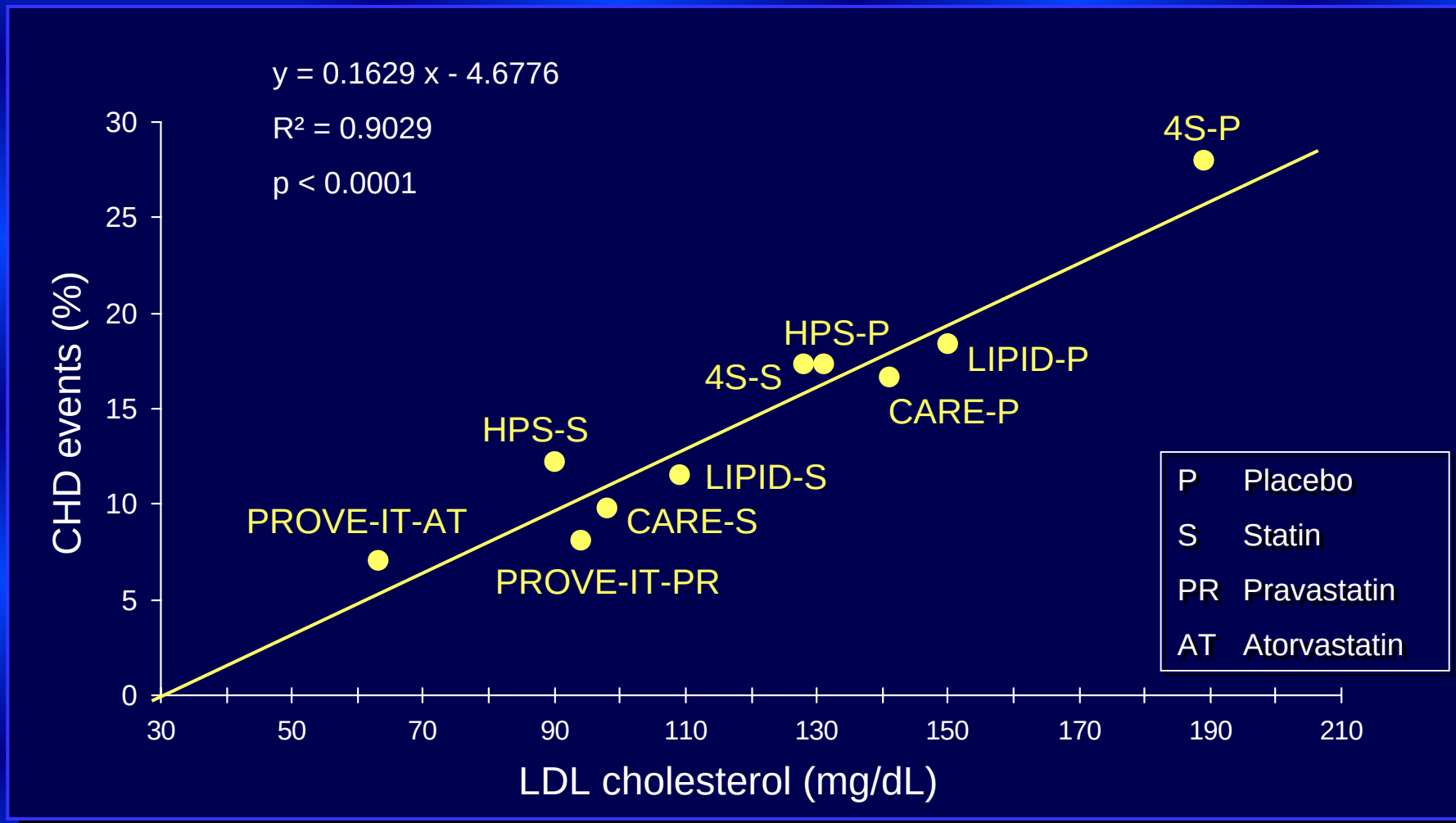
New opportunities for targeting multiple lipid pathways

Michel FARNIER, DIJON, FRANCE

Lipid lowering drug therapy

- 60s and 70s
  - nicotinic acid
  - resins
- 70s to 90s
  - fibrates
- the 90s
  - statins

Coronary heart disease (CHD) event rates in secondary prevention trials are directly proportional to the on-treatment LDL-C levels



O'Keefe et al. JACC 2004; 43: 2142-6

Previous lipid intervention strategies for preventing/reversing atherosclerosis

- Reduce LDL-C - statins
- Increase HDL-C - fibrates, niacin

- Event rates in subjects treated with statins or fibrates are up to 35% lower than in those on placebo.
- But events are by no means eliminated by the therapy.
- The challenge now is to devise therapies that can reduce events by much more than can be achieved by the existing medications.

Lipid lowering drug therapy

- 60s and 70s
  - nicotinic acid
  - resins
- 70s to 90s
  - fibrates
- the 90s
  - statins
- the new millennium
  - combination with novel agents

Future Research in Hyperlipidemia

→ *What are the major targets of new LRD ?*

- Effect on single risk factor
  - → LDL
  - → HDL
- Effect on multiple risk factors
  - → Atherogenic Lipid Profile (ALP)
  - → Type 2 diabetes, Metabolic Syndrome
- Effect on atherogenesis

Combination therapy in hyperlipidemia

→ *What are the present / near future options in clinical practice?*

- Effect on single risk factor
  - → LDL
  - → HDL
- Effect on multiple risk factors
  - → ↑ TG, ↓ HDL, ↑ small dense LDL
- Effect on ~~atherogenesis~~

Combination therapy in hyperlipidemia

→ *What are the present / near future options in clinical practice?*

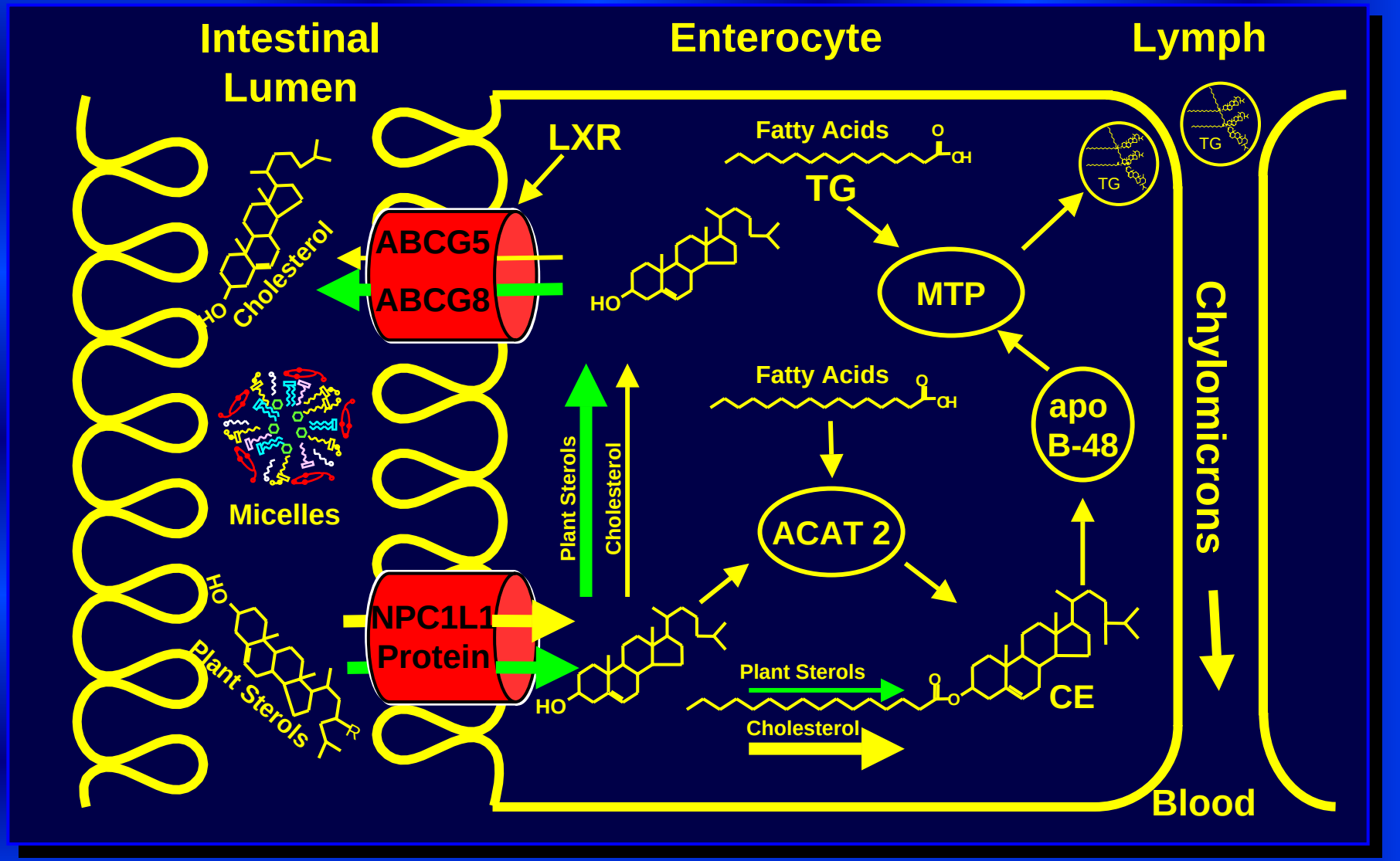
- Effect on single risk factor

  → LDL → Statin + BAS (resin)
  Statin + Ezetimibe

  → HDL

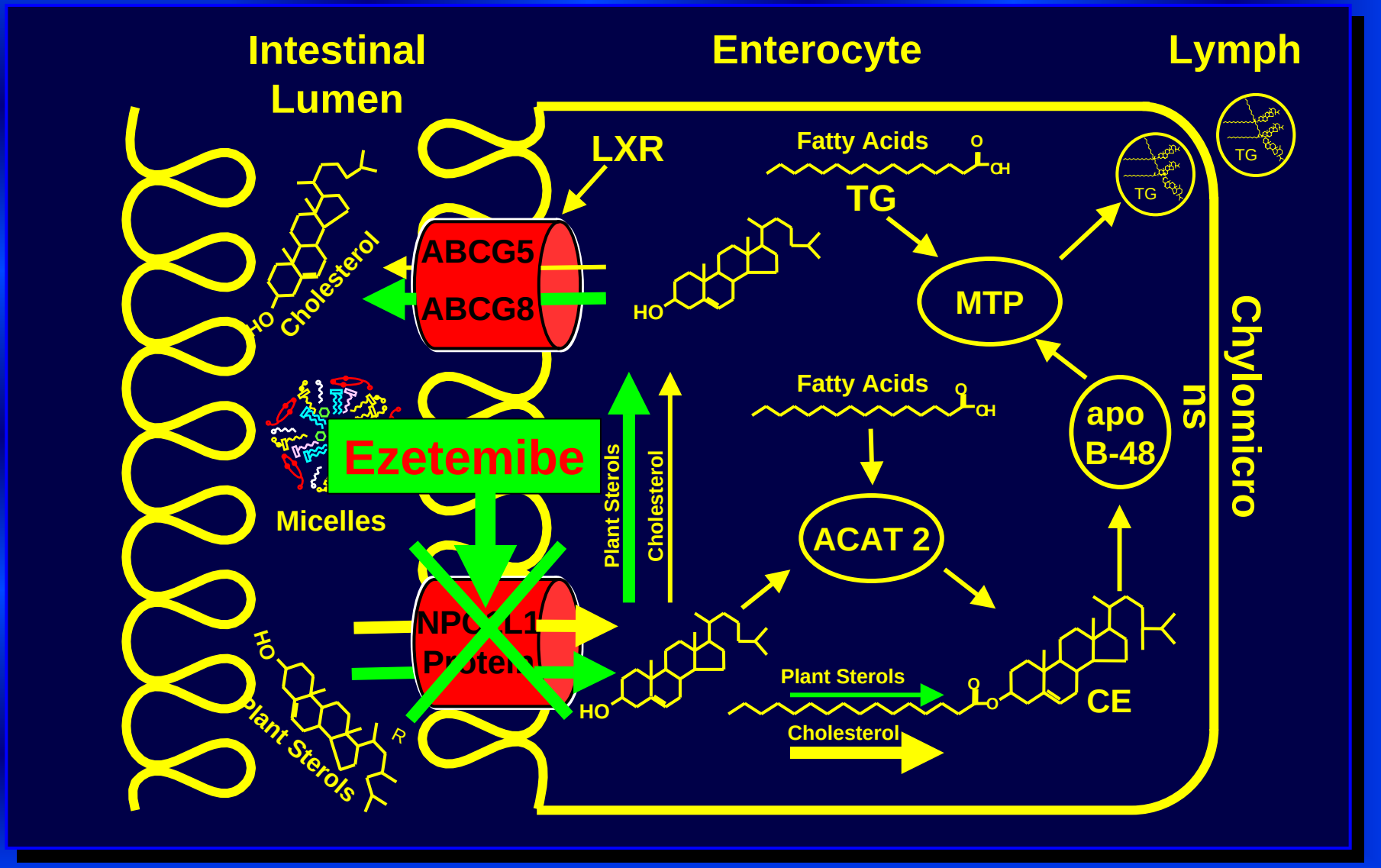
Regulation of intestinal Cholesterol Absorption

(NPC1L1 = Niemann-Pick C1 Like 1 Protein)

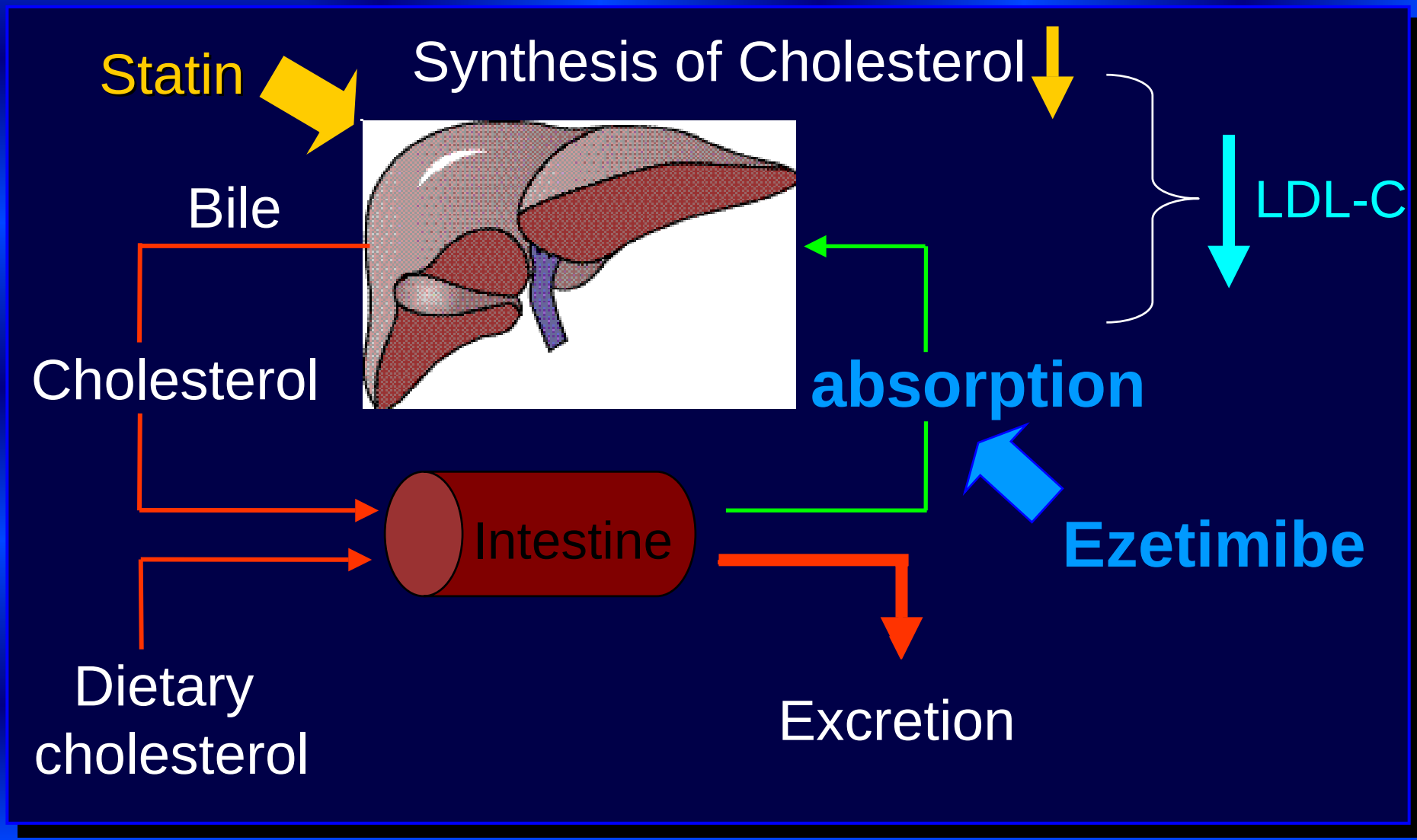


Altmann et al., Science 2004;303:1204

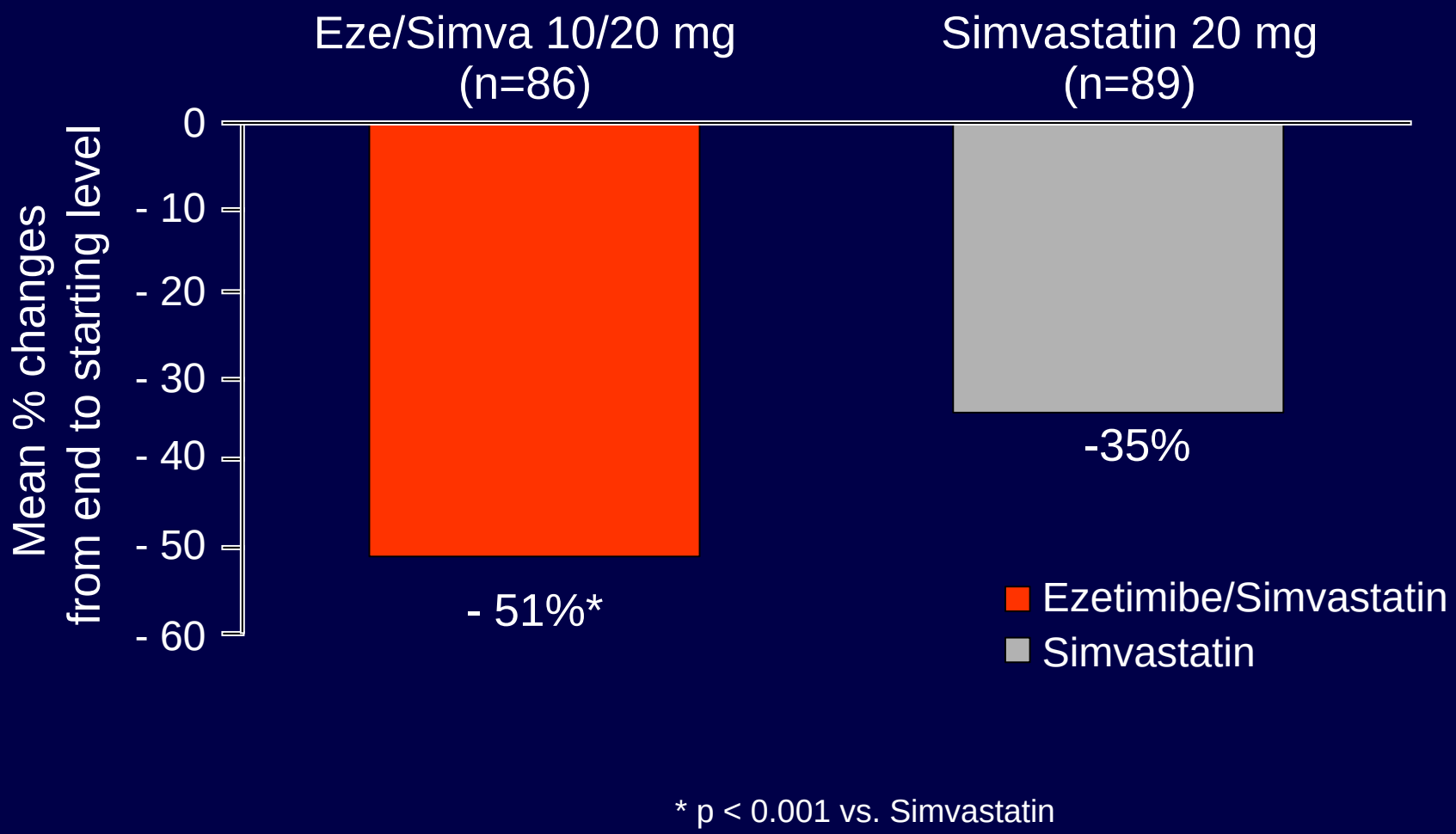
Regulation of intestinal Cholesterol Absorption



Dual Inhibition: Ezetimibe and Statin



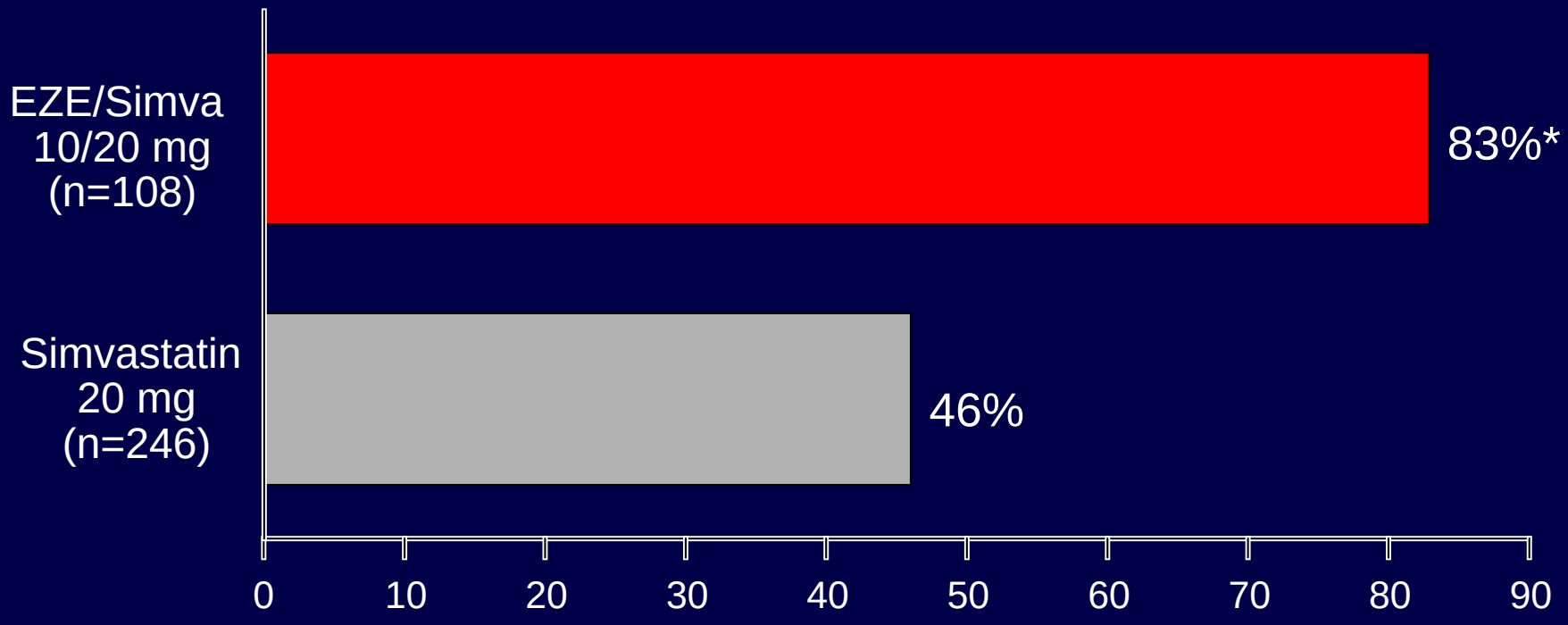
LDL-C Reduction in Usual Doses



* p < 0.001 vs. Simvastatin

Goldberg A et al, Mayo Clin Proc. 2004; 79: 620-629

Percentage of patients reaching target levels of LDL-Cholesterol < 100 mg/dl at a typical dose of Eze/Simva 10/20



** p < 0.001 vs. Simvastatin 20 mg*

Data on file MSD and Schering-Plough

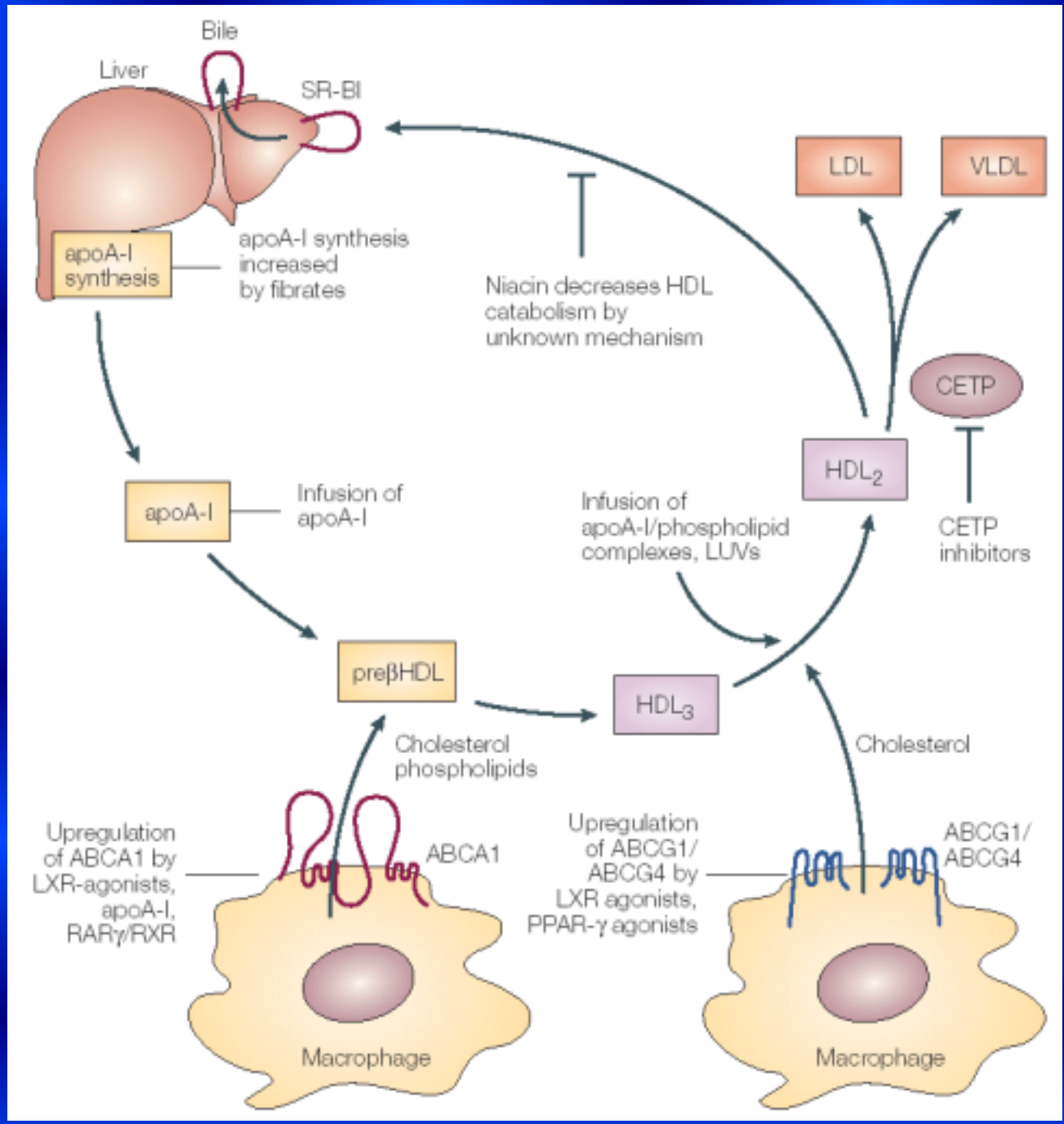
Combination therapy in hyperlipidemia

→ *What are the present / near future options in clinical practice?*

- Effect on single risk factor
  - → LDL
  - → HDL

Established and emerging HDL raising approaches

- New PPARα agonists (fibrates)
- CETP inhibitors
- LXR agonists
- Endothelial lipase inhibitors
- HDL mimetics
- Niacin receptor agonists



Linsel-Nitschke, Tall Nature Reviews/Drug Discovery 2005

Opportunities for novel HDL-raising therapies

Drug target	Class of protein	Expected biochemical mechanism
Niacin receptor agonists	GPCR (PUMA-G, HM74)	TG lowering, HDL increase
LXR agonists	Nuclear receptor	↑ ABCA1 expression, cholesterol efflux and HDL formation
CETP-inhibitors	Lipid transfer protein	↓ HDL clearance
Endothelial lipase inhibitors	Enzyme	↓ HDL clearance
Infusion of peptides related to ApoA1		Increased removal of cholesterol from atheroma

Combination therapy in hyperlipidemia

→ *What are the present / near future options in clinical practice?*

- Effect on single risk factor

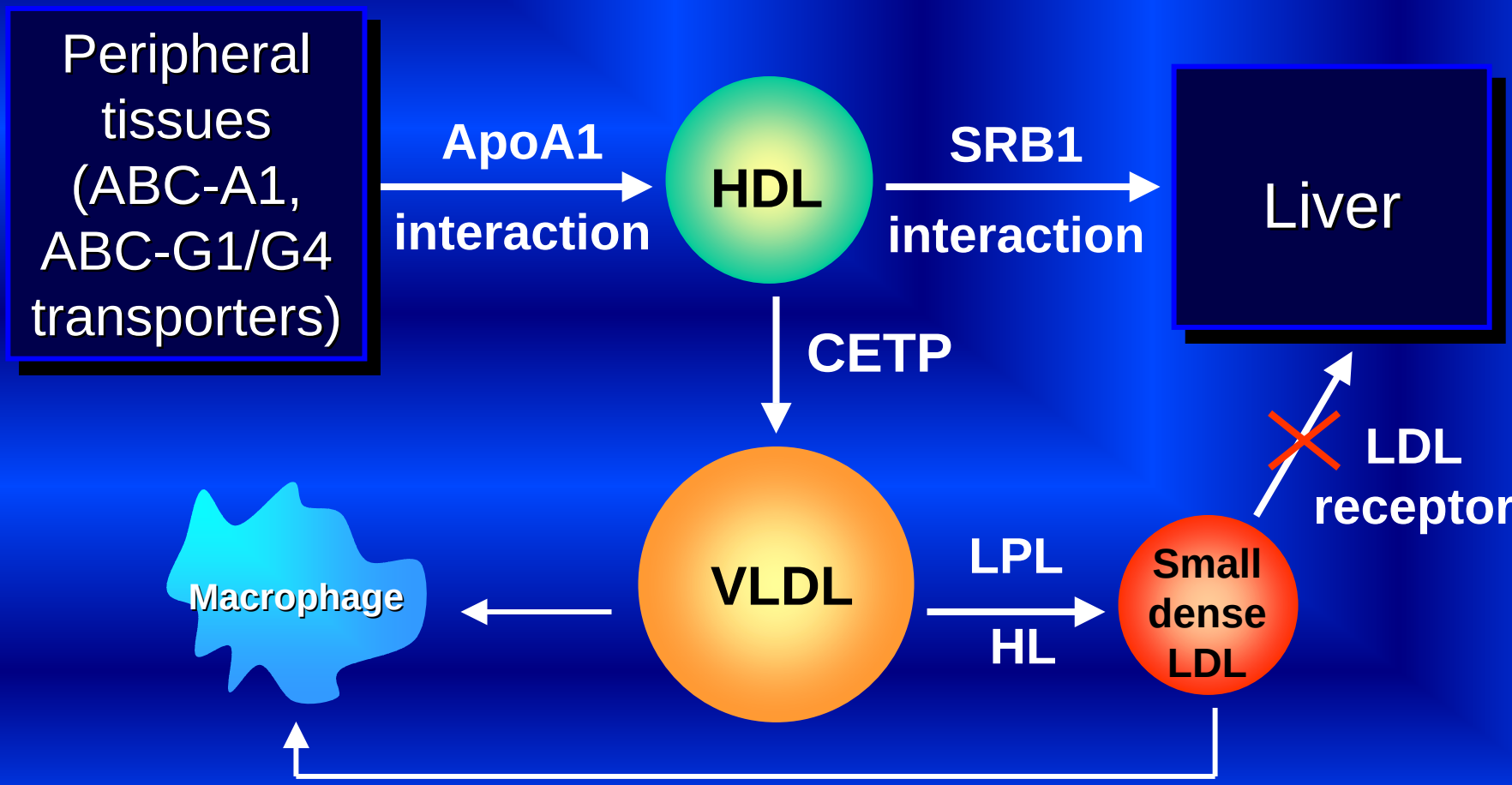
  → LDL

  → HDL → Statin + CETP inhibitor

CETP inhibitors

- Drugs in development :
  - Torcetrapib or CP-529, 414
  - JTT 705

The reverse cholesterol transport route



CETP inhibition as an anti-atherogenic strategy

How strong is the evidence base for CETP inhibition and its relationship to atherosclerosis?

Effect of CETP on Atherogenicity

Transgenic Mice

- No endogenous CETP expression in wild-type mice
- High background HDL levels
- No athero without diet or transgenic induction
- Introduction of CETP lowers HDL-C

Bruce et al. Annu Rev Nutr. 1998;18:297-330.
Foger et al. Circulation. 1997;96:1.
Hayek et al. J Clin Invest. 1995;96:2071-2074.
Marotti et al. Nature. 1993;364:73-75.
Masucci-Magoulas et al. Science. 1997;275:391-394.

Effect of CETP Inhibition on Atherogenicity

Rabbits

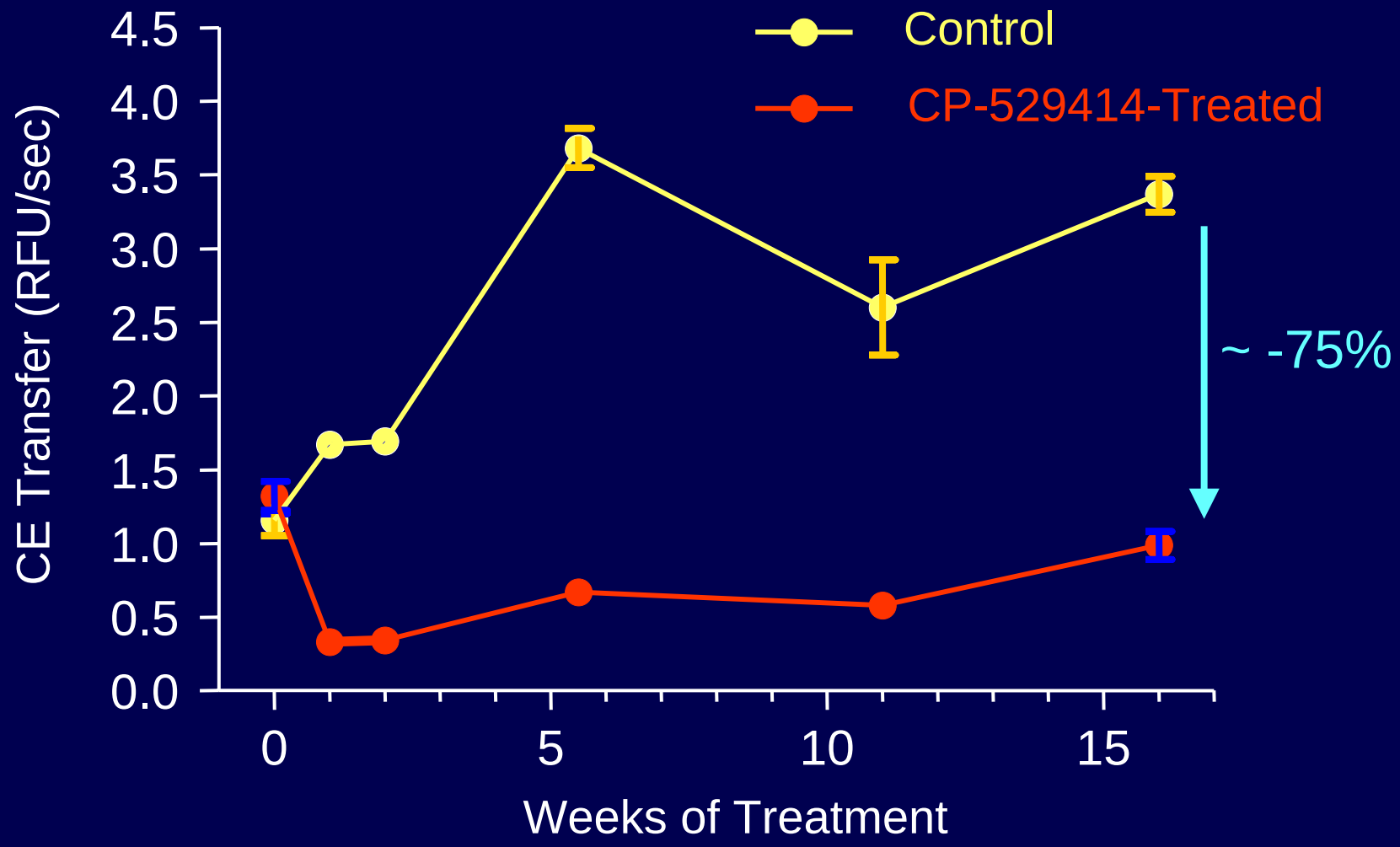
- High endogenous CETP expression
- Cholesterol diet induces atherosclerosis
- CETP inhibition elevates HDL-C

JTT-705, a CETP inhibitor :

- inhibits CETP activity by forming a disulphide bond
- in cholesterol-fed rabbits, increases HDL-C, decreases non-HDL-C and induces a 70% decrease of aortic arch lesions

OKAMOTO et al. Nature 2000; 406: 203-207.

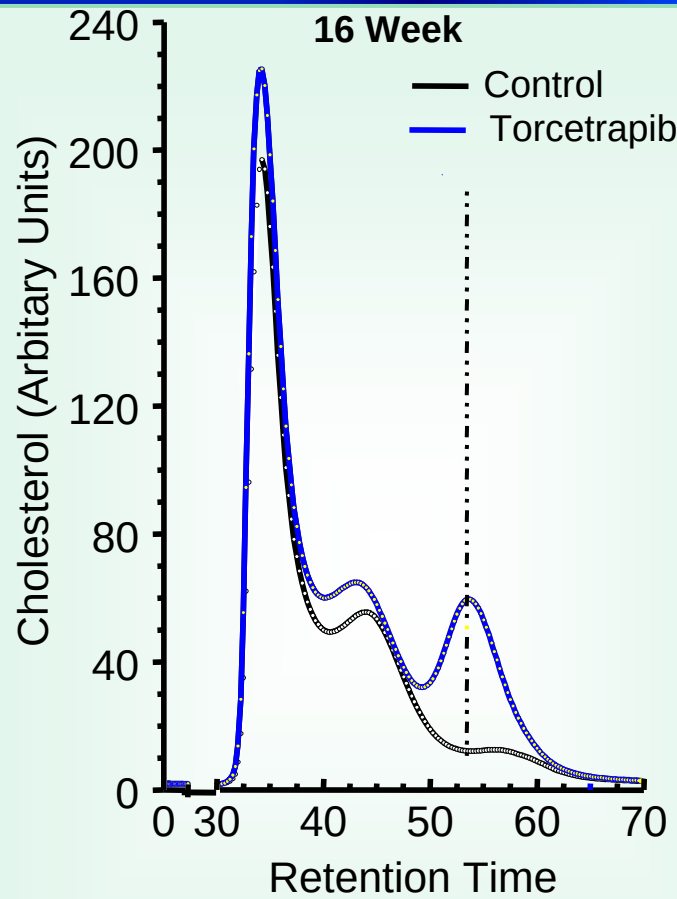
Torcetrapib Treatment Inhibits CETP Activity in Rabbits



From: Morehouse et al.AHA 20004.

Effect of Torcetrapib on Lipids and Atherosclerosis in Rabbits

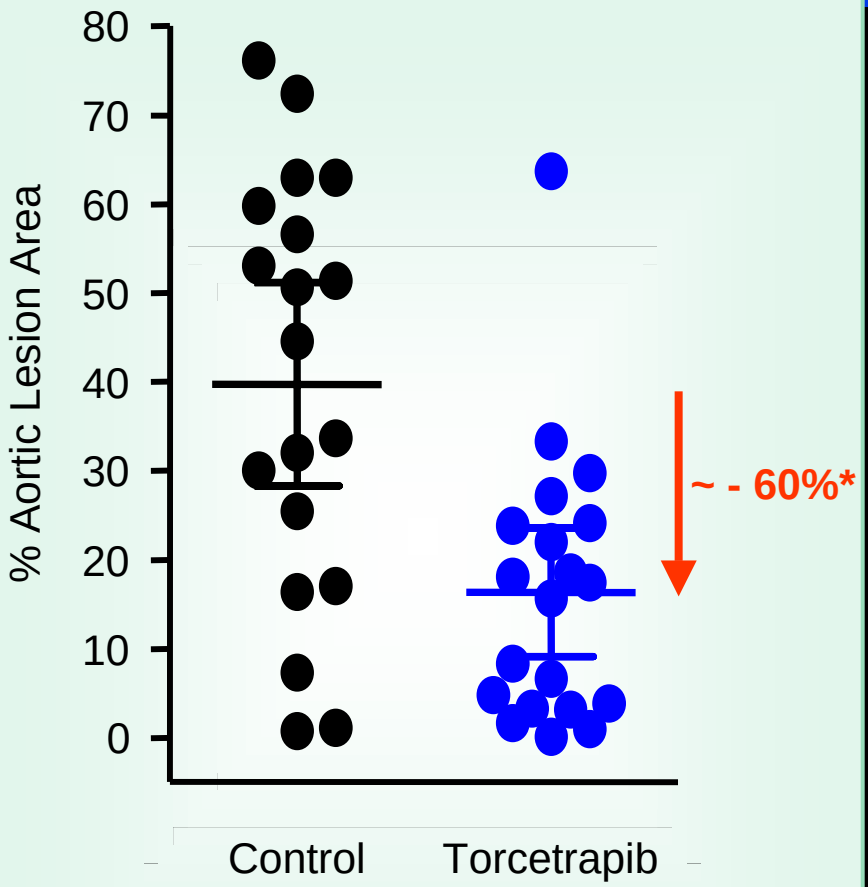
Torcetrapib Increases HDL– No Change in Non-HDL



VLDL	422 ± 75	450 ±68
LDL	224 ± 41	239 ± 43
HDL	57 ± 6	208 ± 32

Lipoprotein values in mg/dl

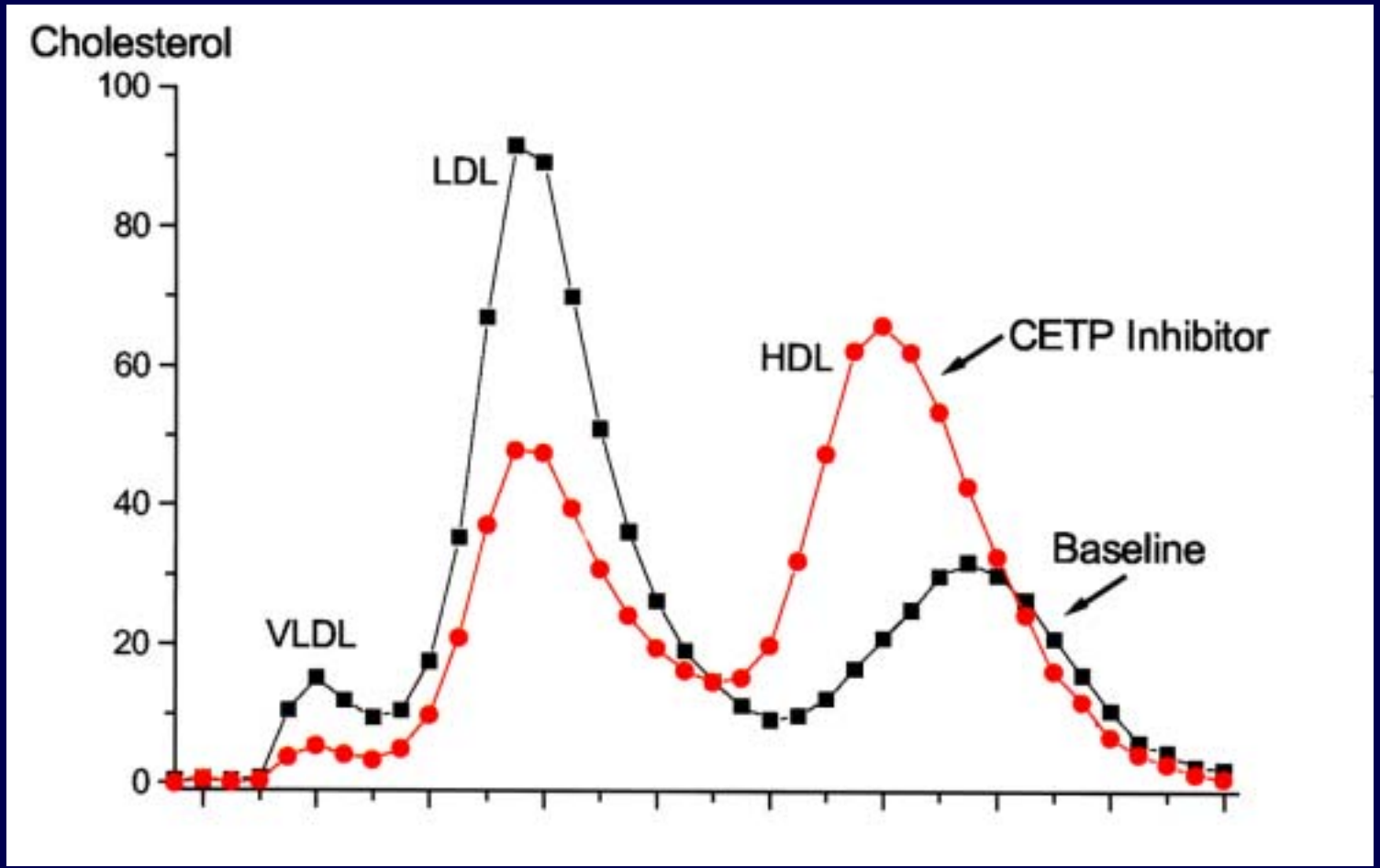
Torcetrapib Reduces Aortic Atherosclerosis



** p = 0.001*

From: Morehouse et al.AHA 20004.

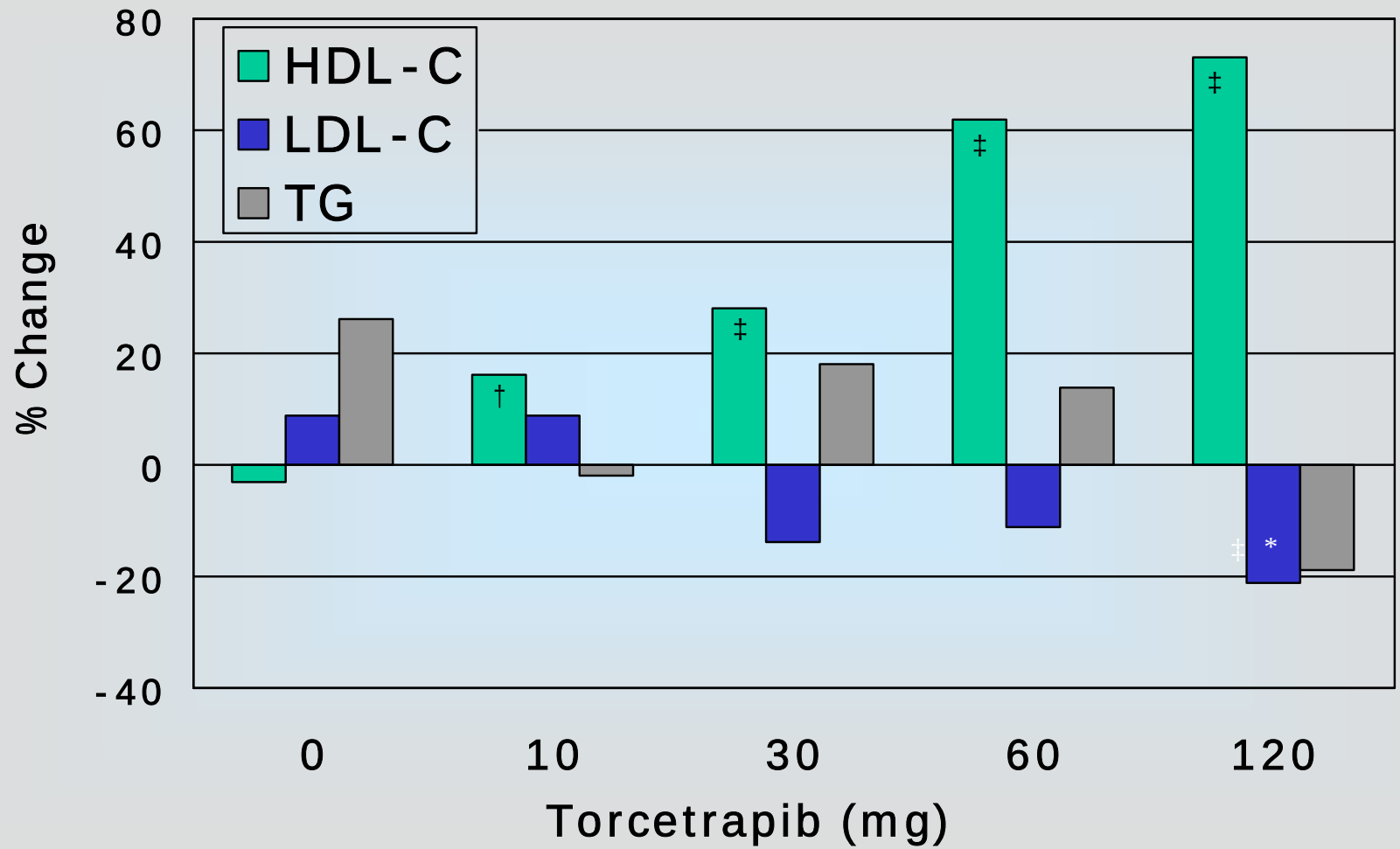
Effects of a CETP inhibitor in normal subjects



Clark et al. ATVB 2004; 24 : 490-497

Torcetrapib: Dose-dependent CETP Inhibition, HDL Raising and LDL Lowering in Healthy Individuals

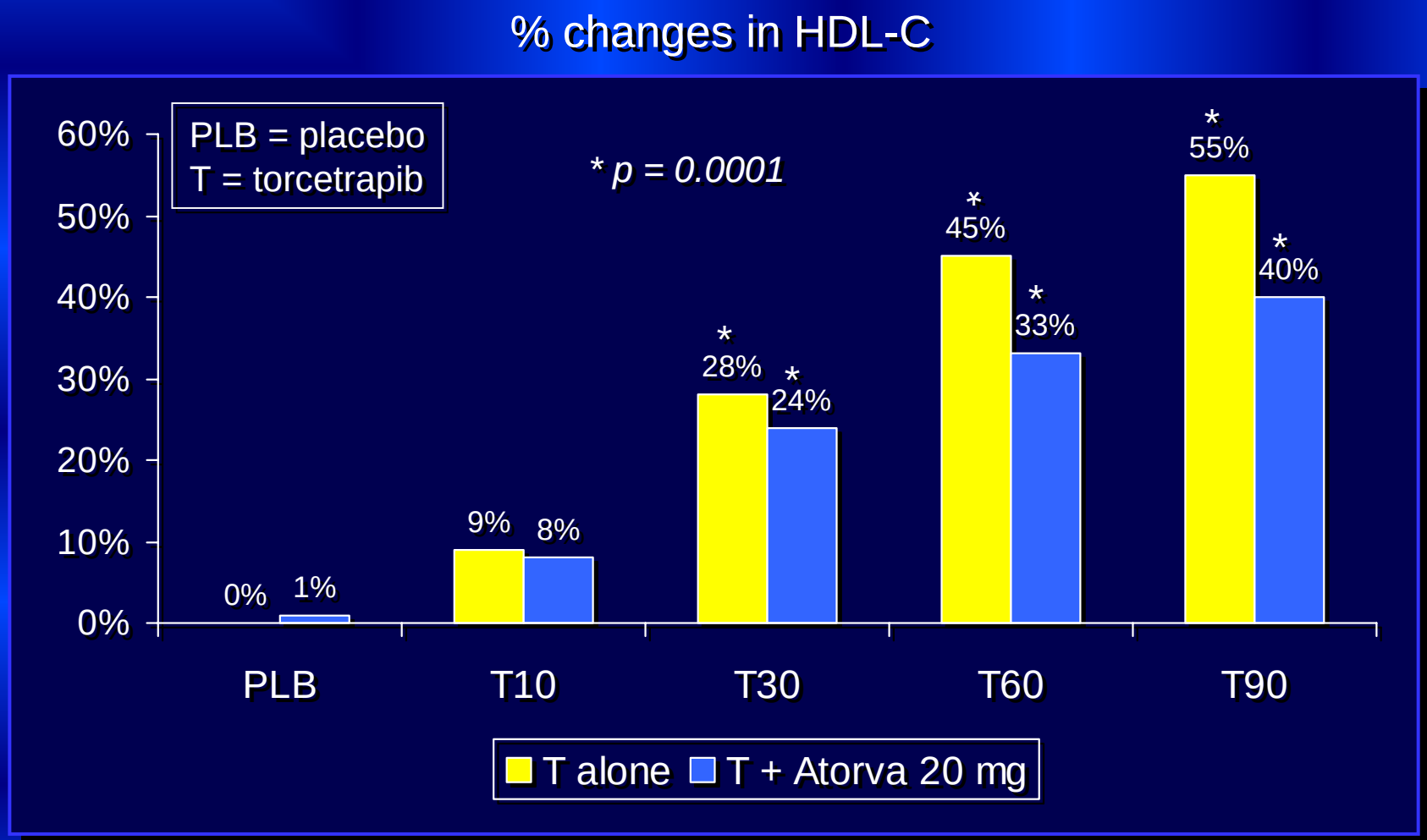
Lipid Profile during Treatment with Torcetrapib versus Placebo for 14 days



* P< 0.05, † P< 0.01, ‡ P< 0.001

Adapted from Clark et al. ATVB 2004, 24:1-9

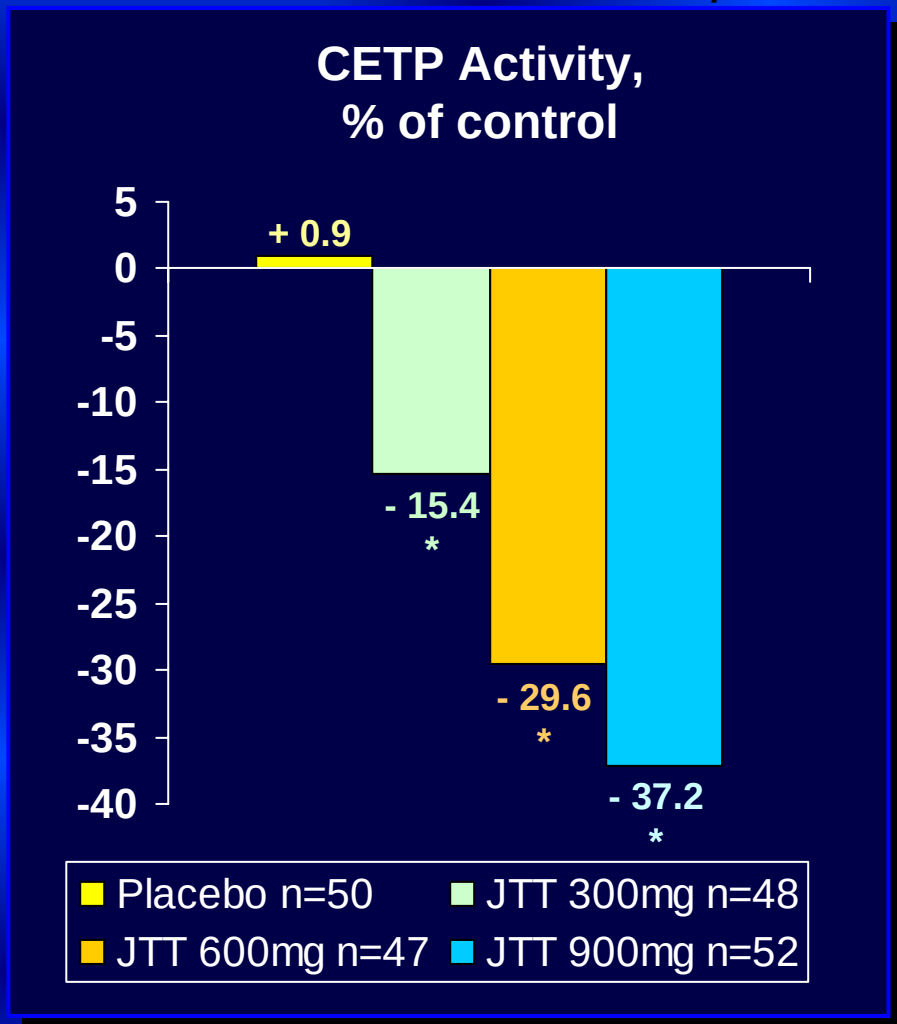
Efficacy of Torcetrapib (with or without Atorvastatin) in subjects with low HDL-C

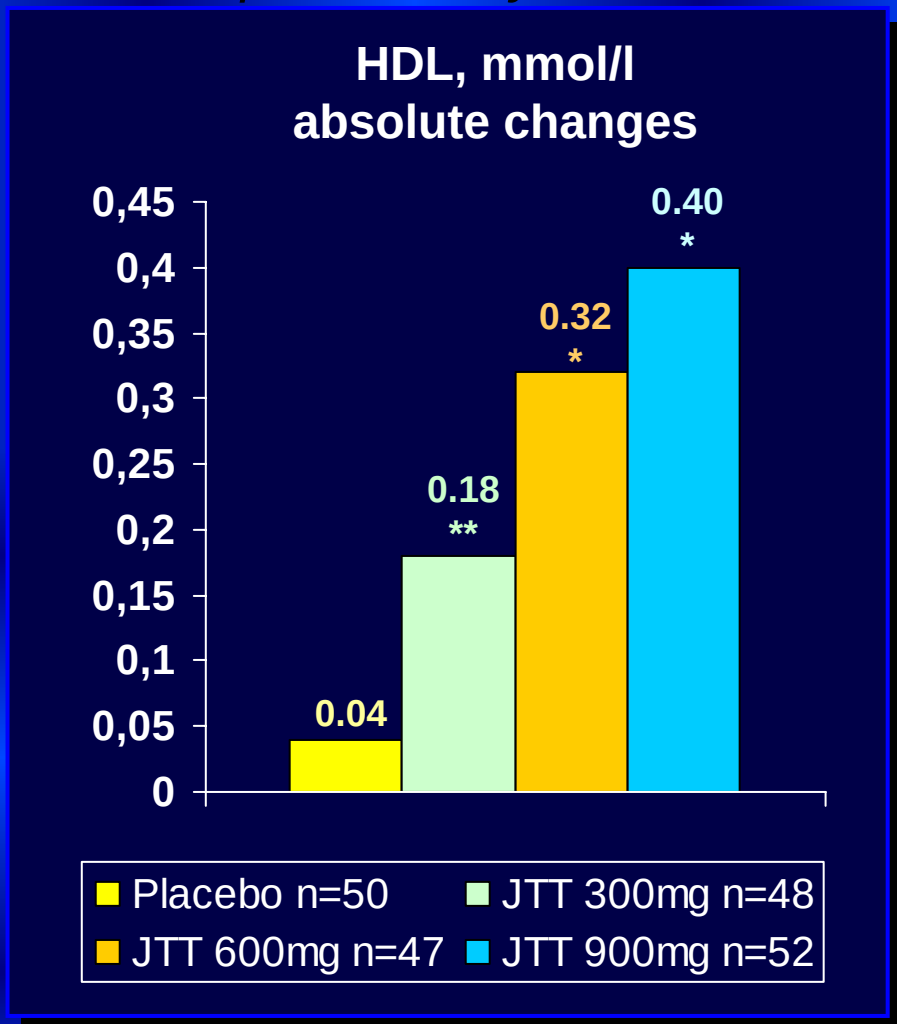


Davidson et al. JACC 2005; 45 (Supplt A) : 394A

Efficacy of JTT-705 in Humans

A randomized phase II Dose-Response Study





* p < 0.0001 vs placebo ** p < 0.001 vs placebo

de GROOTH et al. Circulation 2002; 105: 2159-65.

Efficacy of JTT-705 in Humans

A randomized phase II Dose-Response Study

- Treatment with 900 mg JTT-705 for 4 weeks led to a :

  37% decrease in CETP activity ($p < 0.0001$)

  34% increase in HDL-C ($p < 0.0001$)

  7% decrease in LDL-C ($p < 0.017$)

de GROOTH et al. Circulation 2002; 105: 2159-65.

Combination therapy in hyperlipidemia

→ *What are the present / near future options in clinical practice?*

- Effect on single risk factor
  - → LDL
  - → HDL
- Effect on multiple risk factors
  - → ↑ TG, ↓ HDL, ↑ small dense LDL
    - → Statin + Fenofibrate
    - → Statin + Niacin
    - → Ezetimibe + Fenofibrate

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Statin-Fibrate combination therapy

- Rationale

  Complementary metabolic effects of fibrates and statins

- Efficacy

  Combinations with usual doses of statins and fibrates led to :

  - reductions in LDL-C $\geq$ 40%, TG $\geq$ 50%
  - increase in HDL-C $\geq$ 20%

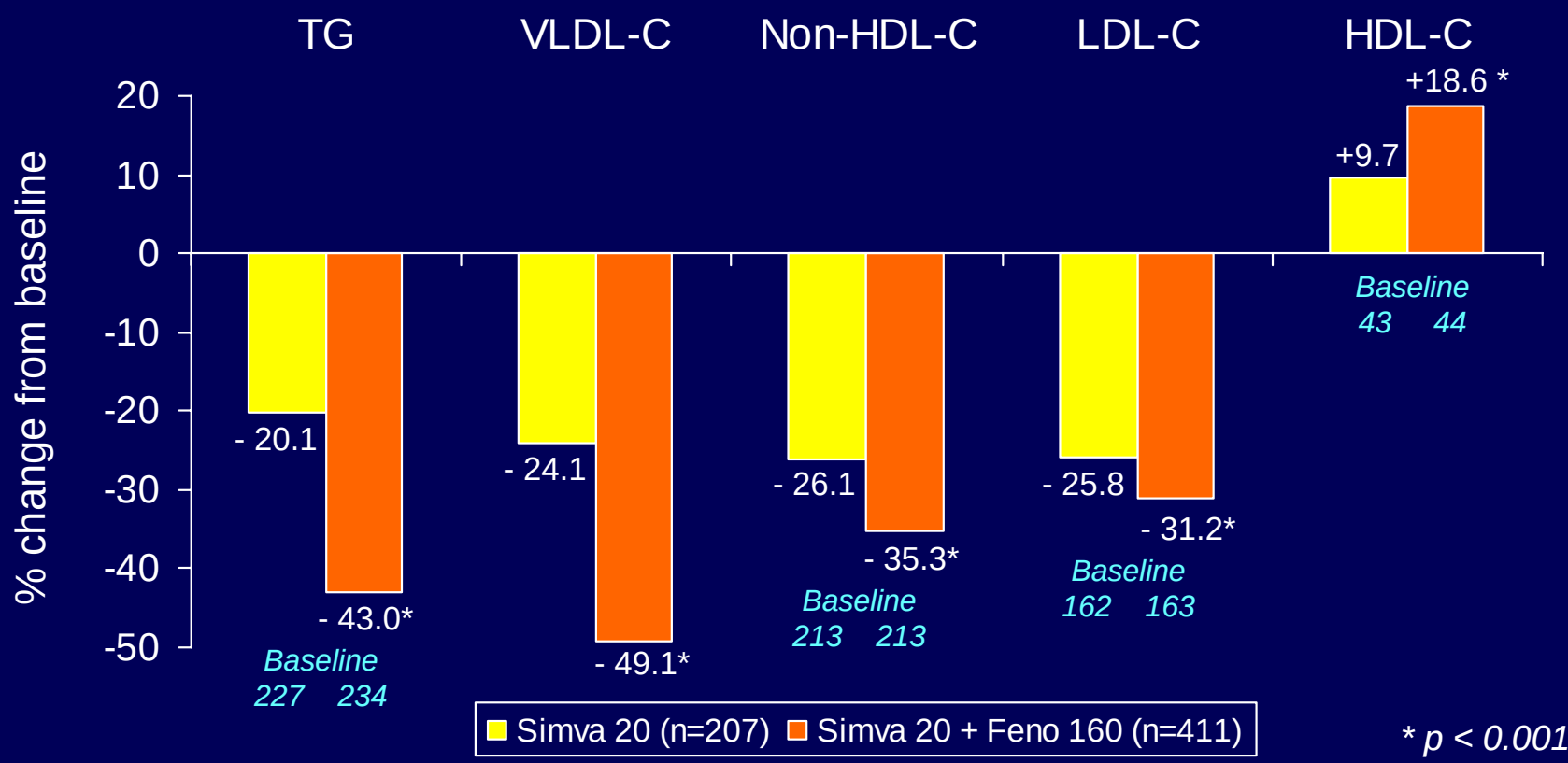
  Farnier. Am J Cardiovasc Drugs 2003; 3: 169

- Targeted populations

  - combined hyperlipidemia
  - type 2 diabetes or metabolic syndrome

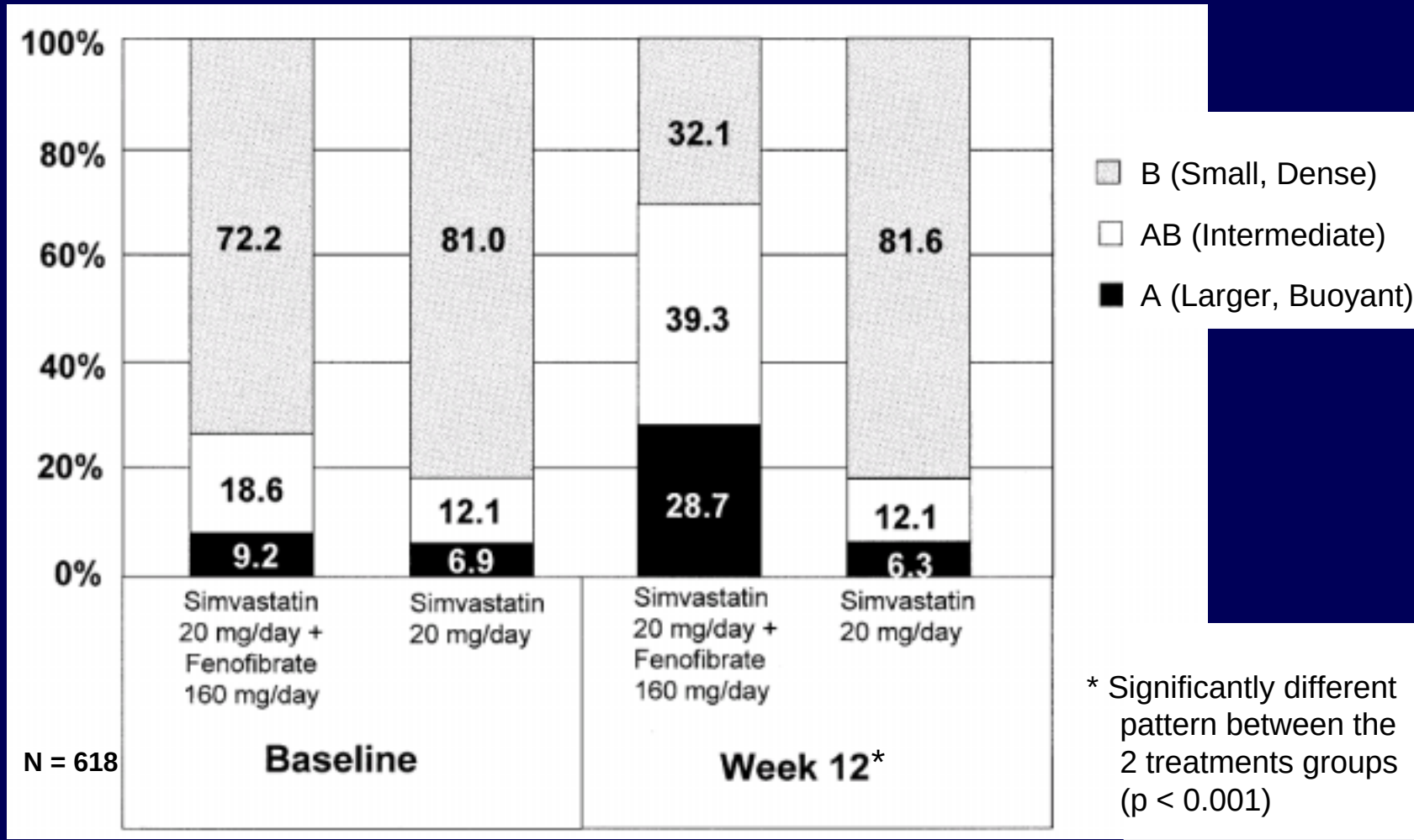
Effectiveness and tolerability of Simvastatin plus Fenofibrate for Combined Hyperlipidemia : The SAFARI trial

12-week, double-blind, randomized study in 619 patients with combined hyperlipidemia (TG 150-500 mg/dl, LDL-C > 130 mg/dl)



Grundy et al. Am J Cardiol 2005; 95: 462-468

SAFARI Trial : effects on LDL-C particle subclasses



* Significantly different pattern between the 2 treatments groups ($p < 0.001$)

Grundy et al. Am J Cardiol 2005; 95: 462-468

Statin-Fibrate combination therapy

- Safety

  use restricted because of severe myopathy and rhabdomyolysis

  associated with statin-gemfibrozil combination therapy

  and with cerivastatin-fibrate combination therapy

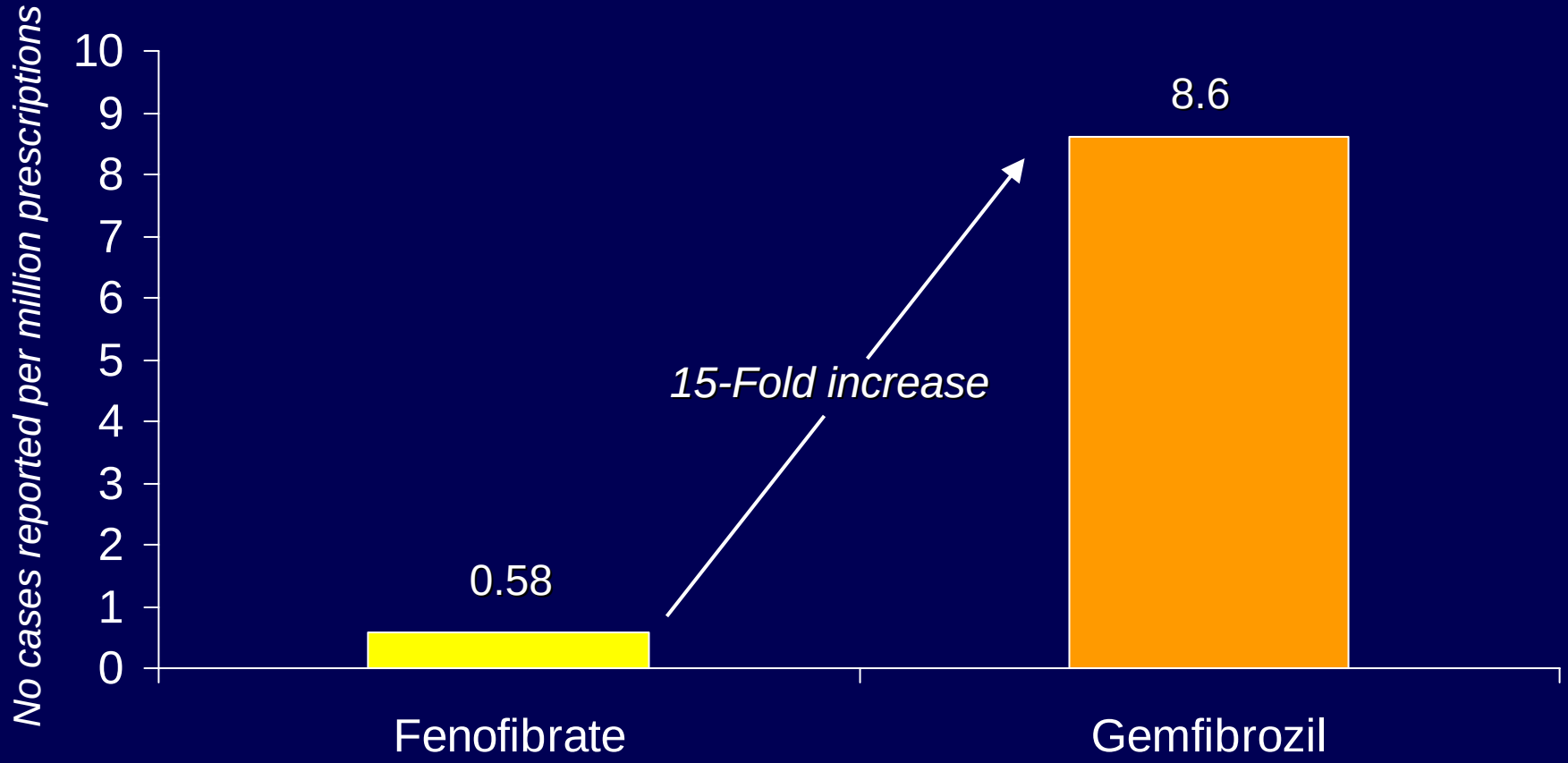
RESULTS : Number of reports of rhabdomyolysis for Fibrate/Statin therapies (1998 to 2002)

Medications	No. Cases reported [1]	No. Prescriptions dispensed [2 3]	No. Cases reported per million prescriptions
Fenofibrate			
with Cerivastatin	14	100 000	140
with other statins	2	3 419 000	0.58
Fenofibrate total	16	3 519 000	4.50
Gemfibrozil			
with Cerivastatin	533	116 000	4600
with other statins	57	6 641 000	8.60
Gemfibrozil total	590	6 757 000	87.00

[1] *Adverse Event Reporting System. U.S. Food and Drug Administration*
[2] *National Prescription Audit Plus report, IMS Health*
[3] *Concomitancy Report, VERISPAN LLC*

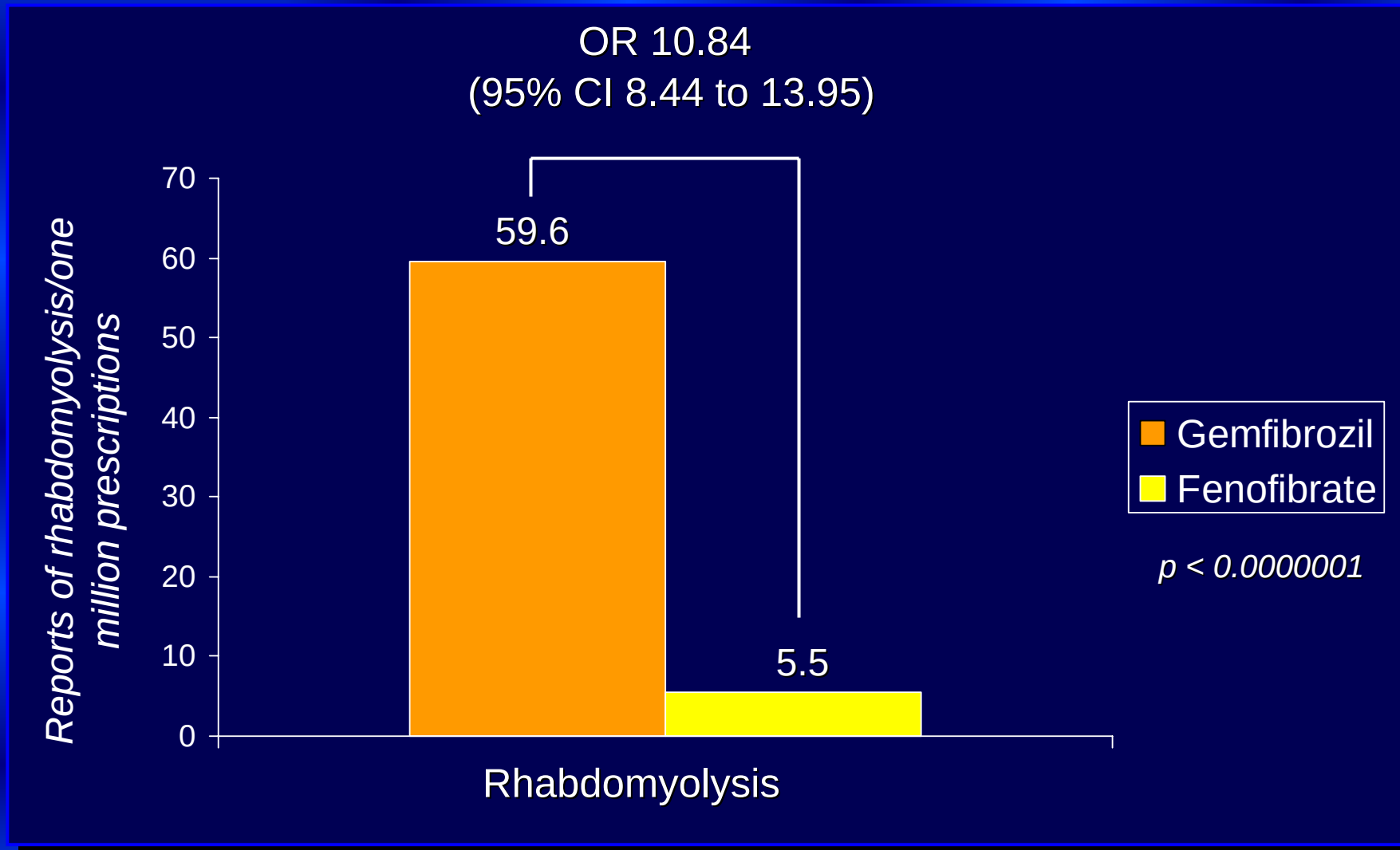
Jones, Davidson. Am J Cardiol 2005; 95: 120-122

Number of cases of rhabdomyolysis in combination therapy with Statins other than cerivastatin



Jones, Davidson. Am J Cardiol 2005; 95: 120-122.

Comparative rates of gemfibrozil- and fenofibrate-associated rhabdomyolysis



Alsheikh-Ali et al. Am J Cardiol 2004; 94: 935-938

VA health care system comparison of Gemfibrozil to Fenofibrate

- 149 cases of rhabdomyolysis in 95,000 patients on statins plus gemfibrozil

  Rate of 0.16%

- No cases of rhabdomyolysis in 1500 patients on fenofibrate plus statins

Presented by Davidson, New York, July 2005

Statin-Fibrate combination therapy : pharmacokinetic interactions

	Gemfibrozil	Fenofibrate
Atorvastatin	↑ in C_{max} (expected)	No effect
Simvastatin	↑ in C_{max} by 2 fold	No effect
Pravastatin	↑ in C_{max} by 2-fold	No effect
Rosuvastatin	↑ in C_{max} by 2-fold	No effect
Fluvastatin	No effect	No Effect
Lovastatin	↑ in C_{max} by 2.8-fold	Not available
Cerivastatin	↑ in C_{max} by 2-3-fold	No effect

Statin-Fibrate interactions

➔ Possible explanation = Glucuronidation

- Glucuronidation is a pathway for the elimination of the active hydroxy acid metabolites of statins
- Gemfibrozil inhibits simvastatin, atorvastatin, rosuvastatin and more prominently cerivastatin glucuronidation
- Fenofibrate has less inhibitory effect on statin glucuronidation

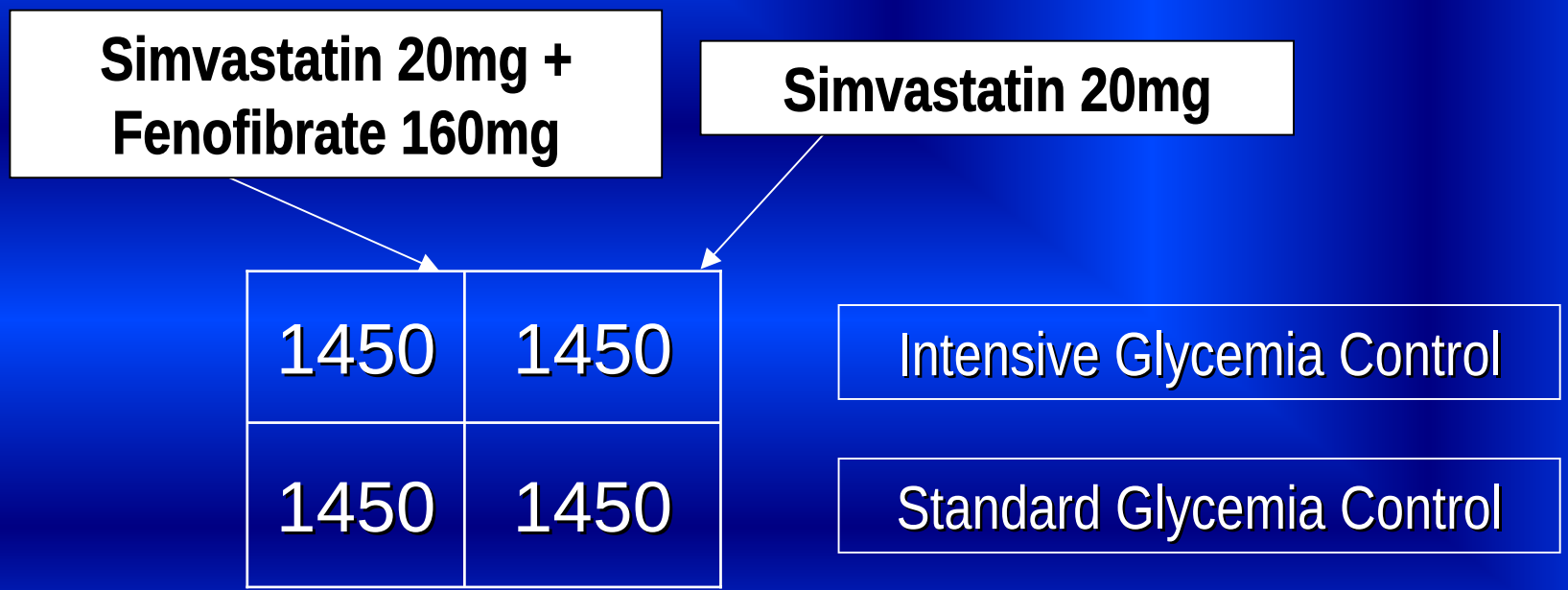
➔ *May explain the lack of significant drug interaction between fenofibrate and statins*

Prueksaritanont et al. JPET 2002; 301: 1042-1051
DMD 2002; 30: 1280-1287

ACCORD: NIH/NHLBI Trial

Action to Control Cardiovascular Risk in Diabetes

- Does a therapeutic strategy that targets HbA1c < 6% reduce the rate of CVD versus a target of 7.5%
- Does a therapeutic strategy of fibrate therapy *plus* statin therapy reduce CVD greater than statin therapy alone



http://www.clinicaltrials.gov/ct/gui/show

Combination therapy in hyperlipidemia

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Lipid-Altering effects of Statin-Niacin regimens

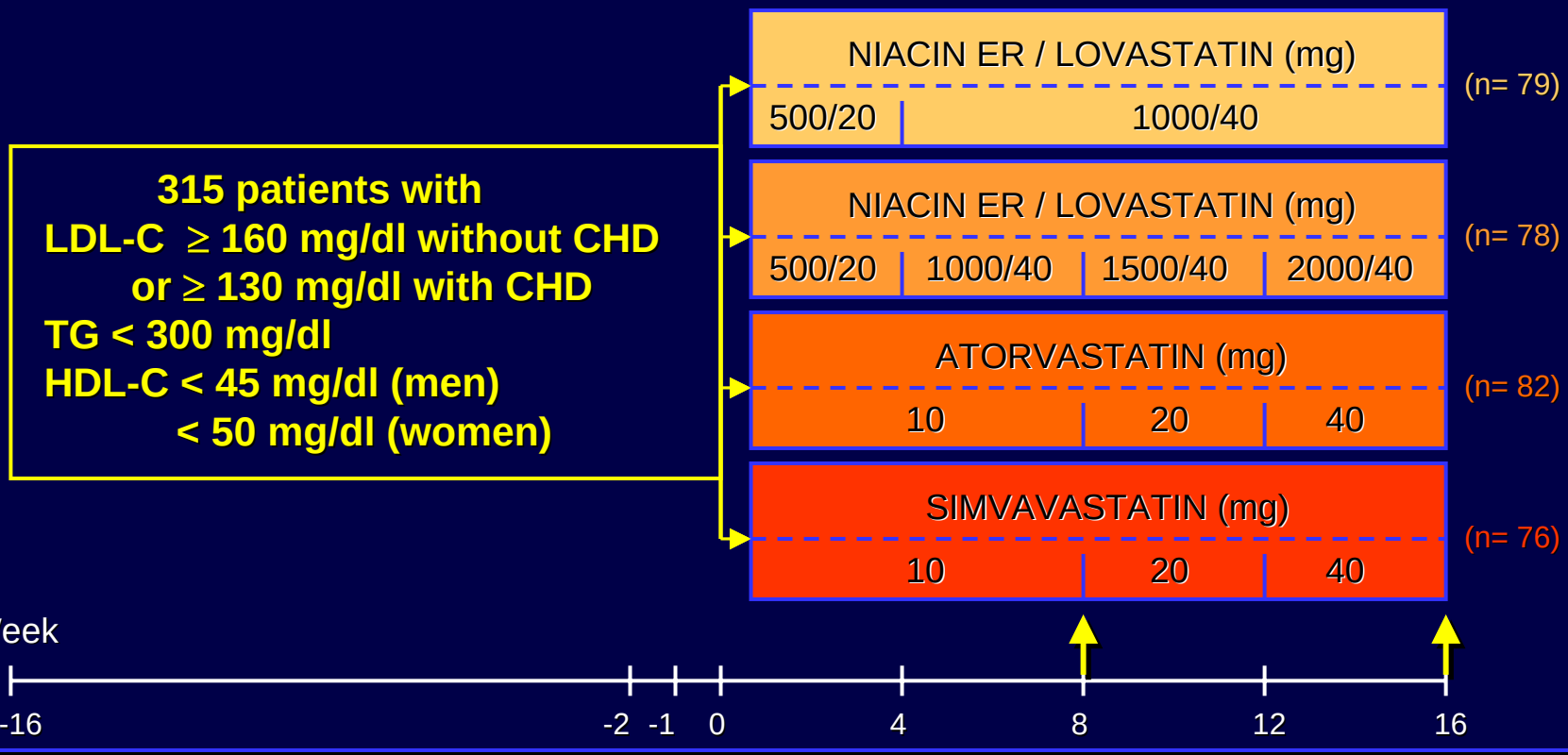
Study /year	Statin/dose, mg/d	Niacin type/dose, g/d	Δ LDL %	Δ HDL %	Δ TG %
Davignon *et al.*/1994	Pravastatin, 40	SR, 1.0-2.0	- 41	16	- 35
Jacobson *et al.*/1994	Fluvastatin, 20	IR, < 3.0	- 40	28	- 30
Vacek *et al.*/1995	Lovastatin, 20	SR, 1.2	- 37	2	- 11
O 'Keefe *et al.*/1995	Pravastatin, 20	IR, 3.0	- 25	29	- 42
Gardner *et al.*/1996	Lovastatin, 20	IR, 1.5	- 30	27	- 19
Pasternak *et al.*/1996	Pravastatin, 40	SR, 1.5-3.0	5	- 3	- 26
Stein *et al.*/1996	Simvastatin, 10	SR, 1.5	- 29	31	- 36
Kashyap *et al.*/2000	Lovastatin, 40	ER, 0.5-2.0	- 47	30	- 42

ER : extended-release; IR : immediate-release; SR : sustained-release

Jacobson. Curr Atheroscler Rep 2001; 3: 373-382.

Comparison of Niacin ER/Lovastatin with standard doses of Atorvastatin and Simvastatin : The Advicor Versus Other Cholesterol-modulating Agents Trial Evaluation (ADVOCATE)

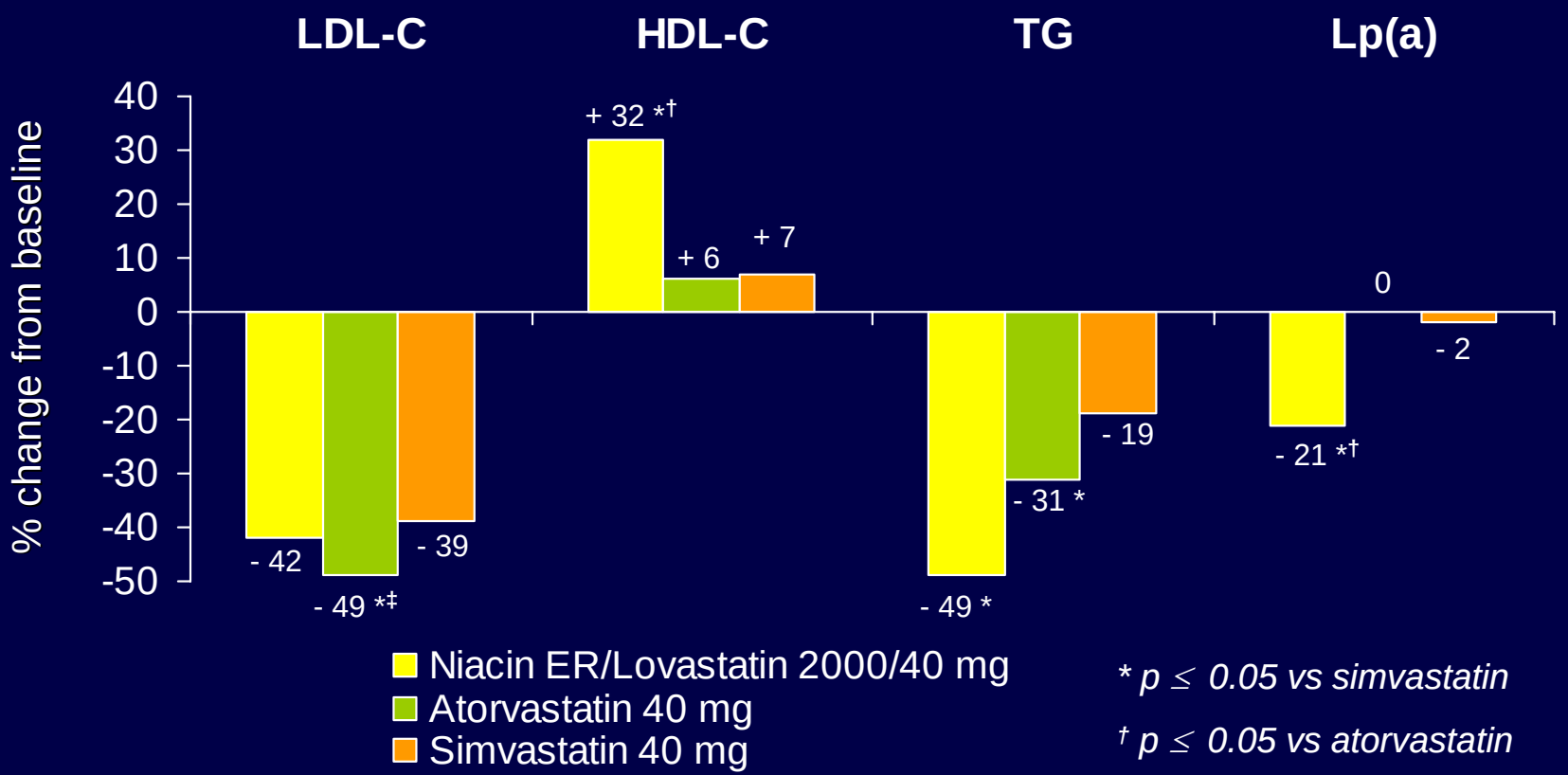
Study Design



Bays et al. Am J Cardiol 2003; 91: 667-72

Comparison of Niacin ER/Lovastatin with standard doses of Atorvastatin and Simvastatin

% change from baseline at week 16



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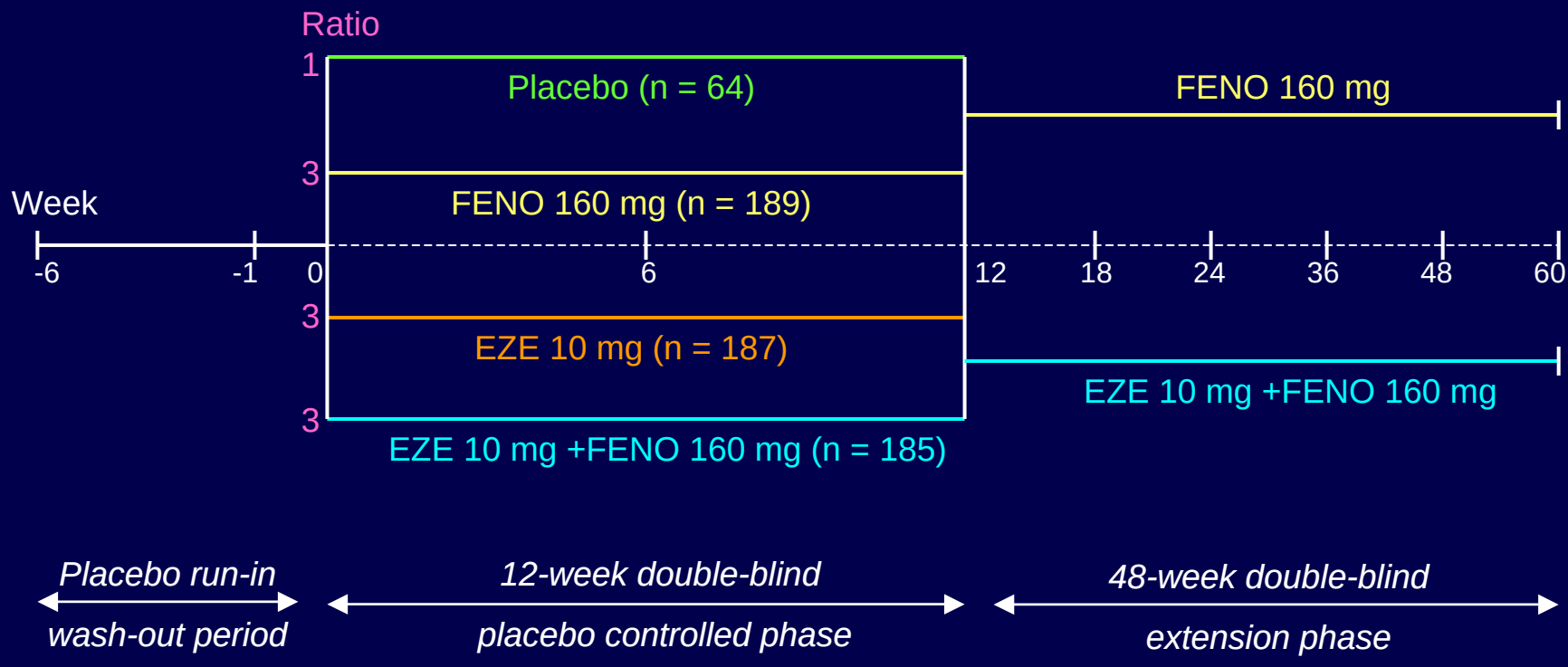
Co-administration of ezetimibe with fenofibrate in patients with mixed hyperlipidemia

Study Design



Short-term

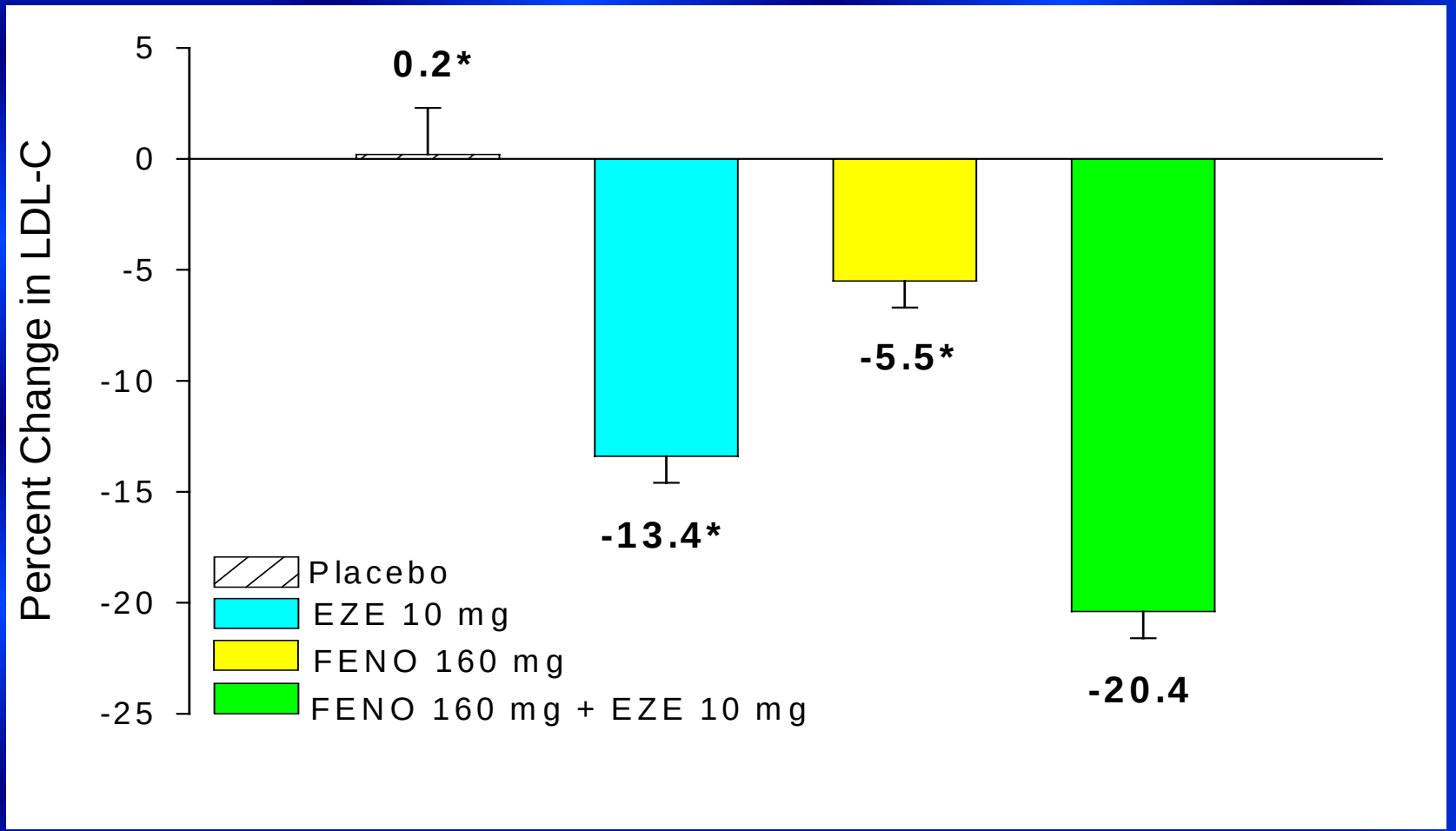
Long-term

Farnier et al. Eur Heart J 2005; 26: 897-905

McKenney, Farnier, JACC, submitted

Co-administration of ezetimibe with fenofibrate in patients with mixed hyperlipidemia (baseline : LDL-C 160 mg/dl, TG 275 mg/dl)

LDL-C Response with Treatment

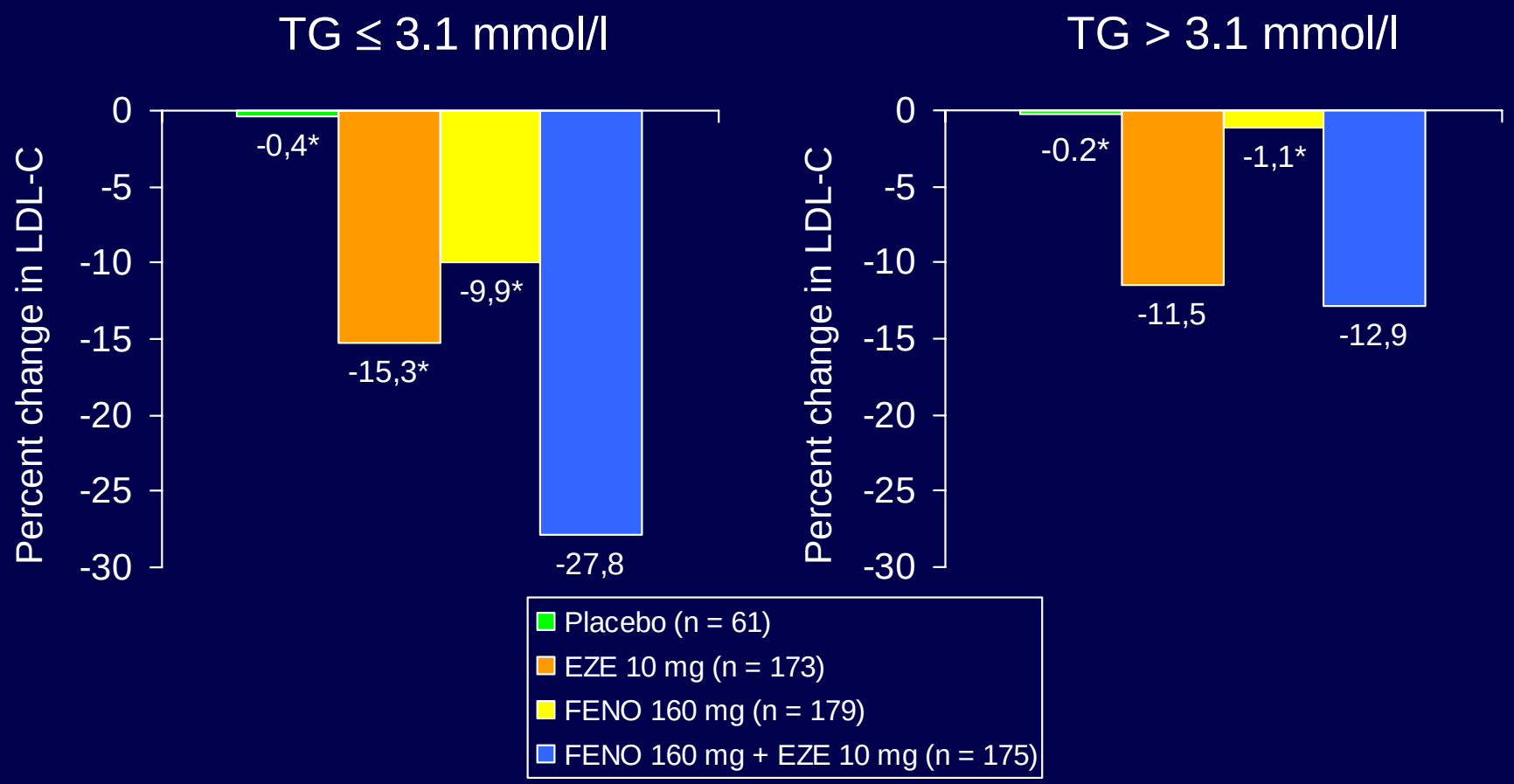


Data are least square mean percent change (standard error); * p < 0.001 compared to FENO+EZE

Farnier et al. Eur Heart J 2005; 26: 897-905

Co-administration of ezetimibe with fenofibrate in patients with mixed hyperlipidemia

LDL-C Response by TG Subgroup

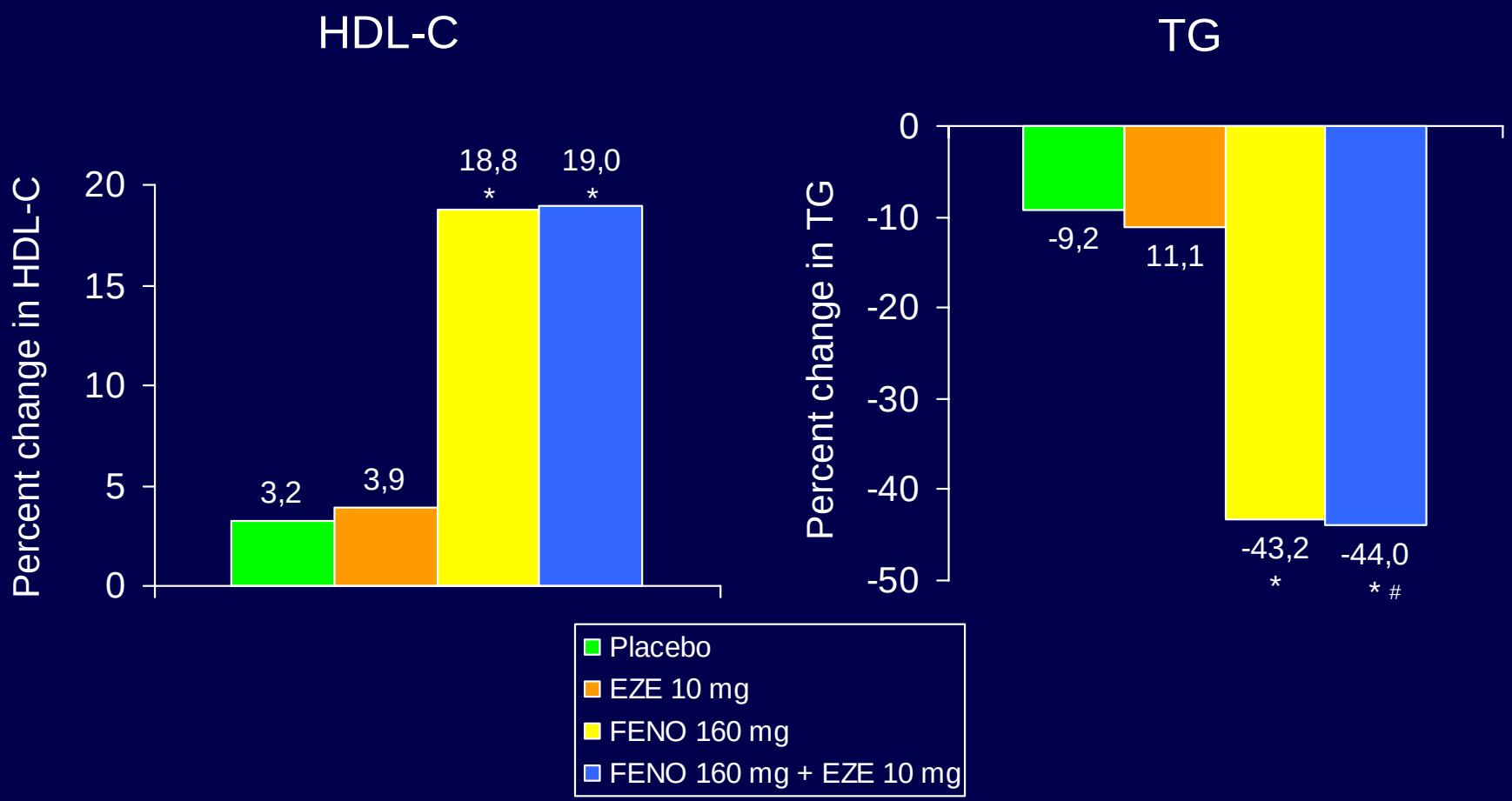


Data are least square mean percent change (standard error); * p < 0.001 compared to FENO+EZE within TG strata

Farnier et al. Eur Heart J 2005; 26: 897-905

Co-administration of ezetimibe with fenofibrate in patients with mixed hyperlipidemia

Percent changes in HDL-C and TG

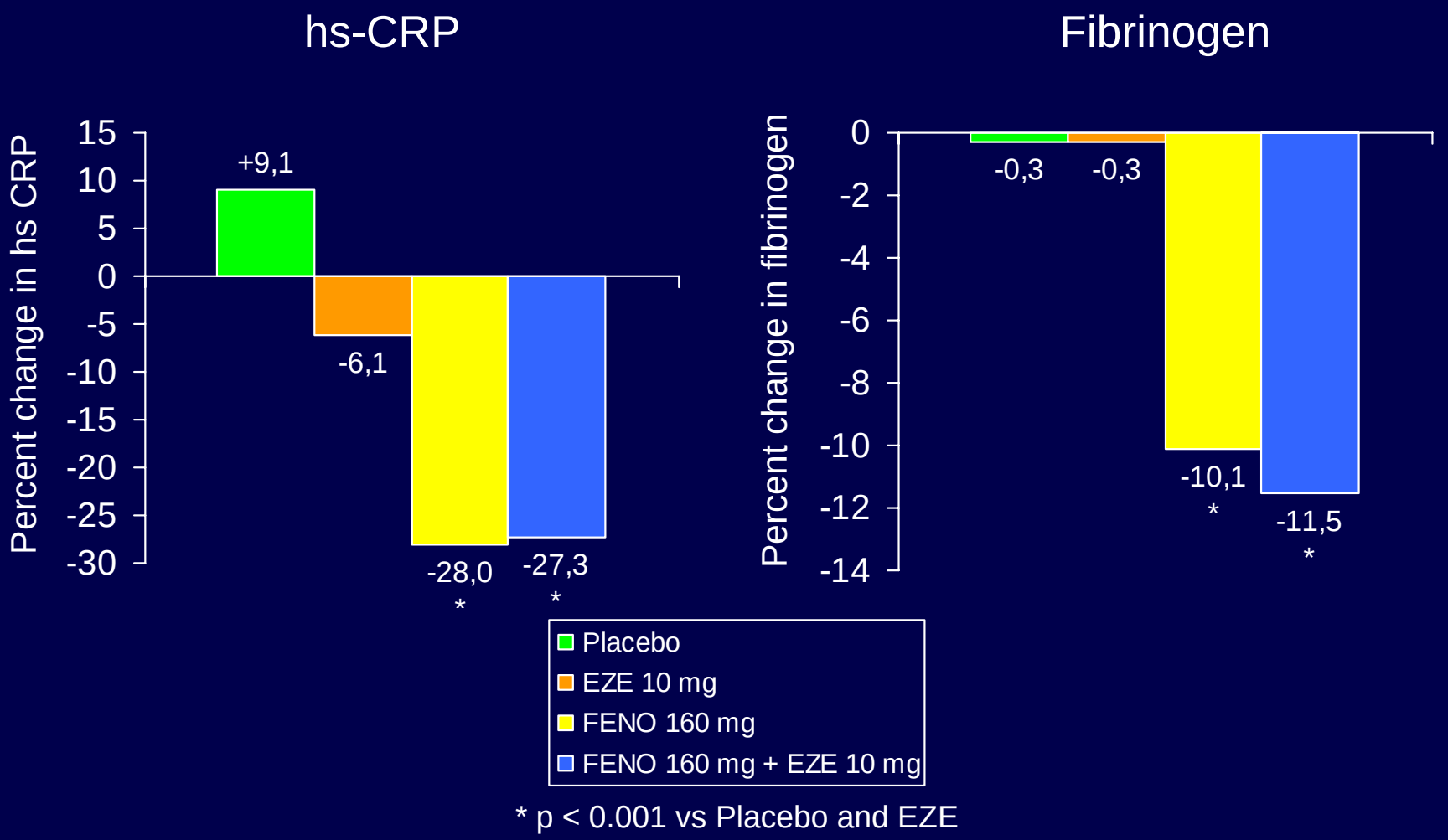


* $p < 0.001$ vs Placebo and EZE, # $p = 0.021$ vs FENO

Farnier et al. Eur Heart J 2005; 26: 897-905

Co-administration of ezetimibe with fenofibrate in patients with mixed hyperlipidemia

Percent change in median hs-CRP and fibrinogen



Farnier et al. Eur Heart J 2005; 26: 897-905

Conclusions (1)

- The use of combination therapy for the treatment of dyslipidemia is becoming increasingly important in the management of patients with CHD and multiple risk factors
- High risk patients often require combined drug therapy to achieve LDL-C and non-HDL-C goals, and also to normalize HDL-C and TG
- Ezetimibe together with a statin is a novel and beneficial approach, providing dual inhibition of two sources of cholesterol.

Conclusions (2)

- Combination therapy with fenofibrate may be of considerable value in combined/mixed hyperlipidemia, in diabetic patients and in patients with MS
- The future of the combined therapies with niacin mainly depends of the tolerability of new forms in development
- Clinical endpoint studies are required to validate the use of these combination therapies