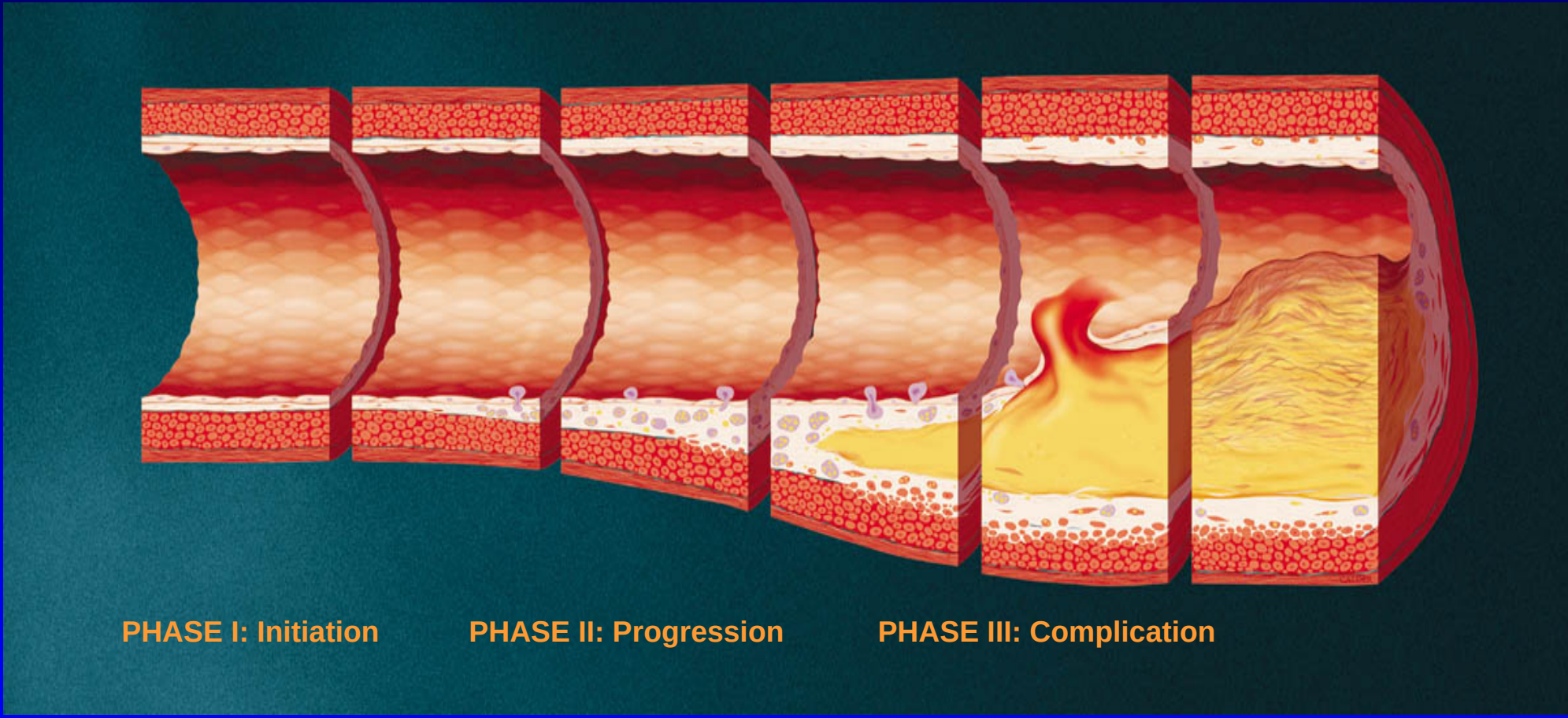
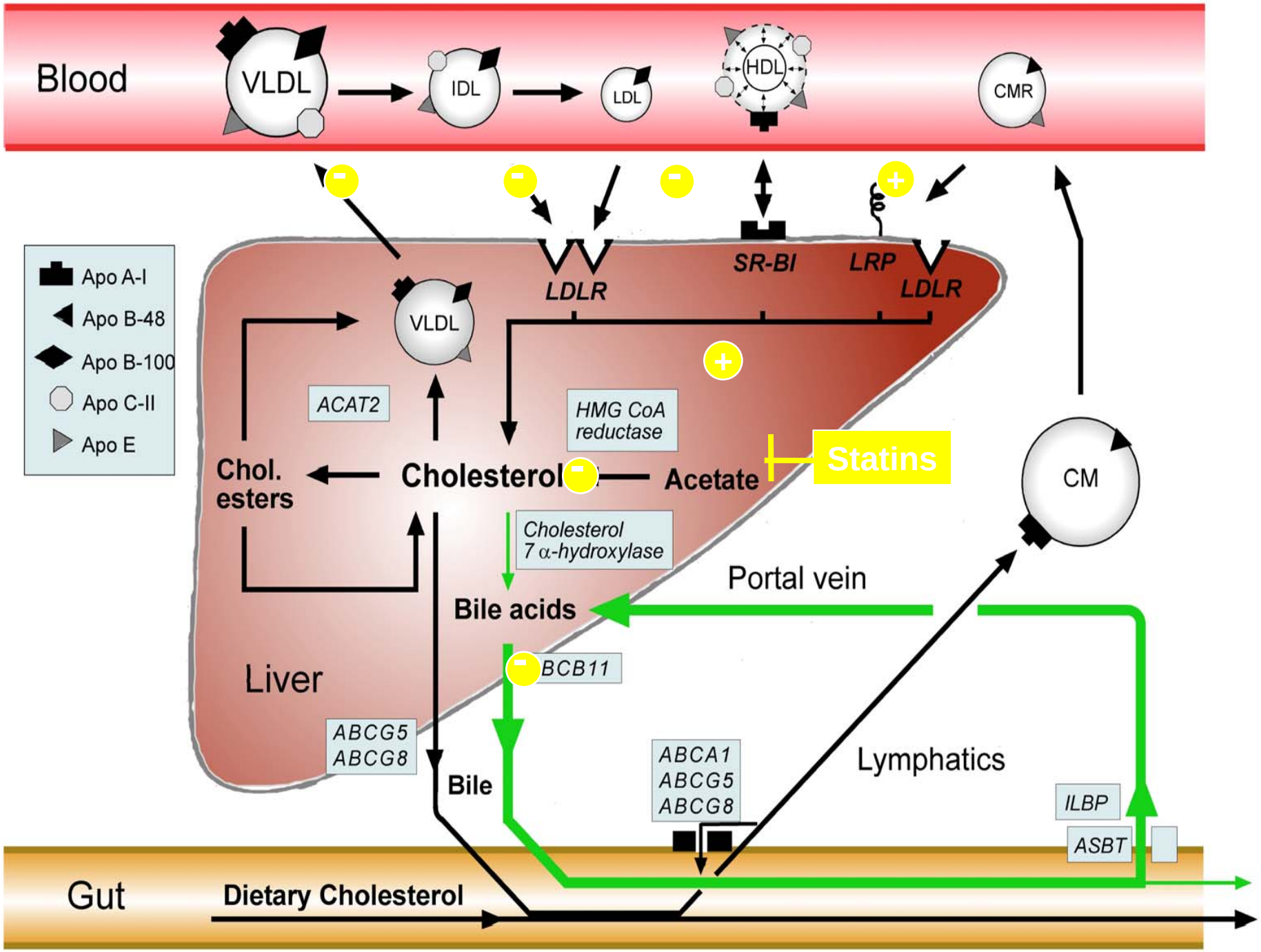
April 2008

Torcetrapib's failure: Find more stories in the ILLUMINATE trial. (Dr. Eriksson MD, PhD)

Atherosclerosis Is a Chronic Inflammatory Disease With LDL-C at the Core



Libby P. J Intern Med. 2000;247:349-358.


Blood
VLDL
IDL
LDL
HDL
CMR
Apo A-I
Apo B-48
Apo B-100
Apo C-II
Apo E
LDLR
SR-BI
LRP
LDLR
VLDL
ACAT2
HMG CoA reductase
Statins
Chol. esters
Cholesterol
Acetate
CM
Cholesterol 7 α-hydroxylase
Portal vein
Bile acids
Liver
BCB11
ABCG5 ABCG8
Bile
ABCA1 ABCG5 ABCG8
Lymphatics
ILBP
ASBT
Gut
Dietary Cholesterol

Only 2 Surrogate Endpoints For Cardiovascular Disease Drugs

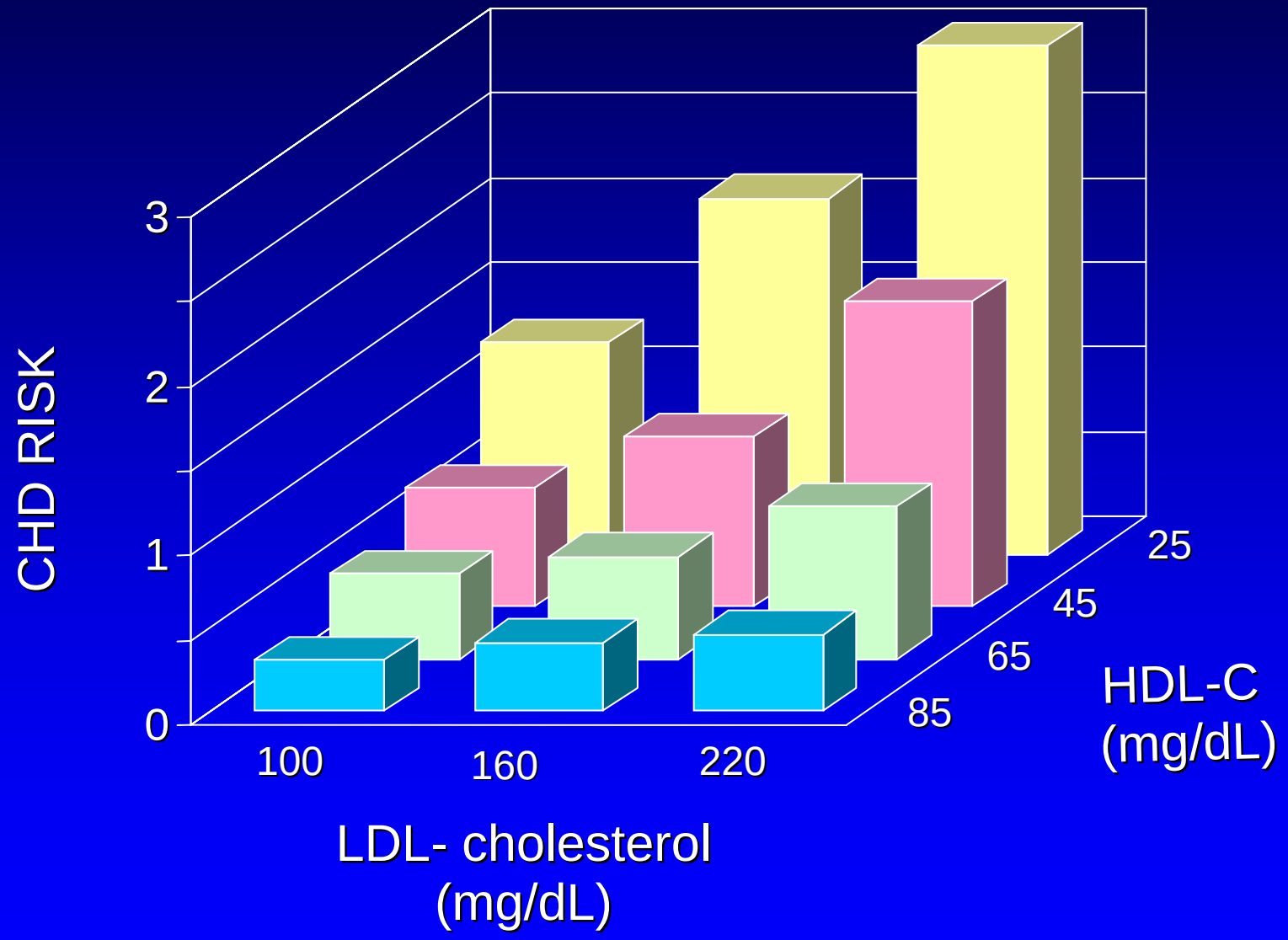
"The only surrogate endpoints currently used as a basis for approval of cardiovascular drugs are blood pressure and serum cholesterol level"

* Temple R: Are surrogate markers adequate to assess cardiovascular disease drugs? JAMA 1999;282:790-95.

LDL-C (apo B) Lowering As a Surrogate Endpoint for Reduced CVD risk

- Epidemiology/pathology/clinical observation
- Experiment of nature: heFH, PCsk9
- The LRC-CPPT and NHLBI trials demonstrated that resins reduced CV events and slowed progression, associated with lowering LDL-C
  - Lovastatin was then approved on the basis of LDL-C reduction in 700 patients
  - Ezetimibe was also approved on the basis of LDL-C reduction

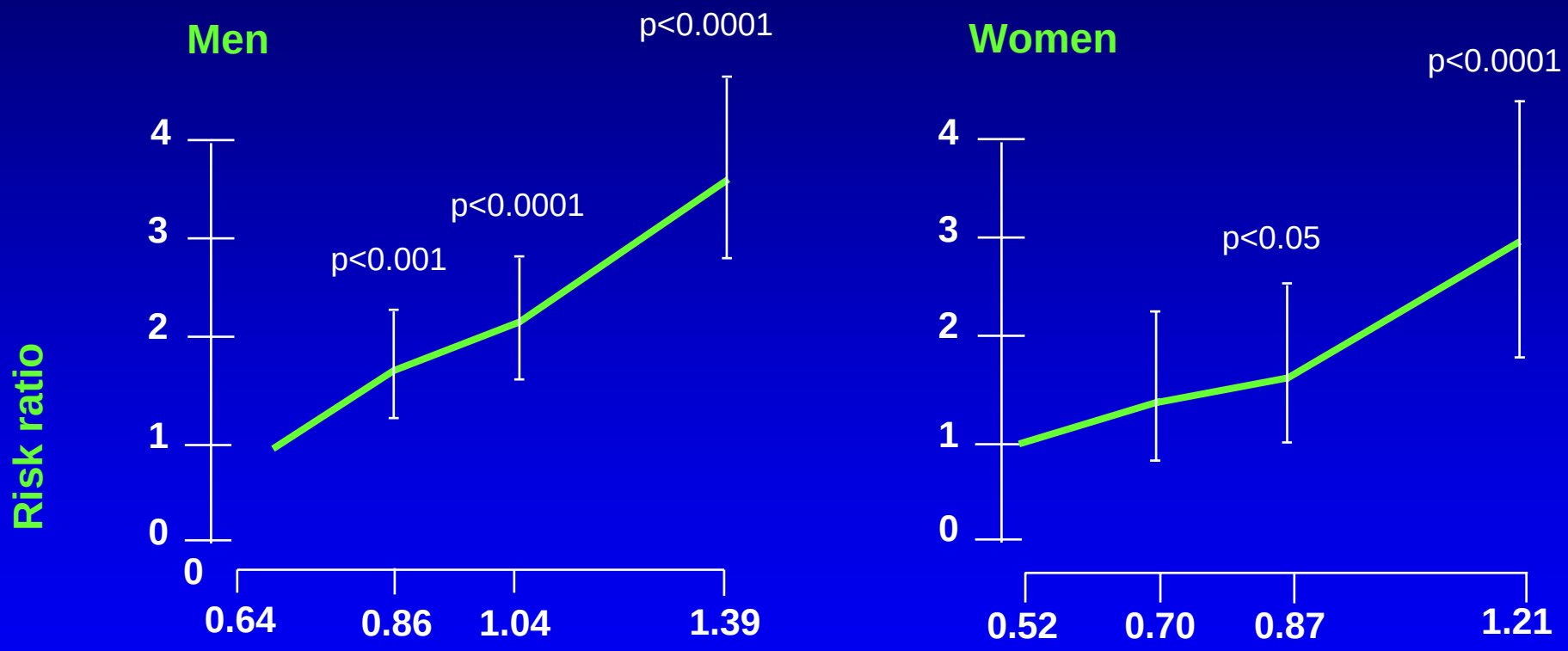
FRAMINGHAM: CHD RISK



* Men aged 50-70

© G.Walldius, I. Jungner

AMORIS, fatal myocardial infarction



Apolipoprotein B/Apolipoprotein A-I

Walldius G, Jungner I, Holme I, Aastveit A, Kolar W, Steiner E. Lancet 2001; 358: 2026-33

Torcetrapib – Final Results of the ILLUMINATE Trial

Philip J Barter[1] for the ILLUMINATE Steering Committee and Investigators

[1]Heart Research Institute, Sydney, Australia

Steering Committee: P. Barter, Chair (Australia), M. Caulfield (UK),M. Eriksson (Sweden),S. Grundy (US), J. Kastelein (The Netherlands),M. Komajda (France), J.-L. Lopez-Sendon (Spain), L. Mosca (US),J.-C. Tardif (Canada), D. Waters (US)

Statistical analysis: The Department of Biostatistics and Medical Informatics at the University of Wisconsin-Madison

Sponsor: Pfizer, Inc

Published online today in the New England Journal of Medicine

Rationale

- **HDL protects against cardiovascular disease**

- **A novel mechanism for raising HDL levels is to inhibit CETP. This protein transfers cholesterol from HDL to LDL fraction and thus retains cholesterol in the protective HDL.**

- **Torcetrapib inhibits CETP and had been shown in humans to raise the level of HDL-C and lower that of LDL-C.**

- **Inhibiting CETP with torcetrapib protects against atherosclerosis in rabbits.**

- **The ILLUMINATE trial was designed to test the hypothesis that inhibiting CETP with torcetrapib would also protect against cardiovascular disease in humans.**

ILLUMINATE: Long-term Outcomes in Patients With CHD or CHD Risk Equivalence

Investigation of Lipid Level Management to Understand its Impact in Atherosclerotic Events

Atorvastatin run-in to LDL <100 mg/dL (2.6 mmol/L) 4-10 weeks

Torcetrapib + titrated atorvastatin dose

Planned 4.5 years of treatment

Titrated atorvastatin dose

Patient Population	Subjects	Primary End Point
♦ Men or postmenopausal women ♦ Statin eligible ♦ Any HDL-C level ♦ CHD or risk equivalent (type 2 DM)	♦ 15,067 ♦ 7 countries	♦ Major cardiovascular events ♦ Power=0.9 for 21% reduction

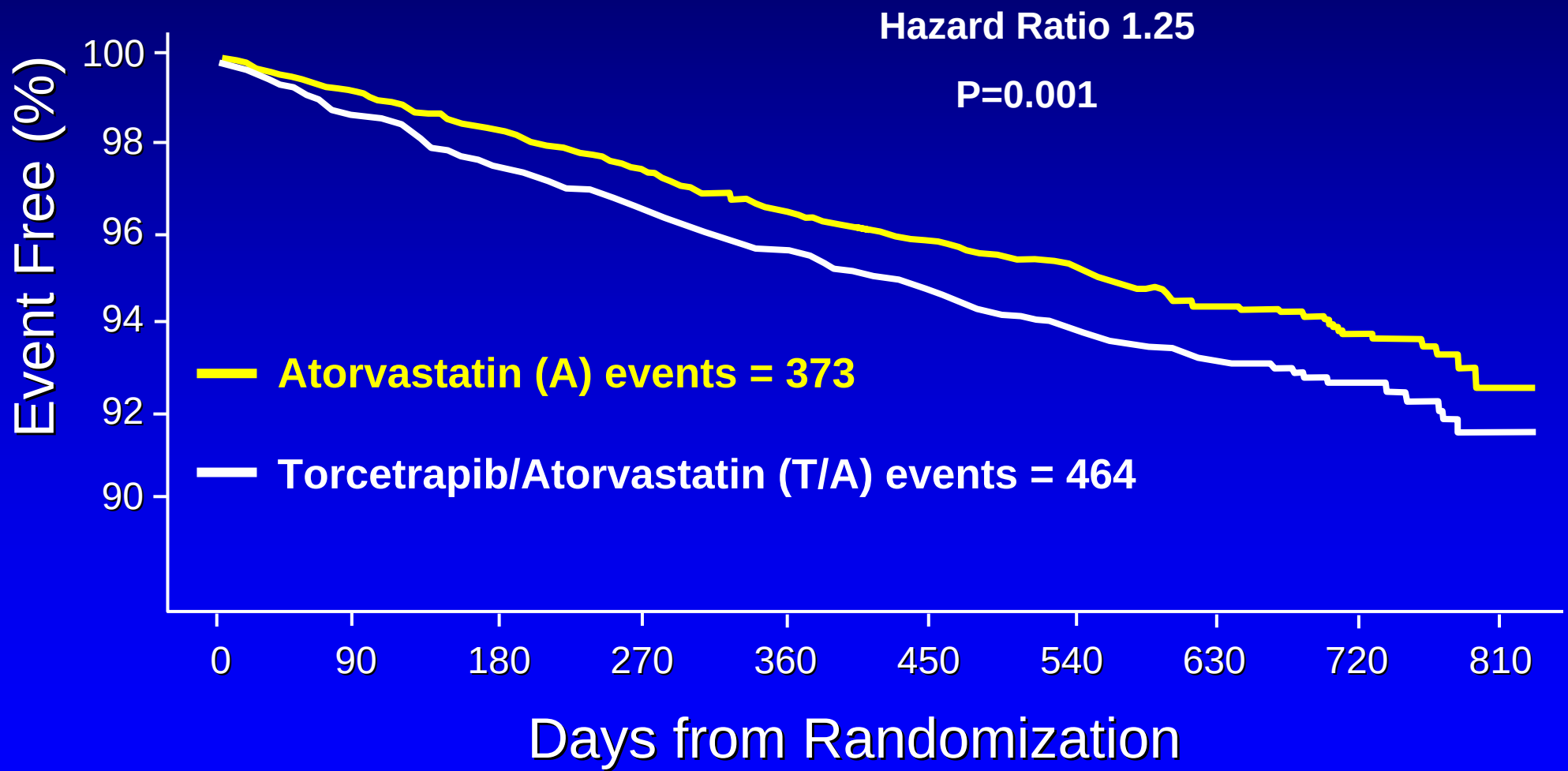
Premature Trial Termination: December 2nd, 2006

On Dec 2, 2006, after a median follow-up on-treatment of 550 days, the sponsor was informed by the Steering Committee, acting on advice from the independent Data Safety Monitoring Board, to terminate the trial based on a statistically significant excess of deaths and cardiovascular events in the group treated with torcetrapib

The sponsor immediately terminated the trial

All data were censored for the primary analyses on December 2, 2006

Primary Endpoint:
Time to First MCVE*: Kaplan-Meier Plot



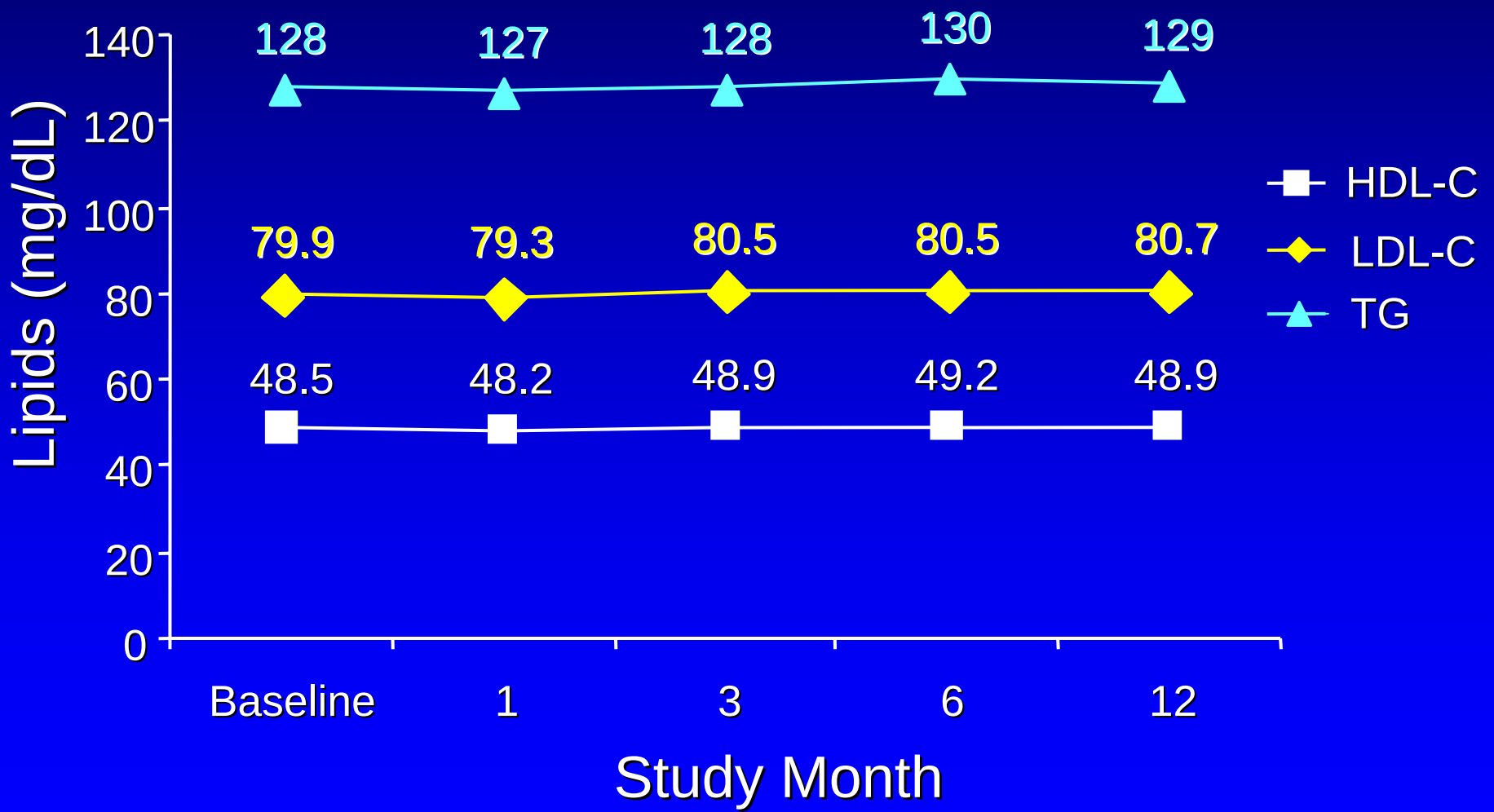
*Major cardiovascular event: CHD death, non-fatal MI, stroke or hospitalization for unstable angina

Baseline Demographics

	Atorvastatin (n=7,534)	Torcetrapib/ Atorvastatin (n=7,533)	P-value
Male (%)	77.8	77.7	0.90
White, n (%)	93.3	93.2	0.82
Age, yrs, mean	61.3	61.3	0.82
BMI, kg/m^2, mean	30.2	30.1	0.14

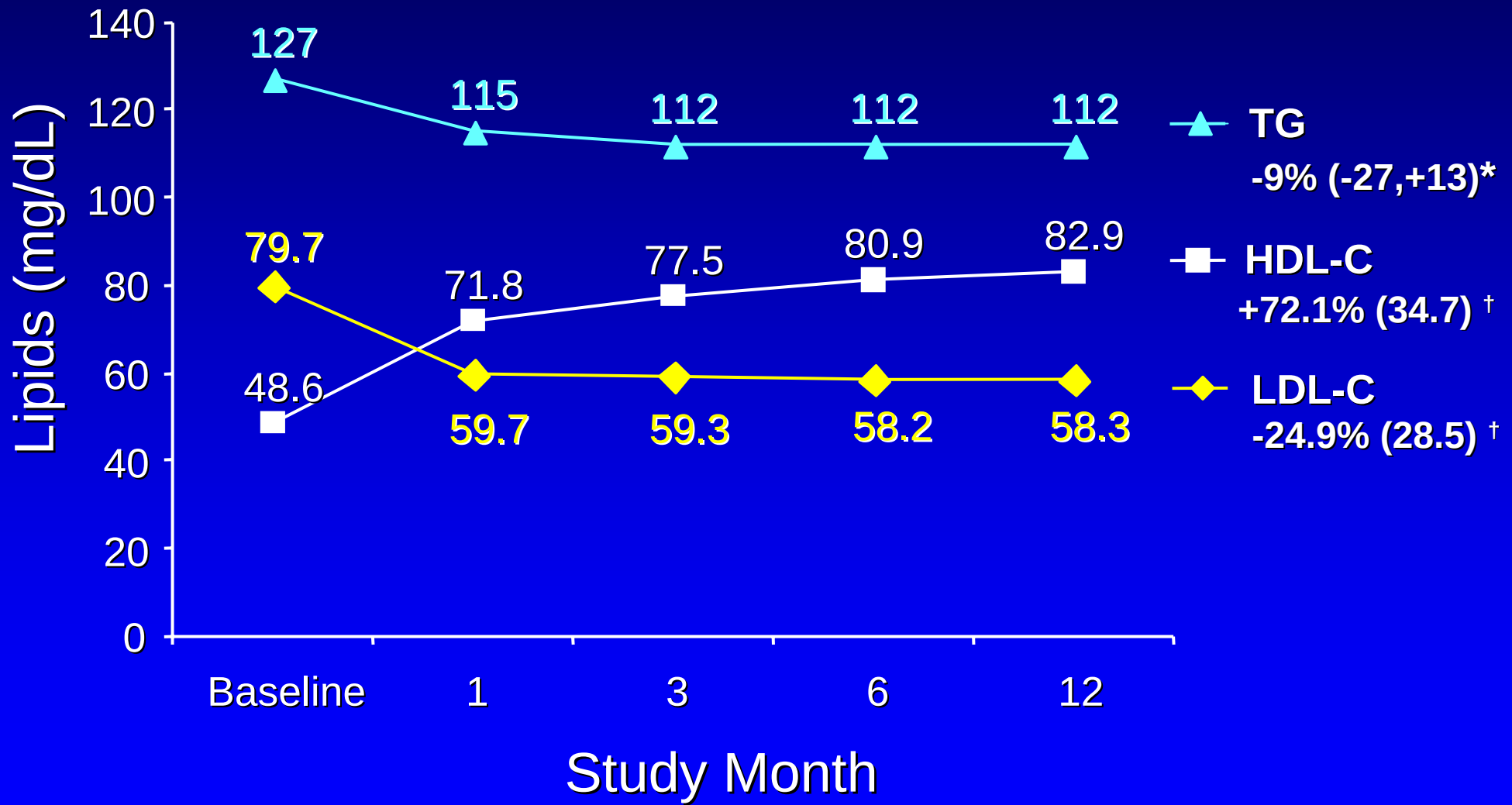
On Trial Lipid Levels By Study Month

Atorvastatin Group (Post Run-In)



On Trial Lipid Levels By Study Month

Torcetrapib/ Atorvastatin Group (Post Run-In)



*median % change (IQR) for TG at month 12; p<0.001 vs atorvastatin

† mean % change (SD) for LDL-C, HDL-C at month 12; p<0.001 vs atorvastatin

Secondary Endpoints

Estimated hazard ratio for pre-specified cardiovascular outcomes				
	Atorvastatin n (%)	Torcetrapib/ Atorvastatin n (%)	Hazard Ratio (95% CI)	P- value
CHD death	33 (0.4)	40 (0.5)	1.21 (0.77, 1.92)	0.41
Non-fatal MI (excluding procedure related)	118 (1.6)	142 (1.9)	1.21 (0.95, 1.54)	0.13
Stroke	40 (0.5)	43 (0.6)	1.08 (0.70, 1.66)	0.74
Hospitalization for unstable angina	201 (2.7)	270 (3.6)	1.35 (1.13, 1.62)	0.001
All-cause mortality	59 (0.8)	93 (1.2)	1.58 (1.14, 2.19)	0.006

Causes Of Death

	Atorvastatin (n=59)	Torcetrapib/ Atorvastatin (n=93)
Any cardiovascular death	**35**	**49**
Sudden cardiac death	25	26
Fatal MI - not procedure related	6	8
Fatal stroke	0	6
Other cardiac death	1	4
Fatal heart failure	1	2
Other vascular death/procedure related MI	2	3
Any non-cardiovascular	**20**	**40**
Cancer	14	24
Infection	0	9
Other non-cardiovascular	2	4
Trauma/suicide/homicide	4	3
Reason unknown	**4**	**4**

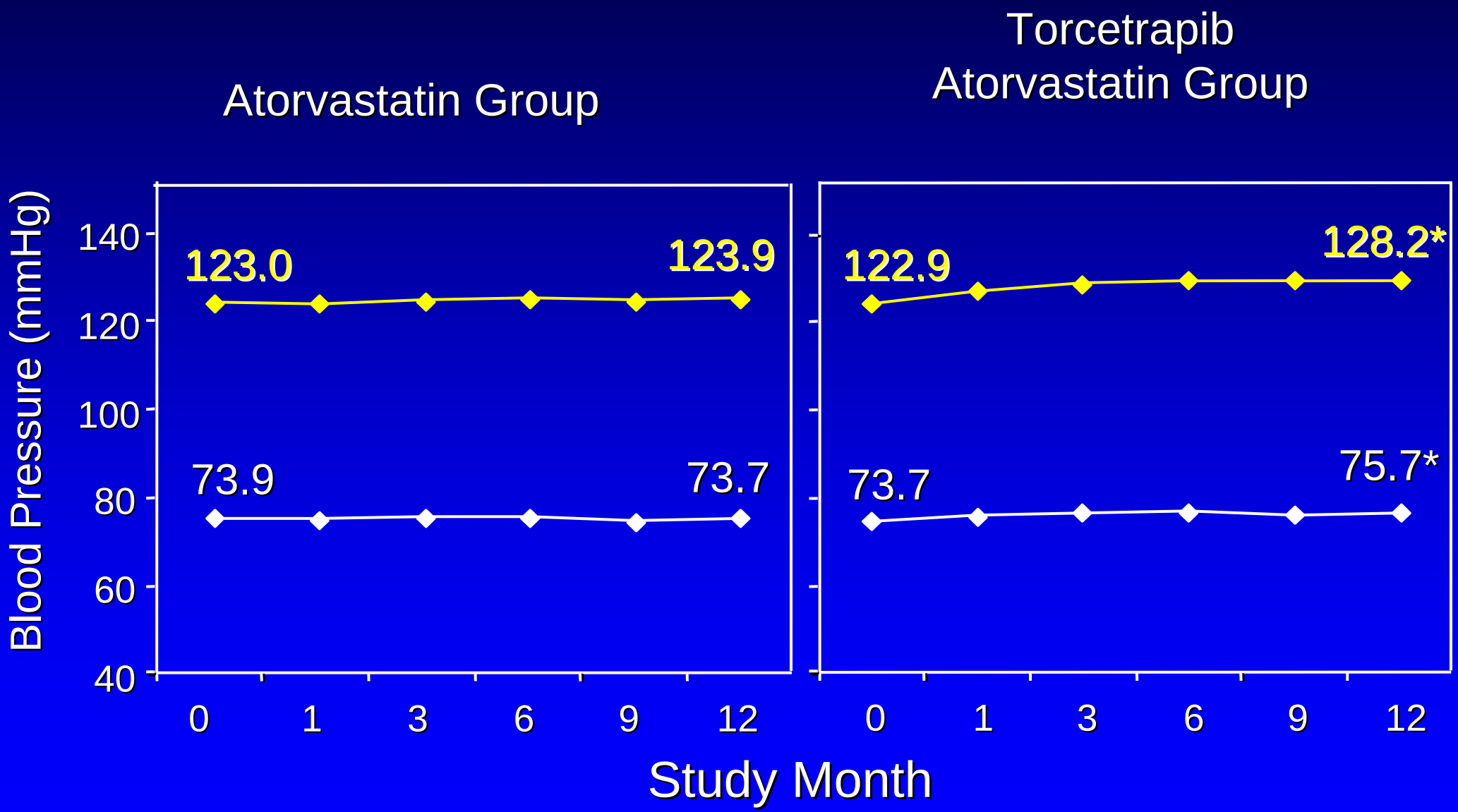
Investigator-reported SAEs of neoplasms

Atorvastatin Group	136
Torcetrapib/atorvastatin Group	128

Investigator-reported SAEs of infections/infestations

Atorvastatin Group	177
Torcetrapib/atorvastatin Group	182

On-Trial Blood Pressure By Study Month



* p<0.001 vs atorvastatin at month 12

Changes in Serum Electrolytes

Patients receiving torcetrapib/atorvastatin had changes in serum electrolytes that differed significantly from those in patients taking atorvastatin alone.

- **Serum potassium was reduced** **($p<0.001$)**
- **Serum bicarbonate was increased** **($p<0.001$)**
- **Serum sodium was increased** **($p<0.001$)**

Serum Aldosterone

Performed after study termination on the 87% of patients with stored baseline and month 3 samples

55% of the analyzed samples had aldosterone levels below the lower limit of quantification by the technique

It was, however, possible to determine unambiguously whether or not an analyzed sample had an aldosterone level of 8 ng/dL or more.

Percentage of patients with aldosterone > 8 ng/dl			
	A Group	T/A Group	P value*
Baseline	**17.1%**	**16.3%**	**0.2**
Month 3	**17.8%**	**21.6%**	**< 0.001**

* Wilcoxon comparisons after truncating the data below 8 ng/dl

Reported events occurring after Dec 2, 2006

The following events were reported up to July 15th 2007:

Deaths

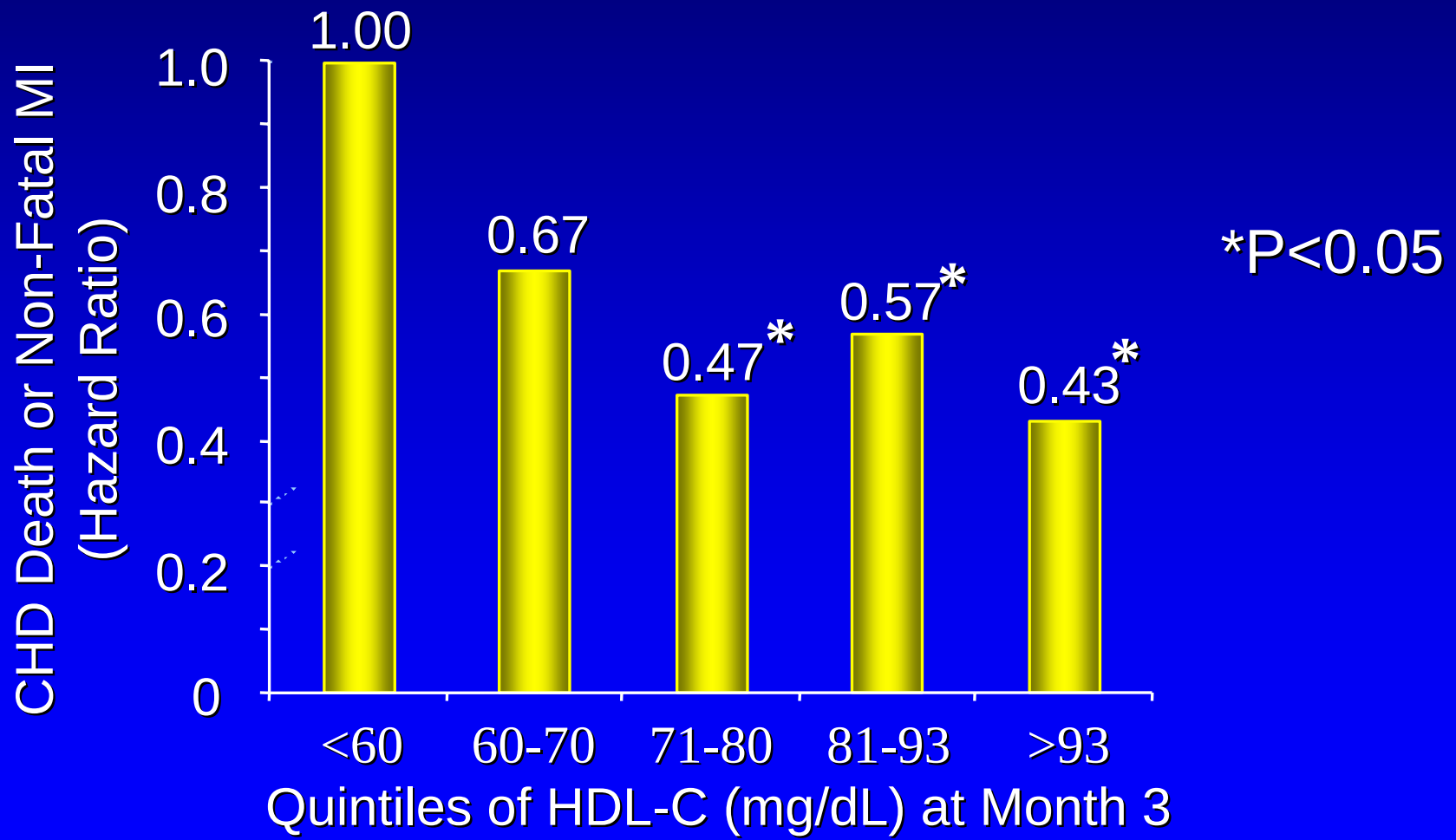
Atorvastatin:	**20**	**(n=7,475)**
Torcetrapib/atorvastatin:	**14**	**(n=7,440)**

MCVEs

Torcetrapib/atorvastatin:	**38**	**(n=7,475)**
Atorvastatin:	**38**	**(n=7,440)**

Post-hoc Exploratory Analyses in the Torcetrapib/Atorvastatin Group

Hazard ratios for CHD Death or Non-Fatal MI by quintile of on-trial HDL-C (referent group is HDL-C < 60 mg/dL stratum)



Cox proportional hazard model adjusted for age, gender and baseline HDL-C. Excludes 265 patients with missing month 3 HDL-C. Preliminary analysis initiated and authorised by P Barter and conducted by Pfizer

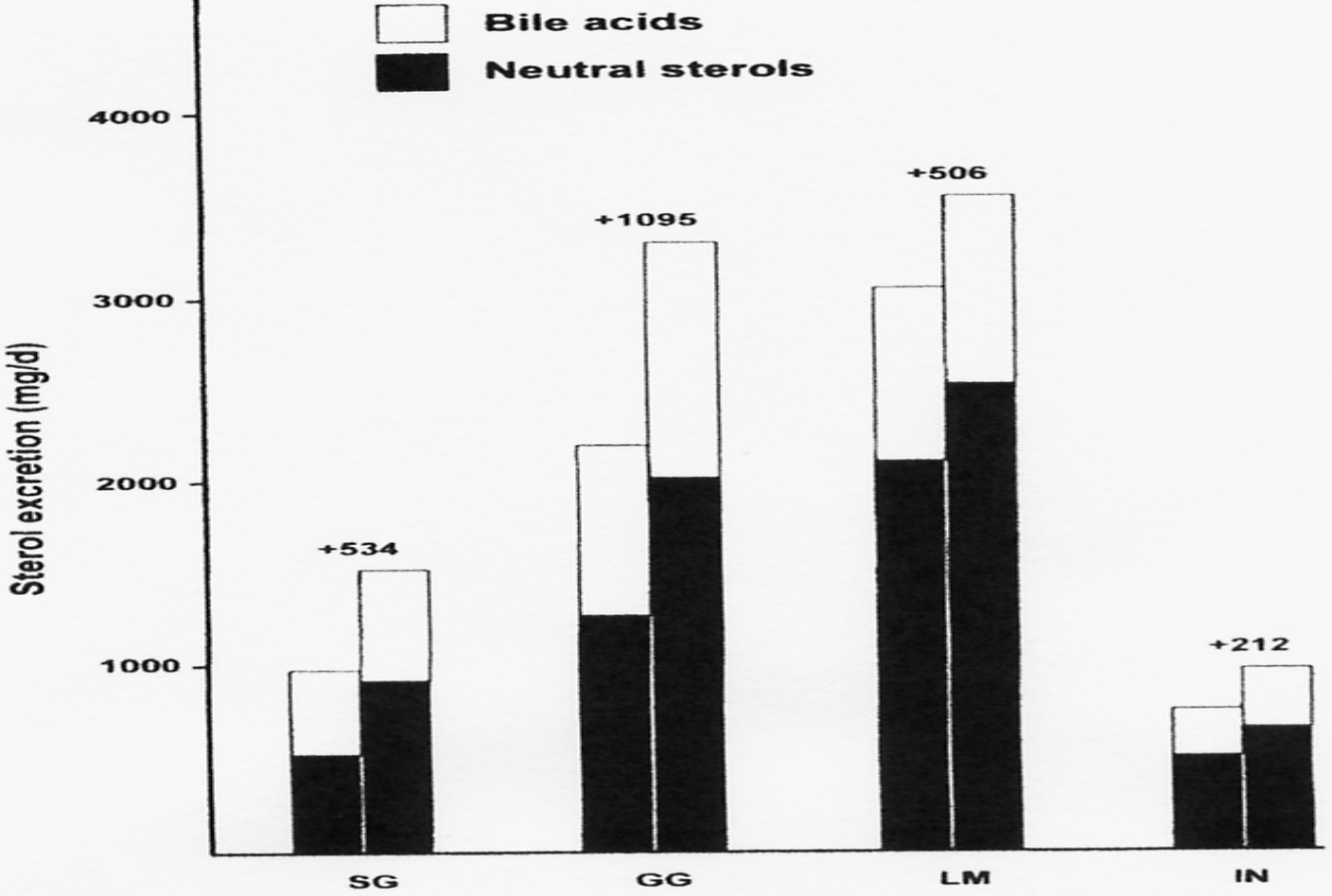


Figure 2. Fecal excretion of bile acids and neutral steroids 9 days before (left bars) and 9 days after (right bars) infusion of proapoA-I liposomes. Individual mean levels are shown for 2 periods; individual changes in total steroid excretion (mg/d) are indicated above each pair of bars. Increase in response to treatment was significant for bile acids ($P<0.03$), neutral sterols ($P<0.03$), and total steroid excretion ($P<0.02$).

Effect of nicotinic acid, cholestyramine, clofibrate and combination on biliary lipids and lithogenic index

	Bile cholesterol (molar %)	Lithogenic index
Nicotinic acid n=13 before	8.5+/-0.7	0.85 +/- 0.07
during	10.0 +/- 0.9 p<0.01	1.00 +/- 0.09 p<0.01
Cholestyramine n=19 before	8.7 +/- 0.5	0.87 +/- 0.05
during	7.0 +/- 0.4	0.71 +/- 0.05 p<0.001
Clofibrate n=11before	8.5 +/-0.3	0.85 +/- 0.3
during	12.1 +/- 0.9 p<0.001	1.30 +/- 0.13 p<0.01
Combination with cholstyramine	9.0 +/- 1.0 p<0.01	0.92 +/- 0.10 p<0.05

Angelin et al 1979

HDL and atherosclerosis

Does the way HDL is increased influence clinical outcome?

ApoA-I infusion

HDL ↑

Fecal BA ↑

Fecal NS ↑

Regression of atherosclerosis!

CETP inhibition

Torcetrapib

Brousseau et al. NEJM 2004

HDL  **106%**

Torcetrapib

HDL **2X**

C4

Latho

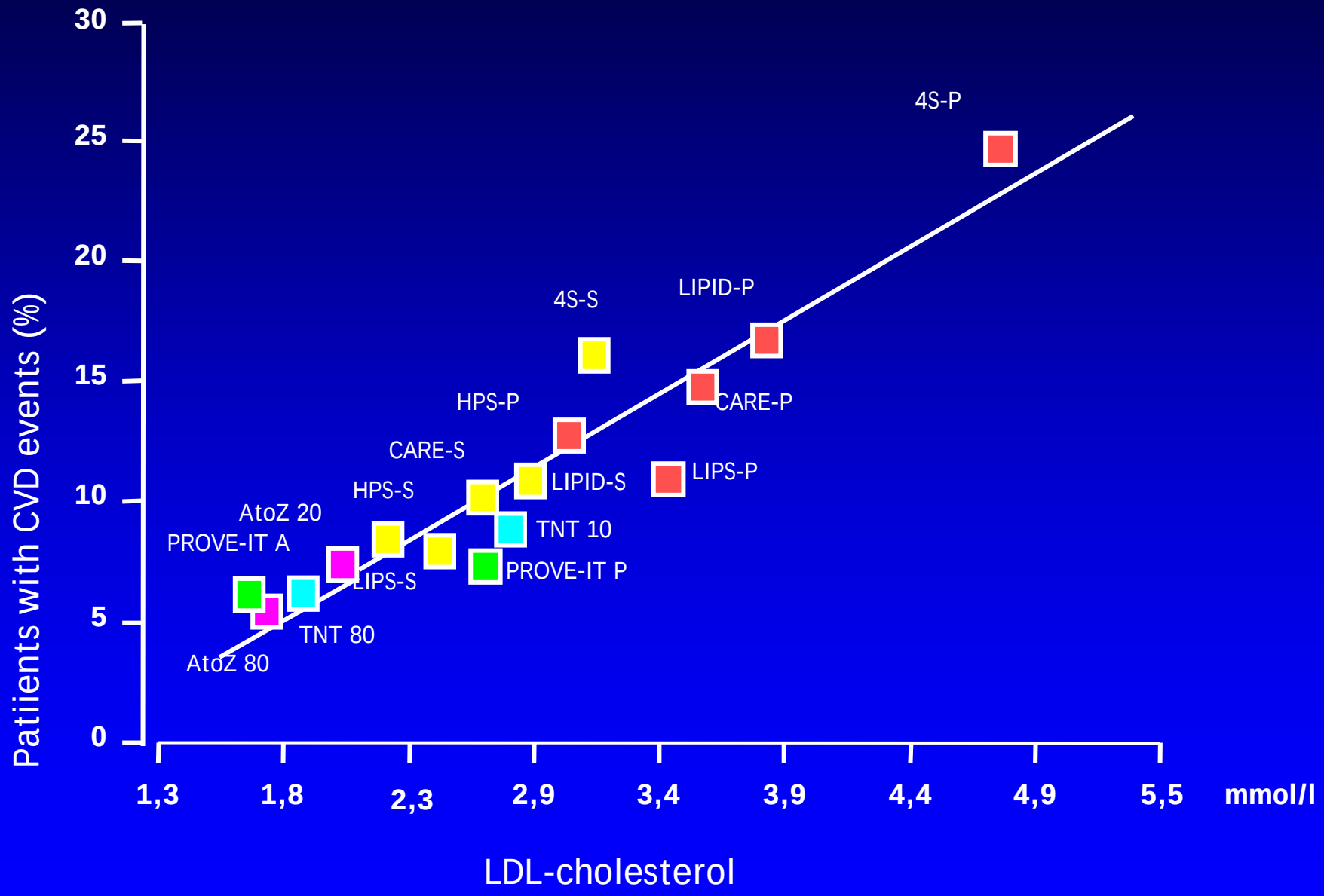
Fecal BA

Fecal NS

Torcetrapib

Negative outcome in illuminate-patient end-point study

LDL-cholesterol cardiovascular disease (CVD) – secondary preventive studies



Ballantyne CM. Am J Cardiol. 1998, O'Keefe JH et al, JACC 2004

Summary and Conclusions

Use of the CETP inhibitor, torcetrapib, in the ILLUMINATE trial was associated with:

- **a predicted substantial increase in HDL-C and decrease in LDL-C**
- **an off-target pharmacology consistent with activation of the renin-angiotensin-aldosterone system**
- **an increased risk of all-cause mortality and CVD morbidity that triggered a premature termination of the trial**

The adverse clinical outcome associated with use of torcetrapib may have been the consequence of an off-target pharmacology but the possibility of an adverse effect of CETP inhibition cannot be excluded by the results of this randomized trial.

Possibilities: 1. Blood pressure

2. No effect on the excretion of sterols from the human body

3. Enrichment of cholesterol in HDL

4. 40 % of the population had diabetes-is increasing HDL among a good thing per se.