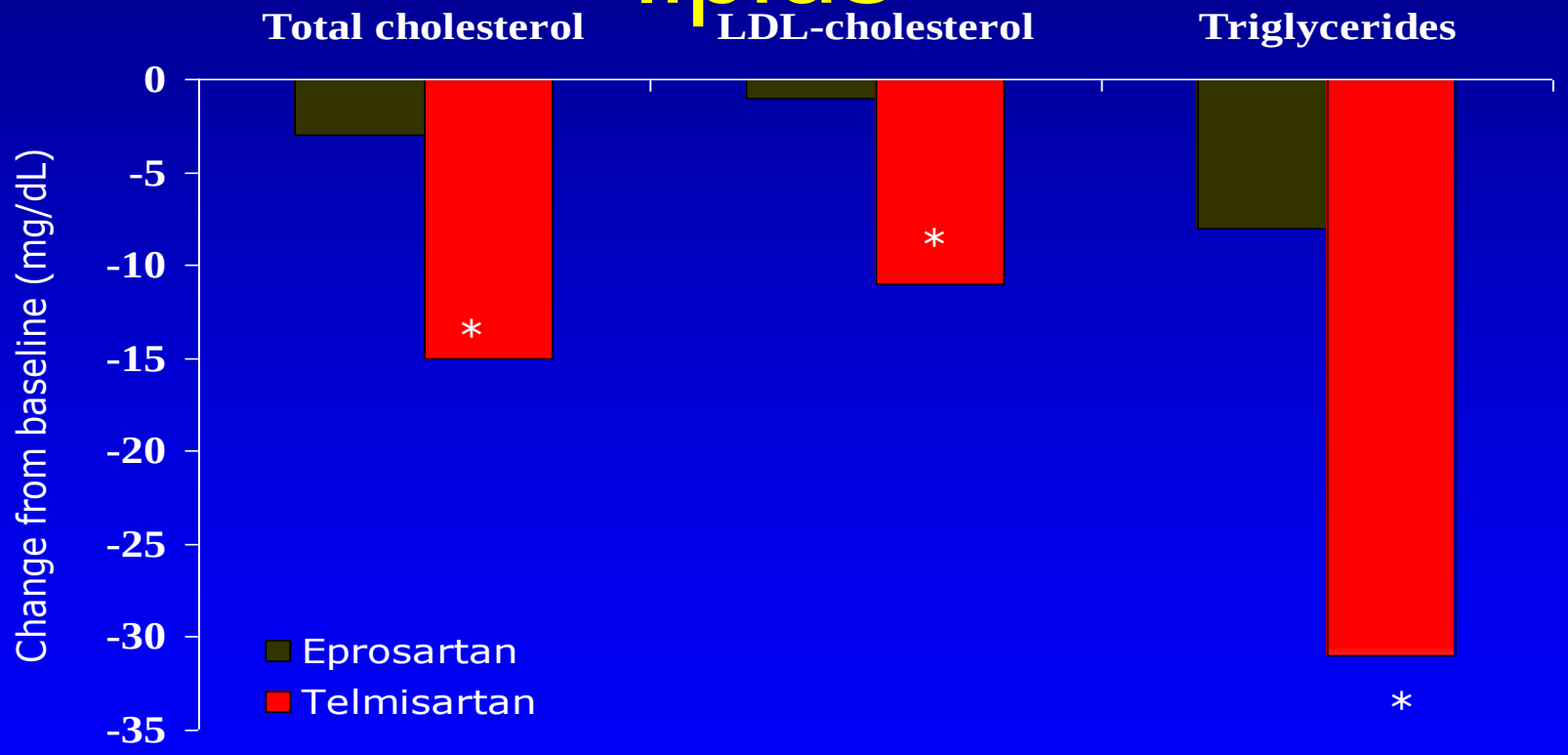


Baseline CIMT LS Mean (SE)	GLM (N=186)	PIO (N=175)	Treatment group difference, Final Visit
	0.779 (0.0085) mm	0.771 (0.0085) mm	−0.013 (95% CI: −0.024,−0.002)

CIMT=carotid intima-media thickness

Adapted from Mazzone T et al. *JAMA* 2006;296:2572–2581.

Telmisartan Improves cholesterol and lipids



* P<0.05 vs Eprosartan

Derosa et al. *Hypertens Res* 2004;27:457–464

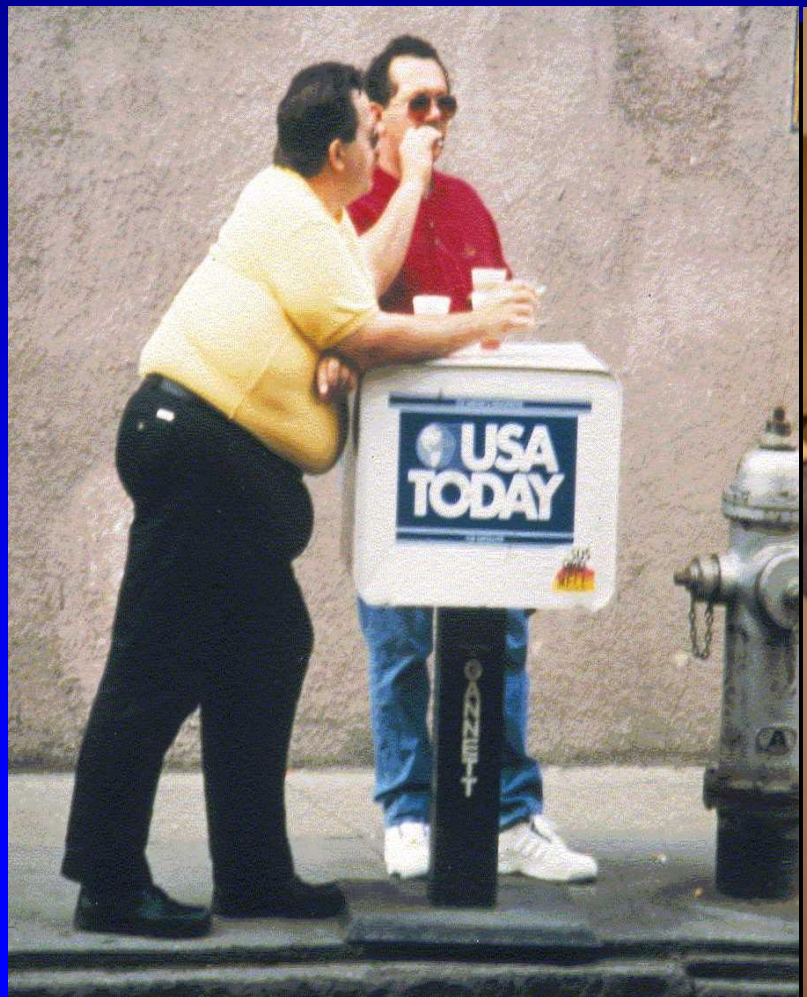
How to influence Residual Risk???

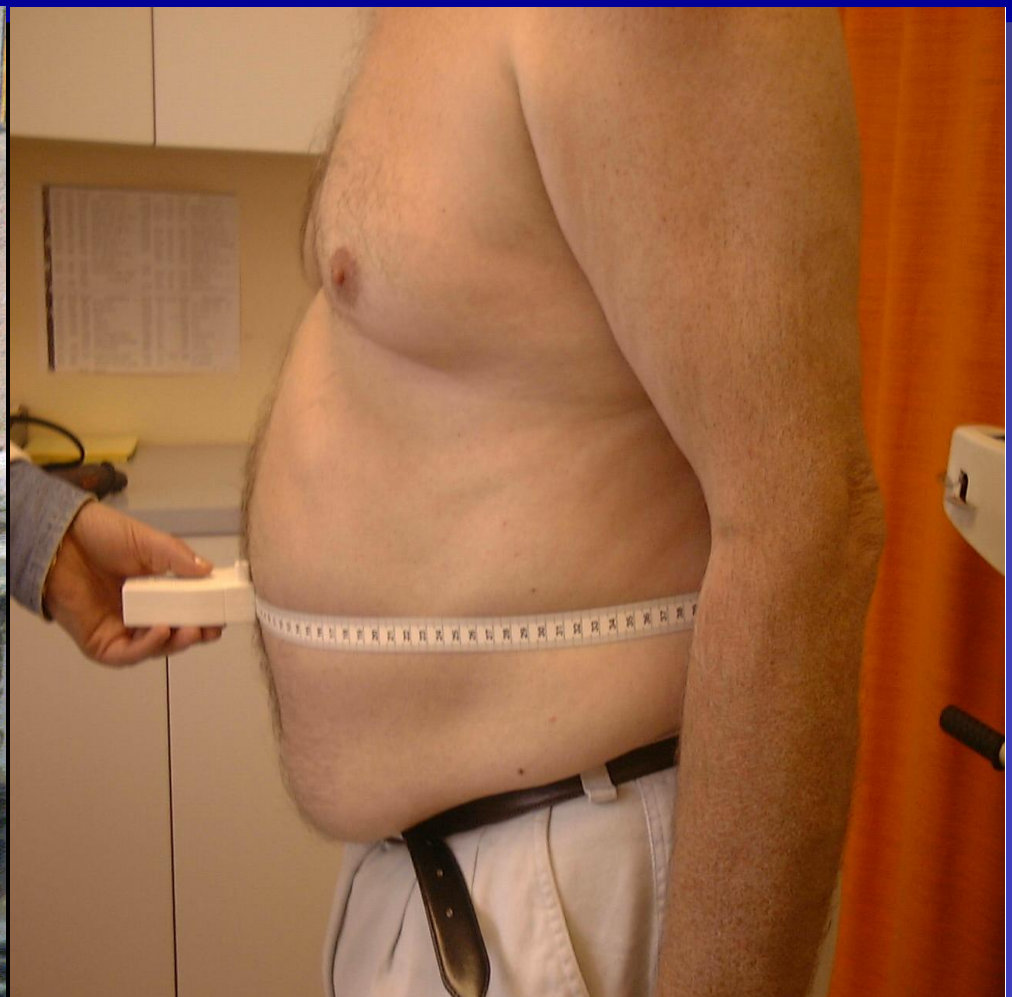
What is the priority

???

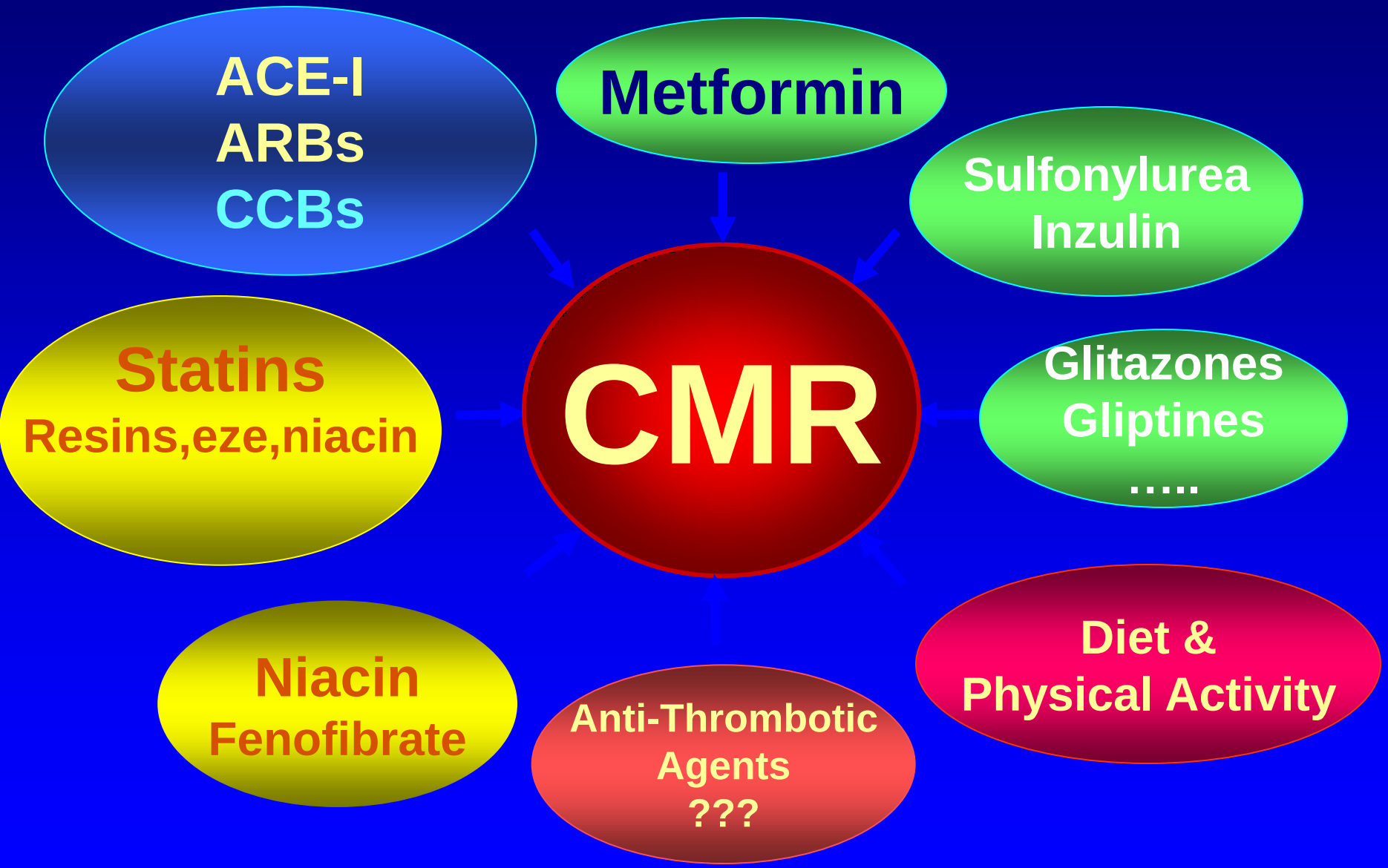
Lifestyle changes,
Lifestyle changes, Lifestyle changes, Lifestyle changes, Lifestyle changes, Lifestyle changes, Lifestyle changes, ***Lifestyle changes , Lifestyle changes,*** ***lifestyle changes,***

BUT!!!???

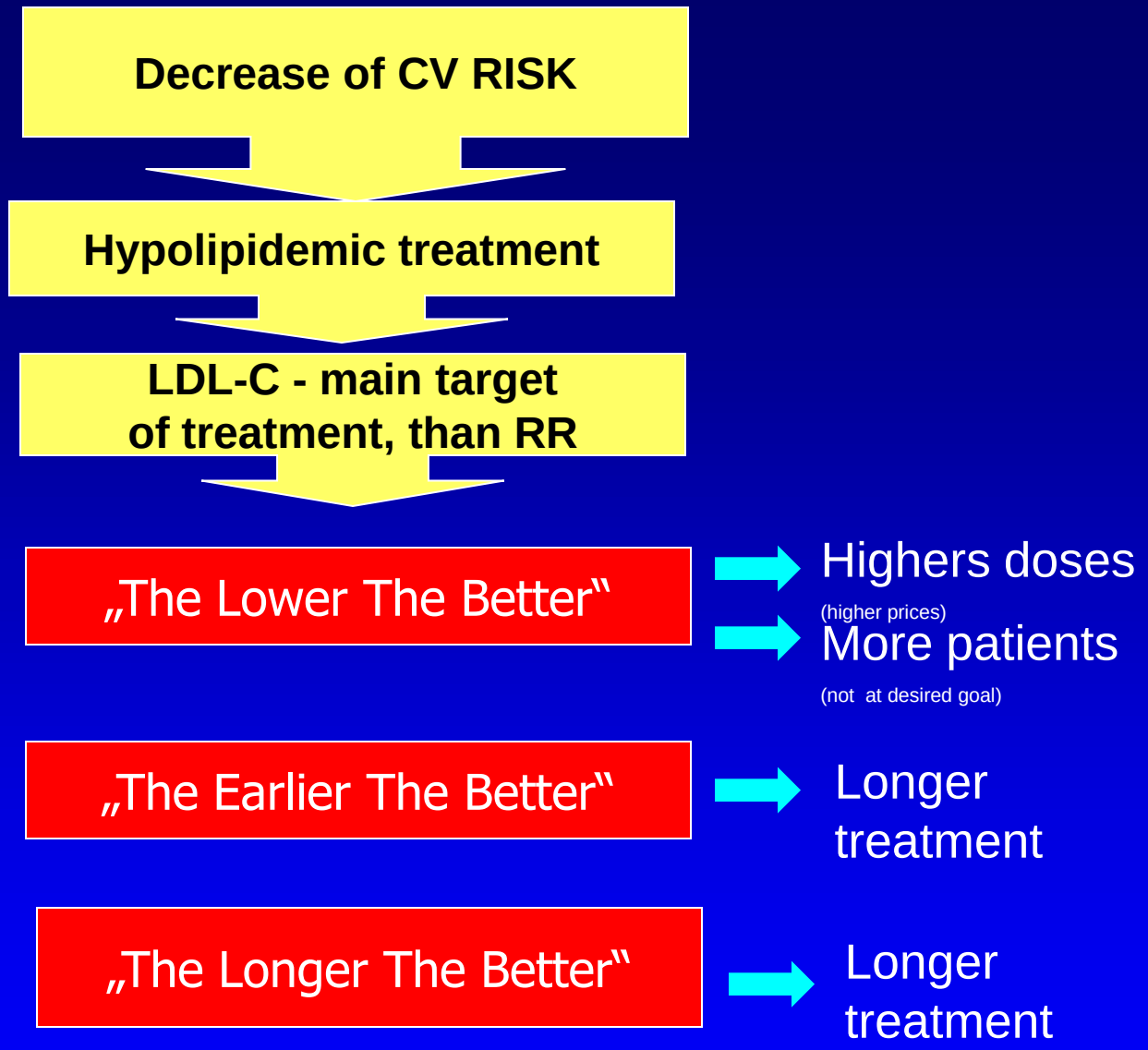




Complex treatment of the patient with „CARDIOMETABOLIC RISK“



Dyslipidemia Management as a part of complex approach



Use therapy which is effective, safe, well tolerated, supported by EBM data in appropriate dose.

Thank you!!!