Fibrate Safety & Metabolism

Thomas Dayspring, MD, FACP

Clinical Assistant Professor of Medicine

University of Medicine and Dentistry of New Jersey
New Jersey Medical School

Attending in Medicine: St Joseph's Regional Medical Center, Paterson and Wayne, NJ

Certified Menopause Practitioner: North American Menopause Society

North Jersey Institute of Menopausal Lipidology
Wayne, New Jersey

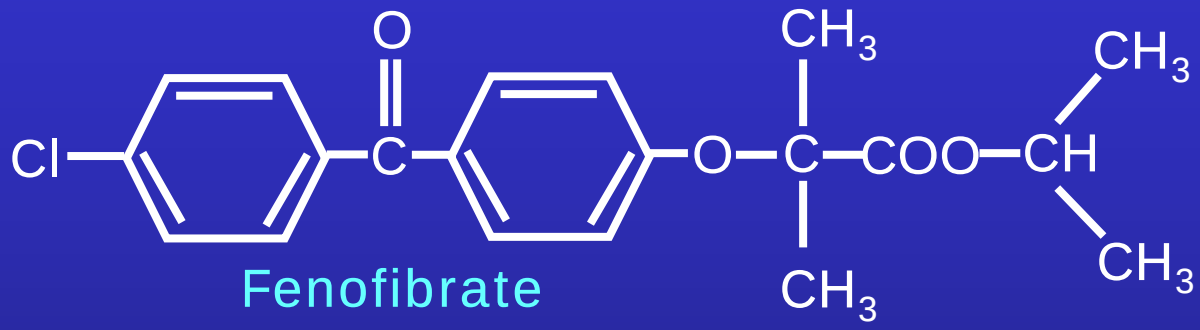
FDA Indications for TriCor

TriCor is indicated as adjunctive therapy to diet to **reduce** **elevated LDL-C**, **Total cholesterol**, **Triglycerides** and **Apo B**, and to **increase** **HDL-C** in adult patients with primary hypercholesterolemia or mixed dyslipidemia

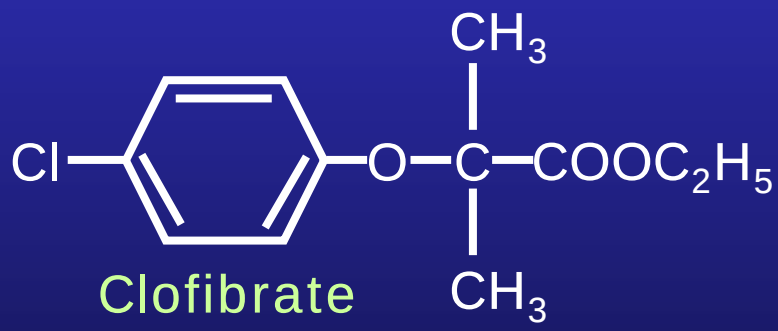
TriCor (fenofibrate) Tablets

- **Contraindicated** in those with a hypersensitivity to fenofibrate, hepatic or severe renal dysfunction and pre-existing GB disease.
- Is associated with rises in aminases: periodic LFT monitoring is required
- May lead to cholelithiasis: if confirmed TriCor should be discontinued
- May increase effects of coumadin

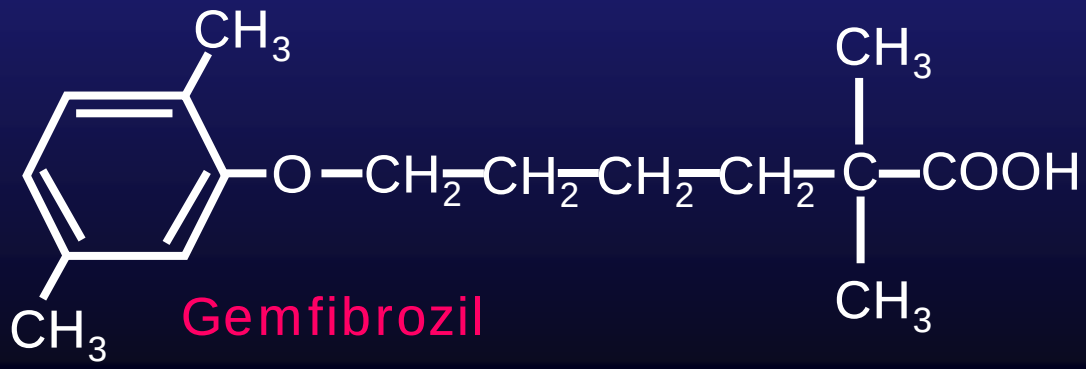
Fibrate Chemical Structures



Fenofibrate



Clofibrate



Gemfibrozil

FDA Indications for TriCor

Phenotype	Occurrence	Lipoprotein Present in Excess	Chol	Trig
I	Rare	Chylomicrons	250-400	>2500
IIA	Common	LDL	>250	<150
IIB	Most common	LDL,VLDL	>250	150-400
III	Rare	VLDL remnants	375-500	600-800
IV	Common	VLDL	225-275	375-500
V	Rare	Chylomicrons, VLDL	350-400	1700-2500

TriCor is indicated in IIA, IIB, IV, V

Drug-Drug Interactions Statins/Fibrates

- Combined use of fibrates and statins has been associated with rhabdomyolysis, markedly elevated creatine kinase levels, and myoglobinuria

- The combined use of fenofibrate and statins should be avoided unless the benefit of further alterations in lipid levels is likely to outweigh the increased risk of this drug combination

Fenofibrate prescribing information, Abbott Laboratories, 1998.

Fenofibrate Pharmacokinetics

- **Well absorbed from GI tract**
- **Peak plasma levels within 6-8 hours**
- **Excreted mainly in the urine**
- **Half-life of 20 hours**
- ***In vivo* data indicate that neither fenofibrate nor fenofibric acid undergoes oxidative metabolism (eg, cytochrome P450) to a significant extent**

Fenofibrate prescribing information, Abbott Laboratories, 1998.

Drug-Drug Interactions

- Potentiation of coumarin-type anticoagulants has been observed, with **prolongation of the INR**
  - Caution should be exercised when coumarin anticoagulants are given in conjunction with TriCor
- Fenofibrate should be taken at least 1 hour before, or 4-6 hours after, taking a bile acid- binding resin, to avoid impeding its absorption

Fenofibrate prescribing information, Abbott Laboratories, 1998.

Fenofibrate Pharmacokinetics

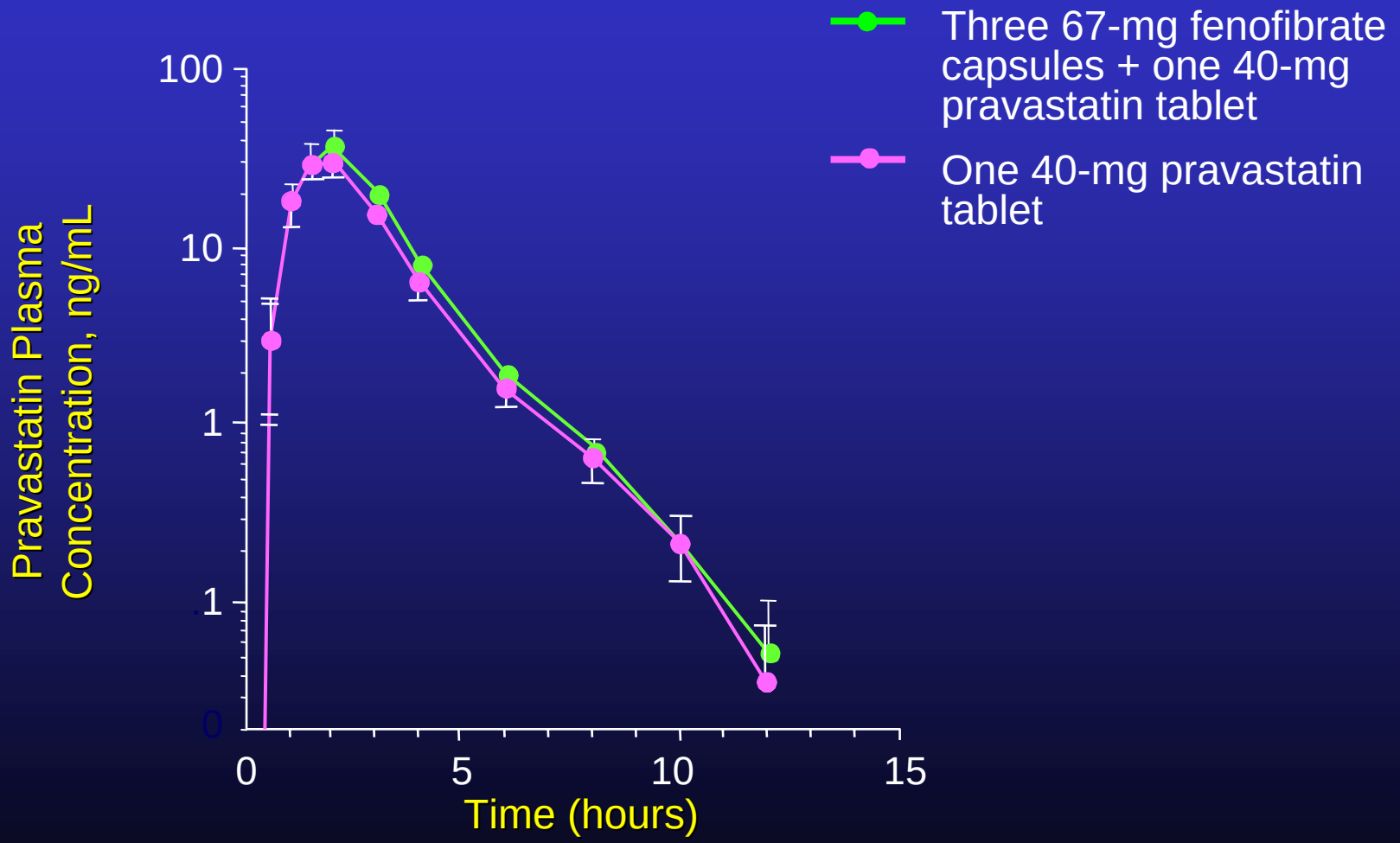
- *In vivo* data indicate that neither fenofibrate nor fenofibric acid undergoes oxidative metabolism (eg, cytochrome P450) to a significant extent.

Fenofibrate prescribing information, Abbott Laboratories, 2003.

FDA Package Insert for Fenofibrate

In a **single-dose drug interaction study** in 23 healthy adults the **concomitant administration of TriCor and pravastatin** resulted in no clinically important difference in the pharmacokinetics of fenofibric acid, pravastatin or its active metabolites, 3a-hydroxy iso-pravastatin when compared to either drug given alone

Fenofibrate Does not Increase Pravastatin Plasma Concentrations

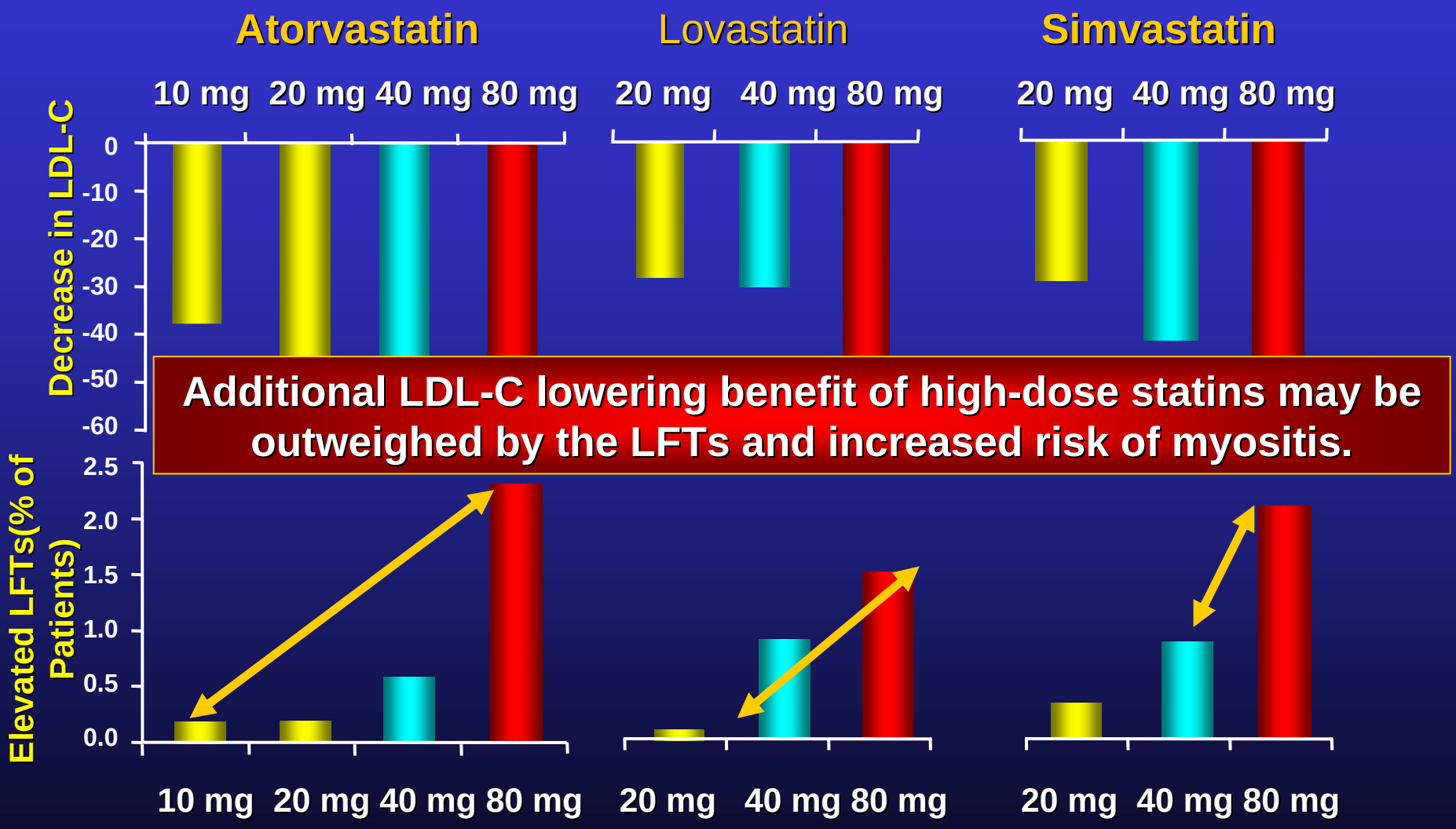


Pan W-J, et al. J Clin Pharmacol . 2000;40:316-323.

Simvastatin Product Information Sheet

- The use of simvastatin should **not exceed 10 mg** daily in patients receiving concomitant gemfibrozil. The combined use of simvastatin and gemfibrozil should be avoided unless benefits are likely to outweigh the risks
- Caution should be used when prescribing simvastatin with other lipid lowering drugs (fibrates or > 1gm niacin)
- The benefits of further alterations in lipids with combined use of fibrates and niacin should be weighed carefully against the potential risk of these combinations

Effects of High-Dose Statins



Davidson MH. *Am J Cardiol.* 2002;90(suppl):50K-60K.

Glucuronidation: Explanation of Fibrate/Statin Interaction

- "Glucuronidation is a pathway for the elimination of the active hydroxy acid metabolites of simvastatin, atorvastatin, and cerivastatin"
- "The most recent evidence suggests that gemfibrozil inhibits simvastatin, atorvastatin, and, more prominently, cerivastatin glucuronidation."
- "**Fenofibrates**, however, appear to have a significantly less inhibitory effect on statin glucuronidation, and this may explain the lack of significant drug interaction between fenofibrate and statins."

Davidson MH. *Am J Cardiol.* 2002;90(suppl):50K-60K.

Glucuronidation: ? Explanation of Fibrate/Statin Interaction

- "Glucuronidation is a pathway for the elimination of the active hydroxy acid metabolites of simvastatin, atorvastatin, and cerivastatin"
- "Initially, the PK interaction between statins and gemfibrozil was thought to be the result of an interaction with cytochrome P450 pathways."
- "The most recent evidence suggests that gemfibrozil inhibits simvastatin, atorvastatin, and, more prominently, cerivastatin glucuronidation."
- "**Fenofibrates**, however, appear to have a significantly less inhibitory effect on statin glucuronidation, and this may explain the lack of significant drug interaction between fenofibrate and statins."

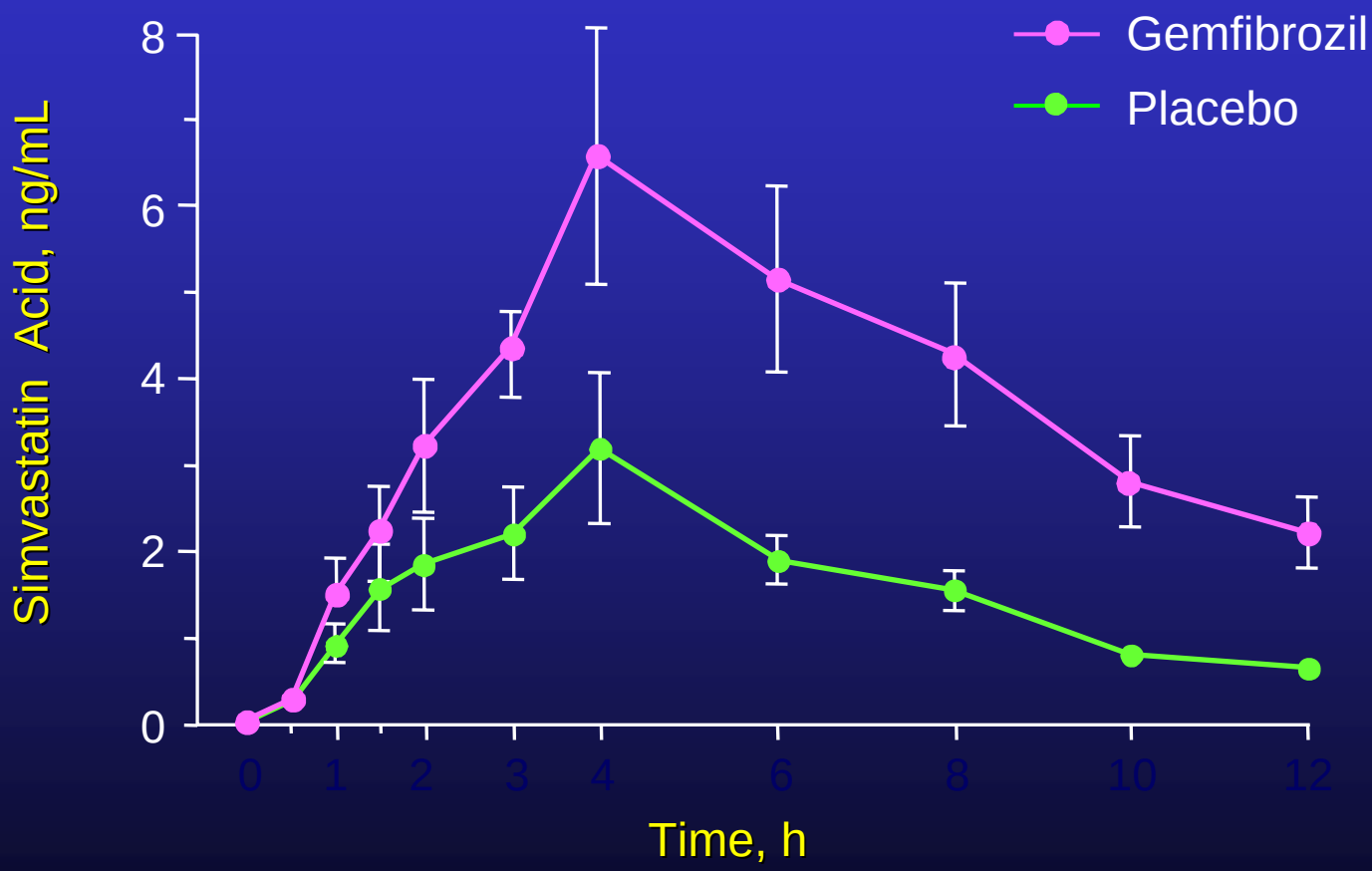
Davidson MH. *Am J Cardiol.* 2002;90(suppl):50K-60K.

Gemfibrozil Interacts with Statin Glucuronidation

- "Further studies conducted in human liver microsomes with atorvastatin showed that, as with simvastatin, gemfibrozil was a less potent inhibitor of the CYP3A4-mediated oxidation of this drug than its glucuronidation."
- "However, with cerivastatin, the glucuronidation as well as the CYP2C8- and CYP3A4-mediated oxidation pathways were much more susceptible to inhibition by gemfibrozil than was observed with simvastatin or atorvastatin."
- "Collectively, the results of these studies provide metabolic insight into the nature of drug-drug interaction between gemfibrozil and statins, and a possible explanation for the enhanced susceptibility of cerivastatin to interactions with gemfibrozil."

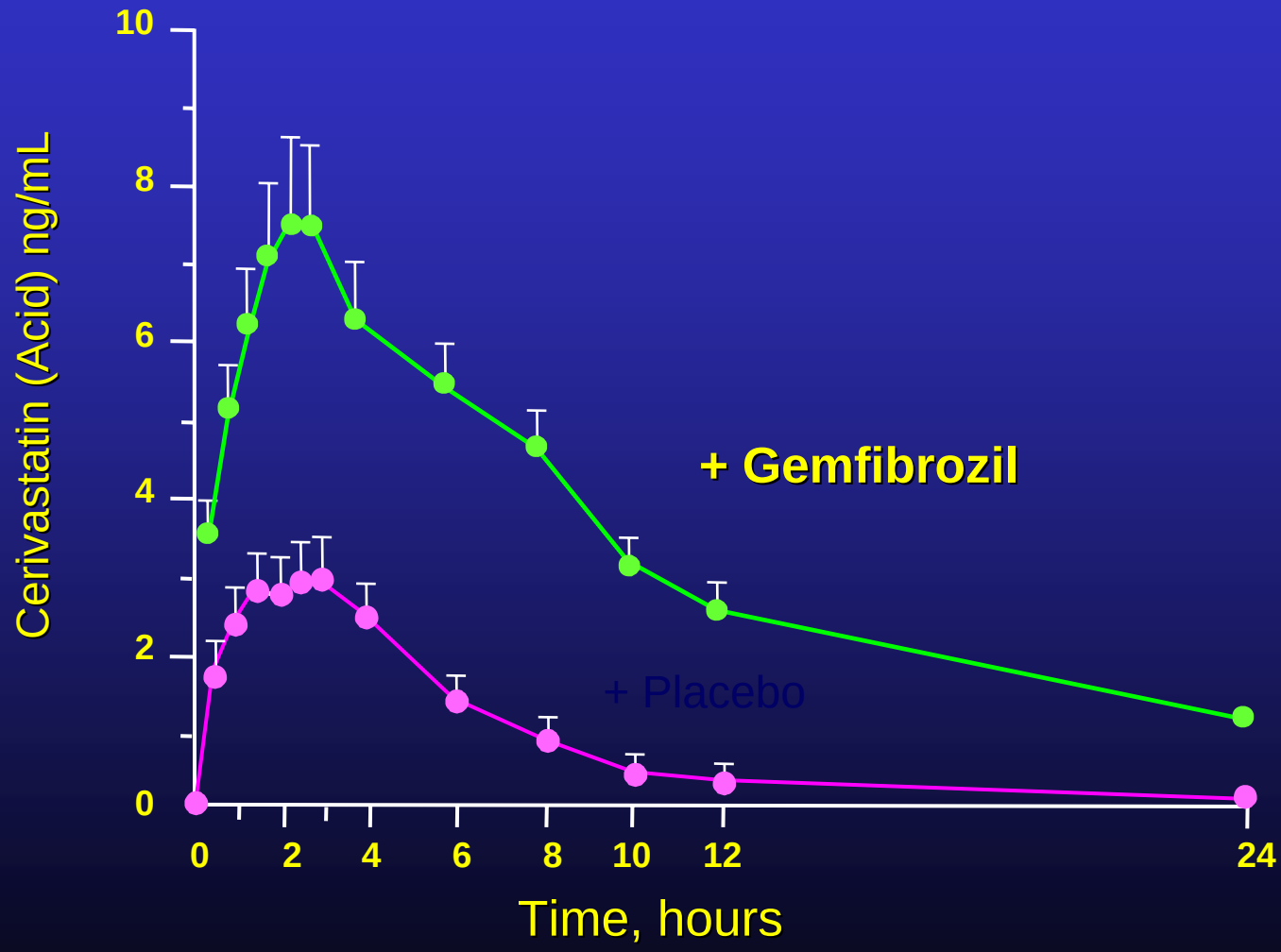
Prueksaritanont T, et al. *JPET.* 301:1042-1051, 2002.

Gemfibrozil Increases Simvastatin Plasma Concentrations



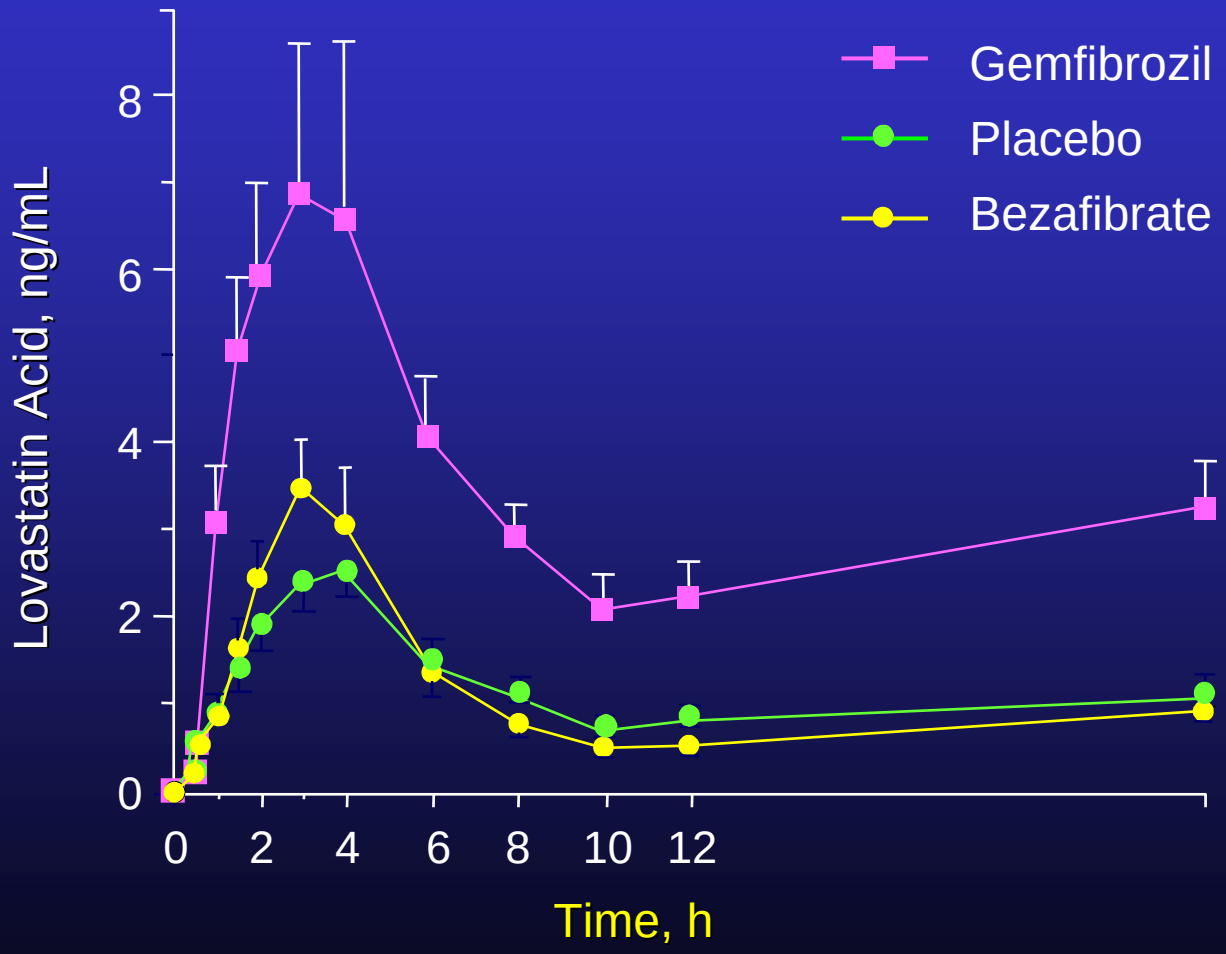
Backman JT, et al. *Clin Pharmacol Ther*. 2000;68:122-129.

Gemfibrozil Increases Cerivastatin Plasma Concentrations



Backman JT, et al. *Clin Pharmacol Ther*. 2002;72:685-691.

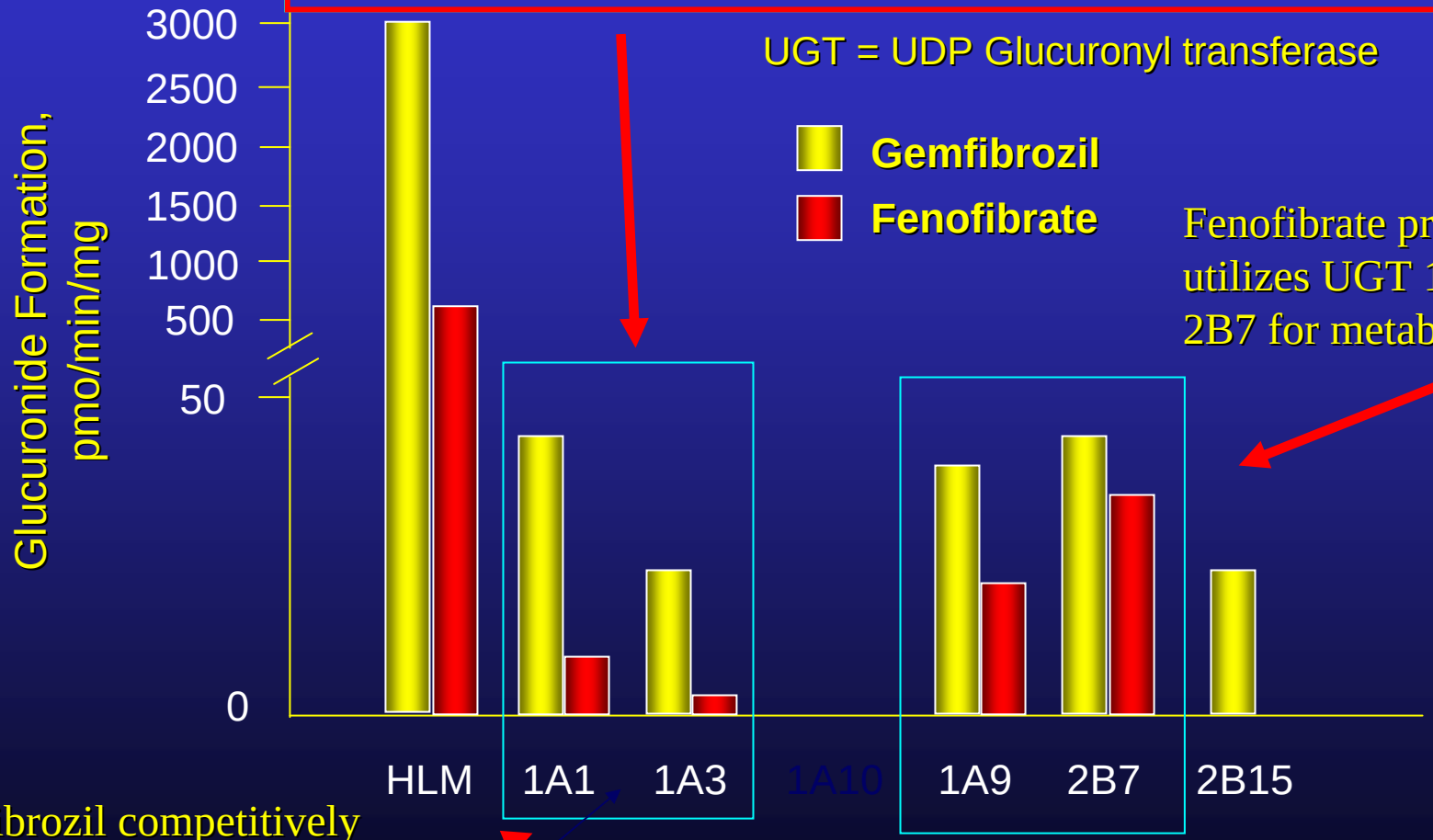
Gemfibrozil, but not Bezafibrate, Increases Lovastatin Plasma Concentrations



Kyrklund C, et al. *Clin Pharmacol Ther*. 2001;69:340-345.

Glucuronidation of Fibrates Gemfibrozil and Fenofibrate

Statins utilize UGT 1A1 and 1A3 for metabolism



Fenofibrate primarily utilizes UGT 1A9 and 2B7 for metabolism

Gemfibrozil competitively competes with statins for UGT 1A1 and 1A3

Prueksaritanont T, et al. *Drug Metab Dispos.* 2002;30:1280-128

Effect on Glucuronidation of Statin Hydroxy Acids - Gemfibrozil Versus Fenofibrate

	Inhibitor	
Substrate	Gemfibrozil IC_{50}* (μM)	Fenofibrate IC_{50}* (μM)
Simvastatin Hydroxy Acid	354	682
Atorvastatin	316	Not Done
Cerivastatin	82	433
	Gemfibrozil C_{max}† (μM)	Fenofibrate C_{max} † (μM)
	100-300	15-55§

*Obtained following coincubation of fibrates and simvastatin hydroxy acid in human liver microsomes.
†Reported values following 600 mg BID gemfibrozil or 200 mg QD fenofibrate in humans.
§Measured as fenofibric acid.

Prueksaritanont T, et al. Poster presented at 2002 AHA.

Effect on Glucuronidation of Statin Hydroxy Acids - Gemfibrozil Versus Fenofibrate

- Although glucuronidation of all statins is inhibited by gemfibrozil: simvastatin, atorvastatin, and rosuvastatin appear to be less susceptible than cerivastatin
- Initial studies indicate the **fenofibrate** is much less inhibitory than gemfibrozil on statin glucuronidation
- For rosuvastatin, the significant effect of gemfibrozil on both glucuronidation and oxidation is similar to cerivastatin, suggestion the potential for a pharmacokinetic interaction between this new statin and gemfibrozil

Prueksaritanont T, et al. Poster presented at 2002 AHA.

Lipophilicity - Hydrophilicity

Most Lipophilic

Simvastatin

Lovastatin

Fluvastatin

Atorvastatin

Rosuvastatin

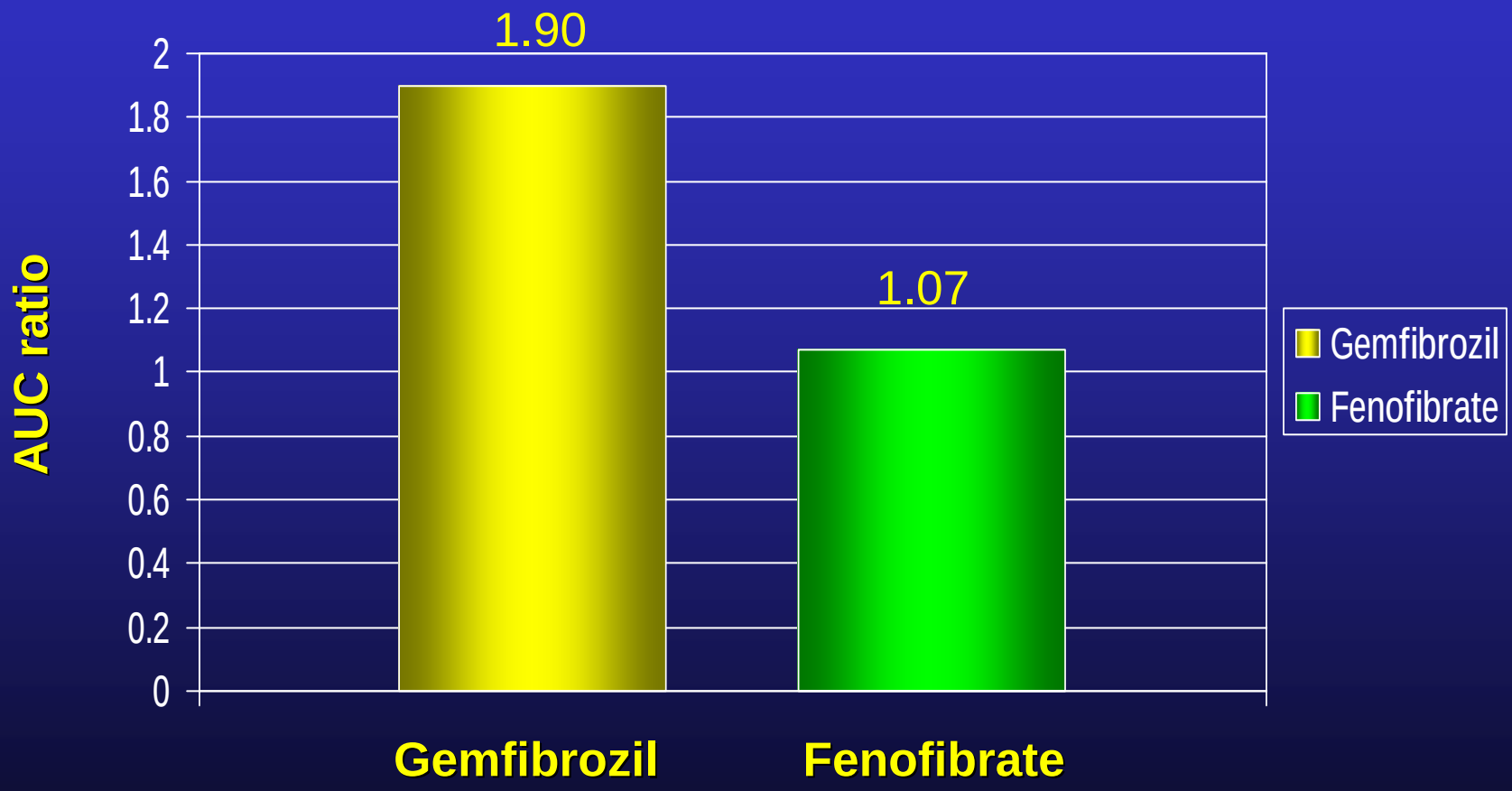
Pravastatin

Most Hydrophilic

Hydrophilic (low lipophilicity) statins may have greater accumulation in the liver via selective membrane carriers and decreased accumulation in peripheral tissues through passive diffusion and thus inhibit greater selective inhibition of liver HMG-CoA reductase.

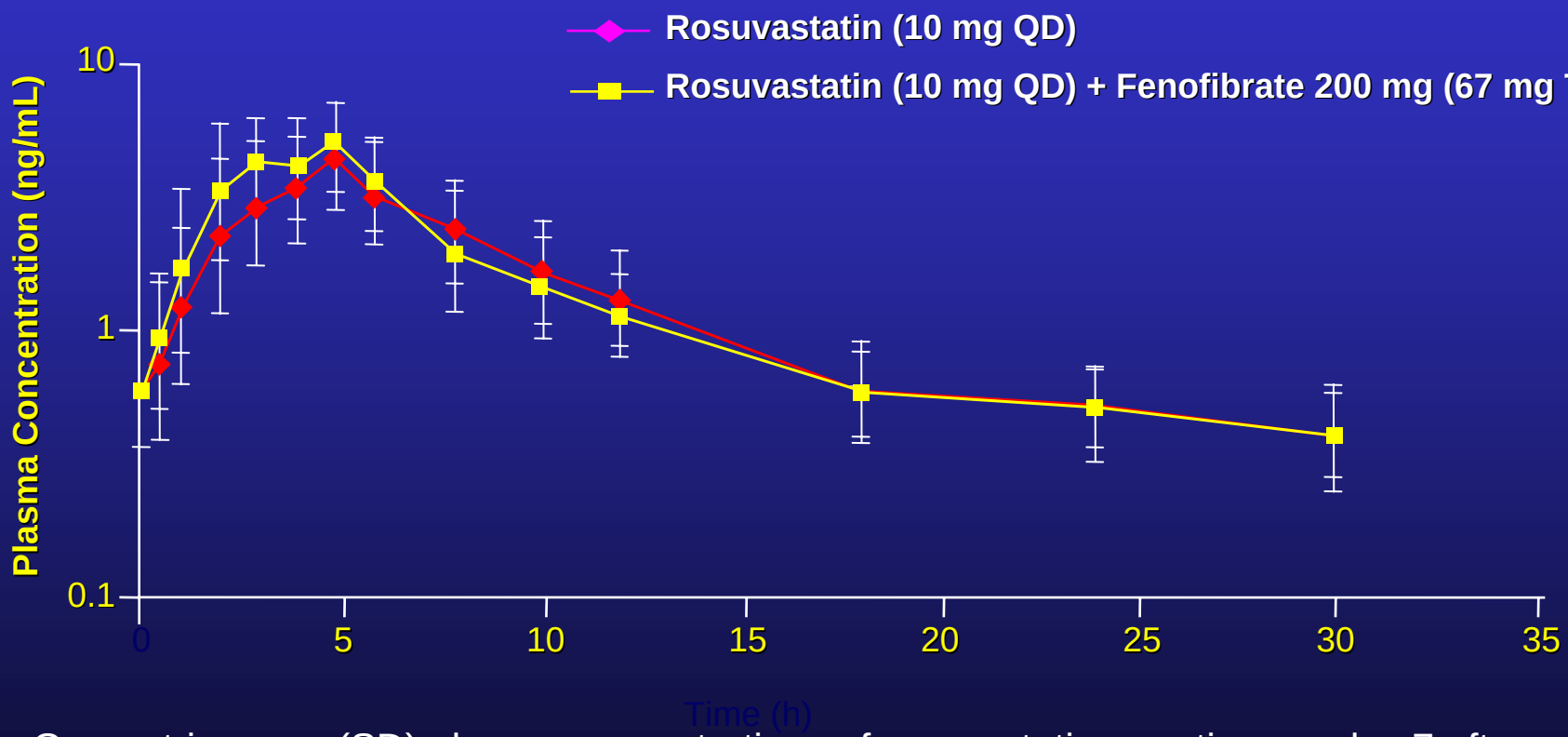
J Pharm Sci 1991;80:830-834Trends Pharmacol Sci 1998;19:26-37
Am J Cardiol 2001;97(suppl):28B-32B

Effect of Gemfibrozil and Fenofibrate on Rosuvastatin Plasma Concentrations



Ratio of rosuvastatin AUC in fibrate-treated patients to AUC in placebo- treated patients

Fenofibrate Does Not Increase Rosuvastatin Plasma Concentrations



Geometric mean (SD) plasma concentrations of rosuvastatin over time on day 7 after dosing of rosuvastatin alone and rosuvastatin in combination with fenofibrate

Martin PD, et al. *Clin Ther*. 2003;25:459-470.

Combination Therapy: Pharmacokinetic Interactions

	Gemfibrozil	Fenofibrate
Pravastatin	↑ in c_{max}	No effect
Fluvastatin	No effect	Not available
Simvastatin	↑ c_{max} by 112%	No effect
Cerivastatin	↑ c_{max} by 2-3-fold	No effect
Rosuvastatin	Not available	No effect

Davidson MH. *Am J Cardiol.* 2002;90(suppl):50K-60K.

Statin/Fibrate Combination Therapy: Pharmacokinetic Interactions

	Gemfibrozil	Fenofibrate
Atorvastatin	Not available	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	No effect
Cerivastatin	↑ in C_{max} by 2-3–fold	No effect

TriCor [package insert]. Abbott Laboratories;2004.
Kyrklund C, et al. *Clin Pharmacol Ther*. 2001;69:340-345.
Pan W-J, et al. *J Clin Pharmacol*. 2000;40:316-323.
Backman JT, et al. *Clin Pharmacol Ther*. 2000;68:122-129.

Backman JT, et al. *Clin Pharmacol Ther*. 2002;72:685-691.
Abbott Laboratories. Data on file; 2005.
Davidson MH. *Am J Cardiol.* 2002;90(suppl):50K-60K.
Prueksaritanont T, et al. *Drug Metab Dispos.* 2002;30:1280-1287.
Martin PD, et al. *Clin Ther*. 2003;25:459-471.
Bergman AJ, et al. *J Clin Pharmacol*. 2004;44:1054-1062.

Lipids in Diabetes Study (LDS)

- 4,191 diabetic patients without known CHD and LDL-C < 160 mg/dL from 30 centers in UK
  - Fenofibrate 200 mg + placebo
  - Cerivastatin .4mg + placebo
  - Cerivastatin.4mg + fenofibrate 200mg
  - Placebo + placebo
- Began May 1999 and closed August 2001
- Data on 1949 followed for a year have been analyzed
  - **No myositis or rhabomyolysis cases**

ADA abstract 317 Neil A et al. The Endocrinologist 2003;13(suppl3):S17

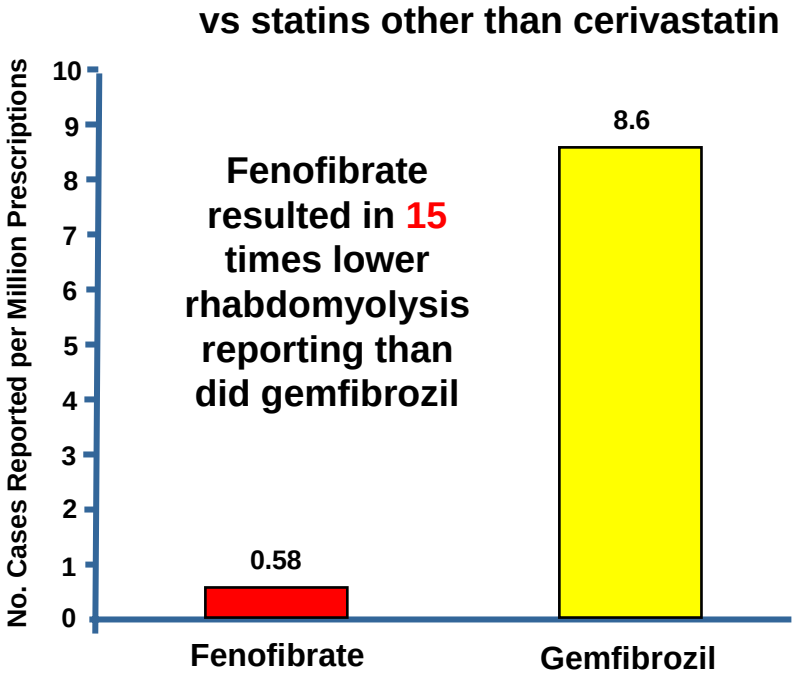
Fibrate/Statin Risk of Rhabdomyolysis

Number of Cases of Rhabdomyolysis

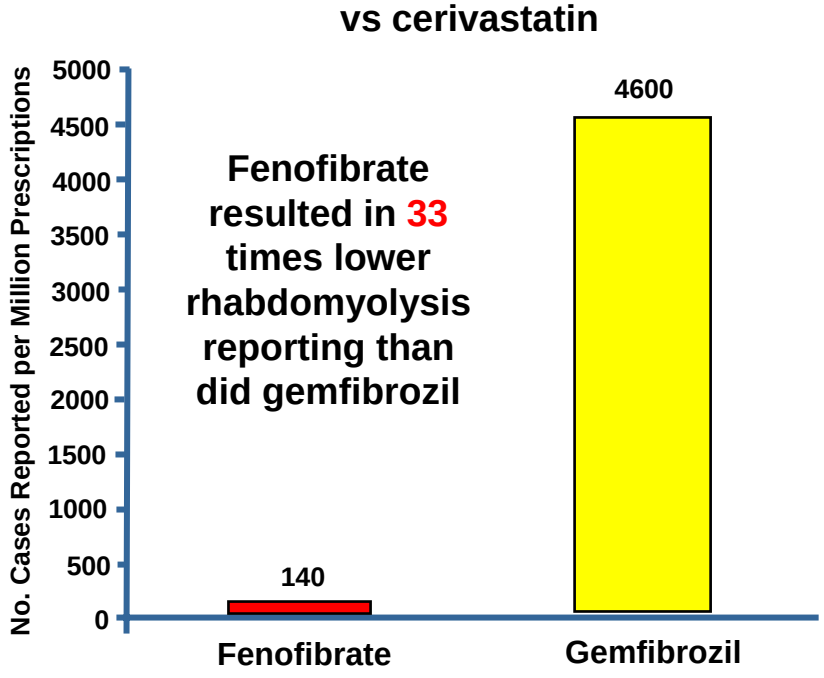
Medication	# Cases Reported	# Rx Dispensed [2,3]	# Cases Reported per Million [1]
Fenofibrate + Any Statin	16	3,519,000	4.55
Fenofibrate + Cerivastatin	14	100,000	140.00
Fenofibrate + Other Statins	2	3,419,000	**0.58**
Gemfibrozil + Any Statin	590	6,757,000	87.32
Gemfibrozil + Cerivastatin	533	116,000	4,594.83
Gemfibrozil + Other Statins	57	6,641,000	**8.58**

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

Risk of Rhabdomyolysis with Fibrates and Statins



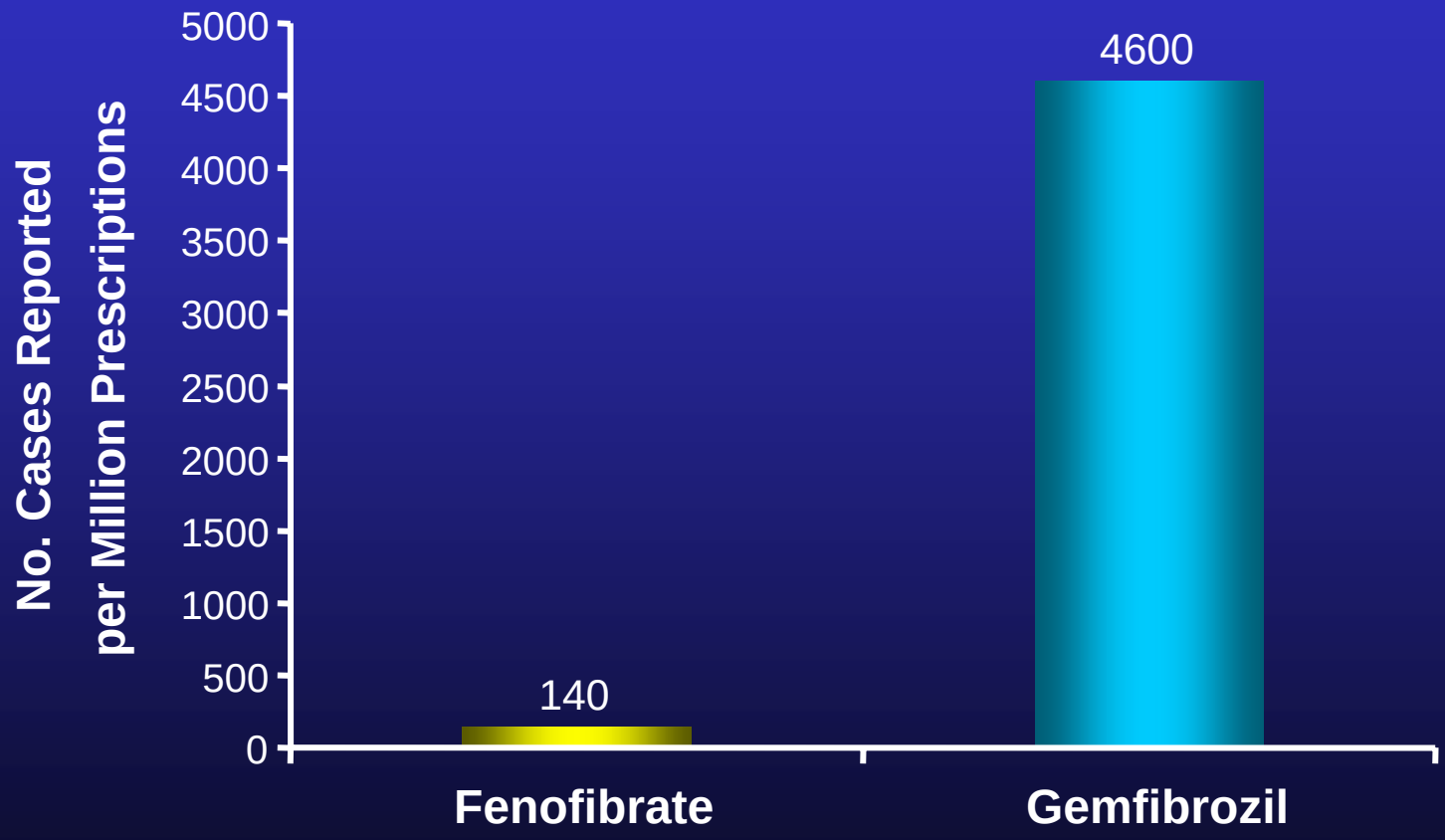
Number of cases of rhabdomyolysis reported per million prescriptions dispensed of statins other than cerivastatin in combination with fibrates.



Number of cases of rhabdomyolysis reported per million prescriptions dispensed of cerivastatin in combination with fibrates.

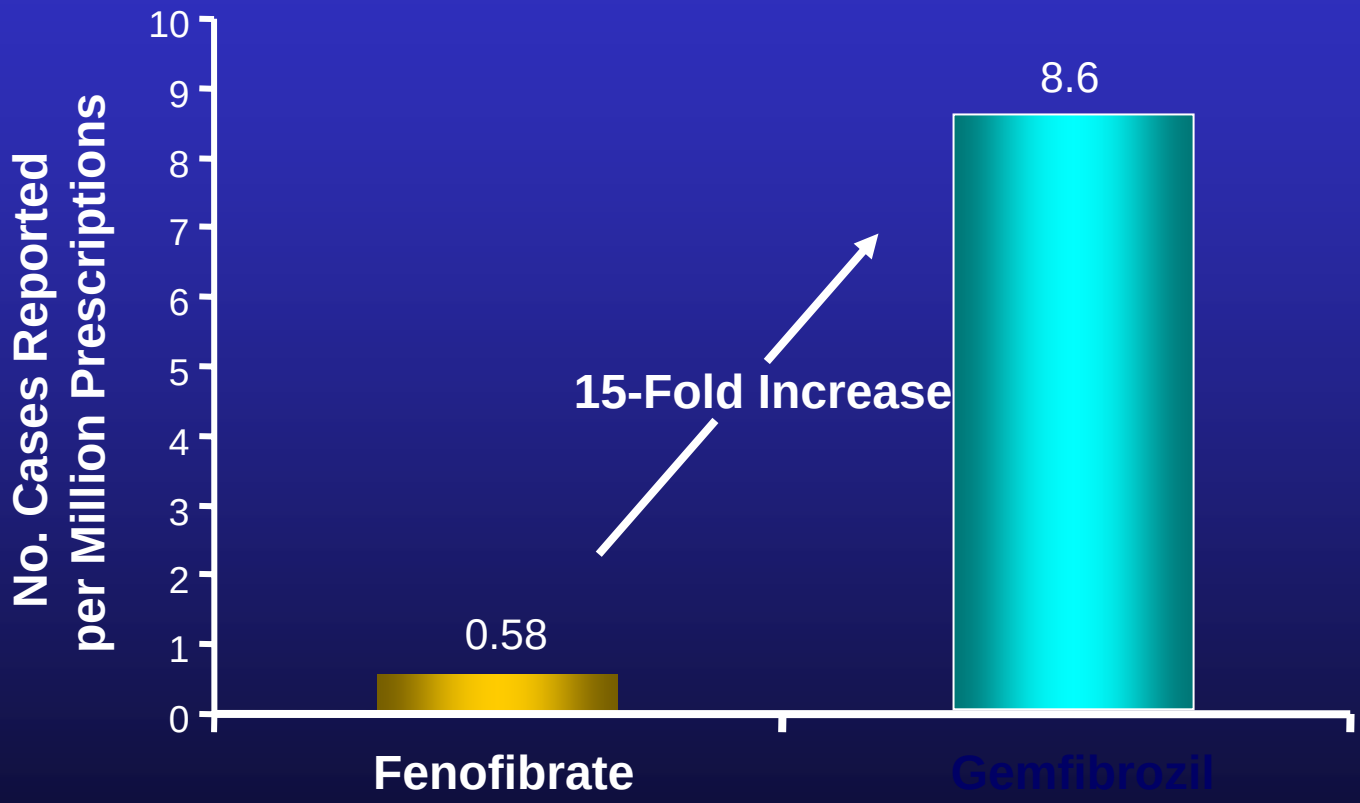
Jones PH & Davidson MH. A J Card 2005;95:120-122

Number of Cases of Rhabdomyolysis in Combination Therapy With Cerivastatin



Jones PH, et al. *Am J Cardiol.* 2005;95:120-122.

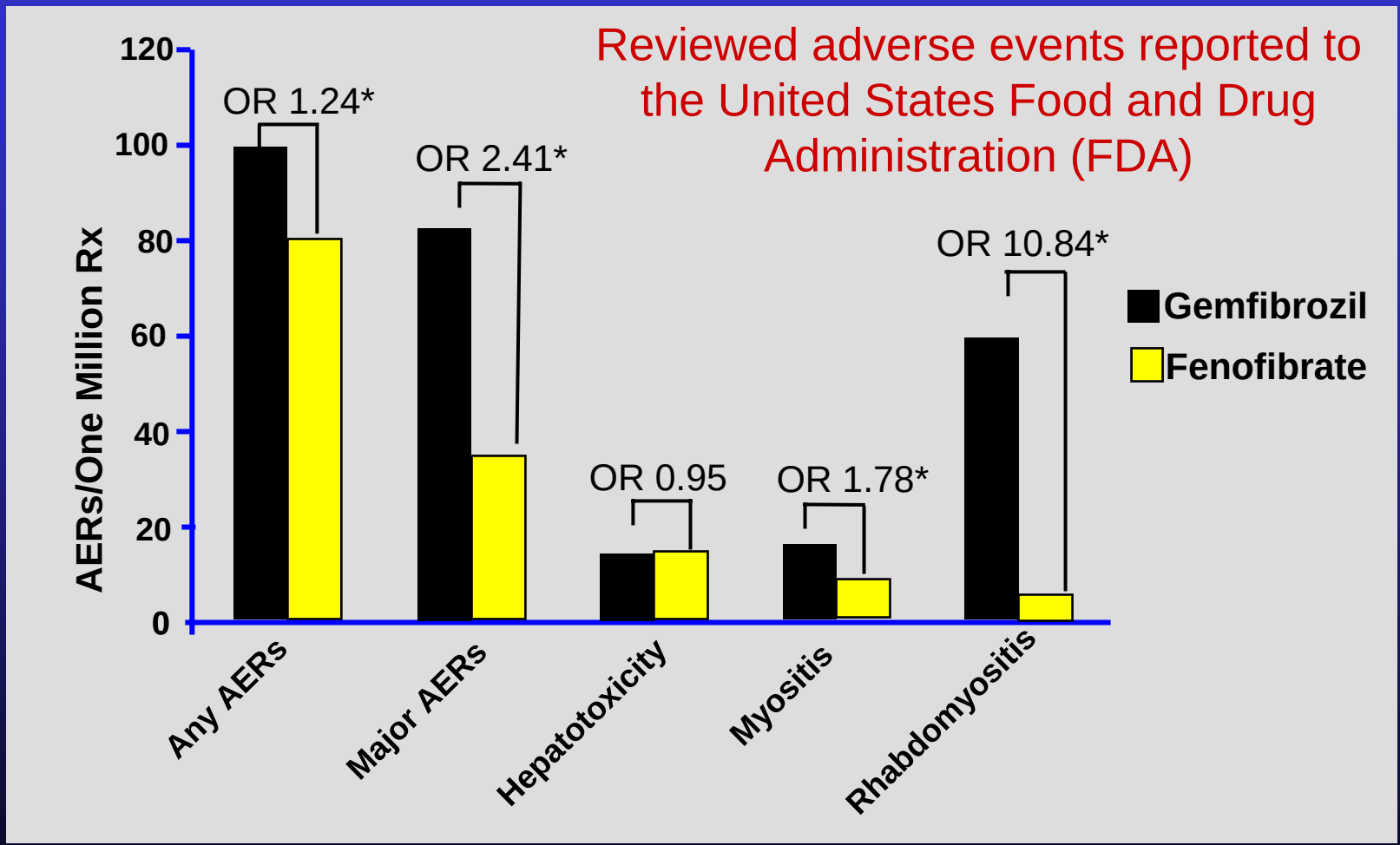
Number of Cases of Rhabdomyolysis in Combination Therapy With Statins*



*Excludes cases involving cerivastatin

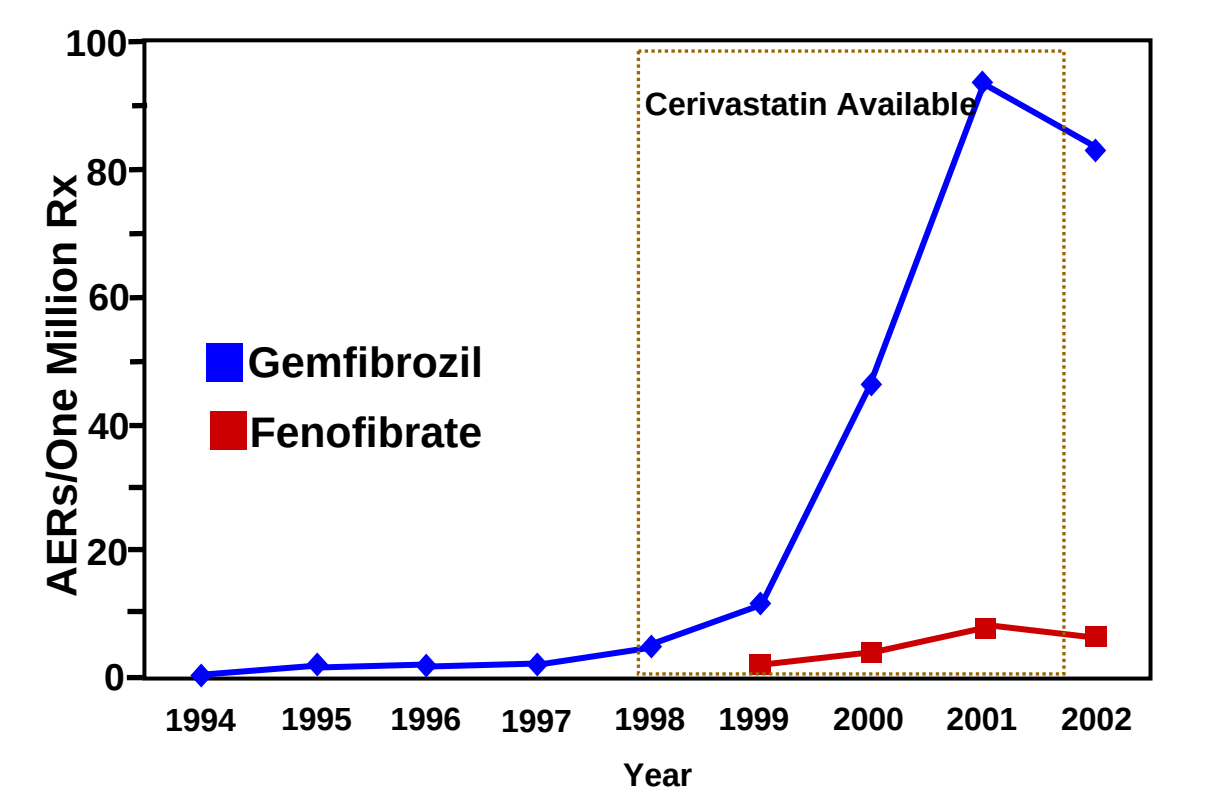
Jones PH, et al. *Am J Cardiol.* 2005;95:120-122.

Risk of Adverse Events with Fibrates



Alsheikh-Ali, A. et al. Amer J Card 2004;59:935-938

Risk of Adverse Events with Fibrates



Alsheikh-Ali, A. et al. Amer J Card 2004;59:935-938

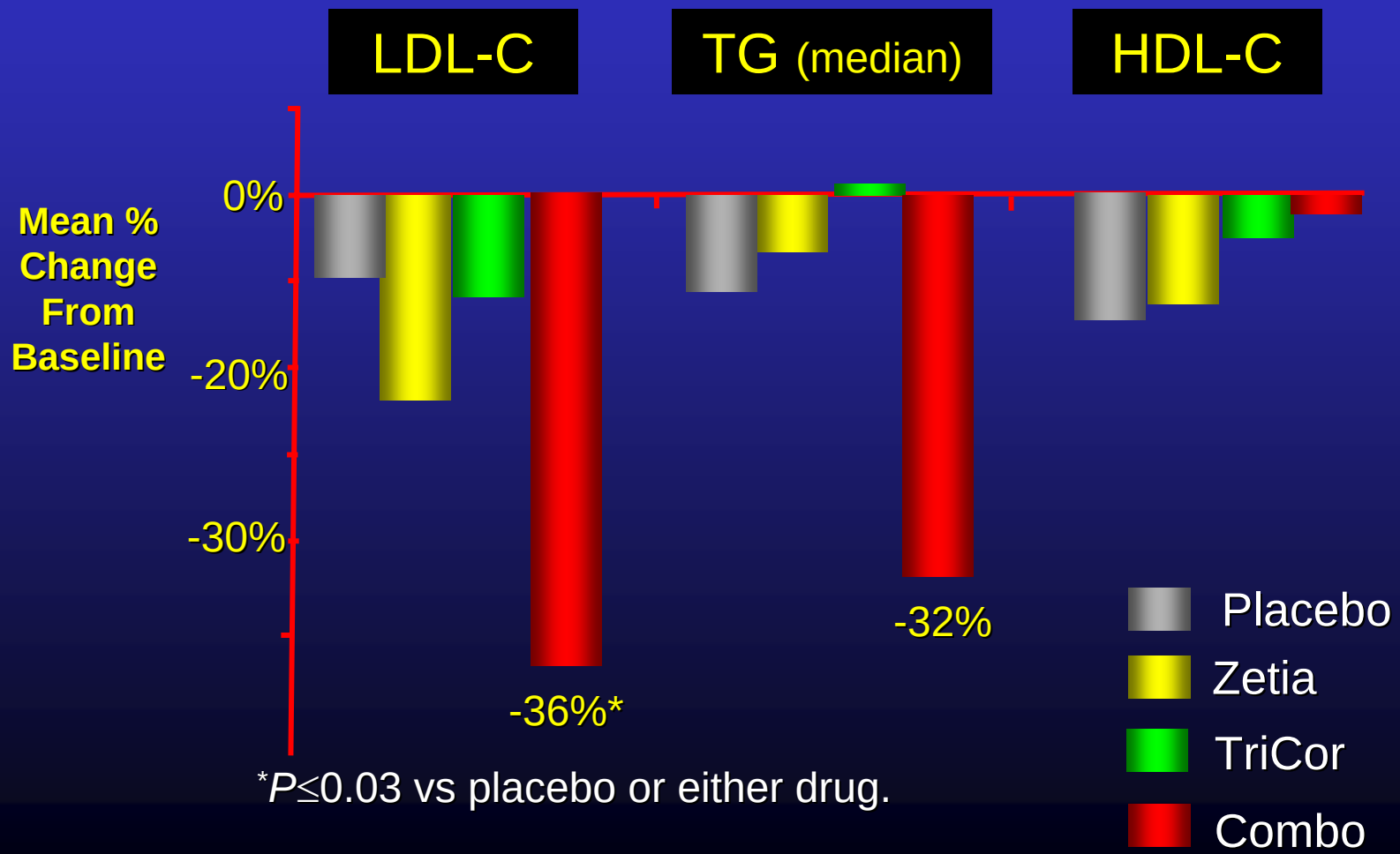
Ezetimibe - Fenofibrate Pharmacokinetic Study

- **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

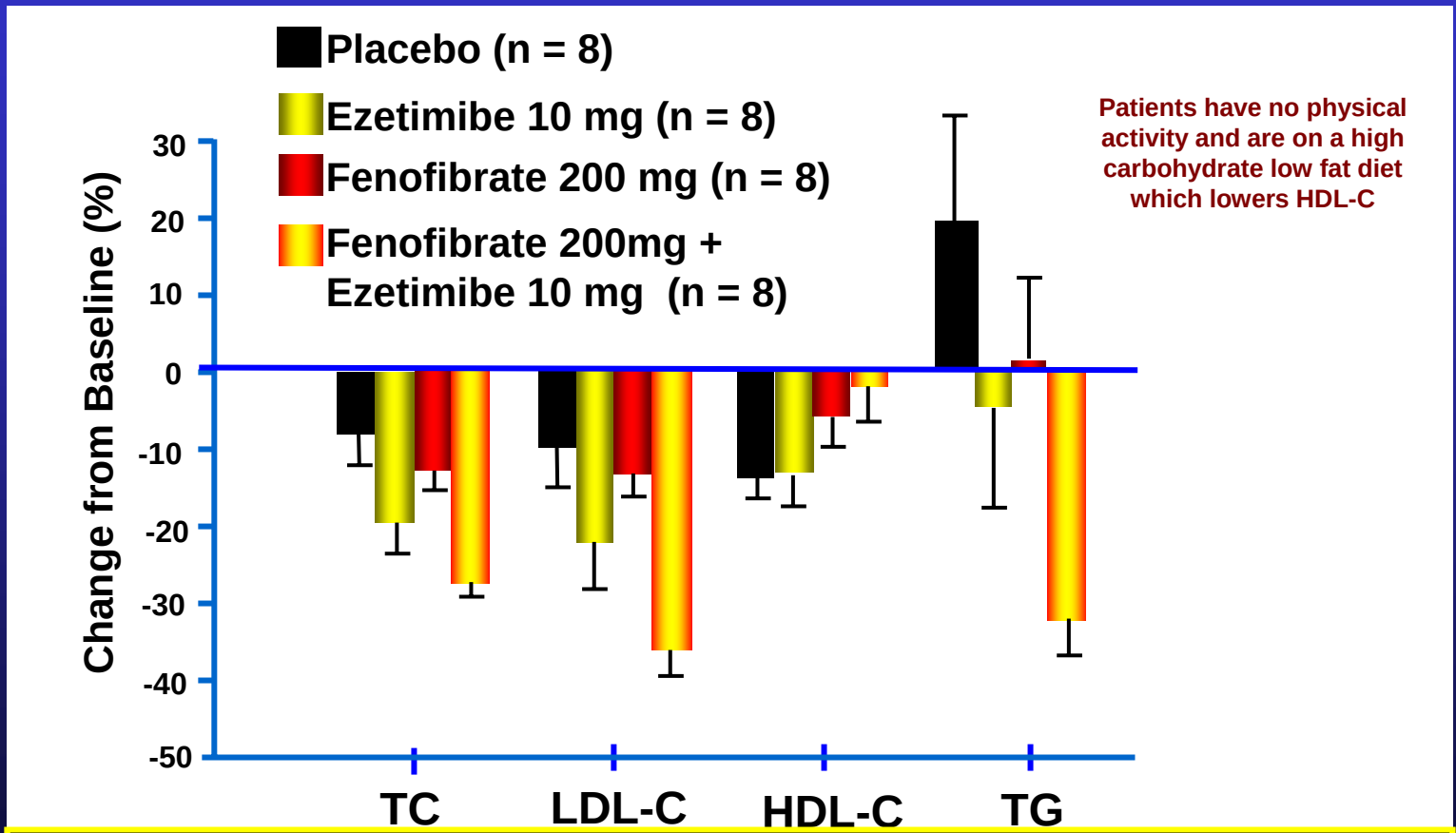
Ezetimibe - Fenofibrate Pharmacokinetic Study

32 patients with hypercholesterolemia for 14 days: on strict diet



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

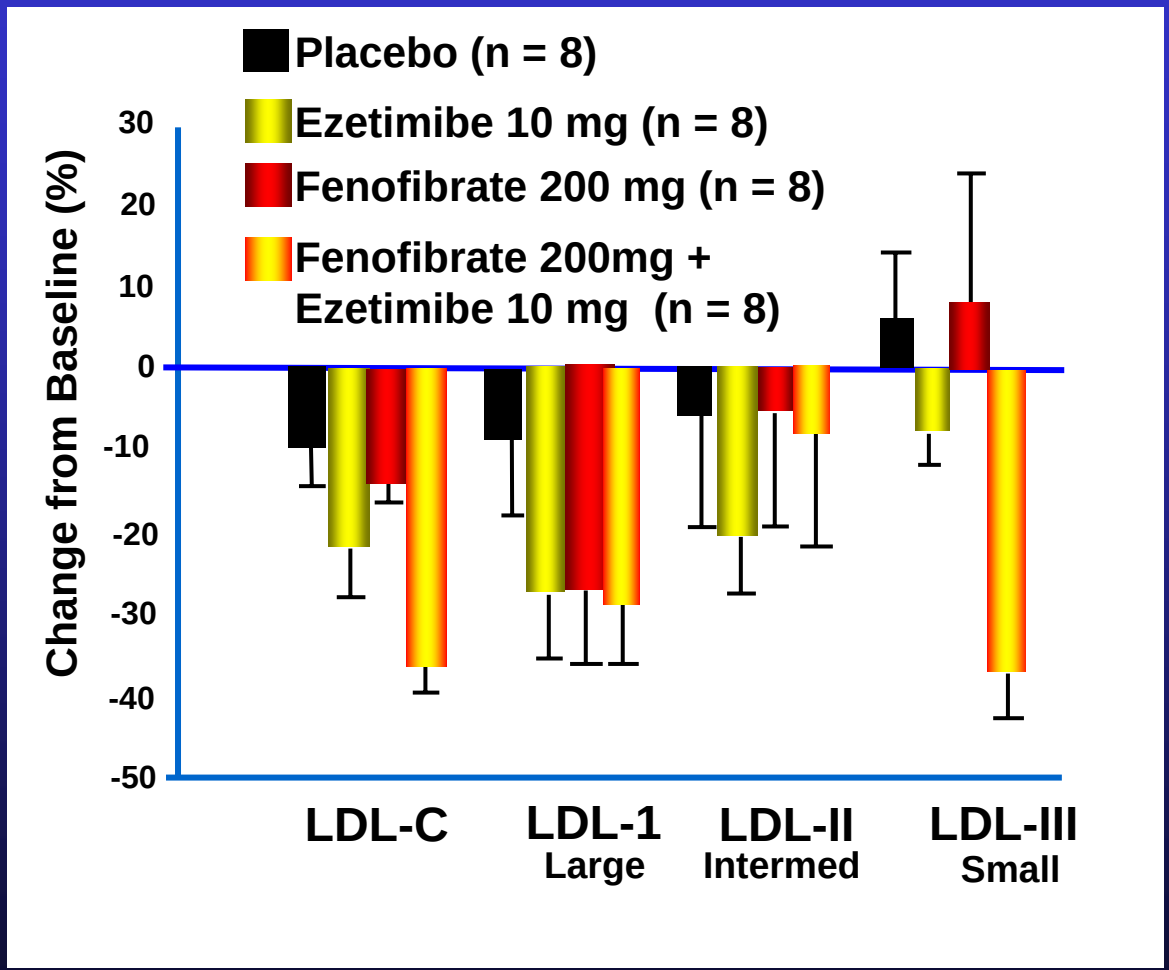
Fenofibrate – Ezetimibe Pharmacodynamic and Pharmacokinetic Interaction Study



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

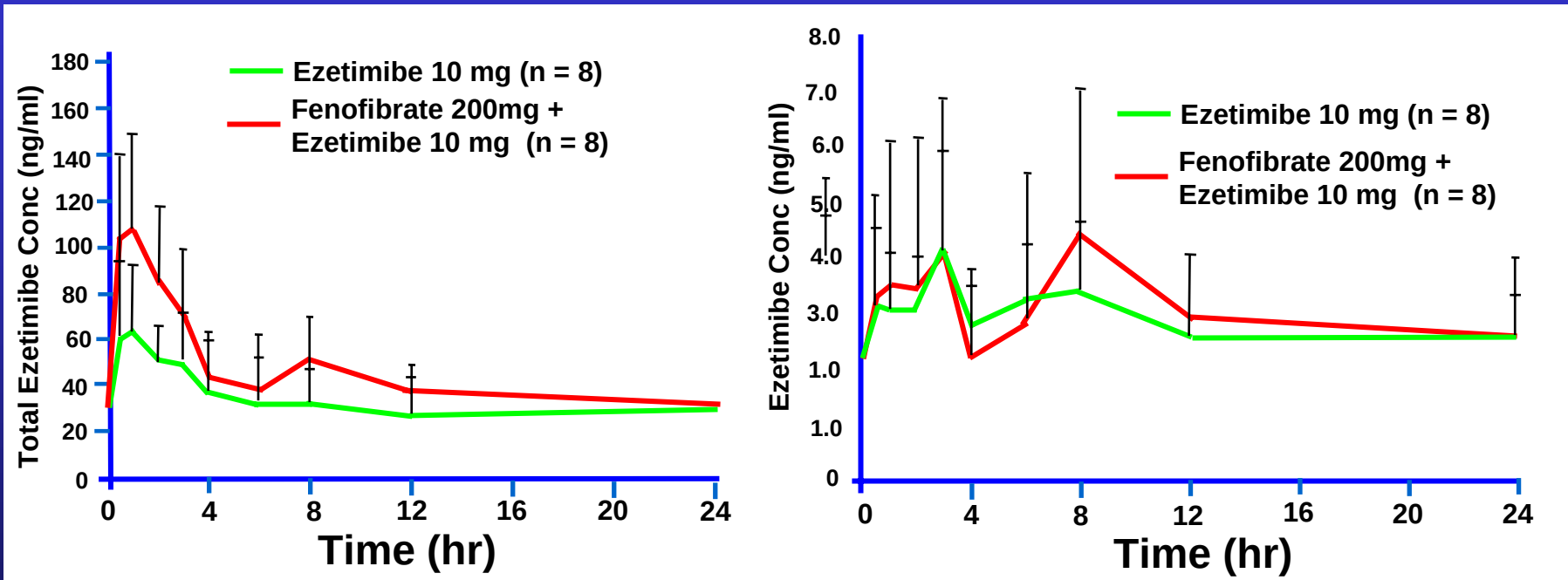


Combination therapy produced significantly greater reductions in LDL-C and in small LDL-III

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