Fenofibrate Ezetimibe Surrogate Trials

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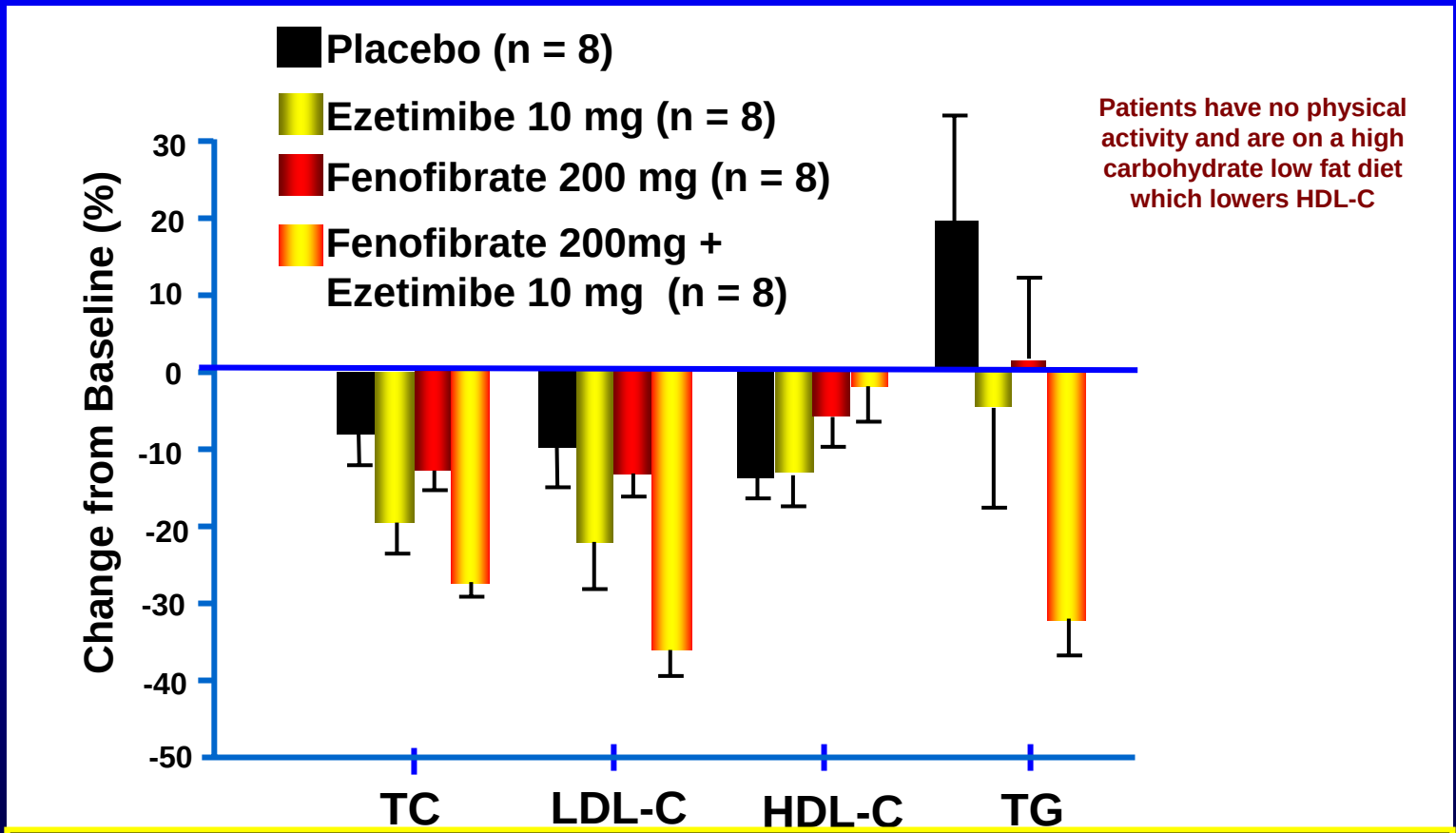
Pharmacokinetic
Data

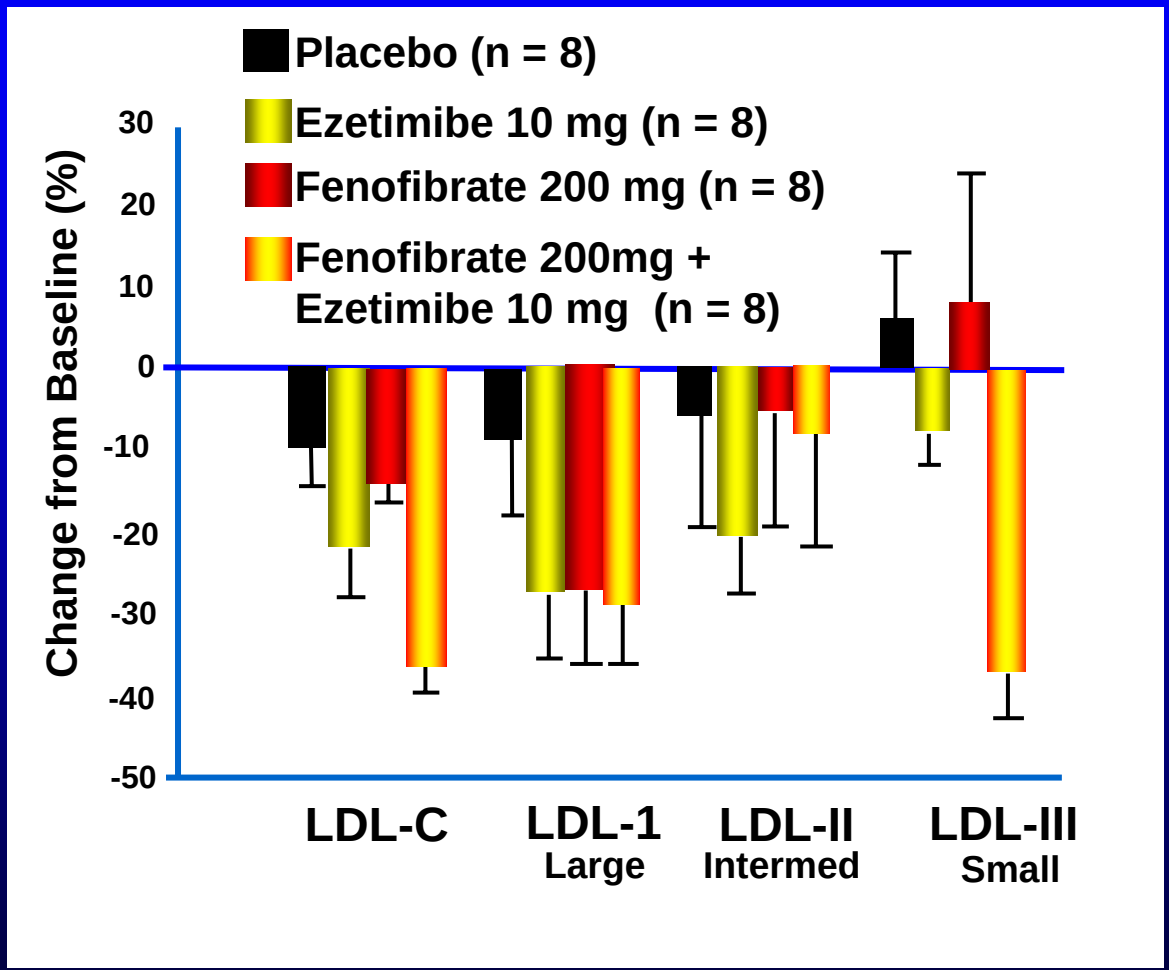
Fenofibrate – Ezetimibe Pharmacodynamic and Pharmacokinetic Interaction Study



Mean (SE) percentage change from baseline in serum lipids on day 14 following oral administration of fenofibrate monotherapy, ezetimibe monotherapy, fenofibrate-ezetimibe co-administration therapy or placebo once daily to 14 healthy subjects with hypercholesterolemia

Kosoglou T et al. Curr Med Res & Opin 2004;20:1185-1195

Fenofibrate – Ezetimibe Pharmacodynamic and Pharmacokinetic Interaction Study

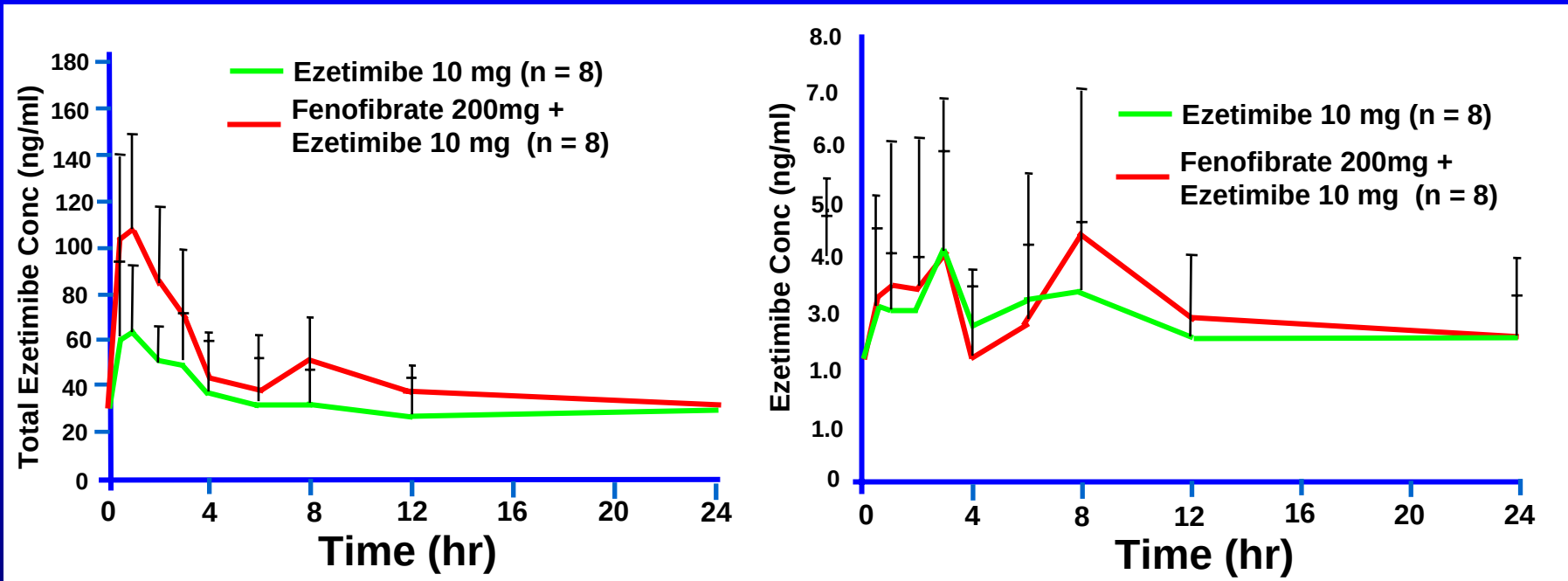


Combination therapy produced significantly greater reductions in LDL-C and in small LDL-III

Levels of apoCIII were also reduced greater than monotherapy with either drug

Kosoglou T et al. Curr Med Res & Opin 2004;20:1185-1195

Fenofibrate – Ezetimibe Pharmacodynamic and Pharmacokinetic Interaction Study



Mean (+SD) plasma concentration-time profiles of total ezetimibe (ezetimibe + ezetimibe glucuronide) and ezetimibe on day 14 following multiple dose, once-daily oral administration of either ezetimibe alone or co-administered with fenofibrate

Concomitant fenofibrate administered as a 200 mg micronized capsule formulation resulted in a significant (~50%) increase in the steady state total ezetimibe exposure. However, this exposure is probably not clinically important. The increased plasma total ezetimibe appear to be due to an increase in ezetimibe bioavailability rather than inhibition of clearance

Kosoglou T et al. Curr Med Res & Opin 2004;20:1185-1195

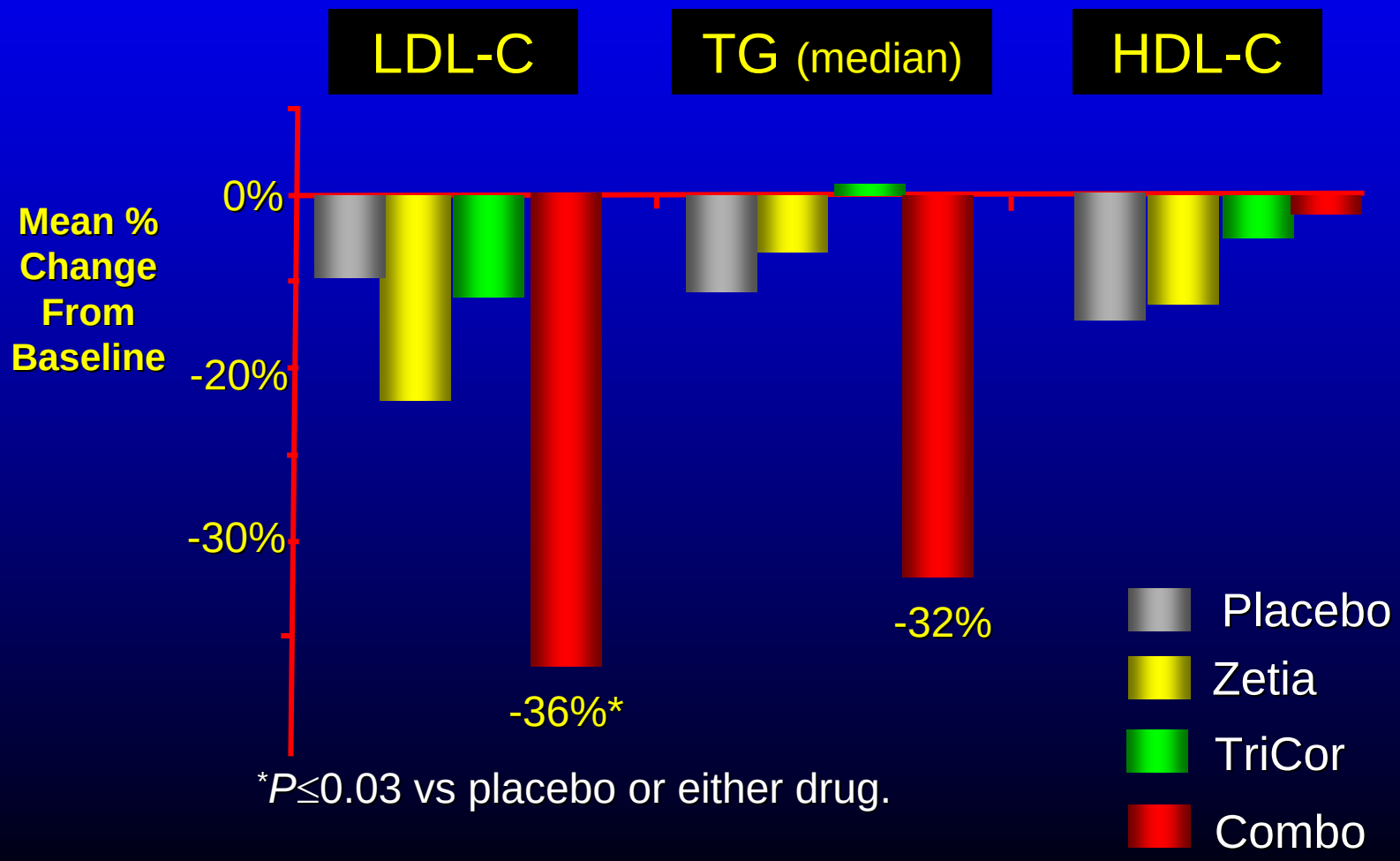
Ezetimibe - Fenofibrate Pharmacokinetic Study

- **Ezetimibe** had no clinically significant effect on the pharmacokinetics (e.g. absorbtion, metabolism and excretion) or pharmacodynamics (e.g. binding action of the drug to certain receptors and consequent effects on CNS, GI tract and other CV parameters) of **fenofibrate or vice versa**.

www.sch-plough.com/news/2001/research/20010521.html

Ezetimibe - Fenofibrate Pharmacokinetic Study

32 patients with hypercholesterolemia for 14 days: on strict diet

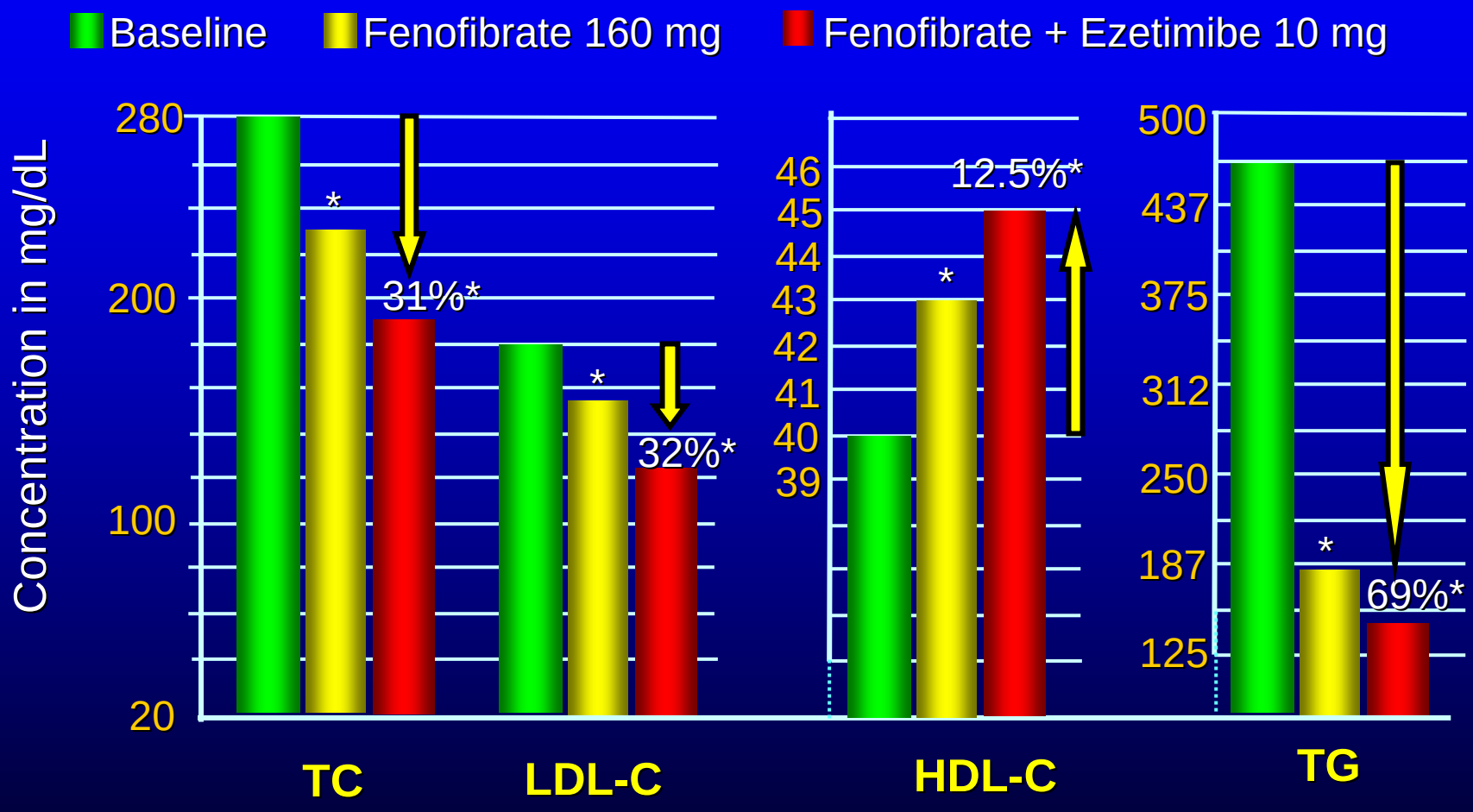


*$P \leq 0.03$ vs placebo or either drug.


Zaijka Study

Fenofibrate – Ezetimibe Combination Therapy

50 Mixed dyslipidemia patients who cannot tolerate a statin



* p<0.01 compared to baseline

Zaijka, P. Poster Presentation NLA Annual Meeting Orlando, Fl Aug 2004

Farnier Study
(Abstract & Publication)

Ezetimibe – Fenofibrate Study

After a six- to eight-week washout period, patients with mixed hyperlipidemia LDL cholesterol between 130 and 220 mg/dL (between 100 and 180 mg/dL for type 2 diabetics) and triglycerides between 200 and 500 mg/dL were randomized in a 1:3:3:3 ratio to one of four daily treatments:

Placebo (n=64).

Ezetimibe 10 mg (n=187).

Fenofibrate 160 mg (n=189).

Ezetimibe 10 mg and fenofibrate 160 mg (n=185).

After the completion of this double-blind, placebo-controlled study, the trial is to be extended for an additional 48 weeks

The primary end point of the study compared the LDL-cholesterol reduction efficacy of fenofibrate plus ezetimibe vs fenofibrate alone at 12 weeks.

Farnier M et al. Drugs Affecting Lipid Metabolism 2004 meeting, October 24-27, 2004; Venice, Italy.

Ezetimibe – Fenofibrate Study

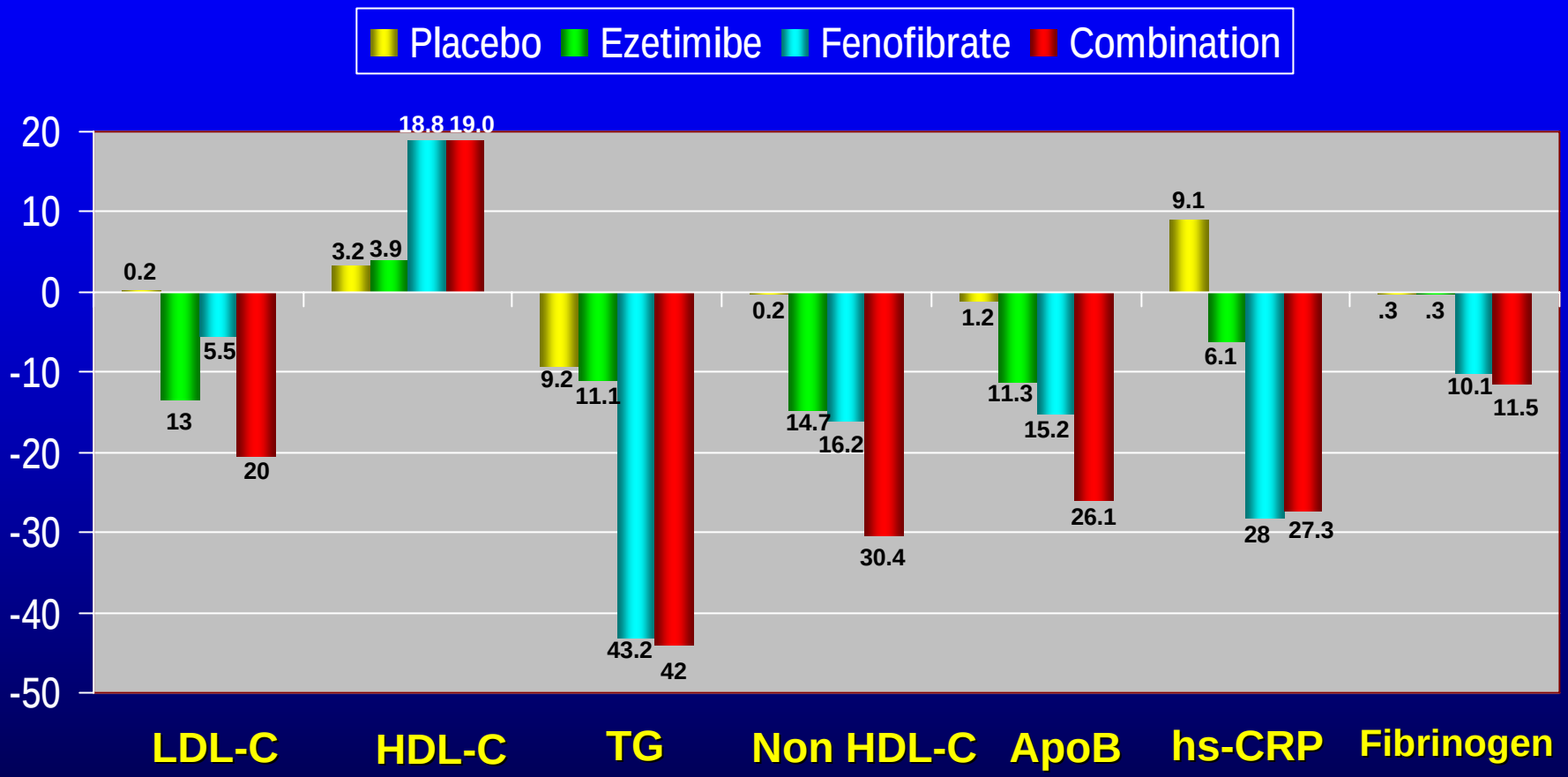
End point	Placebo (n=64)	Ezetimibe 10 mg (n=187)	Fenofibrate 160 mg (n=189)	Ezetimibe 10 mg + fenofibrate 160 mg (n=185)
LDL cholesterol (% change)*	0.2	-13.4	-5.5	-20.4
HDL cholesterol (% change)	3.2	3.9	18.8	19.0
Triglycerides (% change)	-9.2	-11.1	-43.2	-44.0
Non-HDL cholesterol (% change)	-0.2	-14.7	-16.2	-30.4
ApoB (% change)	-1.2	-11.3	-15.2	-26.1
High-sensitivity CRP (% change)	9.1	-6.1	-28.0	-27.3
Fibrinogen (% change)	-0.3	-0.3	-10.1	-11.5

Percent change in study end points

*Indicates primary end point

Farnier M et al. Drugs Affecting Lipid Metabolism 2004 meeting, October 24-27, 2004; Venice, Italy.

Ezetimibe – Fenofibrate Study



Farnier M et al. Drugs Affecting Lipid Metabolism 2004 meeting, October 24-27, 2004; Venice, Italy.

Ezetimibe – Fenofibrate Study

- Fenofibrate and Ezetimibe administered together produced significant, positive benefits on the atherogenic lipid profiles and the inflammation biomarker, hs-CRP, in patients with mixed hyperlipidemia.
- Depending on the study variable, the effects of coadministration of Fenofibrate and Ezetimibe were either additive (LDL-C, TC, non-HDL-C, and apo B) or Fenofibrate-dependent (TG, HDL-C, apo A-I, hs-CRP, fibrinogen, and LDL size pattern shift).
- Moreover, co-administered Fenofibrate and Ezetimibe demonstrated a good safety profile that was comparable to Fenofibrate alone.

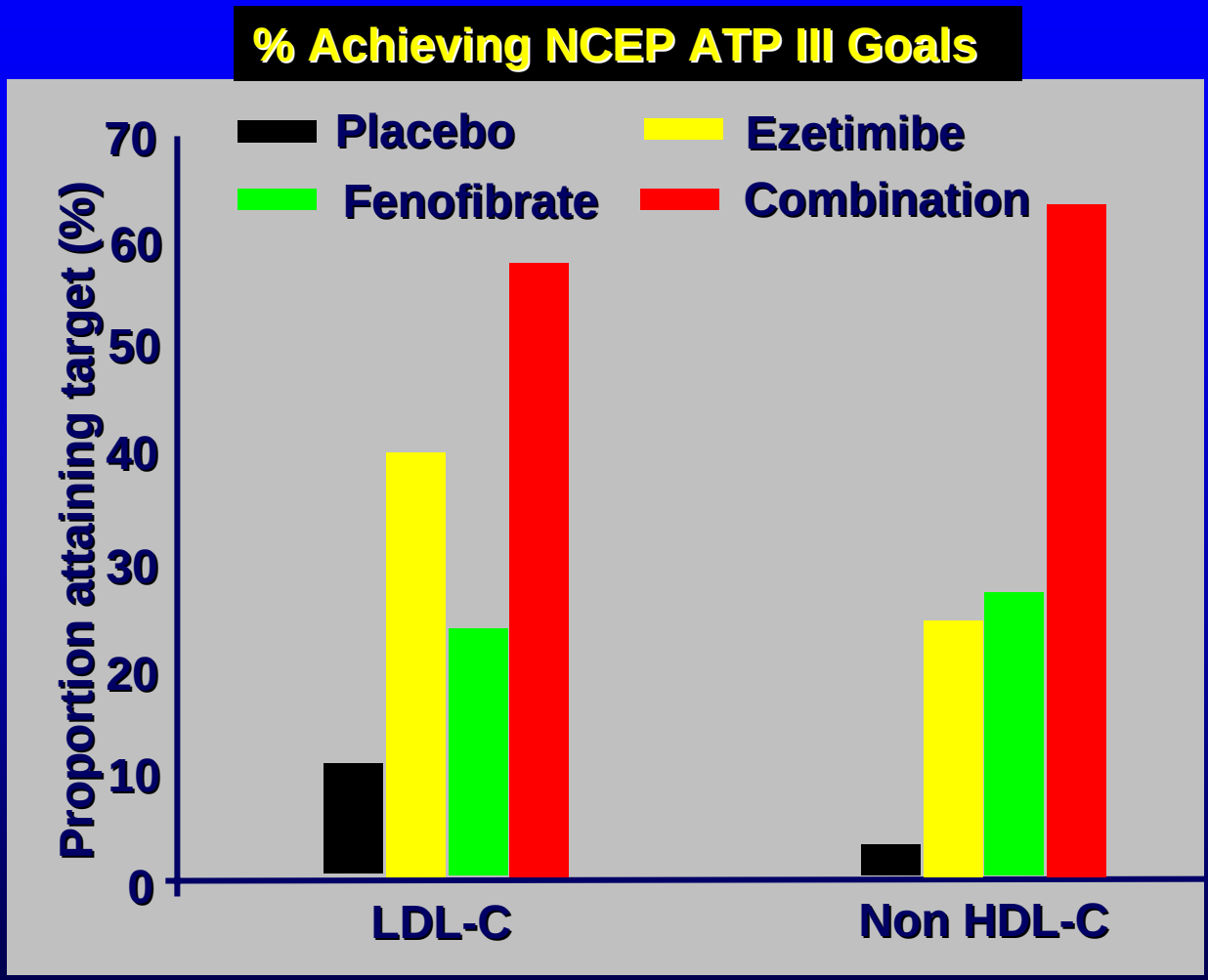
Farnier M, et al. *Eur Heart J.* 2005;26:897-905.

Ezetimibe – Fenofibrate Study

- Per cent reduction in LDL-C was greater with EZE treatment compared with FENO alone, but LDL-C reduction was additive when both FENO and EZE were used together.
- However, the change in LDL-C was influenced by baseline TG levels in patients with mixed hyperlipidemia in the present study.
- Greater LDL-C lowering was noted with all active treatments in patients with baseline < TG 250 mg/dL.
  - In contrast, in the high TG subgroup, FENO treatment produced virtually no change in LDL-C, whereas the effect of EZE was maintained.

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

Ezetimibe – Fenofibrate Study



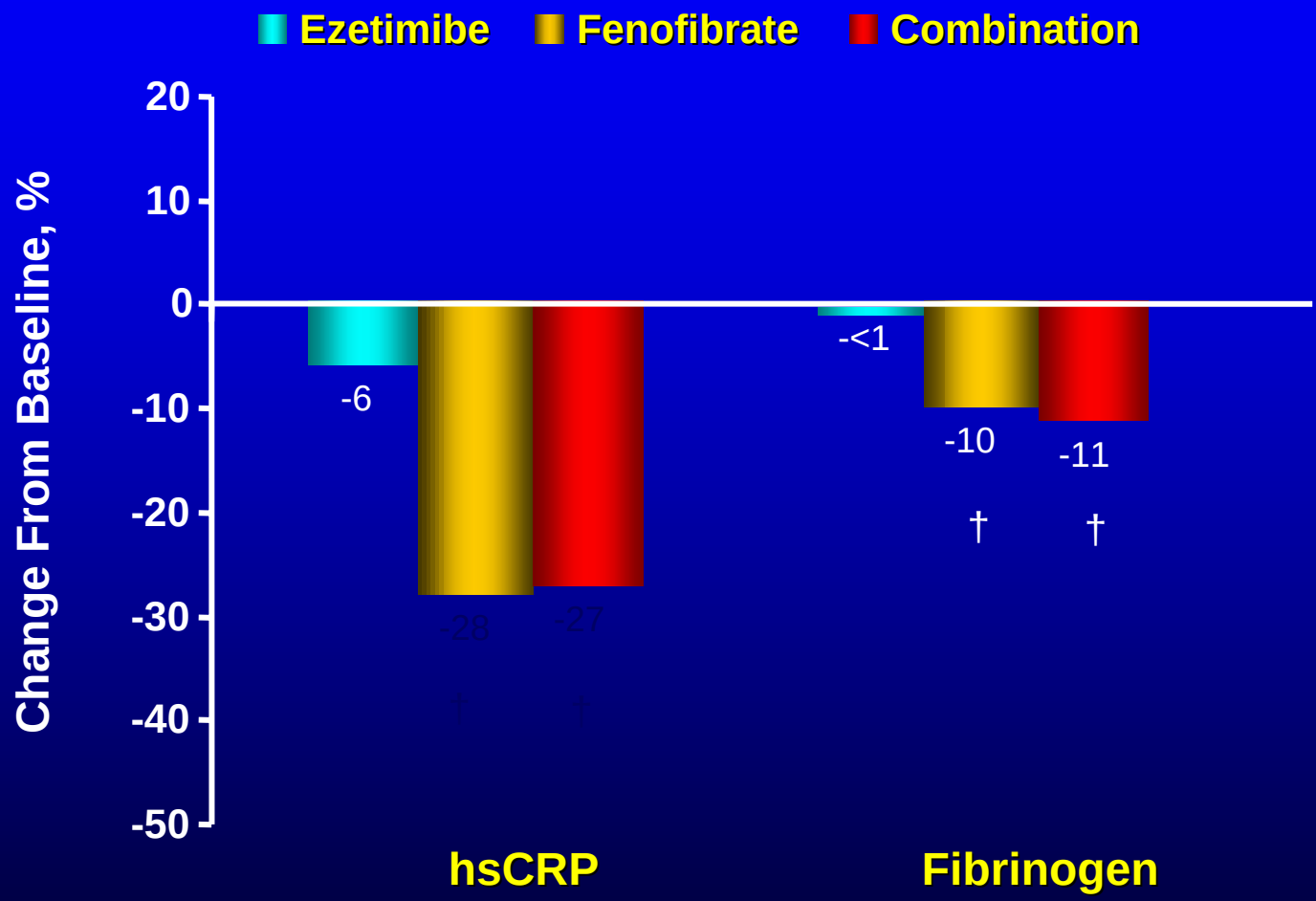
More than 62% of patients shifted to the larger, more buoyant LDL pattern from the smaller, more dense pattern with coadministration, and FENO alone treatments.

The Non HDL-C goal attainment was comparable across baseline TG values

Baseline: LDL-C ~ 140 HDL-C ~ 40 TG ~ 240

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

Fenofibrate and Ezetimibe Combination Effects



†*P*<.05 versus ezetimibe

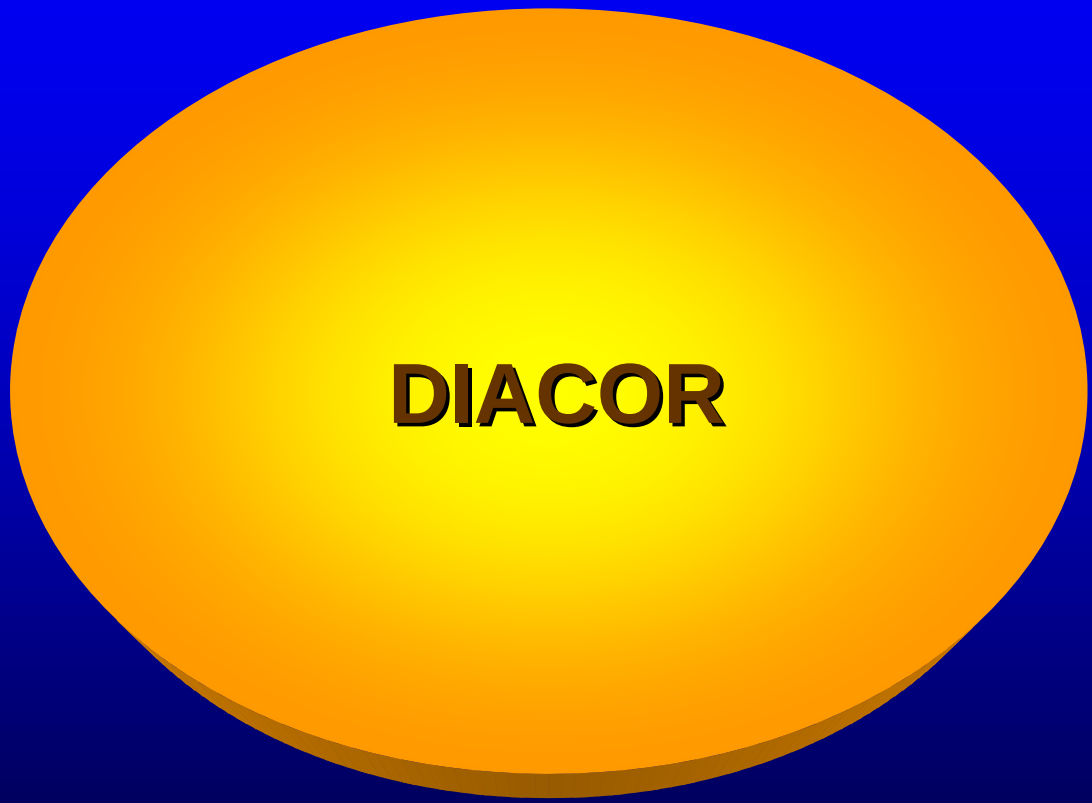
Farnier M, et al. *Eur Heart J.* 2005;26:897-905

Ezetimibe – Fenofibrate Study

The coadministration of Ezetimibe with Fenofibrate offers a well-tolerated new lipid management strategy for patients with mixed hyperlipidemia in this study.

The combined use of these agents provides a therapy with complementary effects to improve the atherogenic lipid profile observed for these patients.

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


DIACOR

The DIACOR Study Triple Therapy with a Statin, Fibrate and Ezetimibe

- Methods: 37 T2DM patients (35% female), mixed dyslipidemia with no CVD. (~age 59)
- After 12 weeks of fenofibrate 160 mg, simvastatin 20m mg or their combination, patients with an LDL-C > 100 mg/dL or TG > 150 mg/dL were randomized to simva/feno plus placebo or ezetimibe 10 mg.
- Followed for 6 weeks

Pearson RR et al. *JACC 2006;47(Suppl) 316A Abstract 808-6*

The DIACOR Study Triple Therapy with a Statin, Fibrate and Ezetimibe

- For combo + Ezetimibe
  - 23.5% vs 0% (placebo) met all 3 NCEP goals
- The likelihood of meeting all three goals was significantly increased in the combo + ezetimibe group (p=0.006)
  - There was an incremental reduction in TC (16%), LDL-C (25.2%) and VLDL-C (14%)
- No serious adversity seen

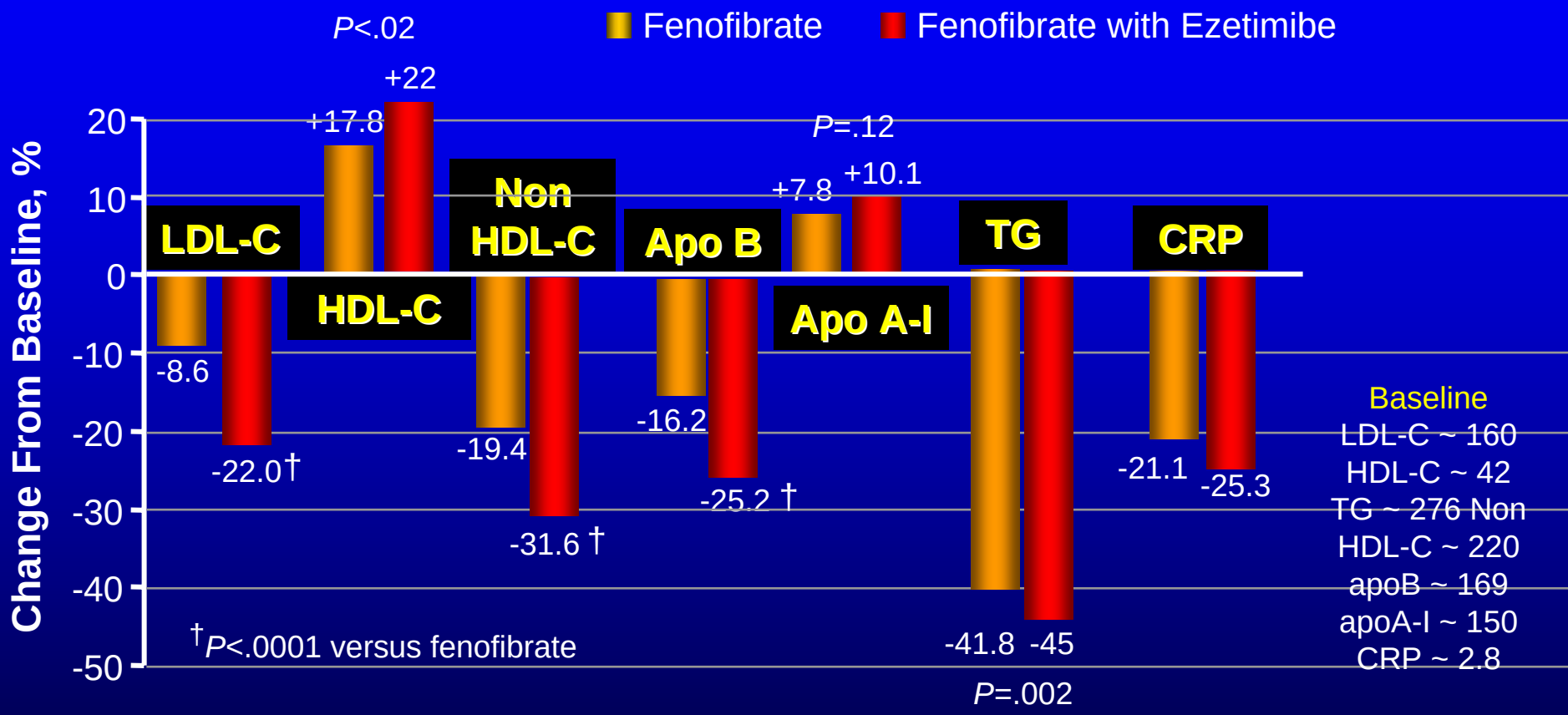
Pearson RR et al. *JACC 2006;47(Suppl) 316A Abstract 808-6*

McKenny Study

Safety and Efficacy of Long-Term Co-Administration of Fenofibrate and Ezetimibe in Patients With Mixed Hyperlipidemia

James McKenney, PharmD; Michel Farnier, MD, PhD; Kwok-Wing Lo, MD; Harold Bays, MD; Inna Perevozkaya, PhD; Gary Carlson, BS; Michael Davies, PhD; Yale Mitchel, MD; Barry Gumbiner, MD

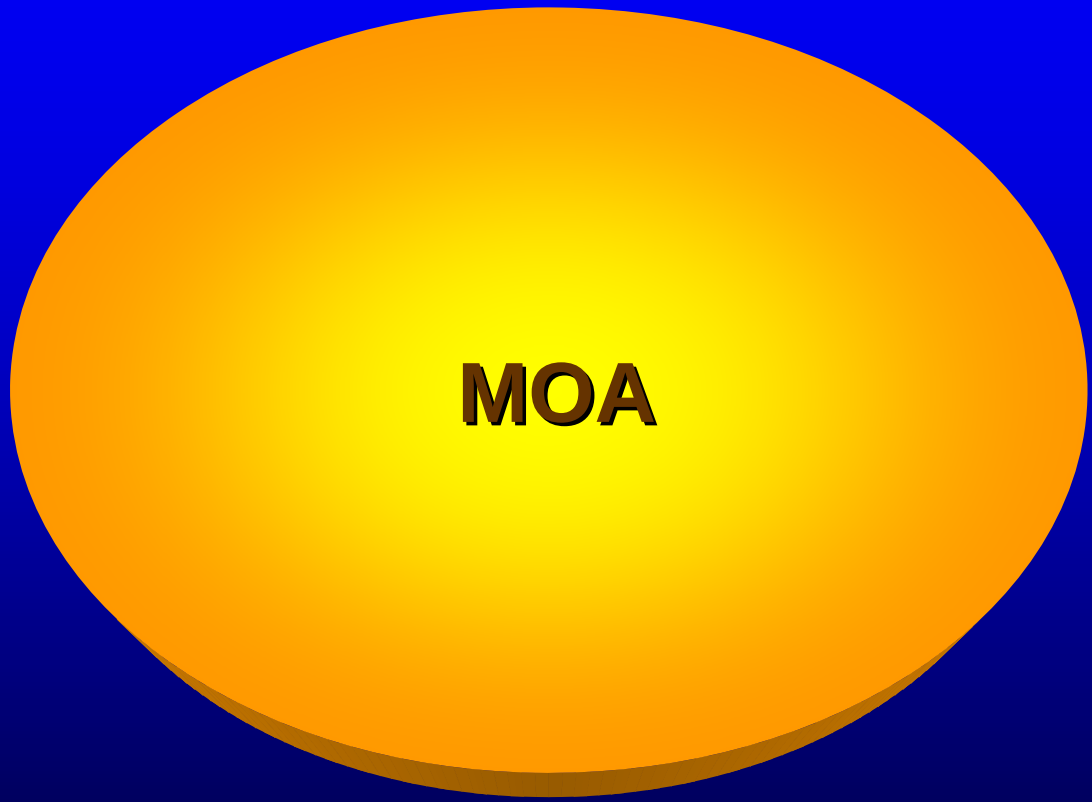
Fenofibrate and Ezetimibe Combination Long Term Effects on Lipid Profile



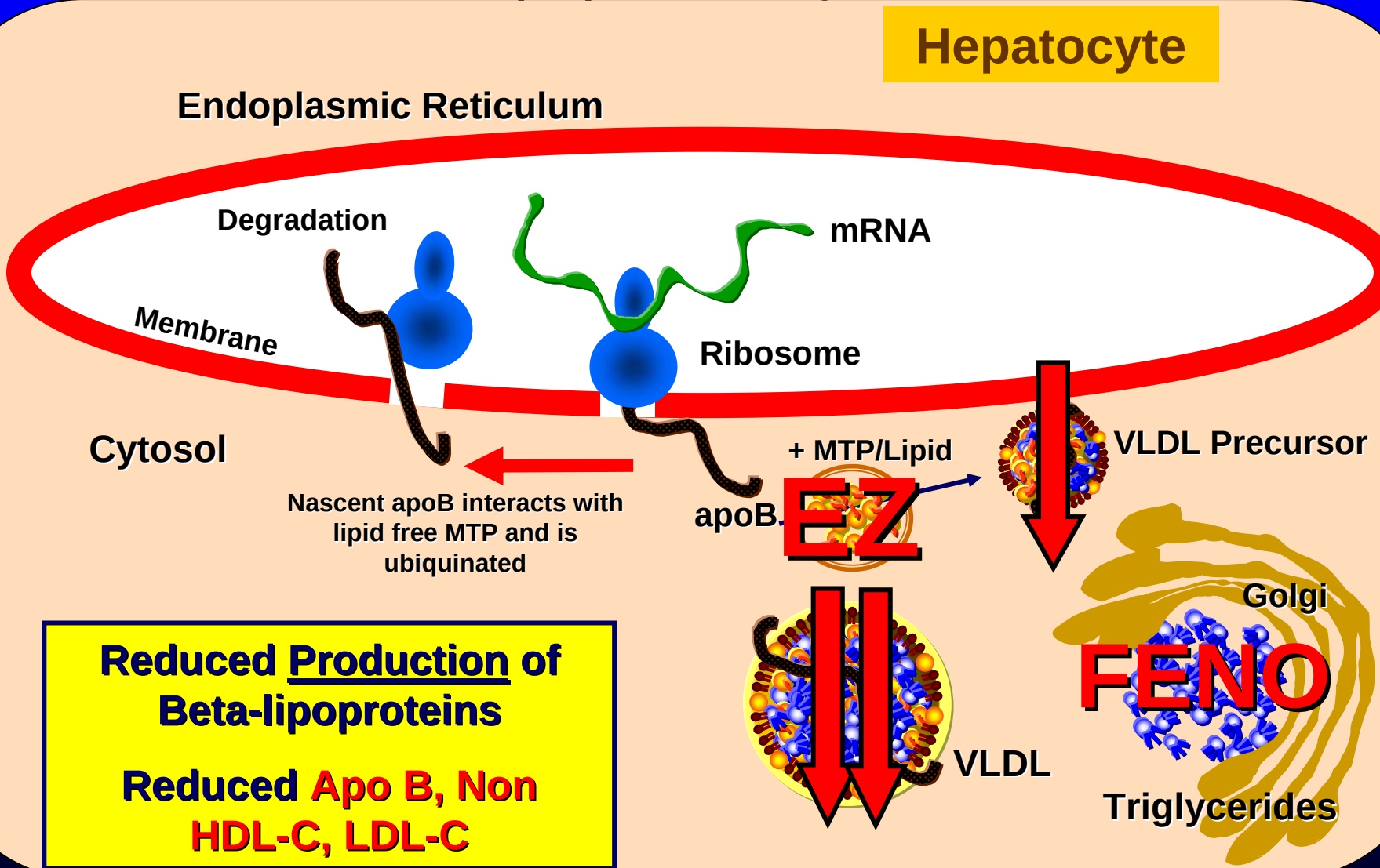
60 weeks in patients with mixed dyslipidemia

Percent change from baseline values to endpoint values:
Values expressed as least squares mean % change

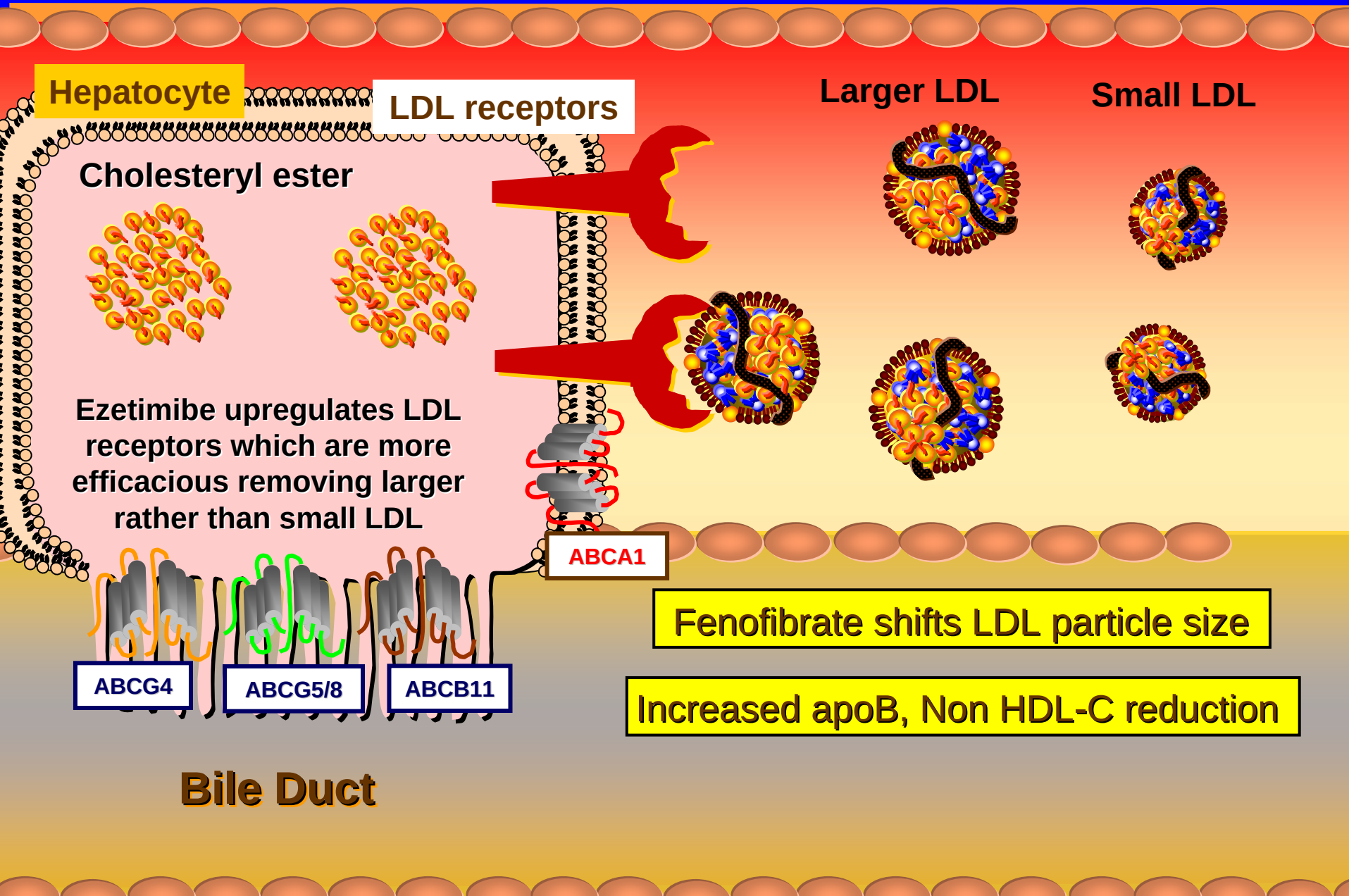
McKenny J et al. JACC 2006; 47:1584-87


MOA

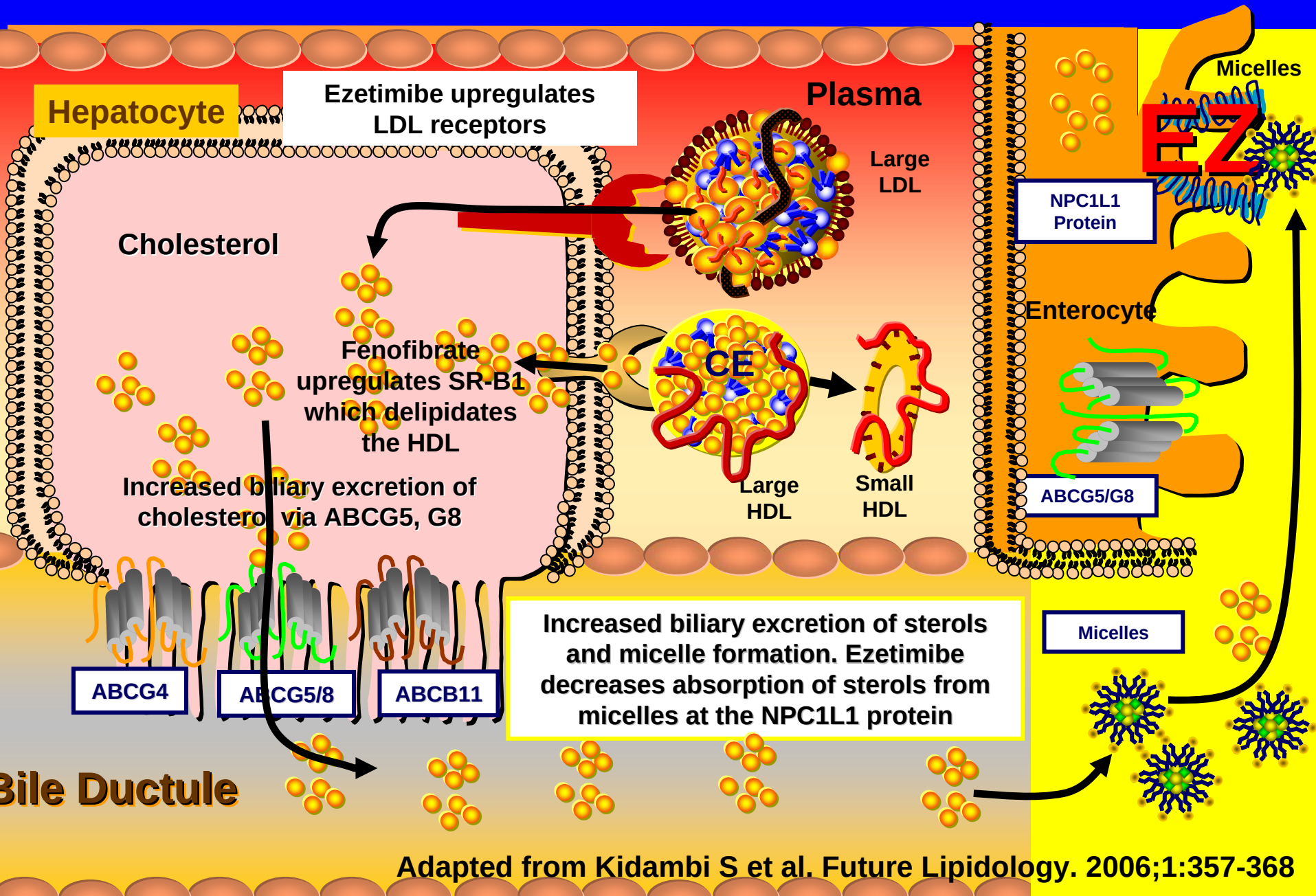
Ezetimibe & Fenofibrate Decrease Beta-lipoprotein Synthesis



Indirect RCT at the Hepatocyte



Ezetimibe and Fenofibrate Increase Stool Cholesterol Excretion



Adapted from Kidambi S et al. Future Lipidology. 2006;1:357-368