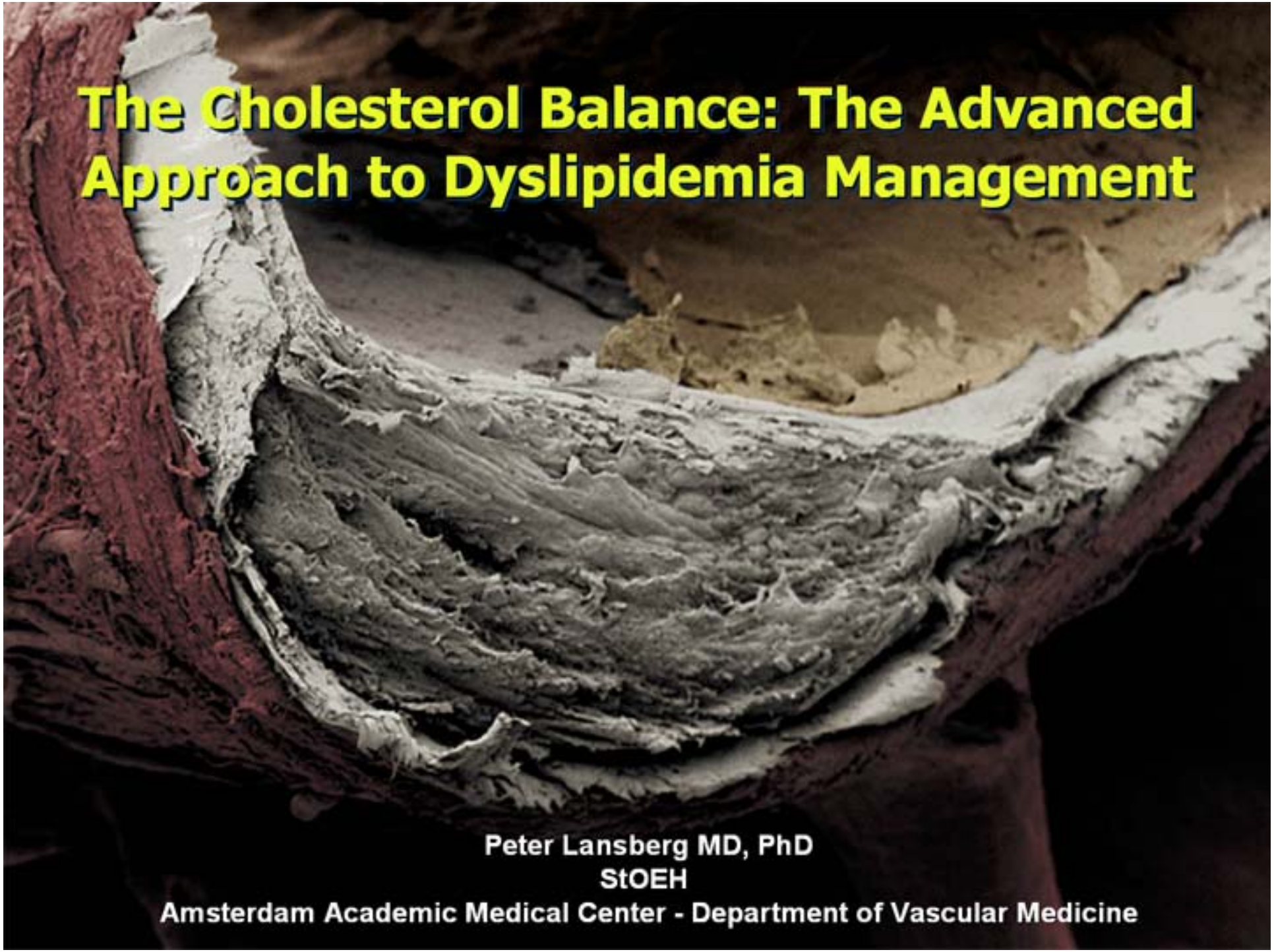
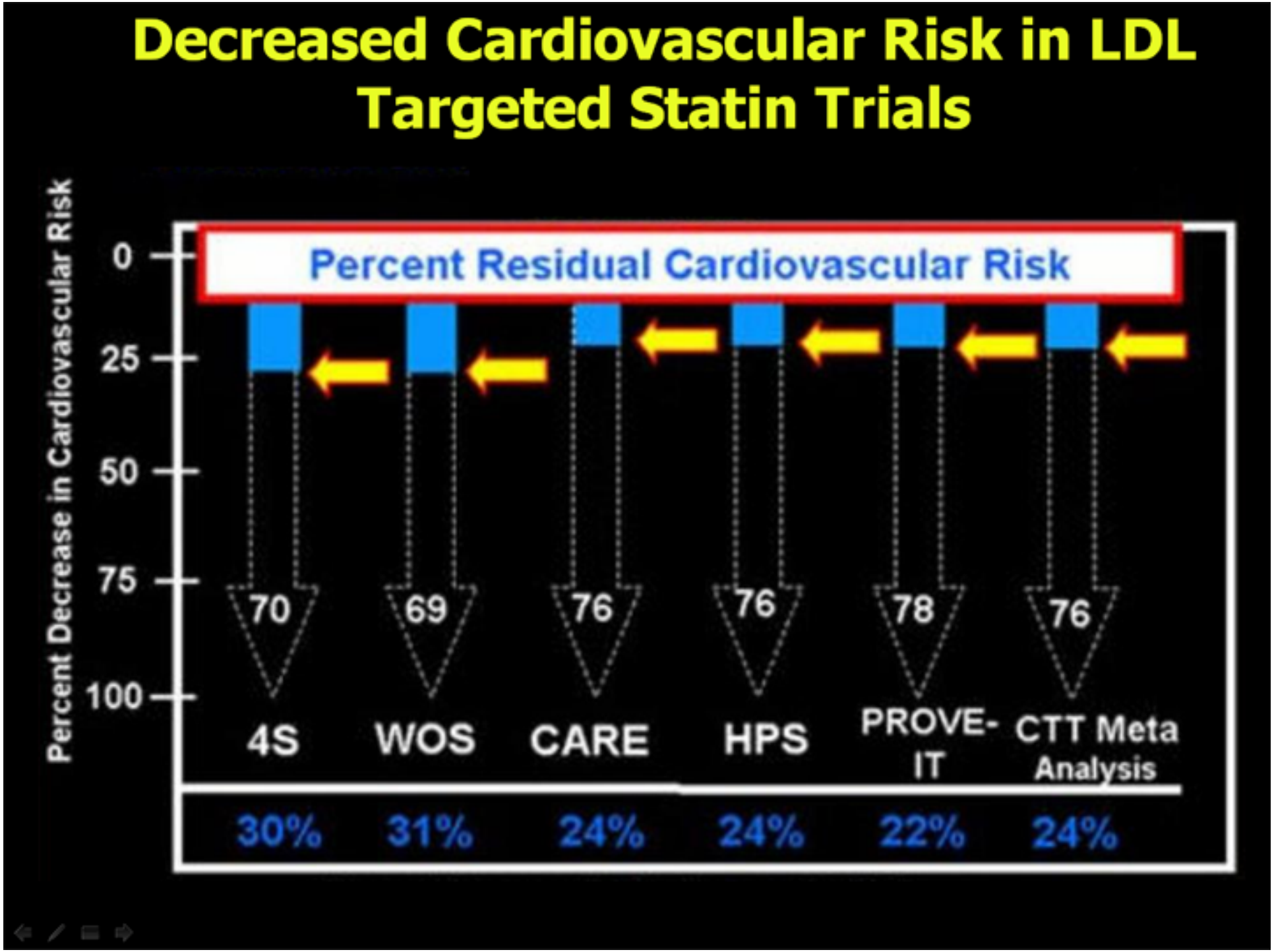
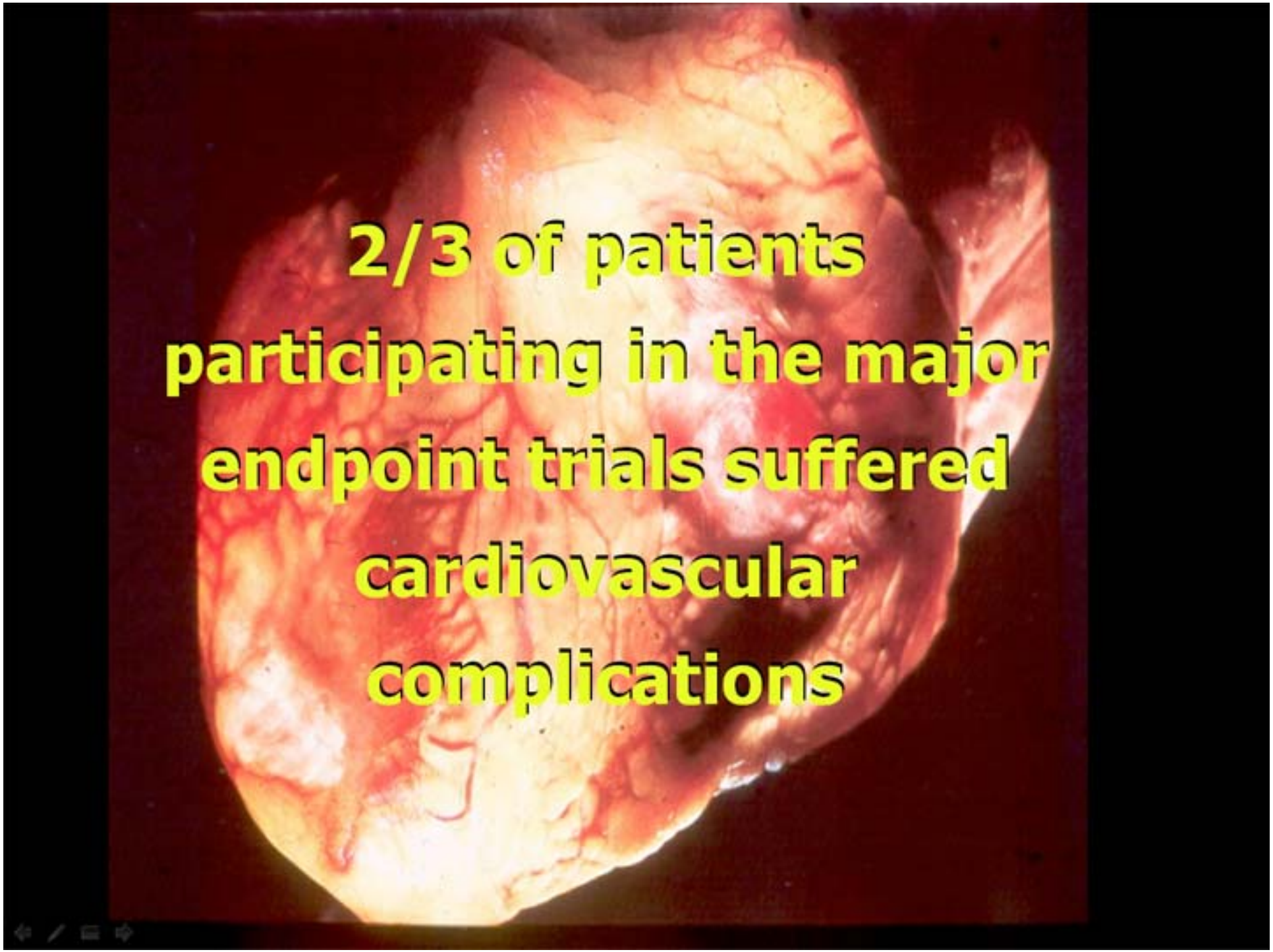

The Cholesterol Balance: The Advanced Approach to Dyslipidemia Management
Peter Lansberg MD, PhD
StOEH
Amsterdam Academic Medical Center - Department of Vascular Medicine

The lessons learned in the 90ies

- (Most) Statins are Safe!
- 25 – 30 % risk reduction
- Benefit extends to
  - Patients with CAD
    - Stable disease
    - ACS
  - Patients with CVD
  - Patients with diabetes and/or multiple risk factors
- Majority of patients not adequately treated!
  - More patients need to be treated
  - Patients are not treated aggressively enough


Decreased Cardiovascular Risk in LDL Targeted Statin Trials
Percent Decrease in Cardiovascular Risk
0
25
50
75
100
Percent Residual Cardiovascular Risk
70
69
76
76
78
76
4S
WOS
CARE
HPS
PROVE-IT
CTT Meta Analysis
30%
31%
24%
24%
22%
24%

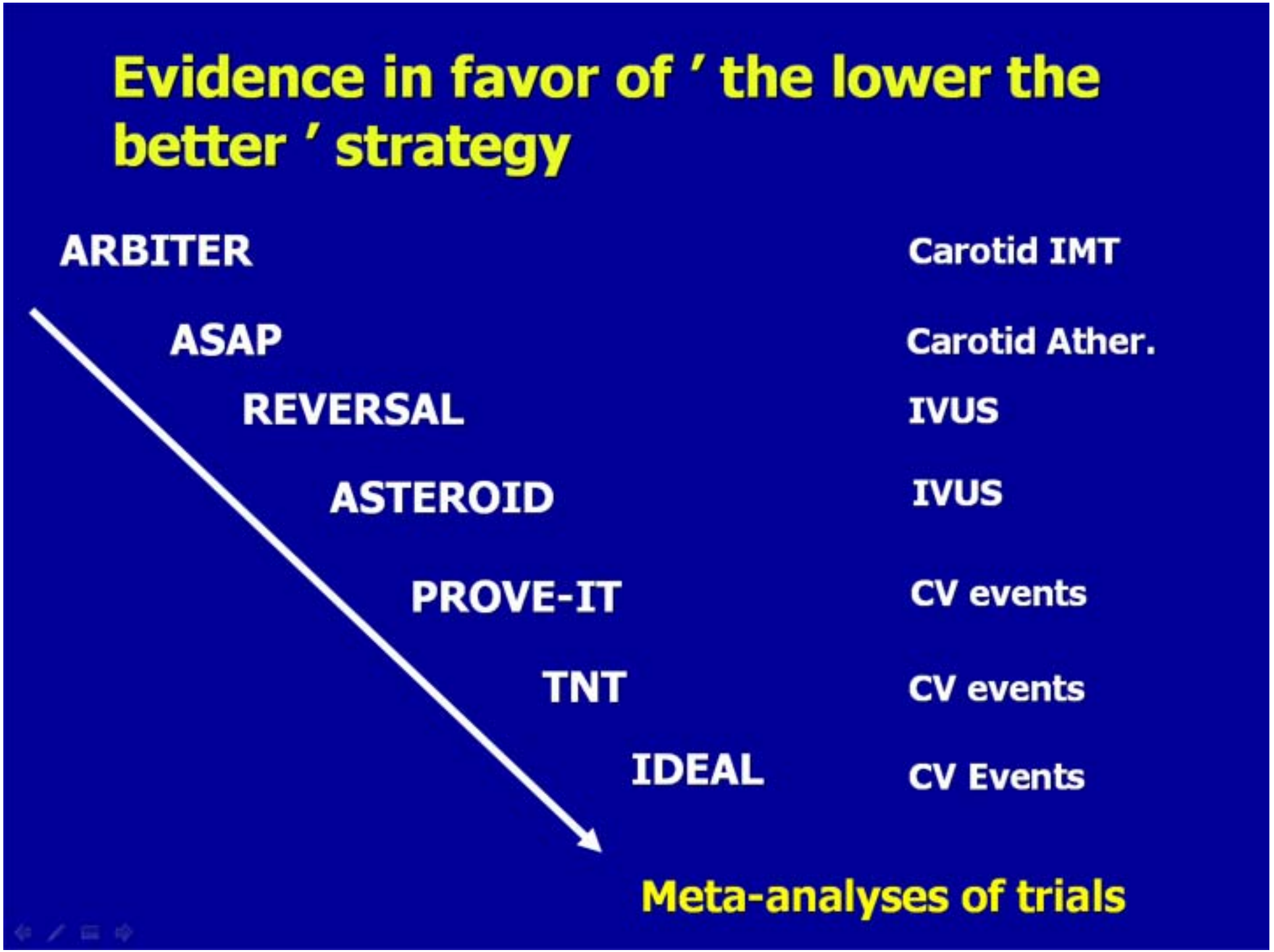

2/3 of patients
participating in the major
endpoint trials suffered
cardiovascular
complications

Why are Patients on Statins still at Risk

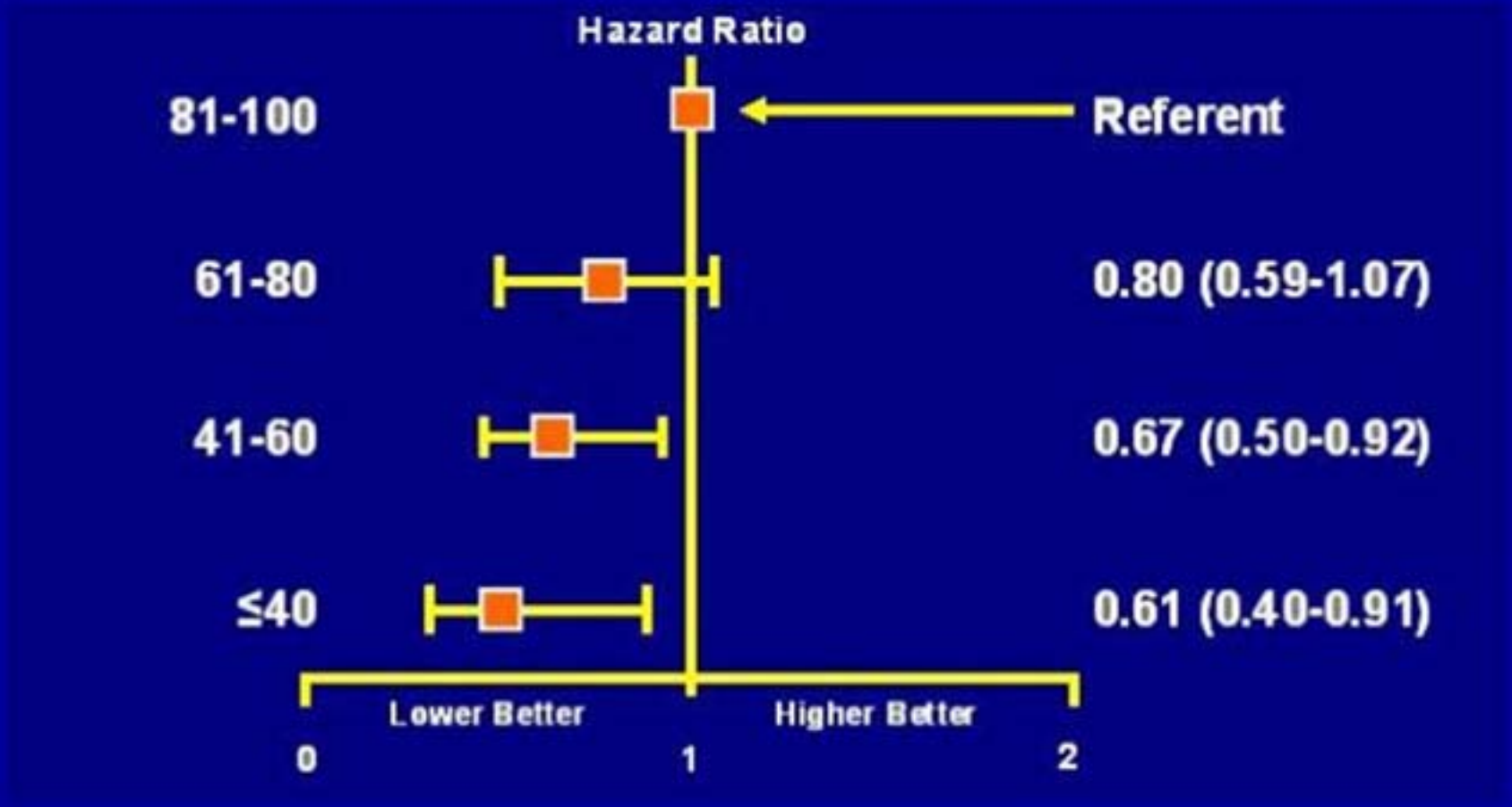
- **Started to Late**
  → Start earlier – Primary prevention
- **Additional (unknown) inadequately treated risk factors**
  → Asses global risk and treat all known risk factors
- **Non compliant**
  → Promote compliance
- **Non responders**
  → Identify and treat with alternative regimen
- **Insufficient treatment**
  → Achieve (lower) targets


More Aggressive Care?

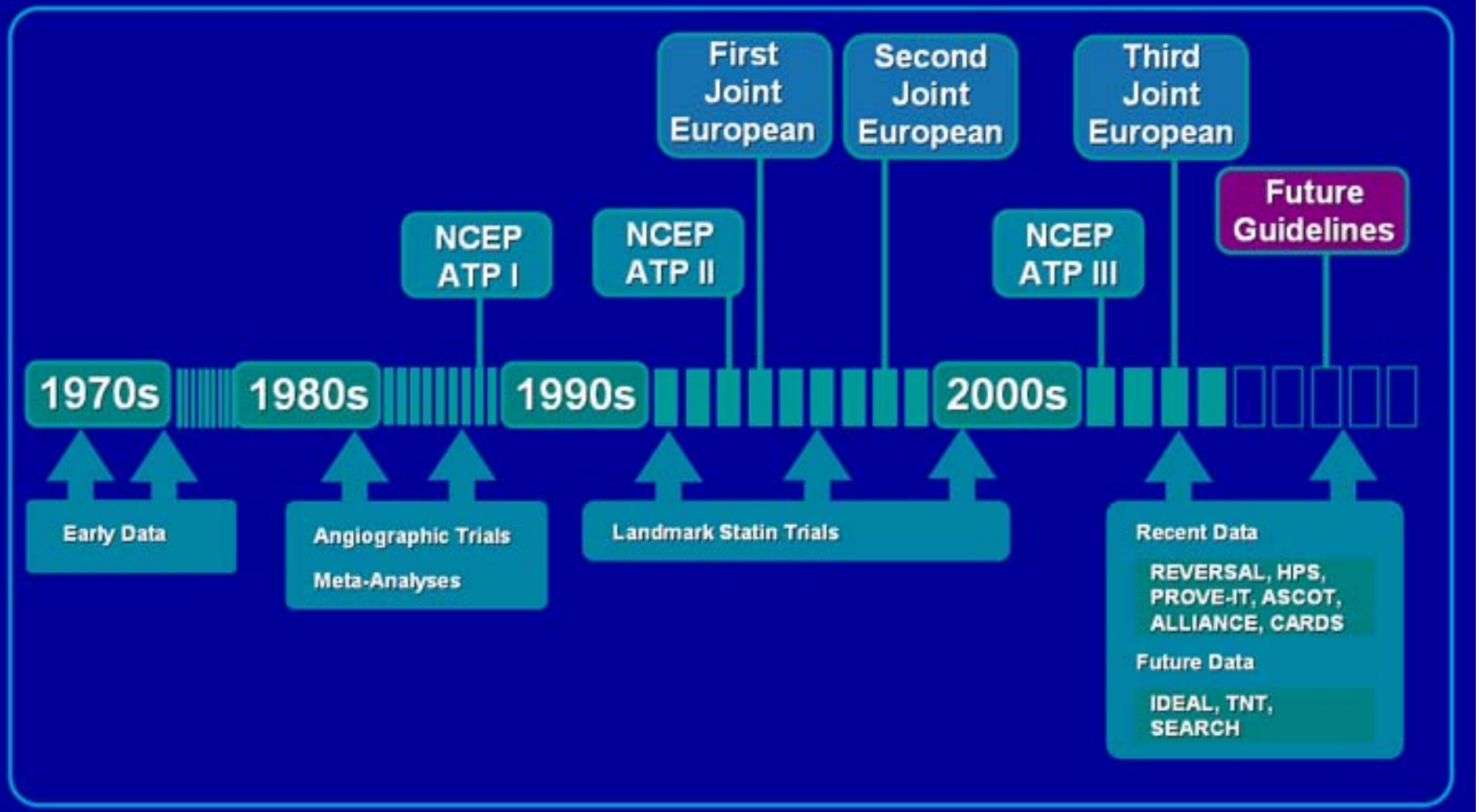
Evidence in favor of ' the lower the better ' strategy



PROVE IT – ON Treatment LDL-Cholesterol



Future evolution of guidelines



Adapted from Fonarow G. Implementation of NCEP/ACC Guidelines.
Presentation available at www.lipidsonline.org.

Lipid-modifying therapy and attainment of cholesterol goals in Europe: Return on Expenditure Achieved for LIpid TherapY (REALITY)

Eric Van Ganse, Laurent Laforest, Evo Alemao, Glenn Davies, Stephen Gutkin and Don Yin

CURRENT MEDICAL RESEARCH AND OPINION VOL. 21, NO. 9, 2005, 1389–1399

Objective

To determine lipid-modifying therapy practices and their effects on LDL-C and/or TC goal attainment in Europeans based on prevailing guidelines at the time of therapy in each country

CURRENT MEDICAL RESEARCH AND OPINION VOL. 21, NO. 9, 2005, 1389–1399

Methods

- Retrospective cohort analysis involving 58 223 patients initiated on lipid-modifying therapies in 10 European countries
- Median patient follow-up on lipid-modifying therapy of 15.3 months
- Analyzed data obtained from healthcare administrative databases and/or patient chart reviews.

CURRENT MEDICAL RESEARCH AND OPINION VOL. 21, NO. 9, 2005, 1389–1399

Cholesterol goal attainment by final statin and dose in the REALITY study

	Number of patients	Number of patients at goal	% goal attainment
Atorvastatin 10 mg	4672	2634	56.4%
Atorvastatin 20 mg	2258	904	40.0%
Atorvastatin 40 mg	485	132	27.2%
Atorvastatin 80 mg	15	1	6.7%
Cerivastatin* 0.1 mg	190	51	26.8%
Cerivastatin* 0.2 mg	34	6	17.6%
Cerivastatin* 0.4 mg	34	11	32.4%
Fluvastatin 20 mg	643	212	33.0%
Fluvastatin 40 mg	683	234	34.3%
Fluvastatin 80 mg	77	22	28.6%
Lovastatin 10 mg	30	6	20.0%
Lovastatin 20 mg	82	13	15.9%
Lovastatin 40 mg	18	1	5.6%
Pravastatin 10 mg	532	191	35.9%
Pravastatin 20 mg	1184	441	37.2%
Pravastatin 40 mg	939	365	38.9%
Simvastatin 10 mg	3847	2018	52.5%
Simvastatin 20 mg	4273	1944	45.5%
Simvastatin 40 mg	805	241	29.9%
Simvastatin 80 mg	44	5	11.4%

CURRENT MEDICAL RESEARCH AND OPINION VOL. 21, NO. 9, 2005, 1389–1399

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CURRENT MEDICAL RESEARCH AND OPINION VOL. 21, NO. 9, 2005, 1389–1399

France
Consequences of Goal Attainment

- **TO+++ group: LDL-C values at treatment objective during all 3 years of observation**
  - mean LDL-C value 2.48 mmol/L 96 mg/dL)
  - The incidence rate of cardiovascular disease was 5.5%
- **TO– group: LDL- C at treatment objective during 1–2 of 3 years**
  - mean LDL-C value 3.33 mmol/L (129 mg/dL)
  - The incidence rate of cardiovascular disease 10.6%
- **TO– – – group LDL- C not at treatment objective during any year of the three**
  - Mean LDL-C 4.32 mmol/L (167 mg/dL)
  - The incidence rate of cardiovascular disease 12.9%

CURRENT MEDICAL RESEARCH AND OPINION VOL. 21, NO. 9, 2005, 1389–1399

Failure to achieve recommended LDL cholesterol levels by suboptimal statin therapy relates to elevated cardiac event rates

A. Baesslera,b, M. Fischera,b, V. Huf a, S. Mella, C. Hengstenberga, B. Mayerc, S. Holmera, G. Rieggera, H. Schunkertc,*

International Journal of Cardiology 101 (2005) 293– 298

Study Design

- A cohort of post MI patients from German MI family registry
- Subjects were identified by screening of patient charts from
  - 17 cardiac rehabilitation centers distributed throughout Germany.
  - Patients with a first MI under the age of 60 years
  - Positive family history for CHD

International Journal of Cardiology 101 (2005) 293– 298

Study Design

- **The quality of statin treatment**
  - optimal: LDL<115 mg/dl
  - suboptimal: LDL>115 mg/dl
  - no statin therapy
- **Incidence of coronary events (coronary death, nonfatal MI, bypass surgery)**
  - 30 months follow-up
  - Large cohort of post MI patients with hypercholesterolemia (n=2045).
- **Analysis was performed in a nested case–control**
  - 173 cases with a coronary event
  - 346 matched controls

International Journal of Cardiology 101 (2005) 293– 298

Effect of Statin Treatment

Treatment	CHD Event	P value
Optimal (<115 mgd/l)	11%	
Sub-optimal (>115 mg/dl mmol/l)	43,4%	0,05
No Statin	45,7%	0,001

International Journal of Cardiology 101 (2005) 293– 298

Effect of Statin Treatment

- Only a small benefit in patients with suboptimal statin therapy (LDL<115 mg/dl) as compared to subjects without statin therapy
- Only 16.1% of patients with previous MI achieved cholesterol levels below 115 mg/dl
- Less than 3% of patients achieved the NCEP goal level of 100 mg/dl

International Journal of Cardiology 101 (2005) 293– 298

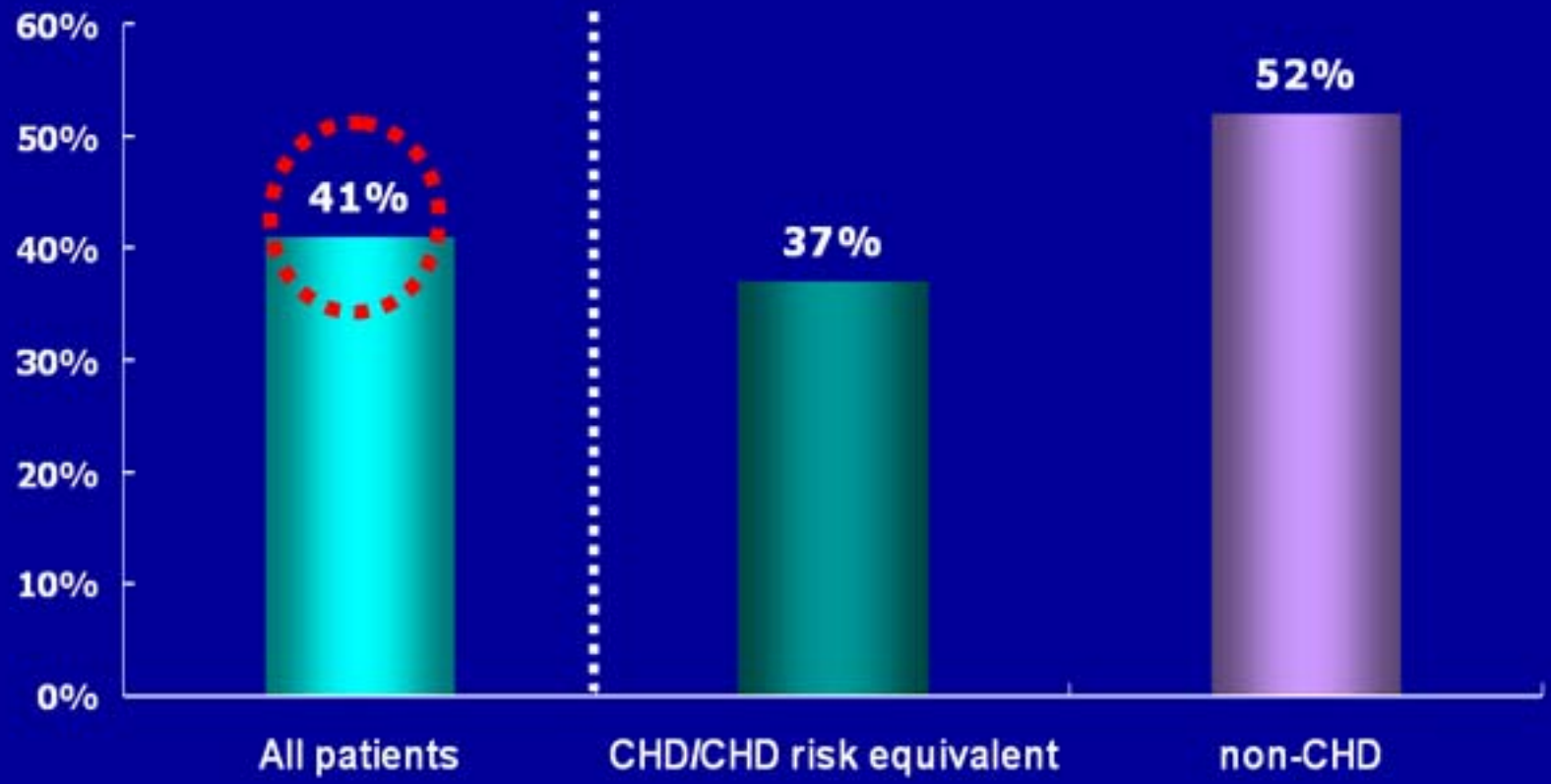
Reality korea

- multi-center retrospective review of medical records
- 100 investigators across Korea
  - 30 Internists working at clinic
  - 30 Endocrinologist working for General Hospitals
  - 40 Cardiologist working for General Hospitals
- 5 patients/investigator, total 500 patients

REALITY: Korea

- Most of the patients are either started with
  - medium (66%) potency statin
  - low (28%) potency statin
- Medium potency statins are the most commonly used initial drugs
  - Atorvastatin 10mg: 34.8%
  - Simvastatin 20mg: 24.4%

REALITY Result: Patients at Goal



Design: Multi-center retrospective review of medical records, 100 investigators across Korea, total 500 patients included. Minimum 1 year follow-up

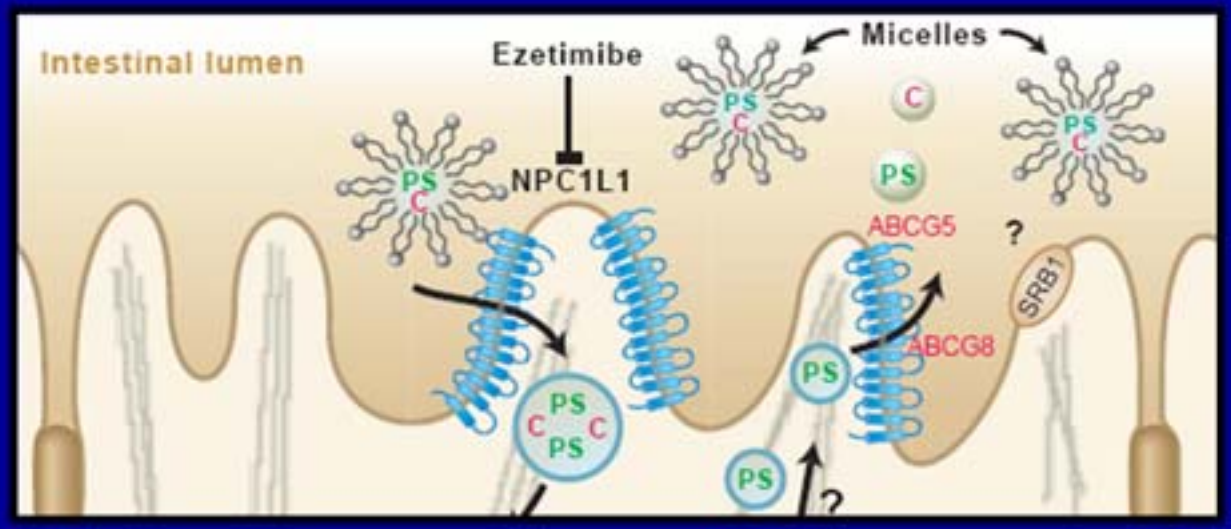
Adapted from HS Kim et al. Presented at *EAS, 2005*

Therapy for atherosclerosis

Do we need a new drug to expand our therapeutic alternatives for LDL cholesterol lowering?

- Many statin patients are treated unsatisfactorily and do not reach their therapeutic goals, even with higher doses
- Physicians are increasingly reluctant to uptitrate statin doses to the highest levels

Niemann-Pick C1L1 (NPC1L1)

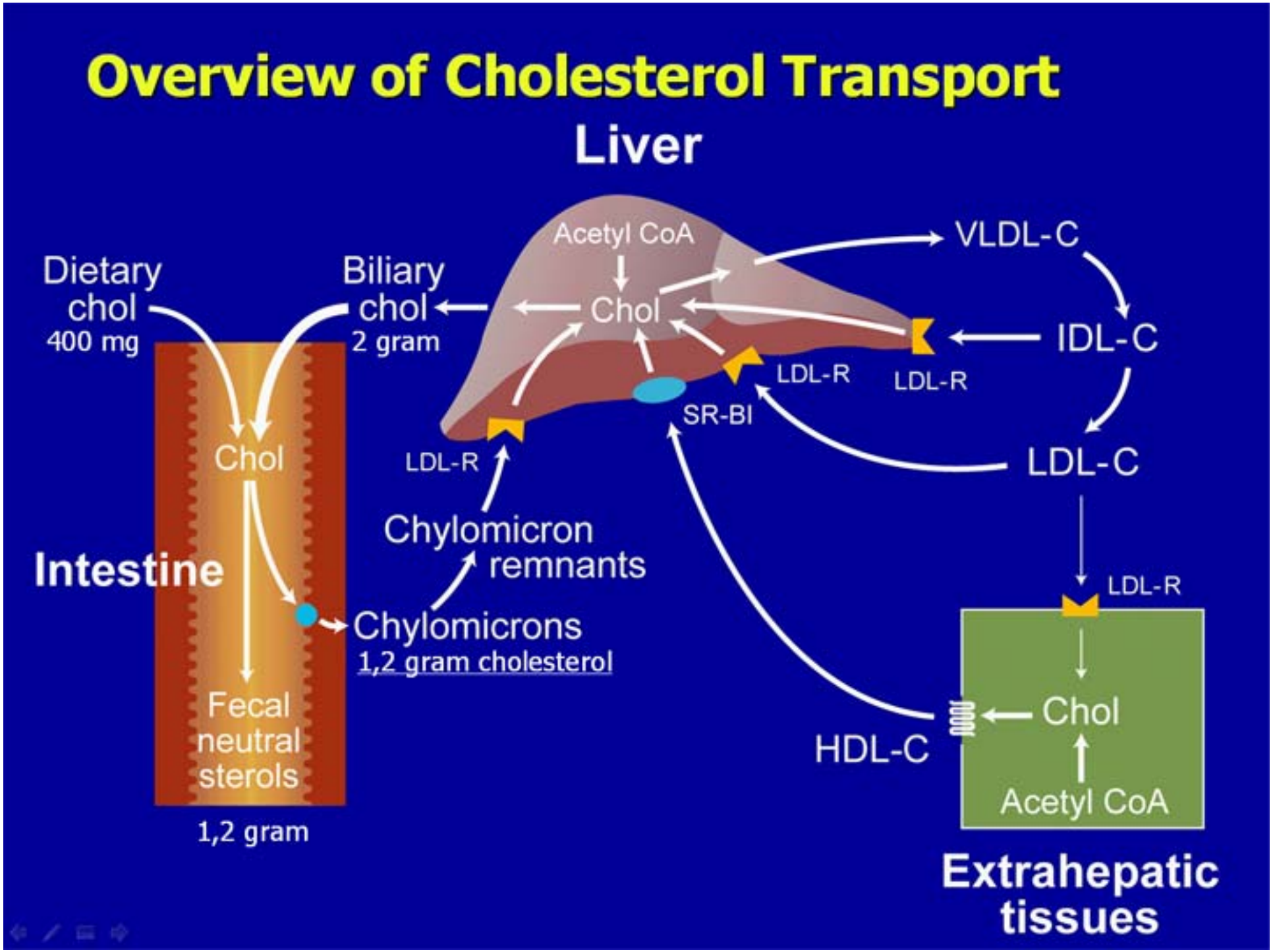


Identified in 2000 by an academic group as a gene of unknown function related to Niemann –Pick C1 protein. It was named NPC1L1.

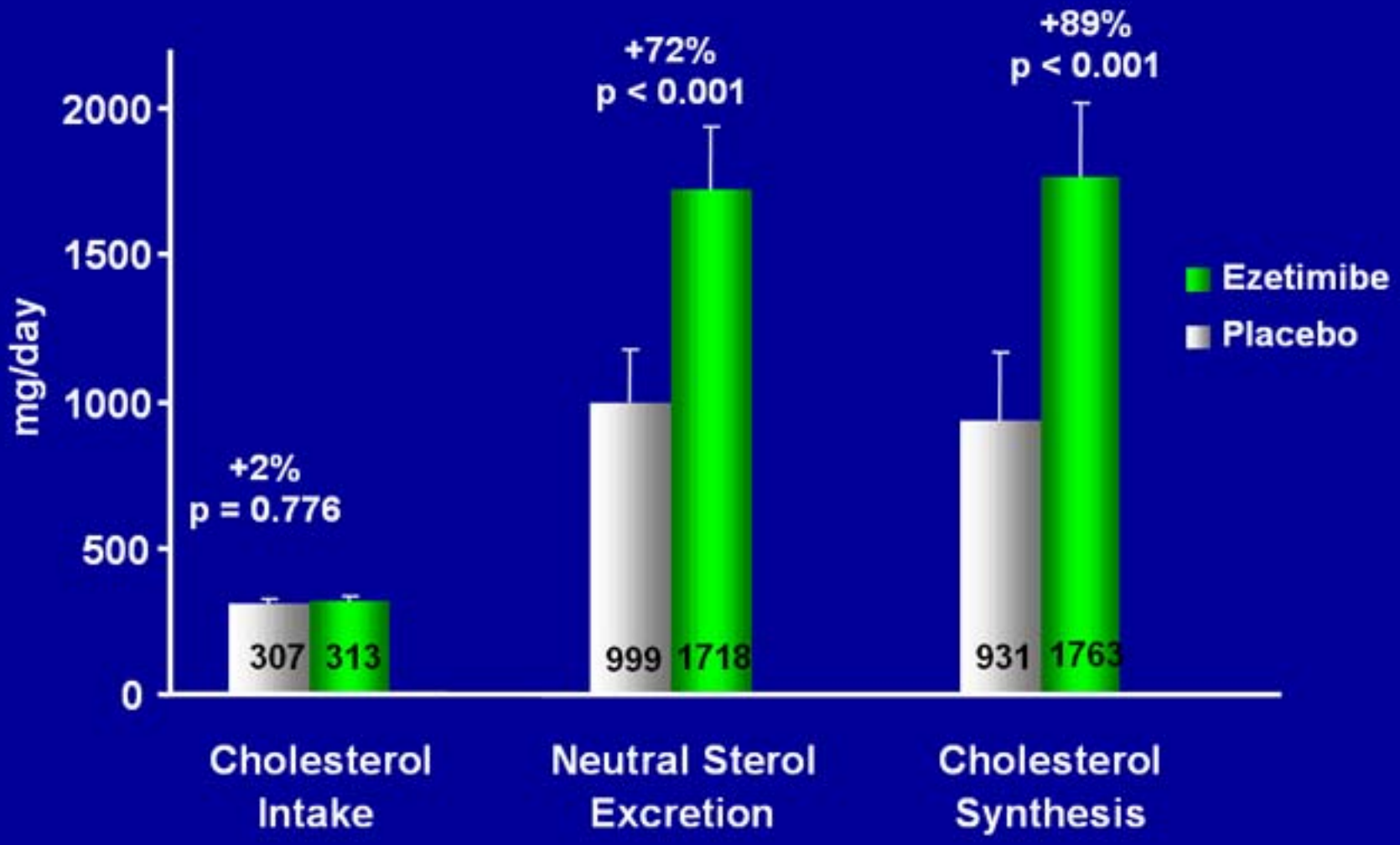
- DNA sequence analysis predicts features of a hypothetical cholesterol transporter
  - Membrane protein expressed on cell surface
  - Homologous to NPC 1 (a protein known to be involved in cholesterol movement)
  - Expression regulated by cholesterol
  - Sterol sensing domain

- Protein expression restricted to the enterocytes of the proximal small intestine

SCIENCE VOL 303 20 FEBRUARY 2004 p. 1201


Overview of Cholesterol Transport
Liver
Acetyl CoA
Chol
VLDL-C
IDL-C
LDL-C
LDL-R
LDL-R
LDL-R
SR-BI
Dietary chol
400 mg
Biliary chol
2 gram
Chol
Intestine
Chylomicron remnants
Chylomicrons
1,2 gram cholesterol
Fecal neutral sterols
1,2 gram
HDL-C
LDL-R
Chol
Acetyl CoA
Extrahepatic tissues

Sterol Excretion and Cholesterol Synthesis



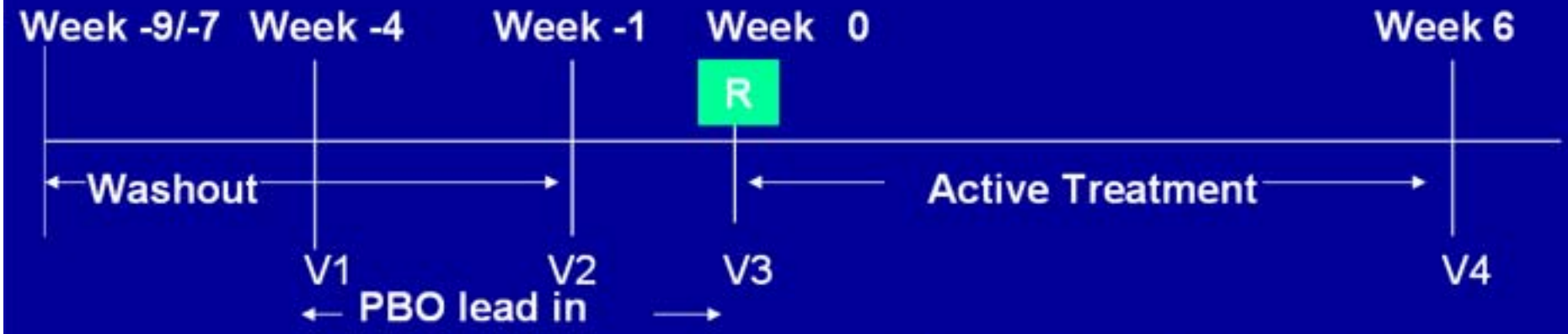
Sudhop et al. Circulation 2002; 106;1943

Vytorin vs. Atorvastatin (VYVA): Study Design

N = 1902 R

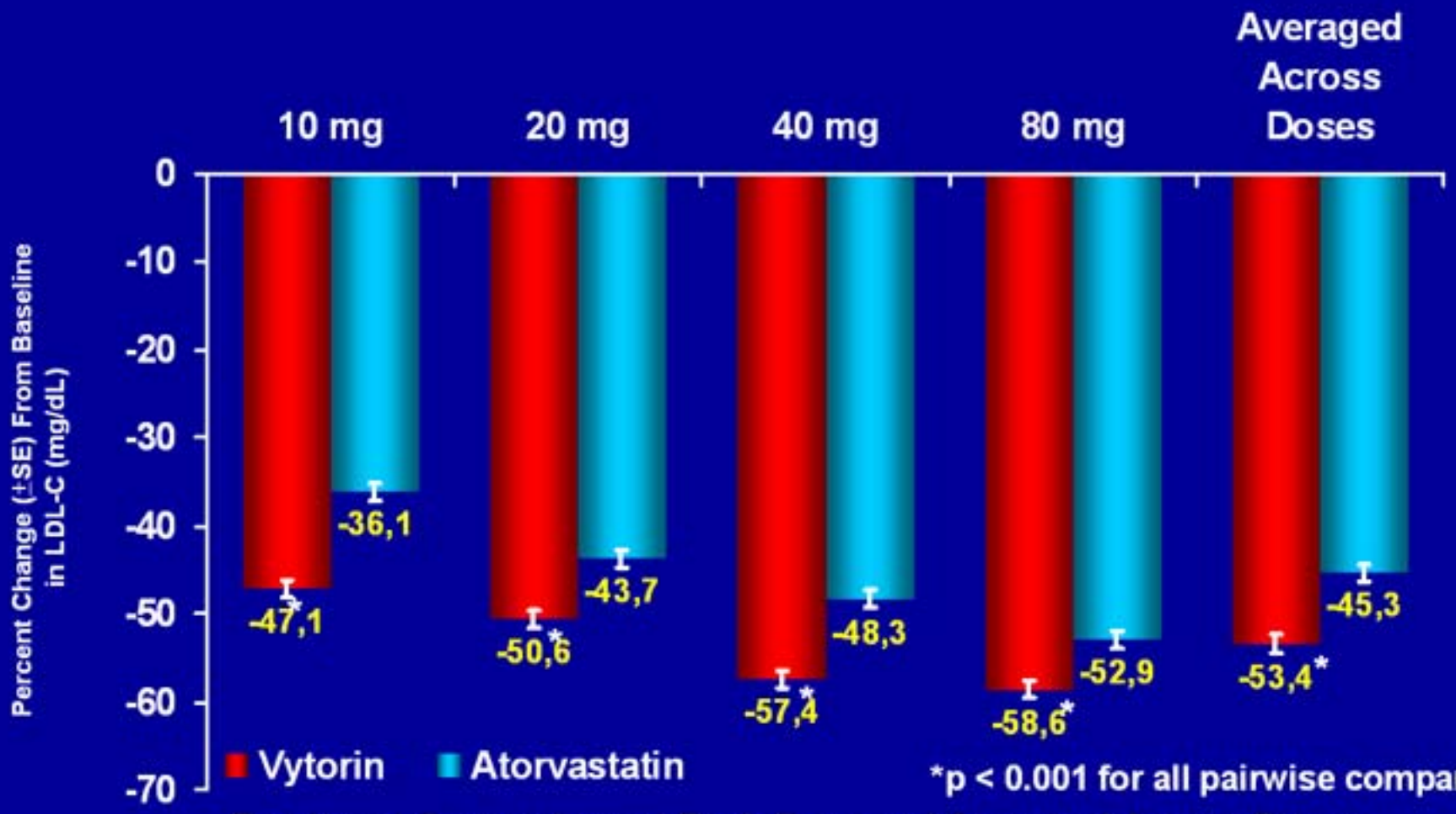
216 Sites

EZE/Simva 10/10	n = 238
EZE/Simva 10/20	n = 238
EZE/Simva 10/40	n = 238
EZE/Simva 10/80	n = 237
Atorva 10	n = 238
Atorva 20	n = 237
Atorva 40	n = 237
Atorva 80	n = 239



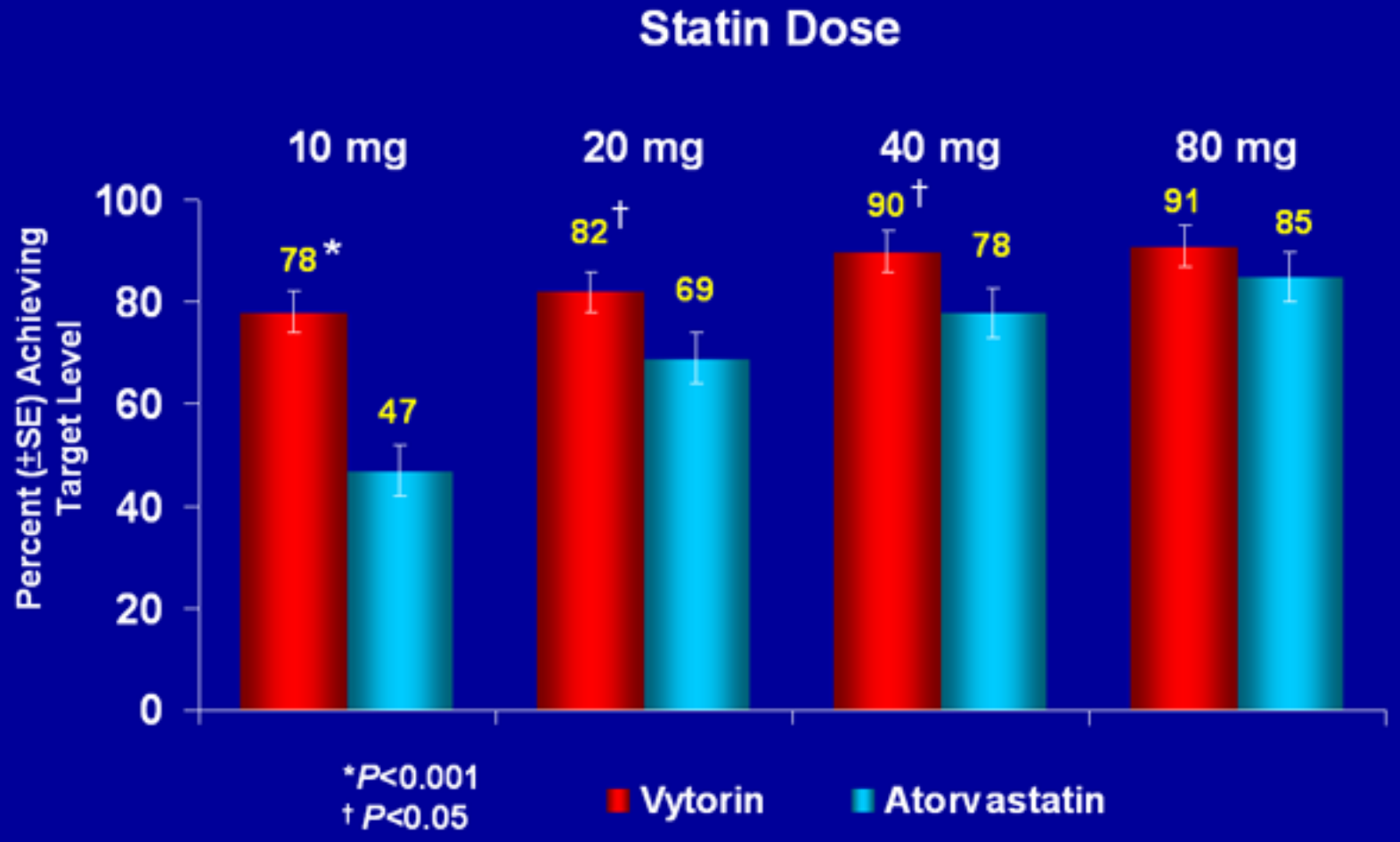
Ballantyne CM et al. Am Heart J 2005;149:464–473.

VYVA: LDL-C Reductions



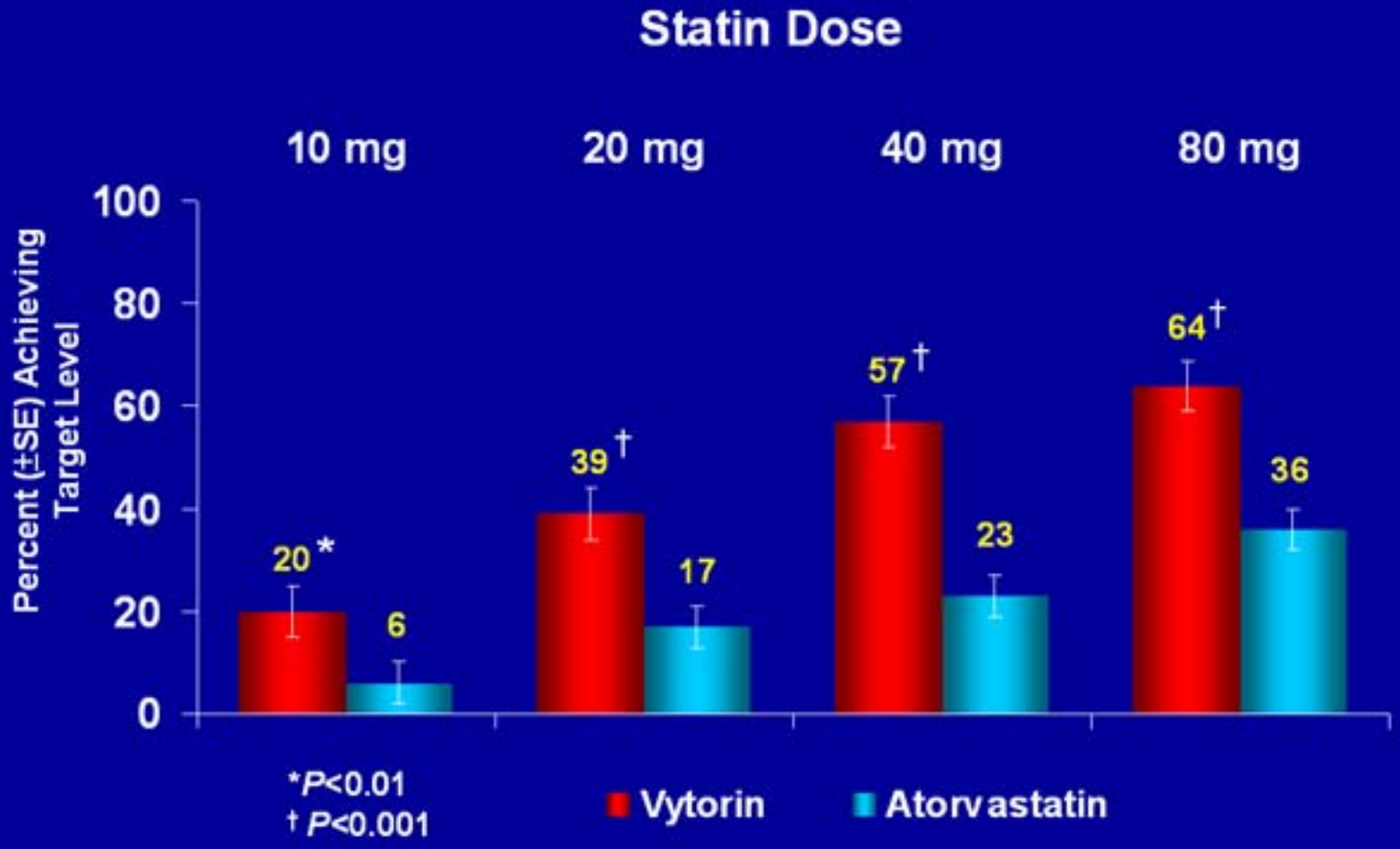
Ballantyne CM et al. Am Heart J 2005;149:464–473.

VYVA: Achievement of LDL-C < 100 mg/dL (2.6mmol/L) in Patients with CHD Risk Equivalent



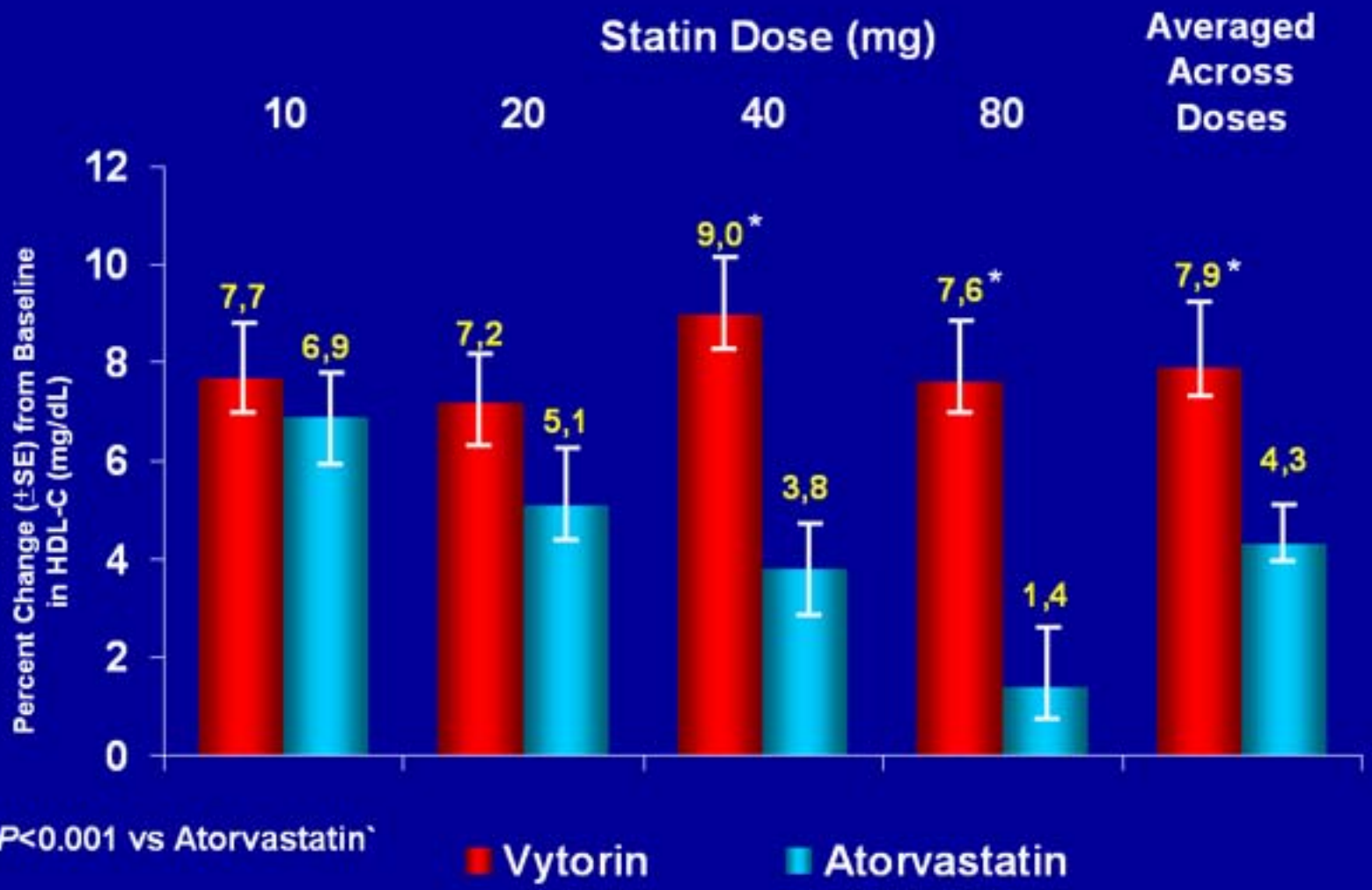
Ballantyne CM et al. Am Heart J 2005;149:464–473.

VYVA: Achievement of LDL-C < 70 mg/dL (1.8 mmol/L) in Patients with CHD Risk Equivalent



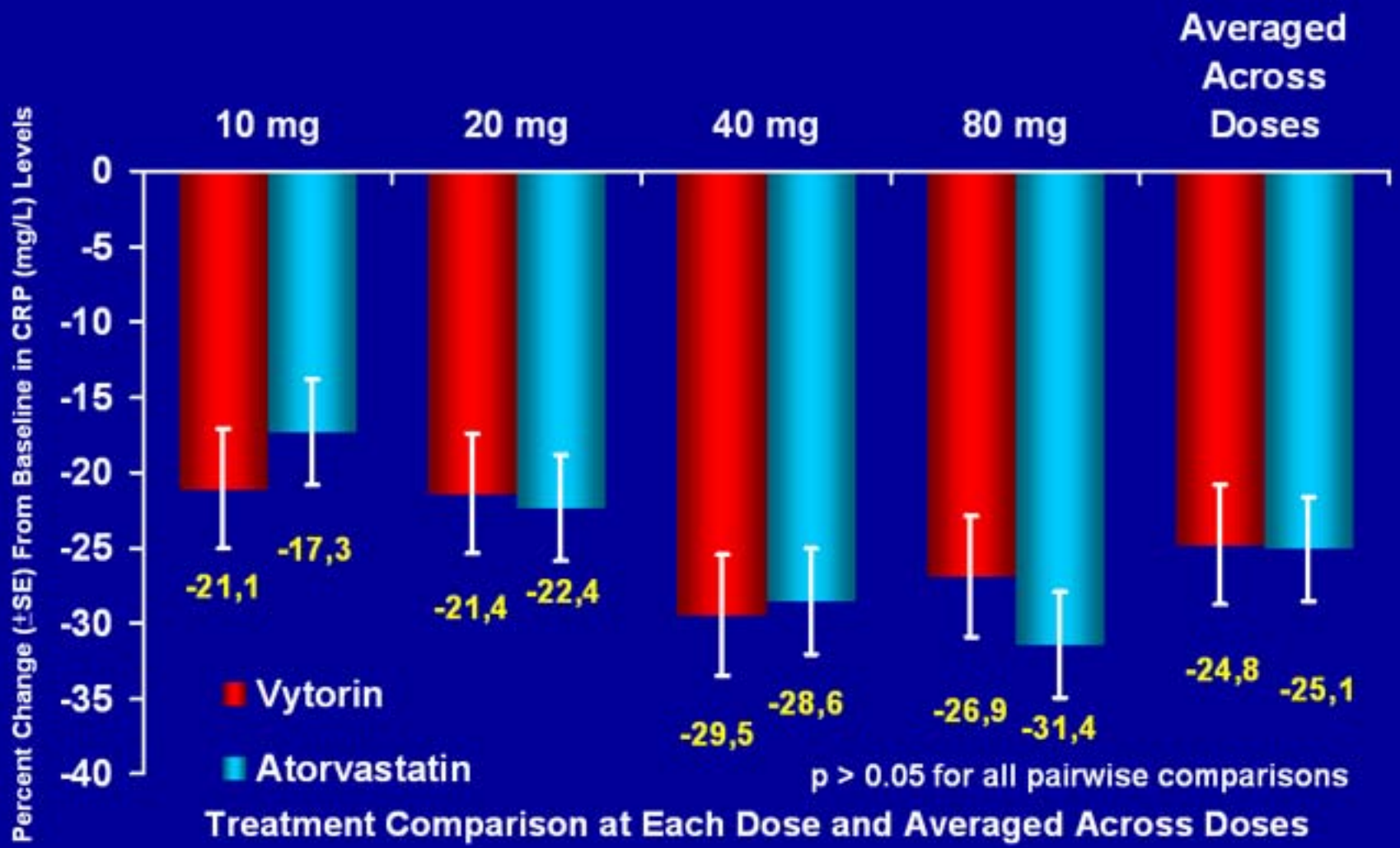
Ballantyne CM et al. Am Heart J 2005;149:464–473.

VYVA: HDL-C Increases



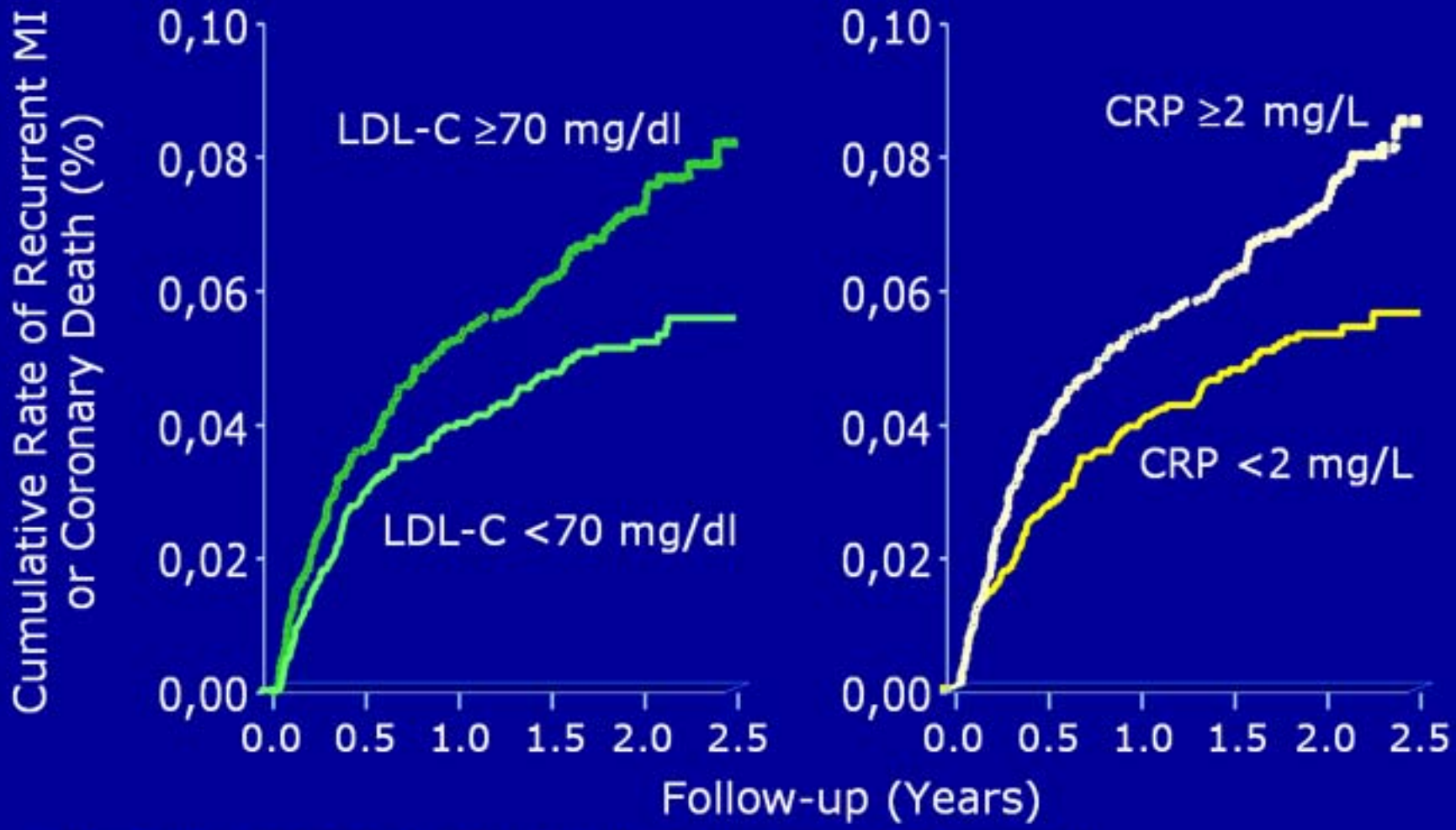
Ballantyne CM et al. Am Heart J 2005;149:464–473.

VYVA: CRP Reductions

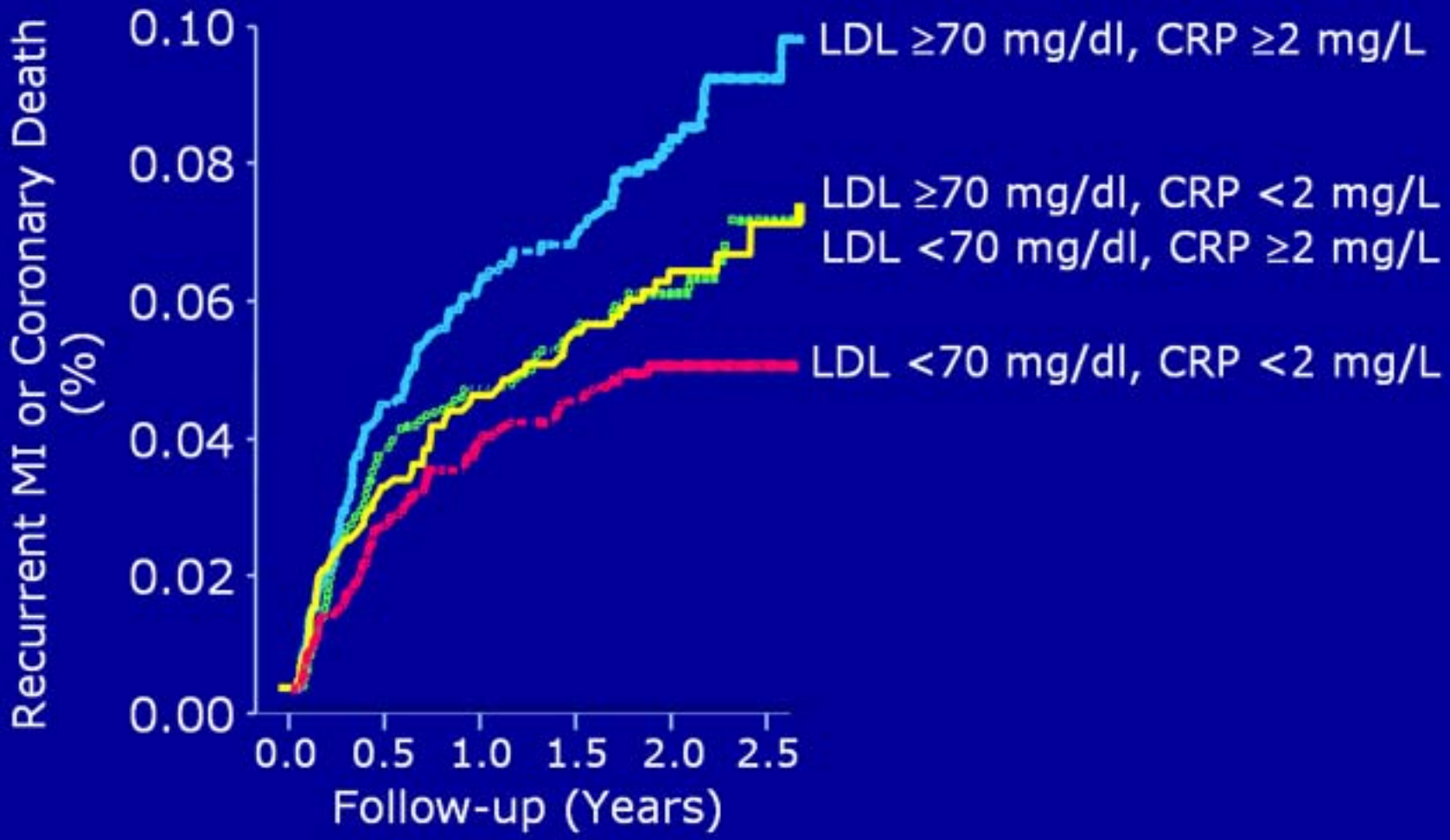


Ballantyne CM et al. Am Heart J 2005;149:464–473.

Incidence of Recurrent MI or CHD Death according to Achieved LDL-C or CRP Levels: PROVE IT–TIMI 22



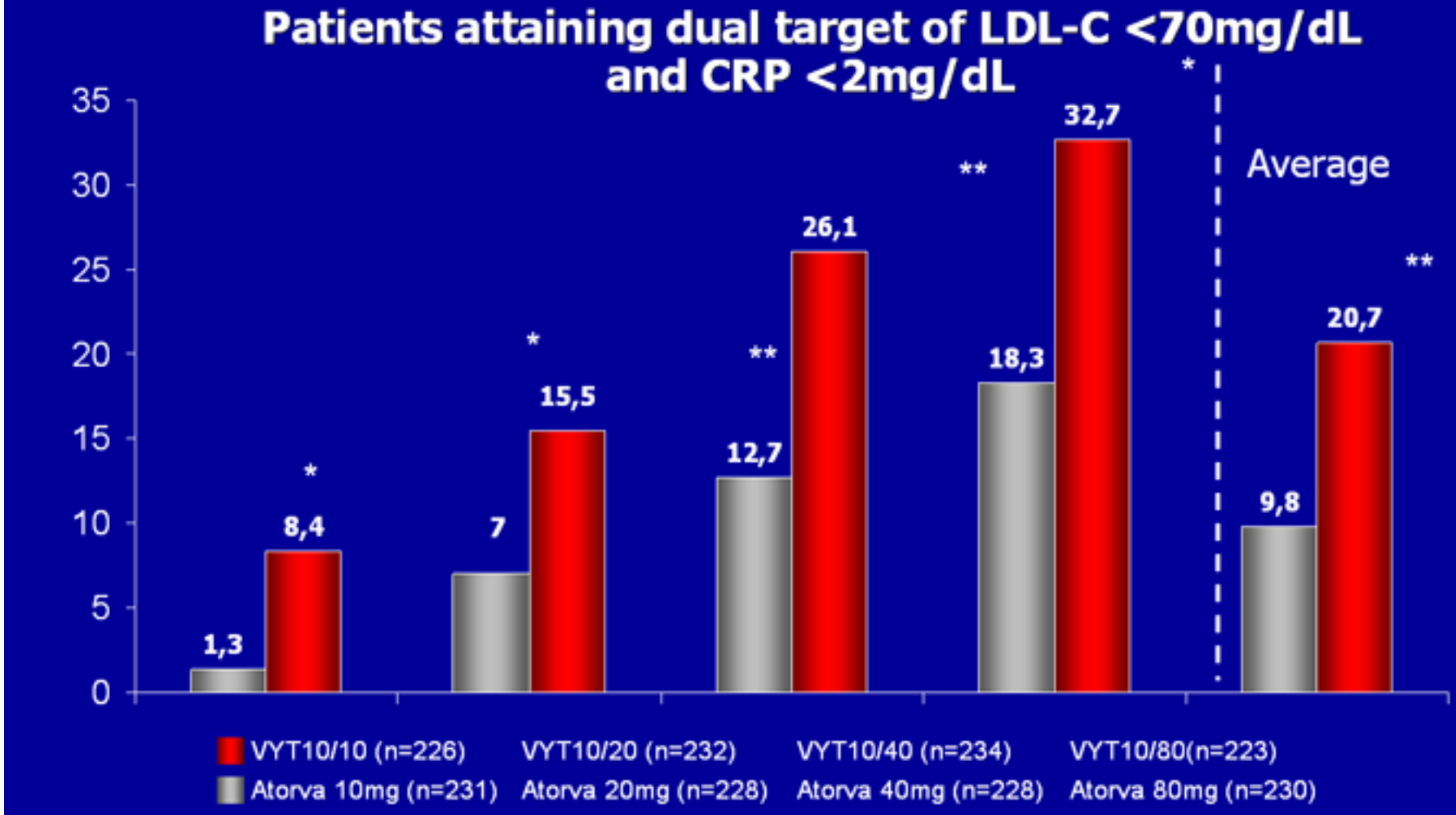
Incidence of Recurrent MI or CHD Death according to Achieved Levels of Both LDL-C and CRP: PROVE IT–TIMI 22



Ridker PM et al. *N Engl J Med* 2005;352:20-28.

VYVA Sub-study

VYT vs. Lipitor: Attainment of CRP and LDL-C



* $p < 0.01$ vs atorvastatin

** $p < 0.001$ vs. atorvastatin

Presented at 2006 ACC

Patients with elevations in ALT & AST and CK

Pooled treatment groups	All Atorva (n=939)	EZE/ All Simva (n=933)	EZE/All Simva minus All Atorva	*P* value
ALT ≥ 3 x ULN	10 (1.1%)	0 (0.0%)	-1.1	0.002
AST ≥ 3 x ULN	7 (0.7%)	1 (0.1%)	-0.6	0.070
ALT and/or AST ≥ 3 x ULN	11 (1.2%)	1 (0.0%)	-1.1	0.006
CK ≥ 10 X ULN	1 (0.1)	0 (0.0)	-0.1	1.000
CK ≥ 10 X ULN With muscle symptoms	0 (0.0)	0 (0.0)	0.0	-

Summary

- History of Statin Landmark Trials
  - Proven efficacy and safety
  - 70% - 75% of high risk patients remain at risk
- Majority of patients at risk not treated to target
  - Risk for CHD remains high
- Shifting targets for LDL-cholesterol
- Dual inhibition in cholesterol metabolism
- Superior efficacy and safety of Inegy in VYVA trial