Epidemiologic and Strategic Assessment of Atherosclerotic Cardiovascular Disease

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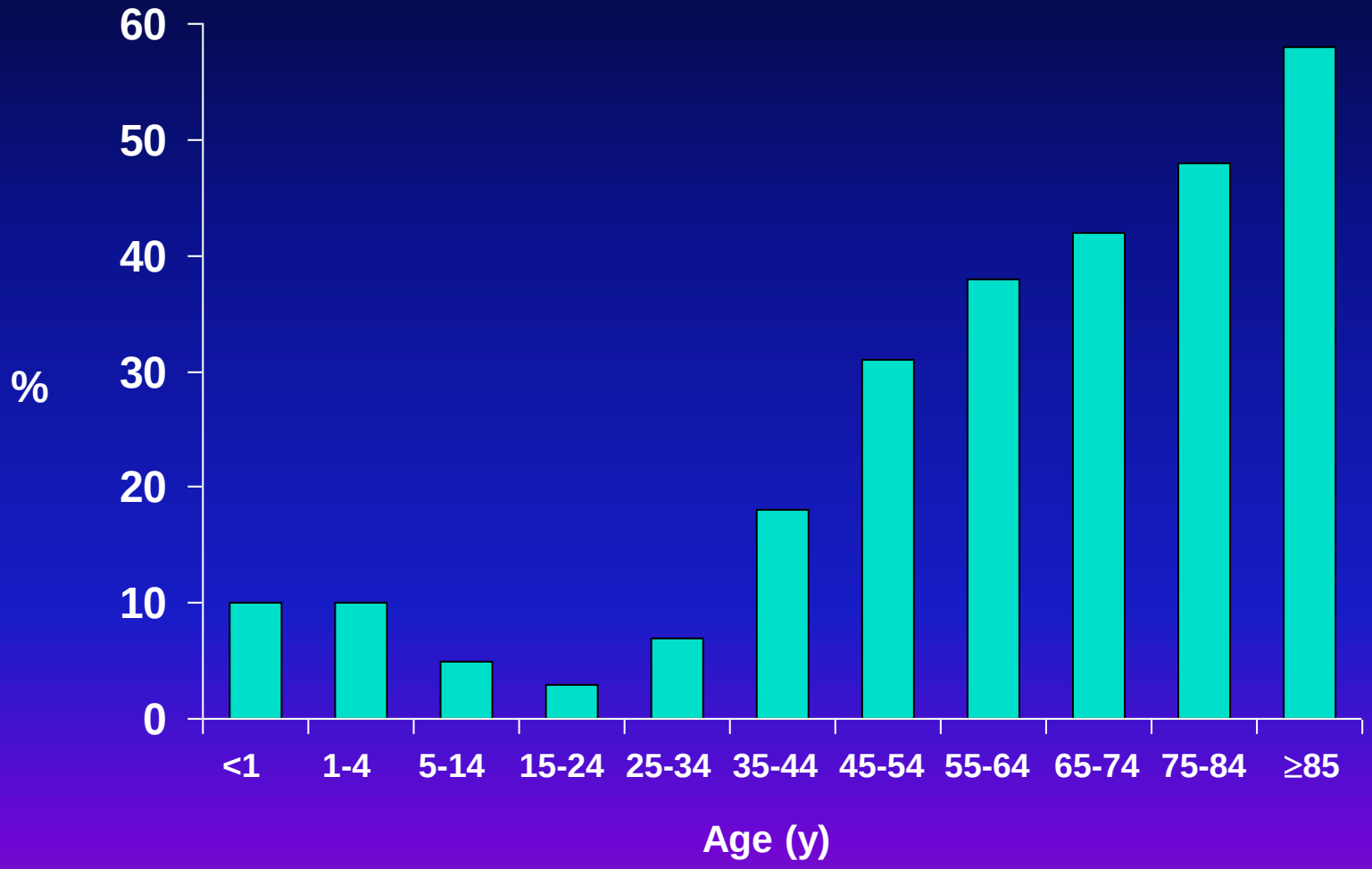
Deaths from Leading Causes (US 1994)

Rank	Disease	Number
1	Heart	734,090
2	Cancer	536,860
3	Cerebrovascular	154,350
4	COPD and allied conditions	101,870
5	Accidents	90,140
6	Pneumonia and influenza	82,090
7	Diabetes	55,390
8	HIV infection	41,930
9	Suicide	32,410
10	Chronic liver disease	25,730
Other	All other causes of death	431,140
Total		2,286,000

NHLBI Factbook 1995.

Percentage of Deaths due to CVD by Age (US 1994)



NHLBI Factbook 1995.

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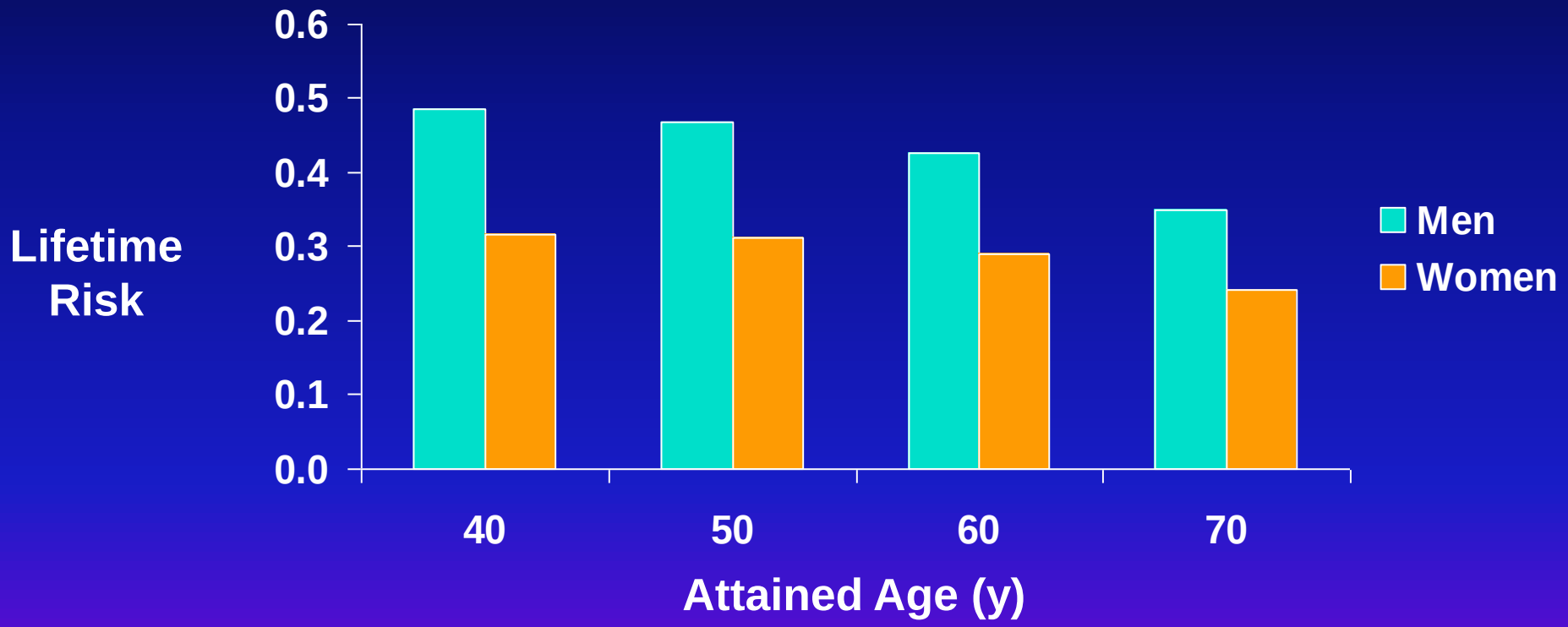
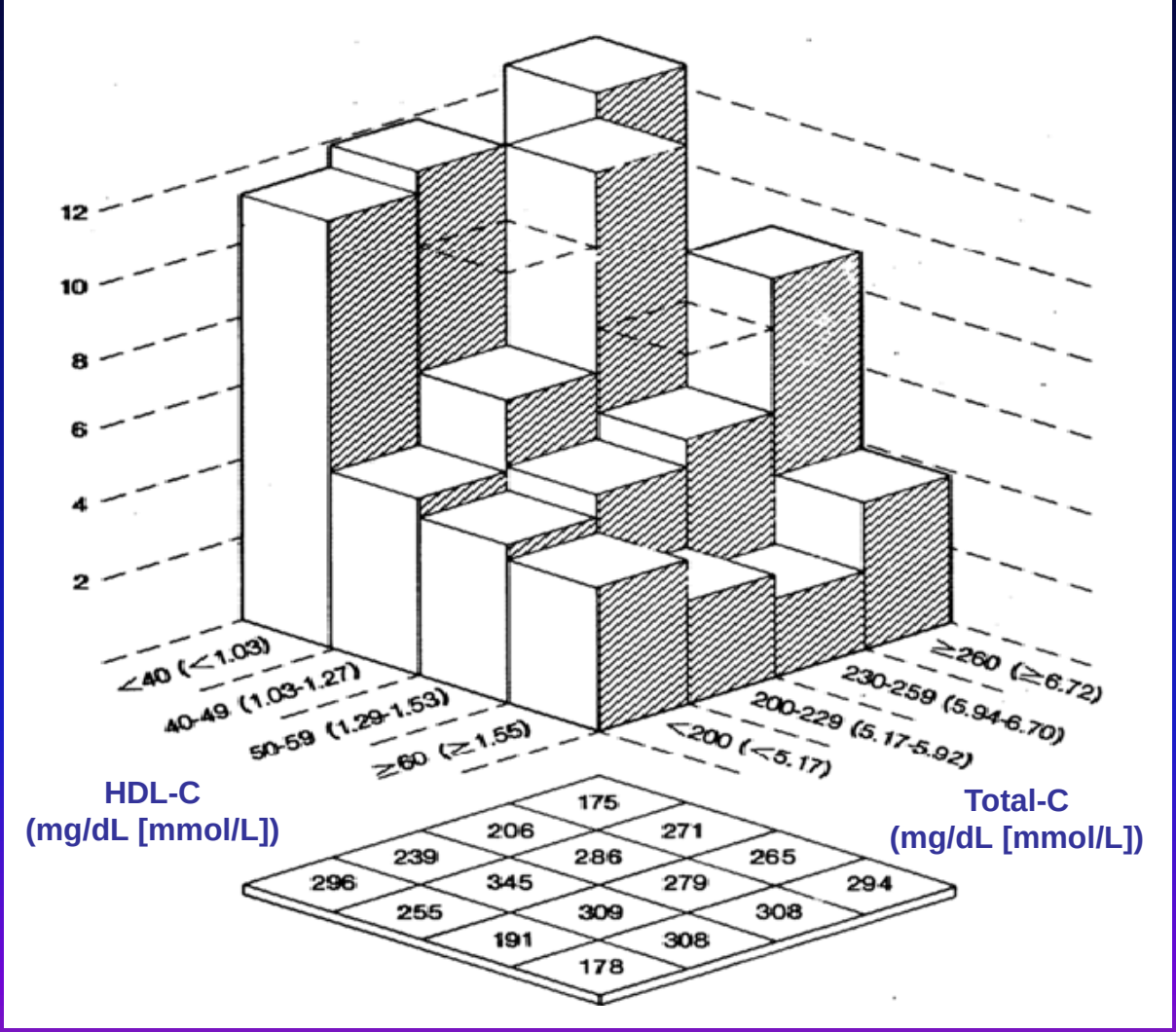
Lifetime Risk of CHD by Age



Lloyd-Jones et al. *Lancet.* 1999;353:89.

4-Year Incidence of CHD by HDL-C and Total-C

% Incidence Rates for CHD



Castelli et al. *JAMA.* 1986;256:2835.

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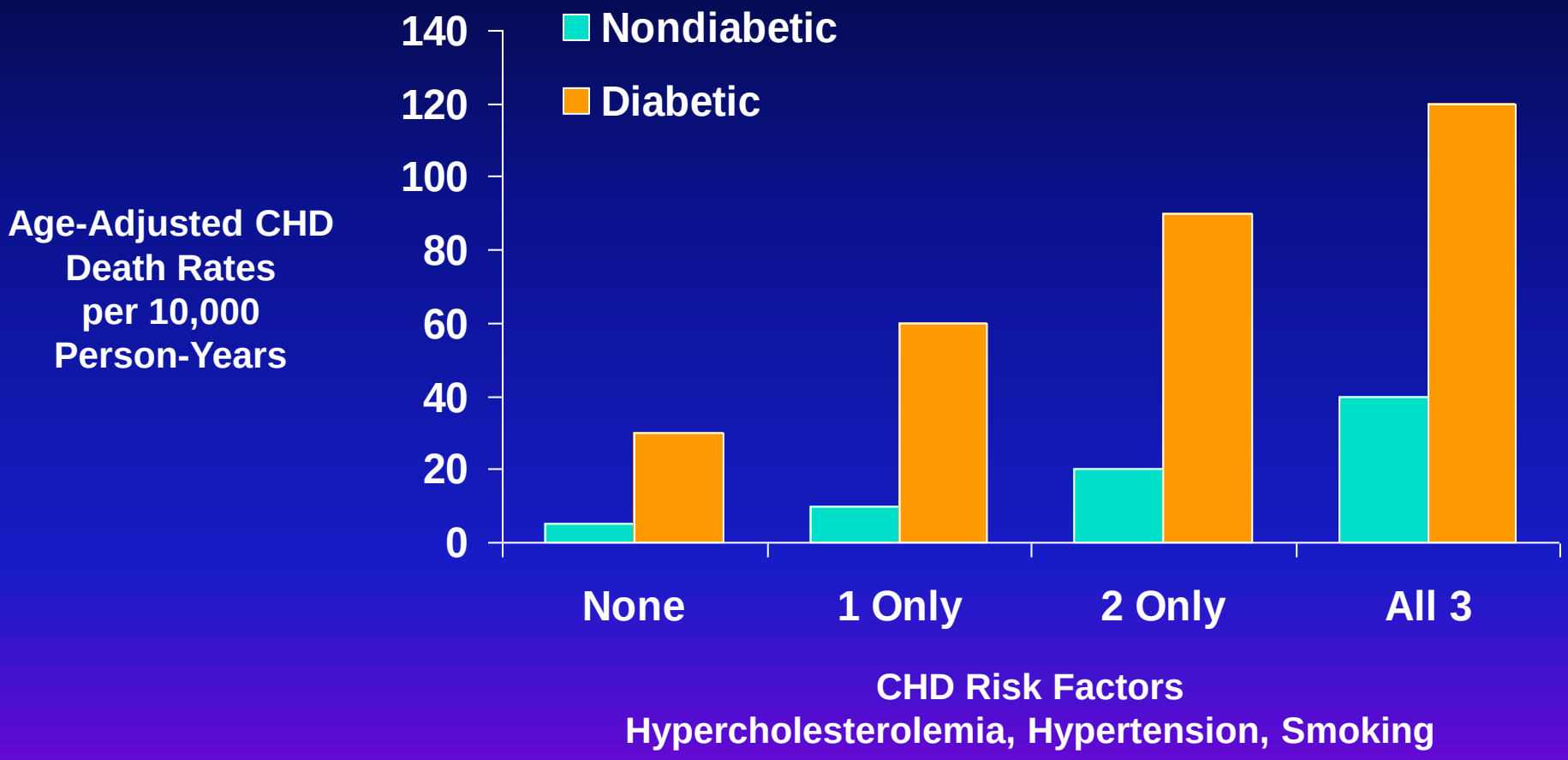
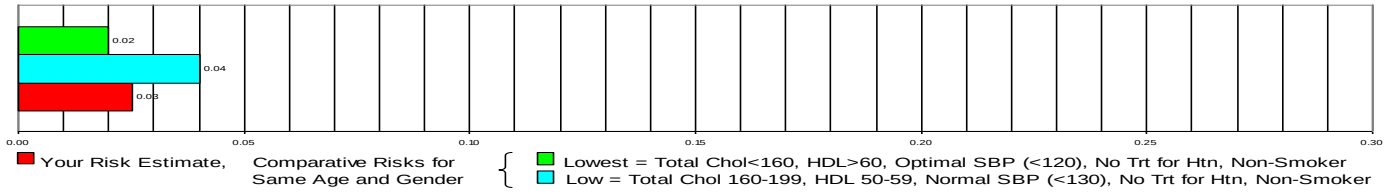
Age-Adjusted CHD Death Rates by CHD Risk Factors in MRFIT



Stamler et al. *Diabetes Care.* 1993;16:434.

ATPiii Risk-Assessment Spreadsheet

From The Framingham Heart Study		Enter Values Here	
CHD(MI and Coronary Death) Risk Prediction			***National Cholesterol Education Program Adult Treatment Panel III***
Risk Factor	**Units**	**(Type Over Placeholder Values in Each Cell)**	**Notes**
Gender	male (m) or female (f)	f	
Age	years	70	
Total Cholesterol	mg/dL	130	
HDL	mg/dL	60	
Systolic Blood Pressure	mmHg	119	
Treatment for Hypertension {Only if SBP≥120}	yes (y) or no (n)	n	
Current Smoker	yes (y) or no (n)	y	
Time Frame for Risk Estimate	10 years	10	
Your Risk (The risk score shown is derived on the basis of an equation. Other NCEP materials, such as ATP III print products, use a point-based system to calculate a risk score that approximates the equation-based one.)	0.03	3%	*If value is < the minimum for the field, enter the minimum value. If value is > the maximum for the field, enter the maximum value.*



These functions and programs were prepared by Ralph B. D'Agostino, Sr., Ph.D. and Lisa M. Sullivan, Ph.D., Boston University and The Framingham Heart Study and Daniel Levy, M.D., Framingham Heart Study, National Heart, Lung and Blood Institute.

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Lipid Modification and Event Reduction

Major Statin Trials

LDL-C Levels ↑

	1º Prevention	2º Prevention
	WOSCOPS	4S
	AFCAPS/ TexCAPS	LIPID CARE

Clinical Trial Findings with Statins

- ↓ In LDL-C required for ↓ in CHD morbidity/mortality
- ↓ In all-cause mortality in 2° prevention and ↓ in cardiovascular mortality in 1° prevention
- Studies support treatment in various subgroups
  - women
  - elderly
  - patients with diabetes

Downs et al. *JAMA.* 1998;279:1615. Goldberg et al. *Circulation.* 1998;98:2513. Lewis et al. *J Am Coll Cardiol.* 1998;32:140. Lewis et al. *Ann Intern Med.* 1998;129:681. Miettinen et al. *Circulation.* 1997;96:4211. Pyörälä et al. *Diabetes Care.* 1997;20:614.

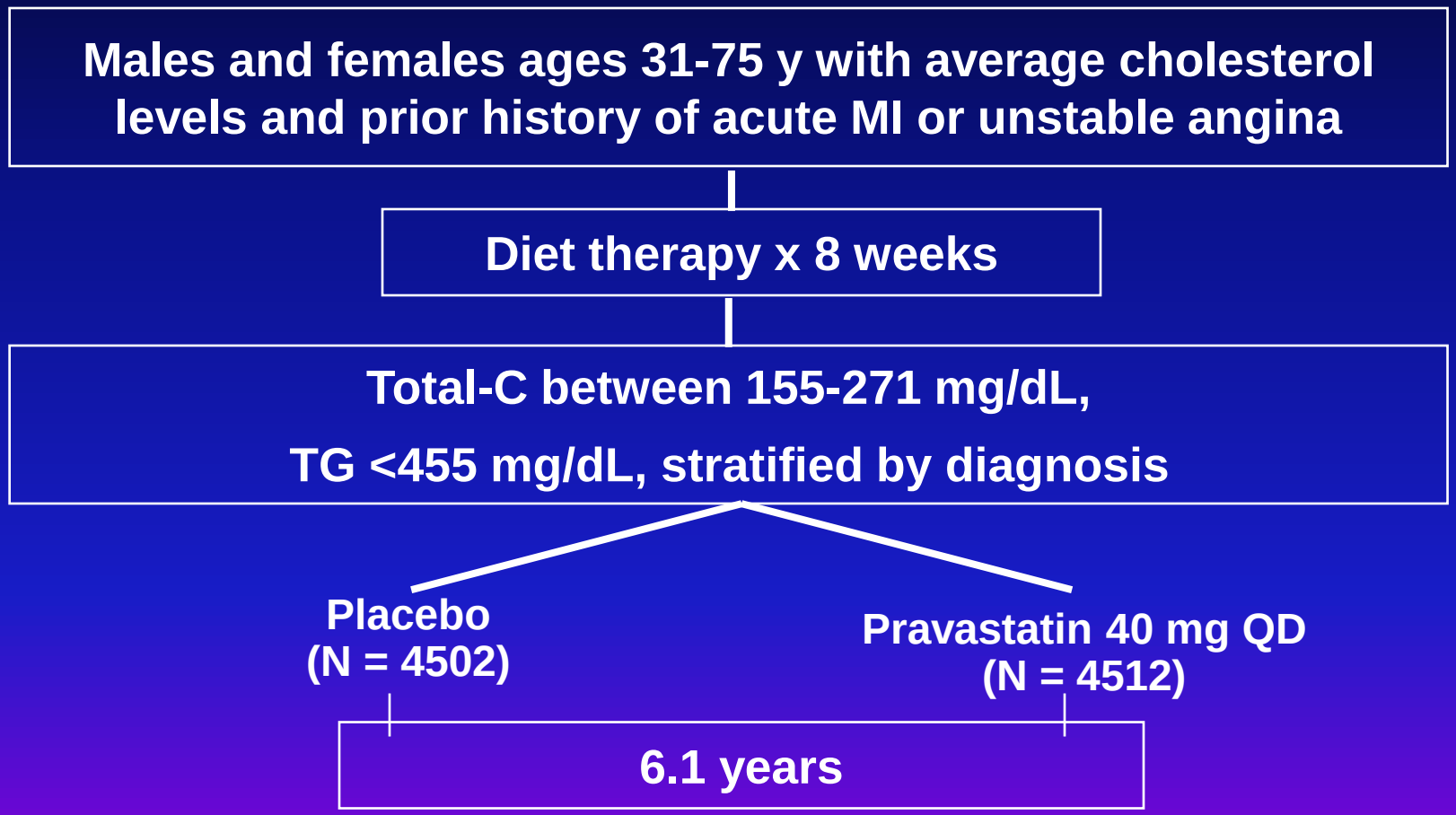
Major Statin Clinical Trials

Secondary Prevention

Study	Study Drug	Number of Patients	Duration (y)	Primary End Point
LIPID	Pravastatin 40 mg/d	9014 (7498 men, 1516 women)	6	CHD death
CARE	Pravastatin 40 mg/d	4159 (3583 men, 576 women)	5	Nonfatal MI/ CHD death
4S	Simvastatin 20-40 mg/d	4444 (3617 men, 827 women)	5	Total mortality

LIPID Study with Pravastatin

Design



LIPID Study Group. *N Engl J Med*. 1998;339:1349.

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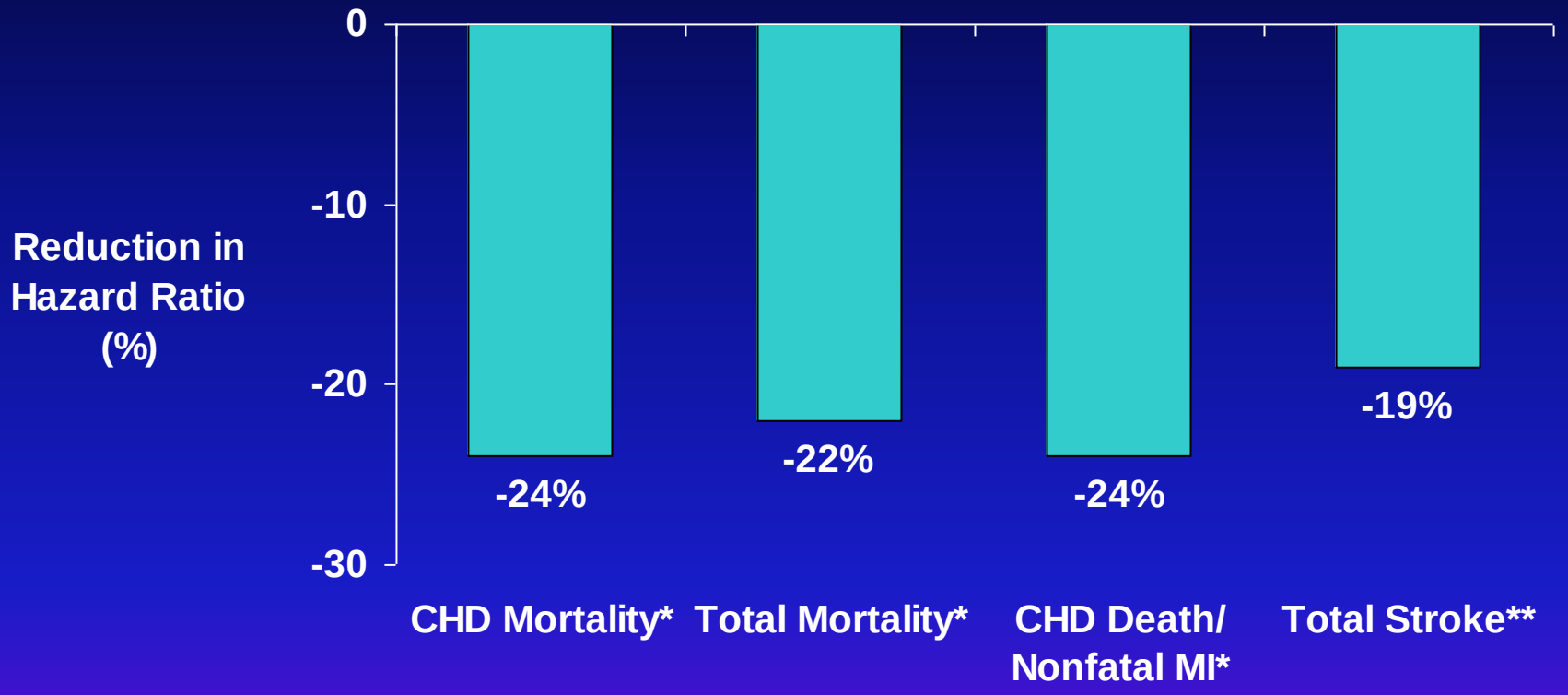
LIPID Study with Pravastatin

Reduction in Cardiovascular Events



* *P*<.001; ** *P*=.048.

LIPID Study Group. *N Engl J Med*. 1998;339:1349.

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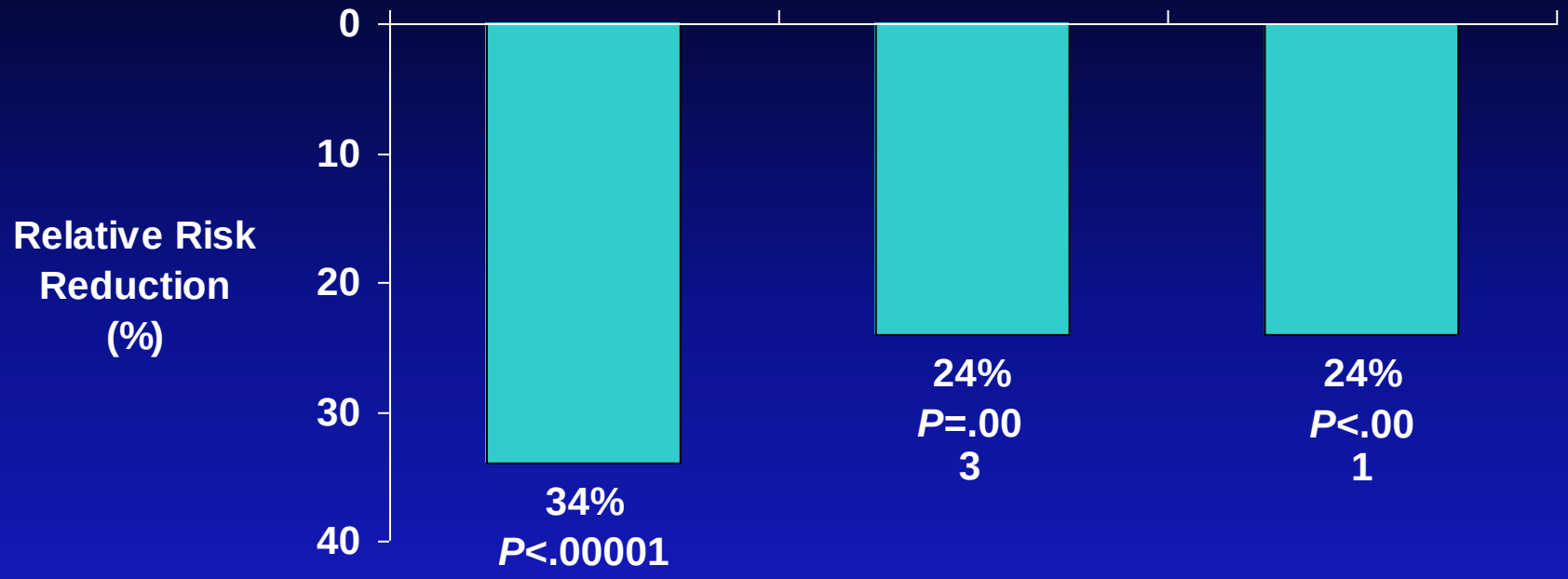
LIPID Study with Pravastatin
Conclusions

- Largest HMG-CoA reductase inhibitor clinical study to date in broadest range of patient types relevant to clinical practice
- Pravastatin significantly ↓ risk of CHD mortality, total mortality, stroke, and need for revascularization procedures
- Benefits of pravastatin demonstrated effectiveness beyond concomitant care with other therapies and across all patient subgroups
- Confirms long-term safety and tolerability of pravastatin

LIPID Study Group. *N Engl J Med*. 1998;339:1349.

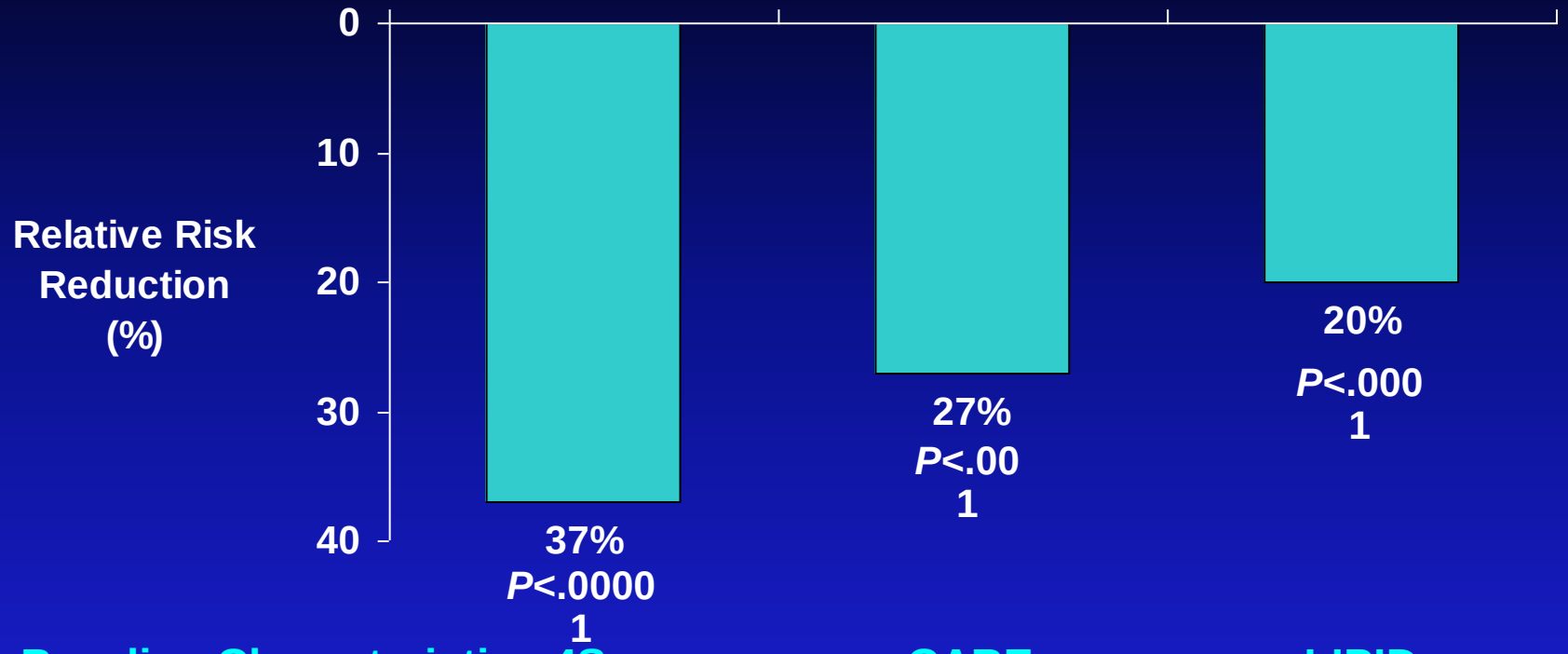
Secondary Prevention Trials
CHD Death and Nonfatal MI



Baseline Characteristics	4S	CARE	LIPID
Total-C (mg/dL)	261	209	218
Aspirin (%)	37	83	83
Revascularization (%)	9	54	41

Lewis et al. *J Am Coll Cardiol.* 1998;32:140. LIPID Study Group. *N Engl J Med*. 1998;339:1349. Pfeffer et al. *J Am Coll Cardiol.* 1999;33:125. Sacks et al. *Circulation.* 1998;97:1446. Scandinavian Simvastatin Survival Study Group. *Lancet.* 1994;344:1383. Scandinavian Simvastatin Survival Study Group. *Lancet.* 1995;345:1274.

Secondary Prevention Trials
Revascularization



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Cerebrovascular Disease in the United States

- Stroke killed 159,942 people in the US in 1996
- Accounts for 1 of every 14.5 deaths
- Third leading cause of death
- Leading cause of serious, long-term disability
- Accounts for more than half of all patients hospitalized for acute neurological disease

American Heart Association. *1999 Heart and Stroke Statistical Update.*

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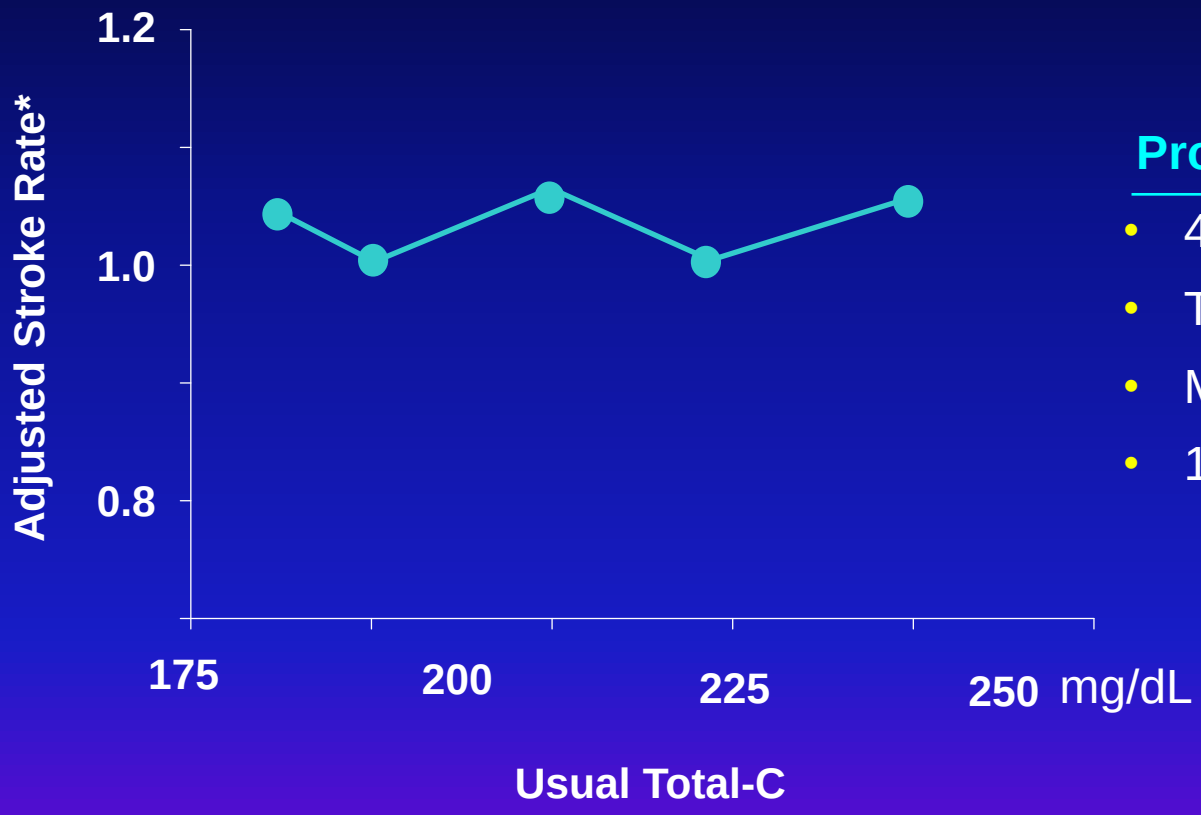
Serum Cholesterol and Stroke Rates Observational Studies



Prospective Studies Collaboration

- 45 prospective observational cohorts
- Total of 450,000 individuals
- Mean follow-up of 16 years
- 13,397 strokes recorded

* Adjusted for study, age, sex, DBP, CAD history, and ethnicity.

Prospective Studies Collaboration. *Lancet*. 1995;346:1647.

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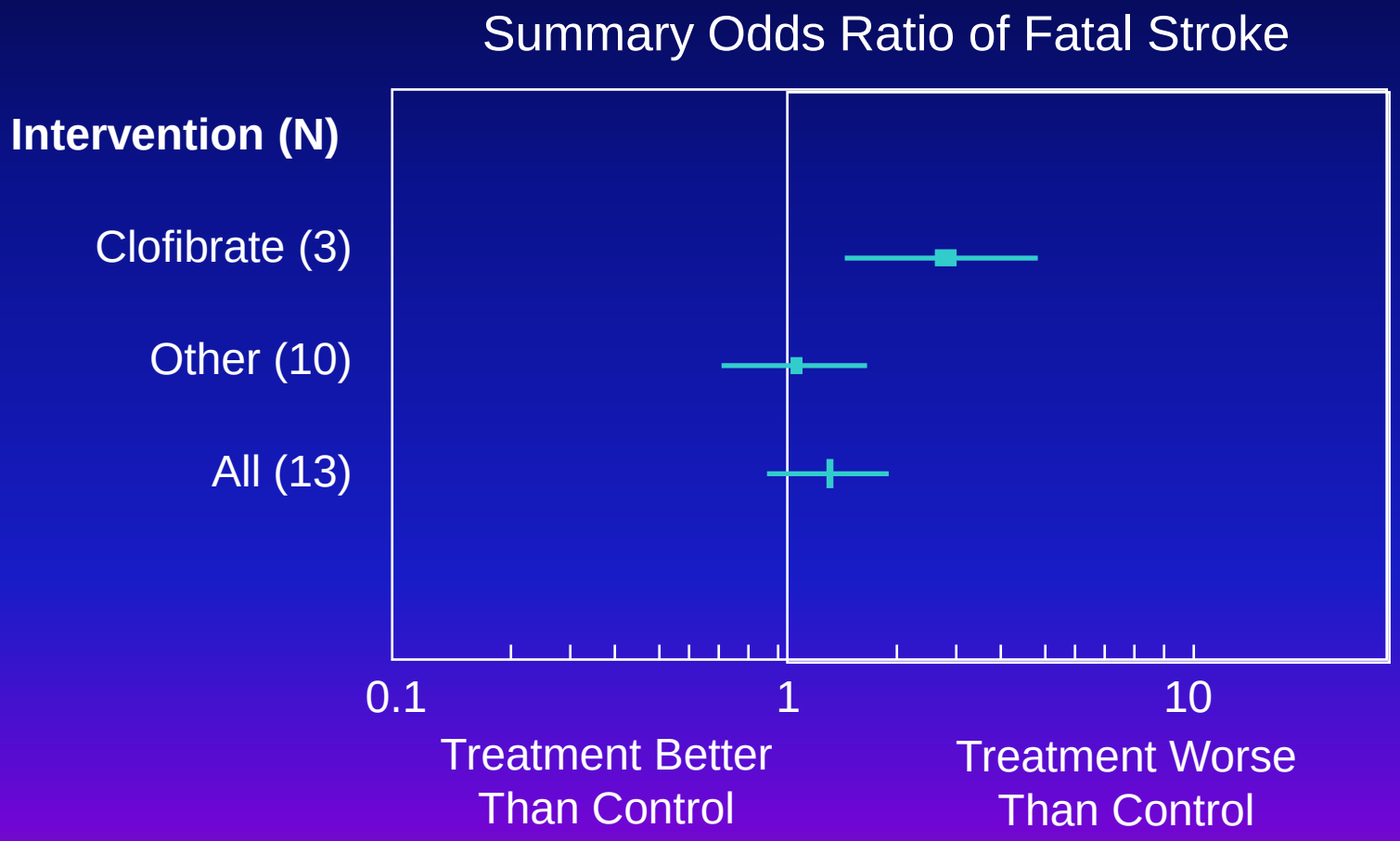
Cholesterol Reduction and Risk of Stroke in Men

Nonstatin Trials



Atkins et al. *Ann Intern Med.* 1993;119:136.

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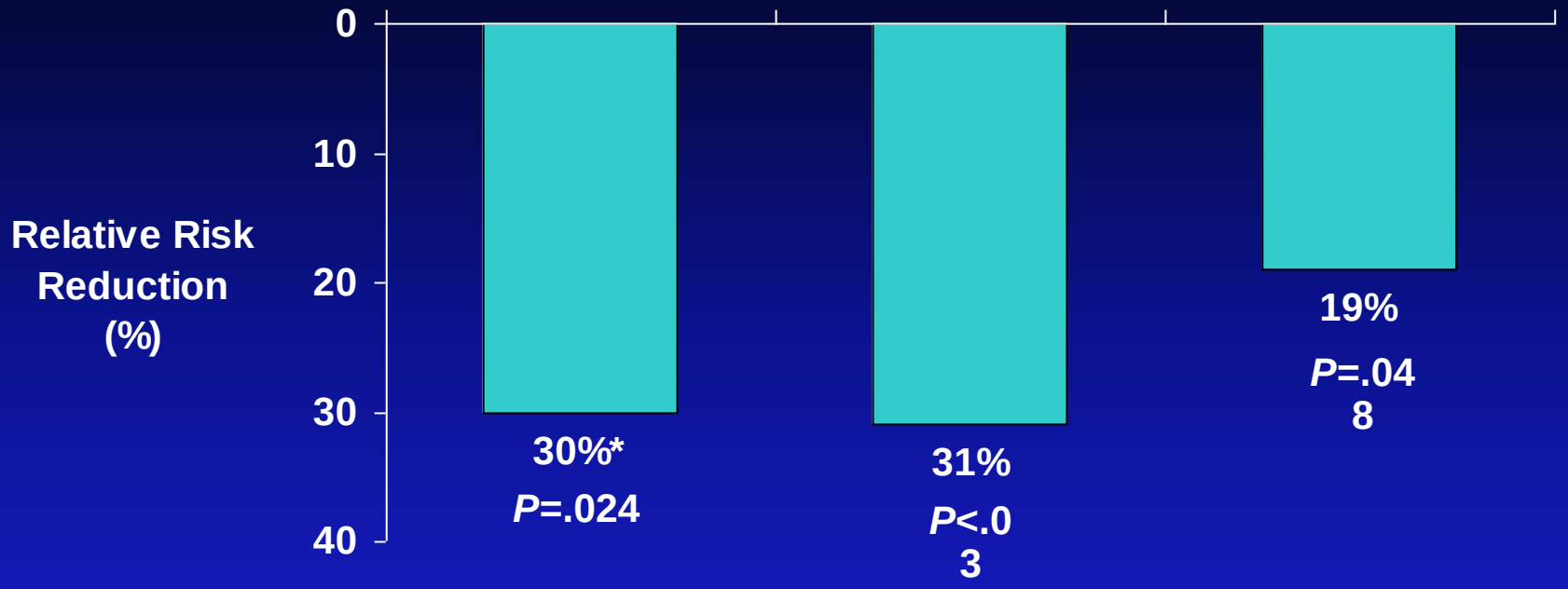
Secondary Prevention Trials

Stroke



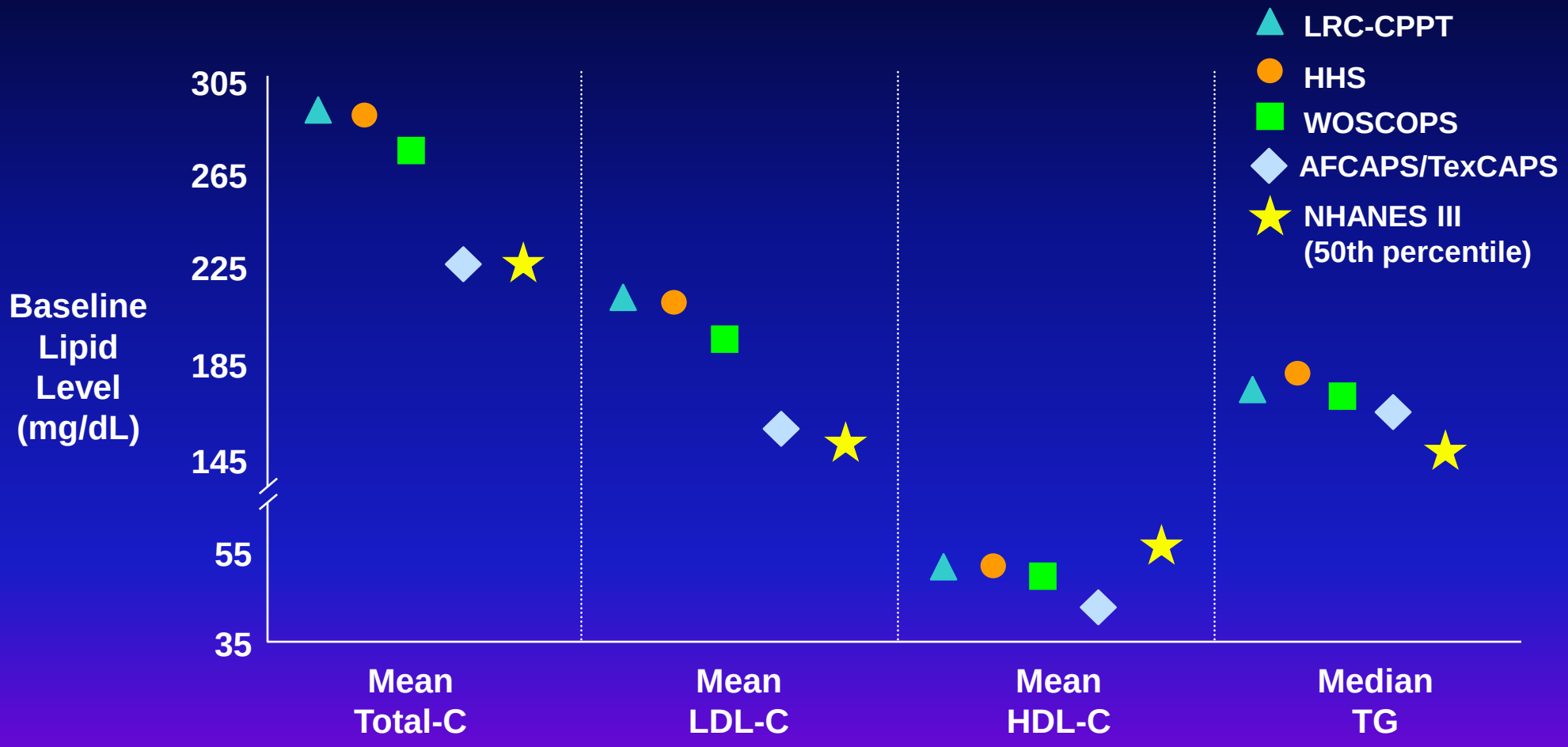
Baseline Characteristics	4S	CARE	LIPID
Total-C (mg/dL)	261	209	218
Aspirin (%)	37	83	83
Revascularization (%)	9	54	41

* Post hoc analysis including transient ischemic attacks (TIAs).

Lewis et al. *J Am Coll Cardiol.* 1998;32:140. LIPID Study Group. *N Engl J Med*. 1998;339:1349. Pfeffer et al. *J Am Coll Cardiol.* 1999;33:125. Plehn et al. *Circulation.* 1999;99:216. Sacks et al. *Circulation.* 1998;97:1446. Scandinavian Simvastatin Survival Study Group. *Lancet.* 1994;344:1383. Scandinavian Simvastatin Survival Study Group. *Lancet.* 1995;345:1274.

Comparison of Primary Prevention Studies

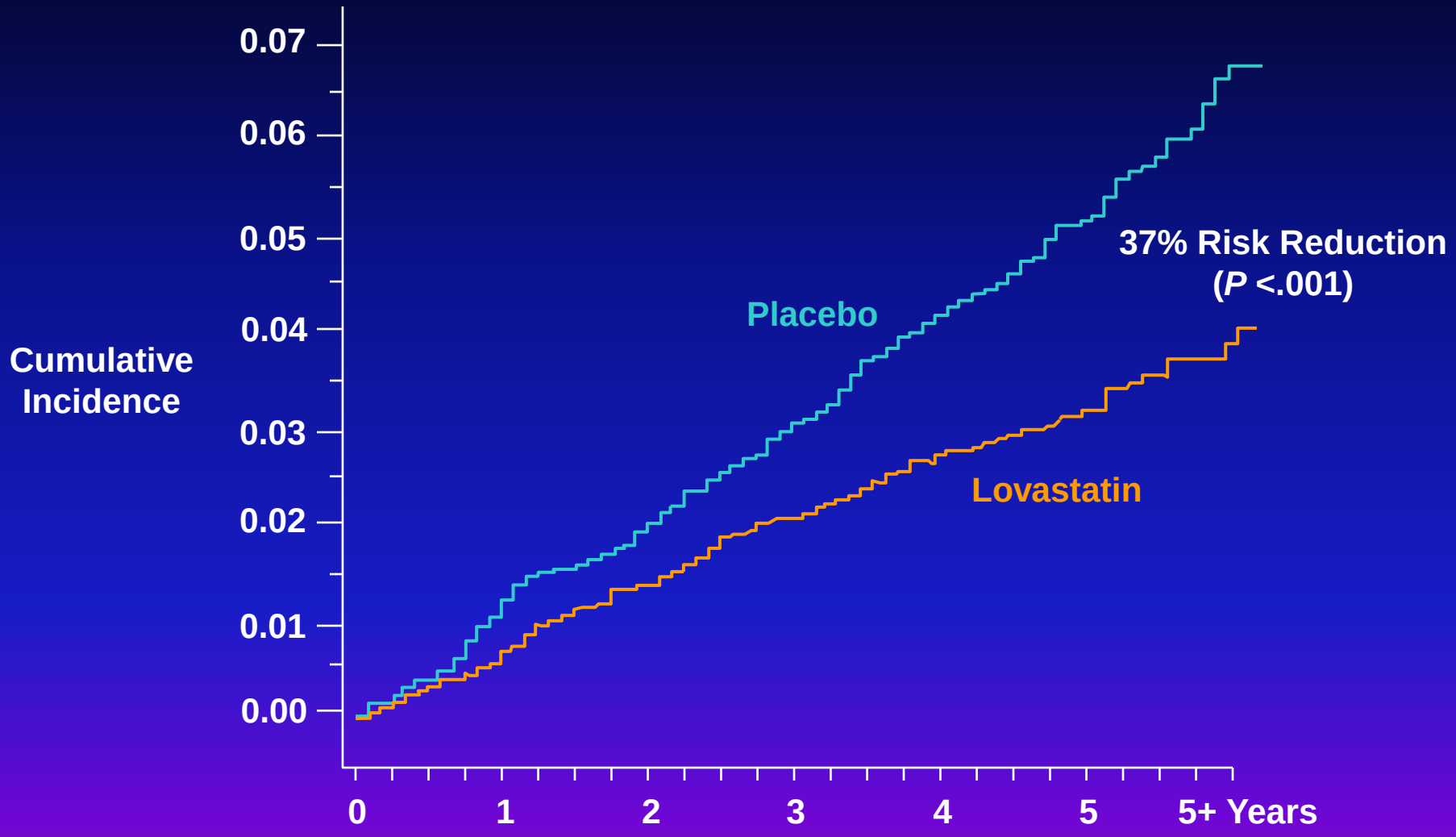
Lipid Parameters



Downs et al. *JAMA.* 1998;279:1615. Lipid Research Clinics Program. *JAMA.* 1984;251:351. Manninen et al. *JAMA.* 1988;260:641. National Center for Health Statistics. 1996. Shepherd et al. *N Engl J Med.* 1995;333:1301.

AFCAPS/TexCAPS

First Acute Major Coronary Event

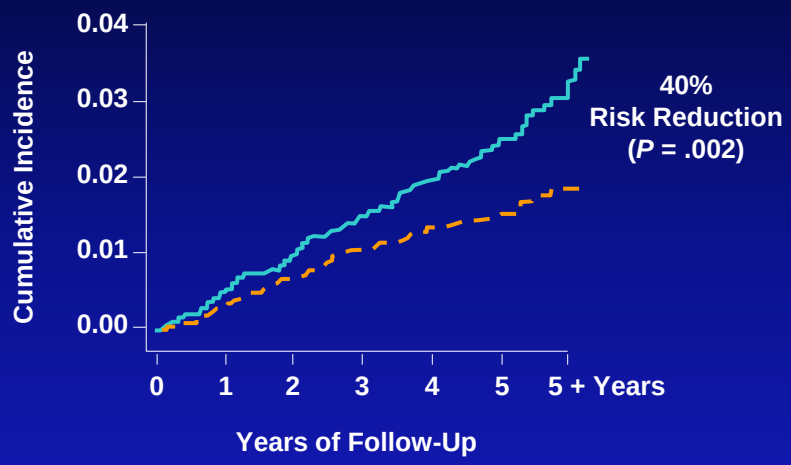


Downs et al. *JAMA.* 1996;279:1615.

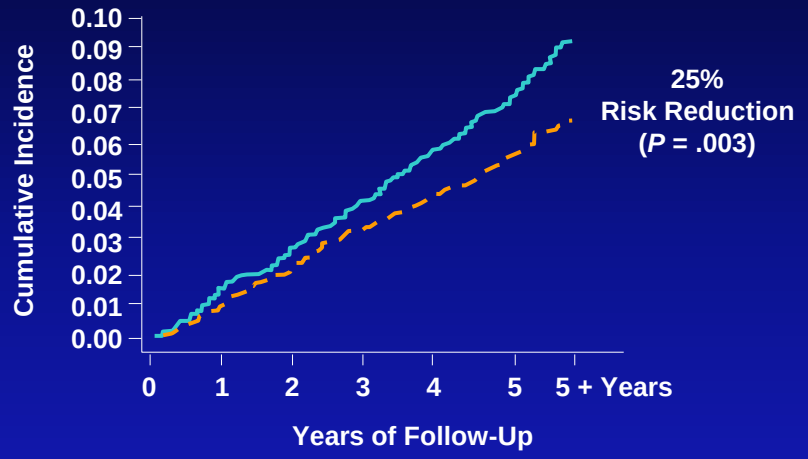
AFCAPS/TexCAPS

Secondary End Point Analyses

Fatal and Nonfatal MI



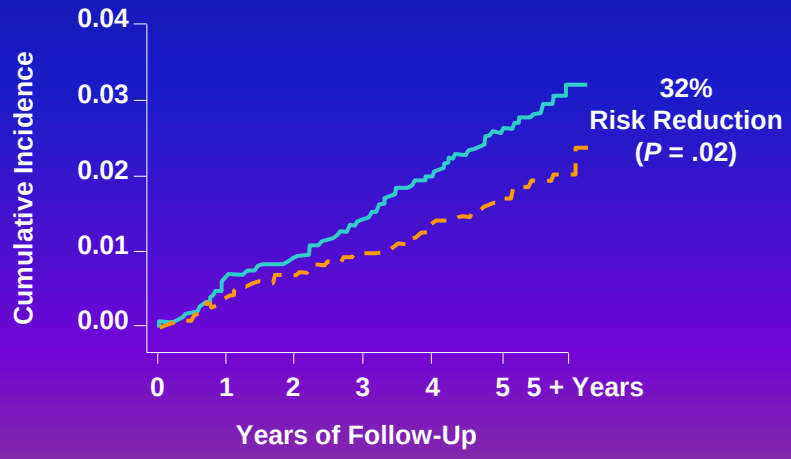
Cardiovascular Events



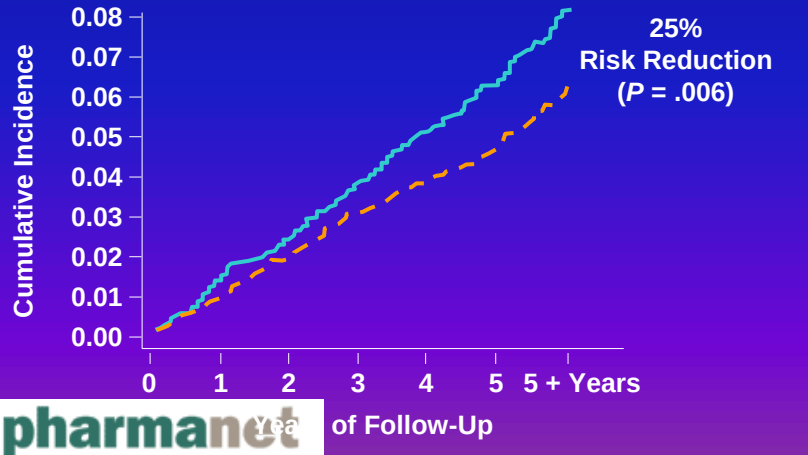
Placebo

Lovastatin

Unstable Angina



Coronary Events



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Downs et al. *JAMA.* 1998;279:1615.

AFCAPS/TexCAPS Summary of Results

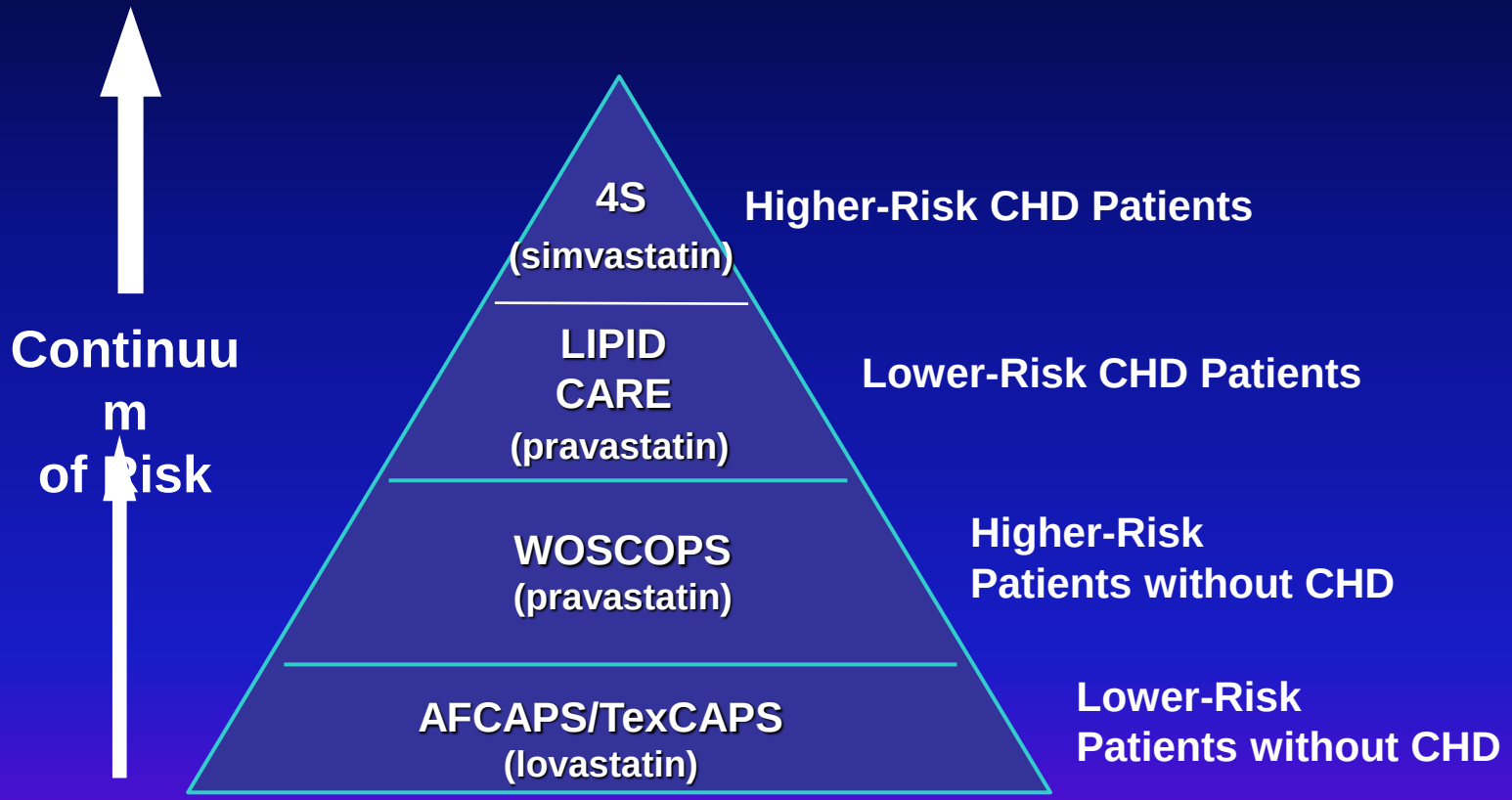
- Clinical benefit within first year of treatment and continued thereafter
- Benefit apparent for all LDL-C tertiles
  - range 90 - 235 mg/dL
- Benefit apparent for all HDL-C tertiles
  - greatest in lower 2 tertiles (<40 mg/dL)
- Clinical benefit consistent for subgroups
  - women
  - risk factors: age, NIDDM, HTN, smoking, family history
- ***No total mortality benefit***

Downs et al. *JAMA.* 1998;279:1615.

AFCAPS/TexCAPS Conclusions

- In conjunction with prudent diet, regular exercise, and risk factor modification, lovastatin lowered the risk of first acute major coronary event
- Significant benefit apparent across spectrum of clinical events frequent in the manifestation of atherosclerotic cardiovascular disease
- Treatment beneficial for women and persons with active risk factors

Statin Clinical Outcome Trials
Relevance to Clinical Practice



Downs et al. *JAMA.* 1998;279:1615. LIPID Study Group. *N Engl J Med*. 1998;339:1349. Pfeffer et al. *J Am Coll Cardiol.* 1999;33:125. Scandinavian Simvastatin Survival Study Group. *Lancet*. 1994;344:1383-1389. Shepherd et al. *N Engl J Med.* 1995;333:1301.

Potential Mechanisms of Benefit for Cardiovascular Event Reduction

- Lipid modification
  - ↓ LDL
  - ↓ chylomicron remnants
  - ↓ VLDL remnants
  - ↓ IDL
  - ↑ HDL
- Plaque stabilization
  - ↓ macrophage mobilization
  - ↓ smooth muscle cell proliferation
  - ↓ immunologic response
  - ↓ lipid core
  - ↓ oxidized LDL
- Improved endothelial function
- Reduced platelet aggregation
- Reduced thrombotic and enhanced fibrinolytic state

Rosenson and Tangney. *JAMA*. 1998;279:1643.

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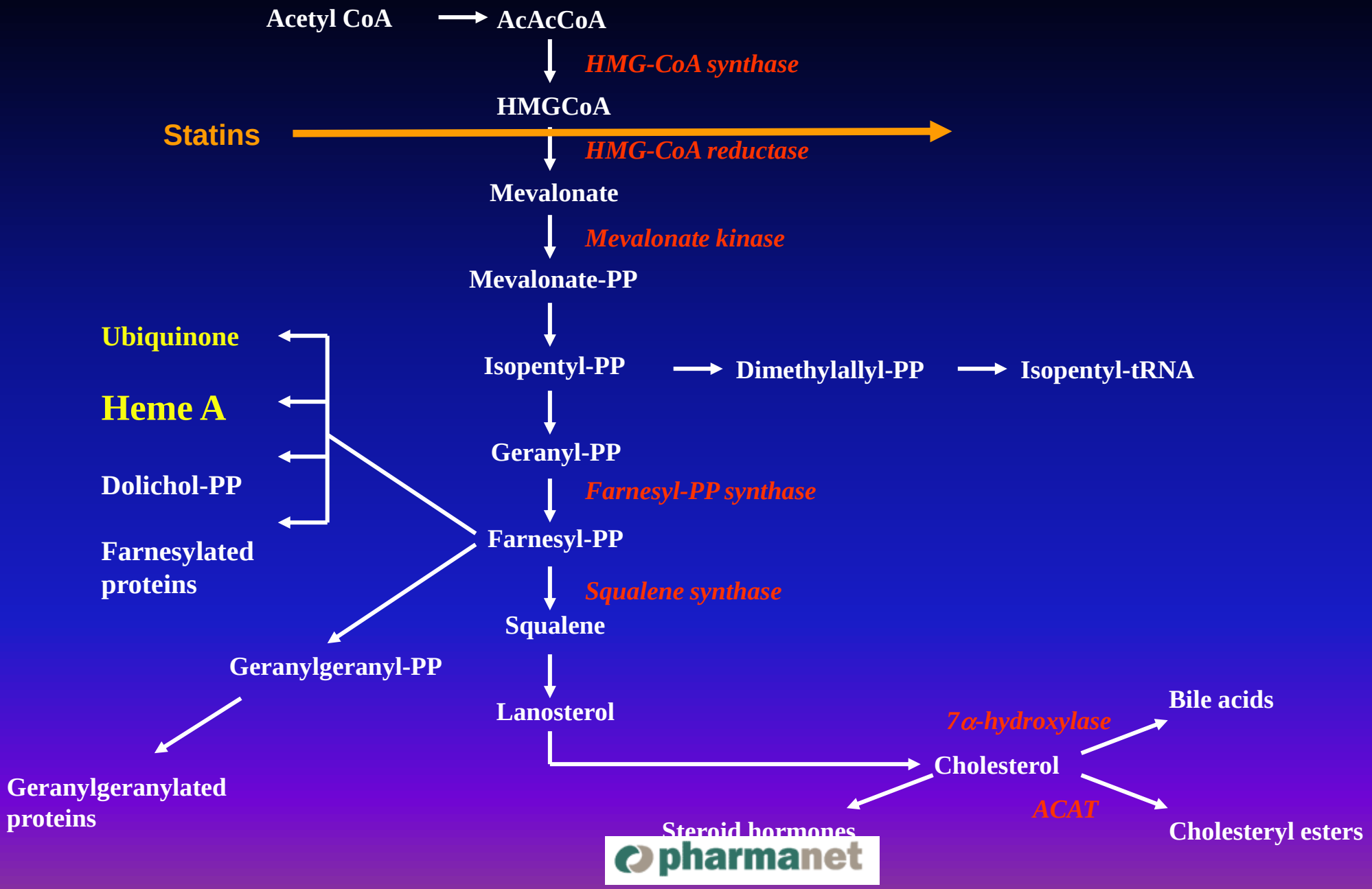
CHOLESTEROL AND ISOPRENOID BIOSYNTHESIS

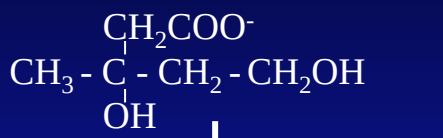


CHOLESTEROL BIOSYNTHESIS

Hydroxymethylglutaryl CoA

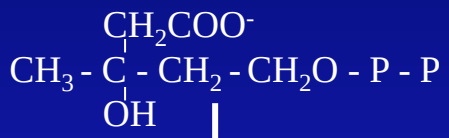
Statins

HMGCoA Reductase

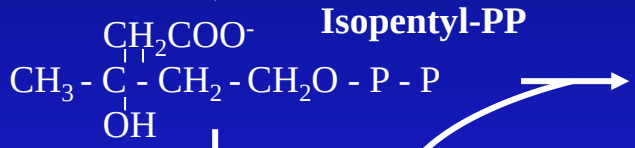


Mevalonate

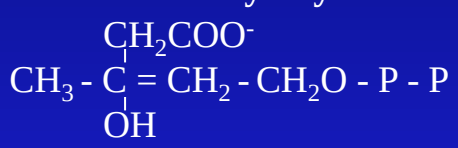
Mevalonate kinase



Mevalonate-PP



Isopentyl-PP



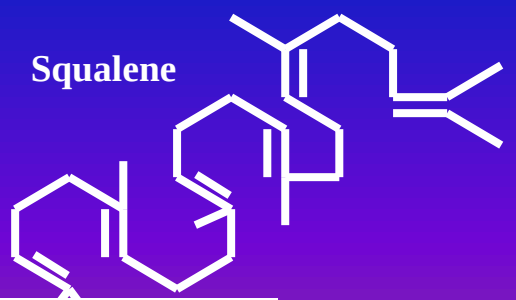
Dimethylallyl-PP

Geranyl-PP

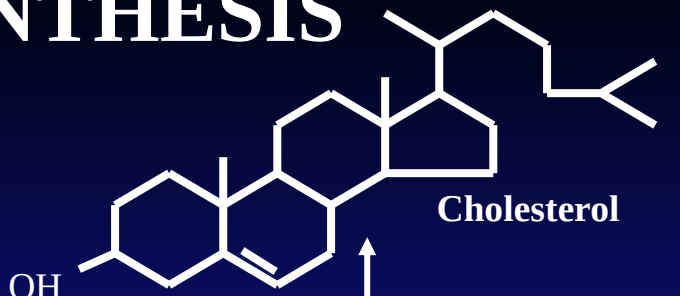
Farnesyl-PP synthase

Farnesyl-PP

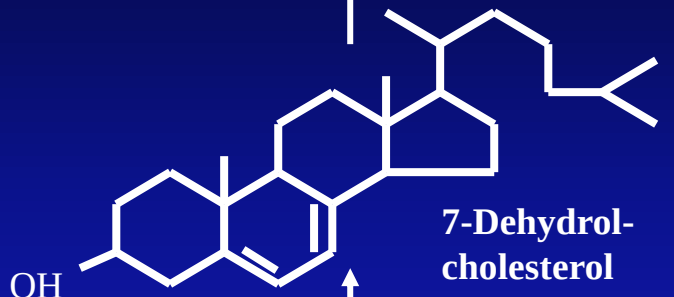
Squalene synthase



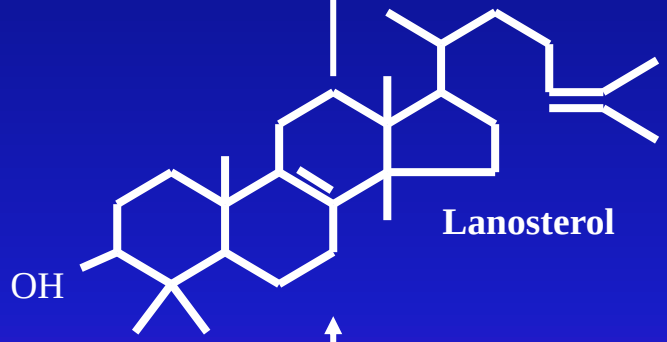
Squalene



Cholesterol



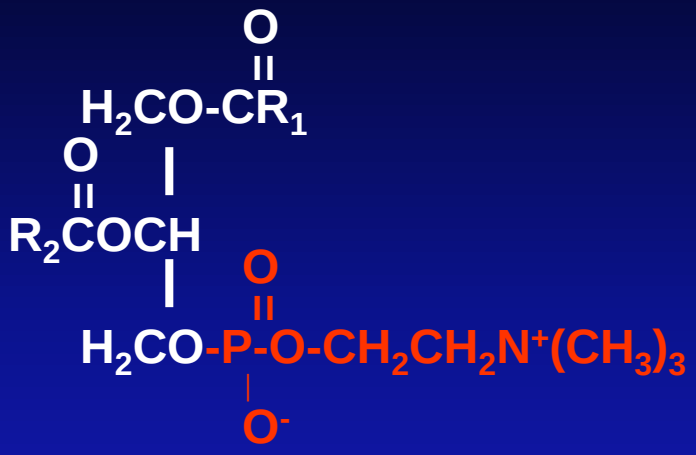
7-Dehydrol-cholesterol



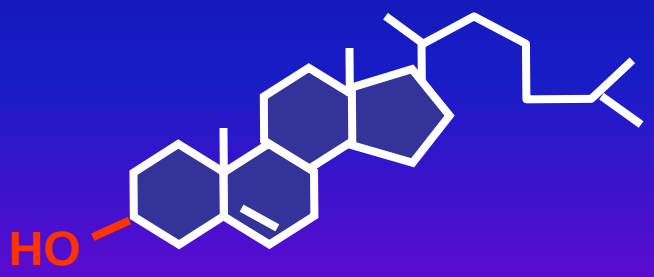
Lanosterol

MAJOR LIPIDS OF PLASMA LIPOPROTEINS

AMPHIPATHIC LIPIDS

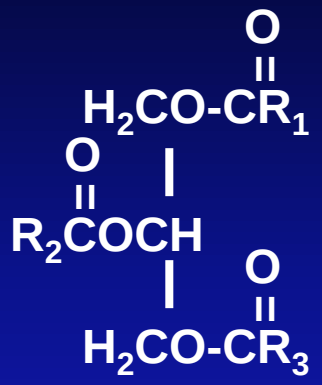


Phospholipid

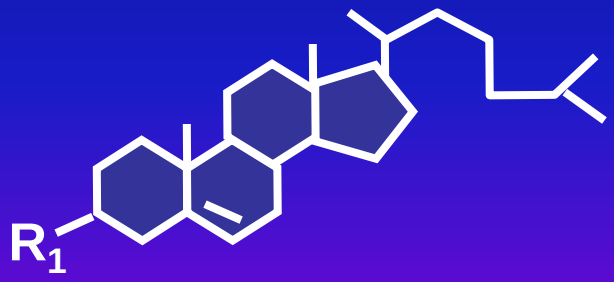


Cholesterol

NEUTRAL LIPIDS

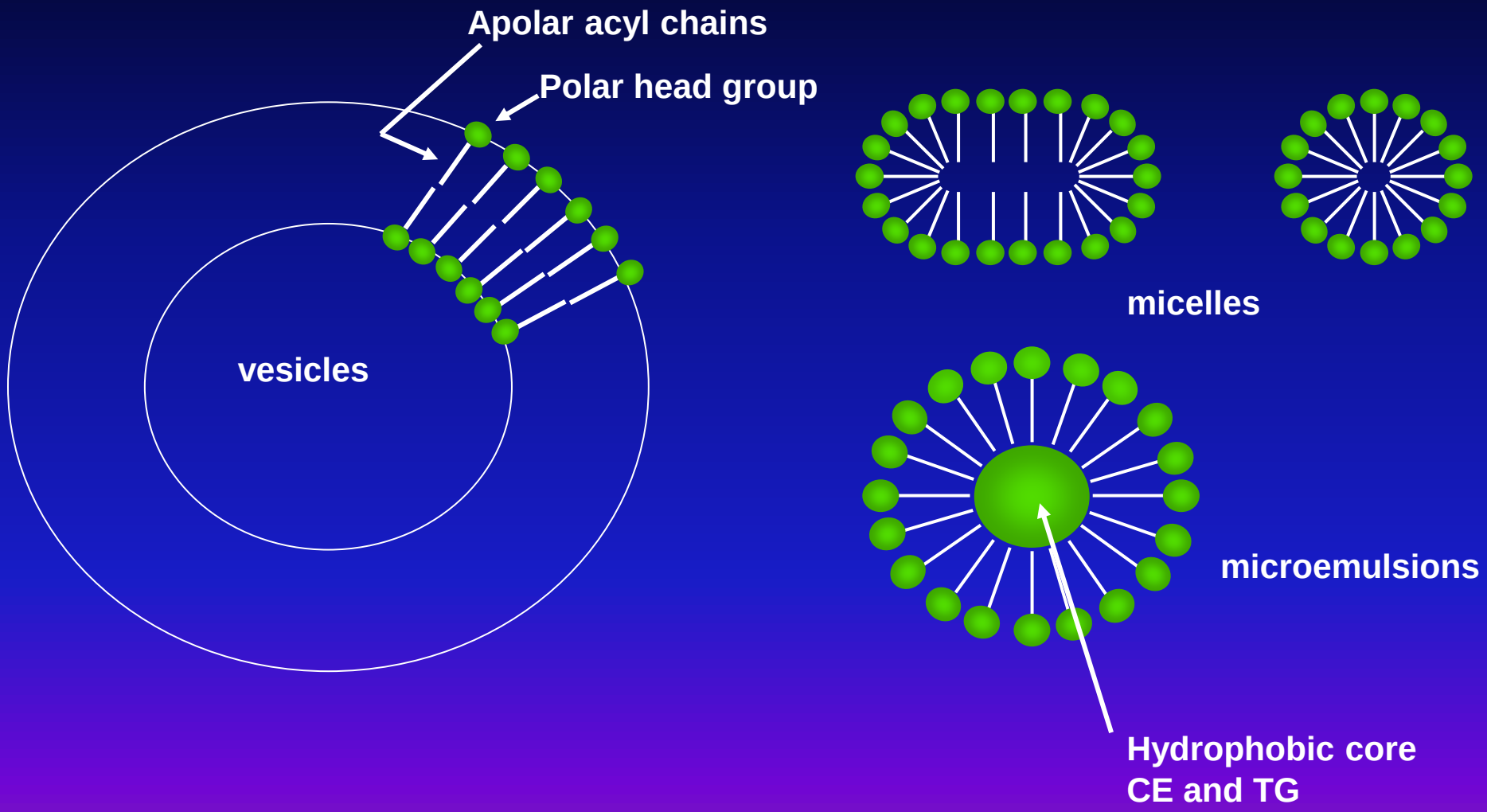


Triglyceride

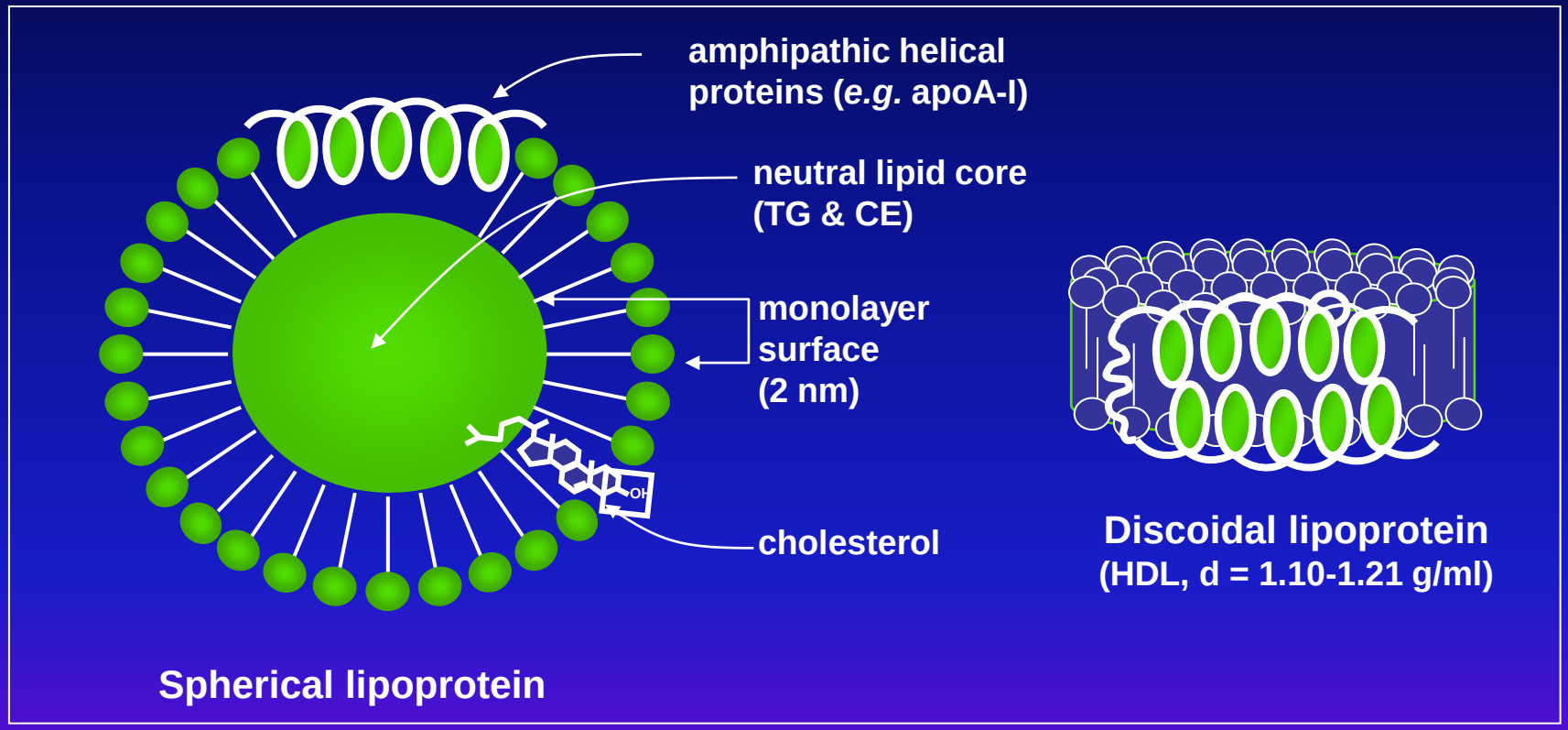


Cholesteryl ester

Lipids in Aqueous Solution



Schematic Representation of Plasma Lipoproteins



Fredrickson Classification

Fredrickson Classification of Lipid Disorders†

Phenotype I – Serum concentration of chylomicrons elevated; triglycerides concentrations are elevated to >99th percentile

Phenotype IIa – Serum concentration of LDL cholesterol elevated; the total cholesterol concentration is >90th percentile. Concentrations of triglyceride and/or apolipoprotein B may also be ≥90th percentile.

Phenotype IIb – Serum concentrations of LDL and VLDL cholesterol elevated; total cholesterol and/or triglycerides may be ≥90th percentile and apolipoprotein B ≥90th percentile

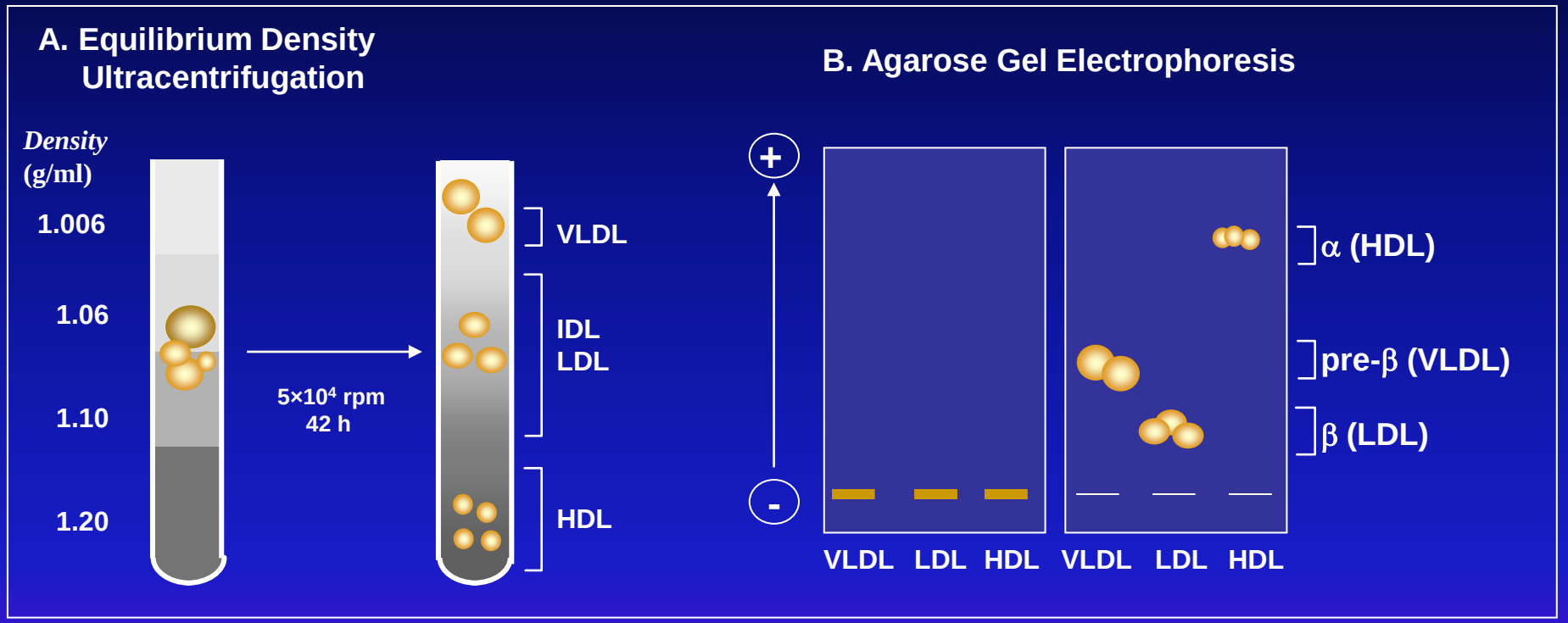
Phenotype III – Serum concentration of VLDL remnants and chylomicrons elevated; total cholesterol and triglycerides >90th percentile

Phenotype IV – Serum concentrations of VLDL elevated; total cholesterol may be >90th percentile and may also see triglyceride concentrations >90th percentile or low HDL

Phenotype V – Elevated serum concentrations of chylomicrons and VLDL; triglycerides >99th percentile

†Adapted from Fredrickson, DS, Ann Intern Med 1971; 75:471.

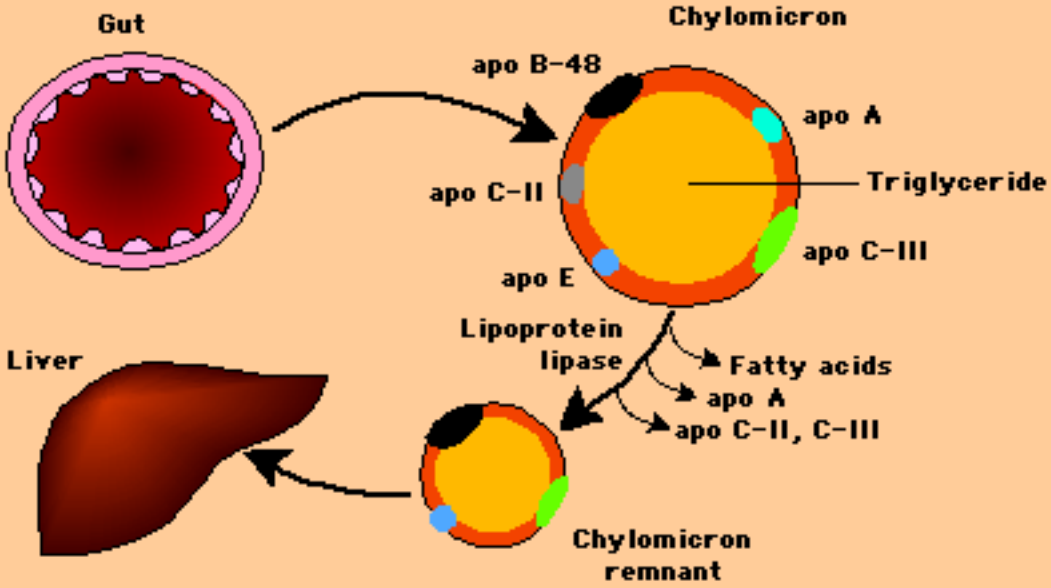
Separation of Plasma Lipoproteins as a Function of their Buoyant Density or their Surface Charge



CHARACTERISTICS AND FUNCTIONS OF APOLIPOPROTEINS IN NORMAL HUMAN PLASMA

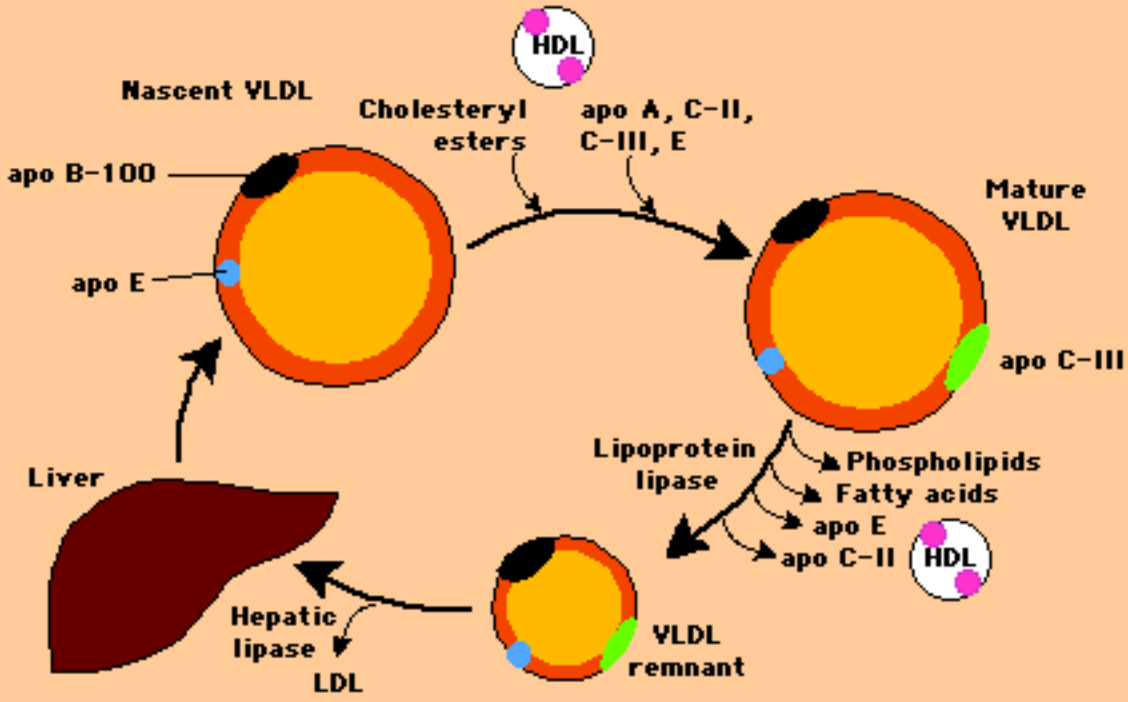
	Plasma concentration *mg/dL*	Distribution in lipoproteins *mol %* HDL	LDL	VLDL	Major tissue source	Molecular weight (polypeptide)	Function
ApoA-I	130	100			Liver	29,016	LCAT activation
ApoA-II	40	100			&	17,414	Unknown
ApoA-IV					intestine	44,465	Unknown
ApoB48					Intestine	240,800	Chylomicron assembly
ApoB100	80		80	10	Liver	512,723	VLDL assembly, LDL receptor ligand
ApoC-I	6	97		3		6,630	Unknown
ApoC-II	3	60		30	Liver	8,900	LPL activator
ApoC-III	12	60	10	30		8,800	Inhibitor of LPL and VLDL binding to LDLr
ApoE	5	50	10	40	Liver etc.	34,145	Ligand for cell surface receptors

Exogenous Pathway of Lipid Metabolism



Exogenous pathway of lipid metabolism In the intestinal cell, absorbed free fatty acids combine with glycerol to form triglycerides, and, to a lesser degree, absorbed cholesterol is esterified to form cholesteryl esters. These lipids are assembled as chylomicrons; the main apolipoprotein (apo) is B-48, but apo C-II and E are acquired as the chylomicrons enter the circulation. Apo C-II is a cofactor for lipoprotein lipase which makes the chylomicrons progressively smaller in part by hydrolyzing the core triglycerides and releasing free fatty acids. The chylomicron remnants that are cleared from the circulation by hepatic chylomicron remnant receptors for which apo E is a high-affinity ligand.

Endogenous Pathway of Lipid Metabolism

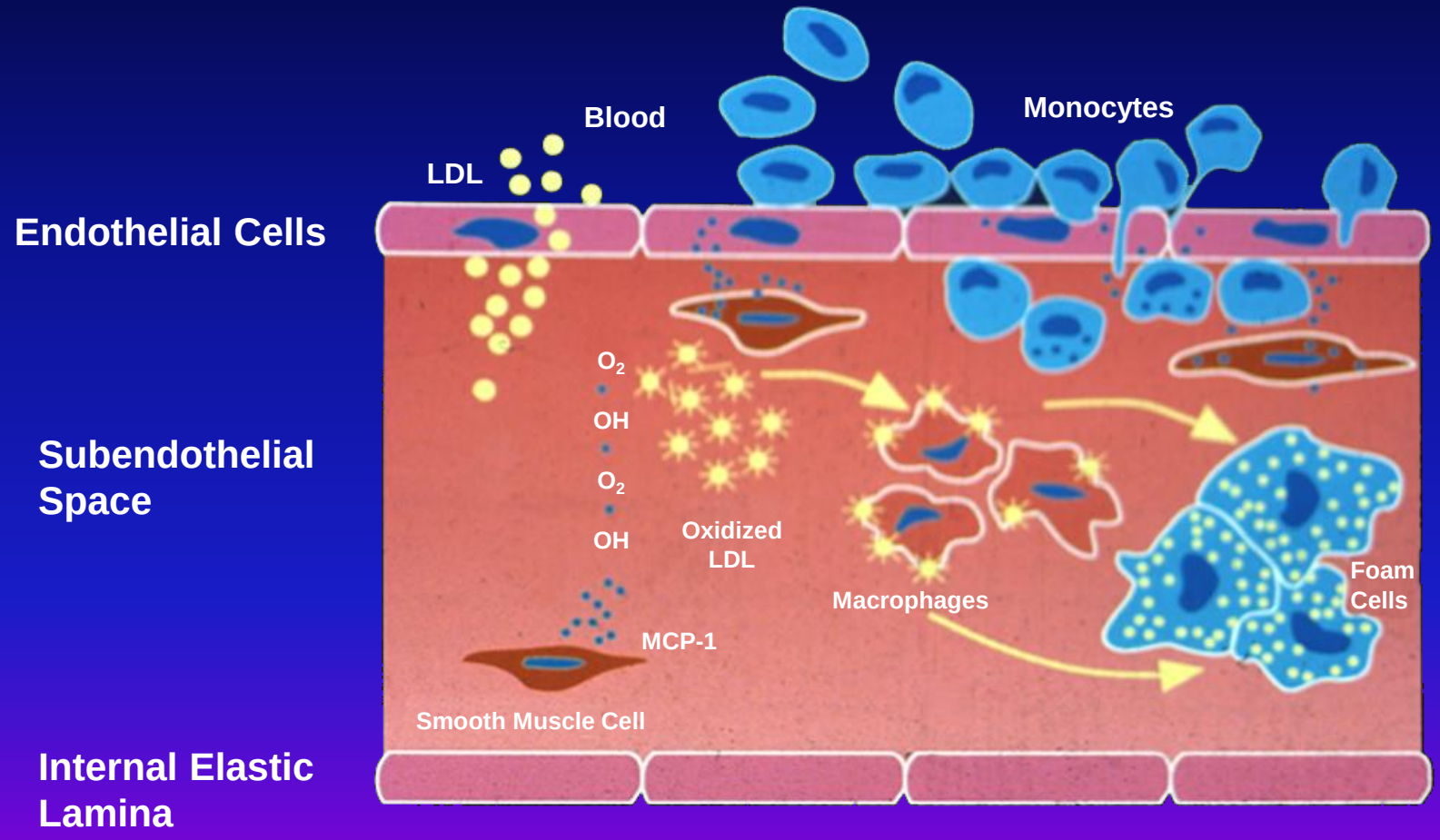


Endogenous pathway of lipid metabolism The endogenous pathway begins with the synthesis in the liver of nascent VLDL particles, containing apolipoproteins (apo) B-100 and E. Cholesteryl esters and other apolipoproteins, some of which are derived from HDL catabolism, are added to form the mature VLDL particle. The lipolytic action of lipoprotein lipase (for which apo C-II is the primary ligand) cleaves VLDL into smaller VLDL remnants that are enriched in apo B-100 and E. The remnants are either cleared by the LDL and remnant receptors in the liver or hydrolyzed by hepatic triglyceride lipase to yield LDL particles containing apo B-100.

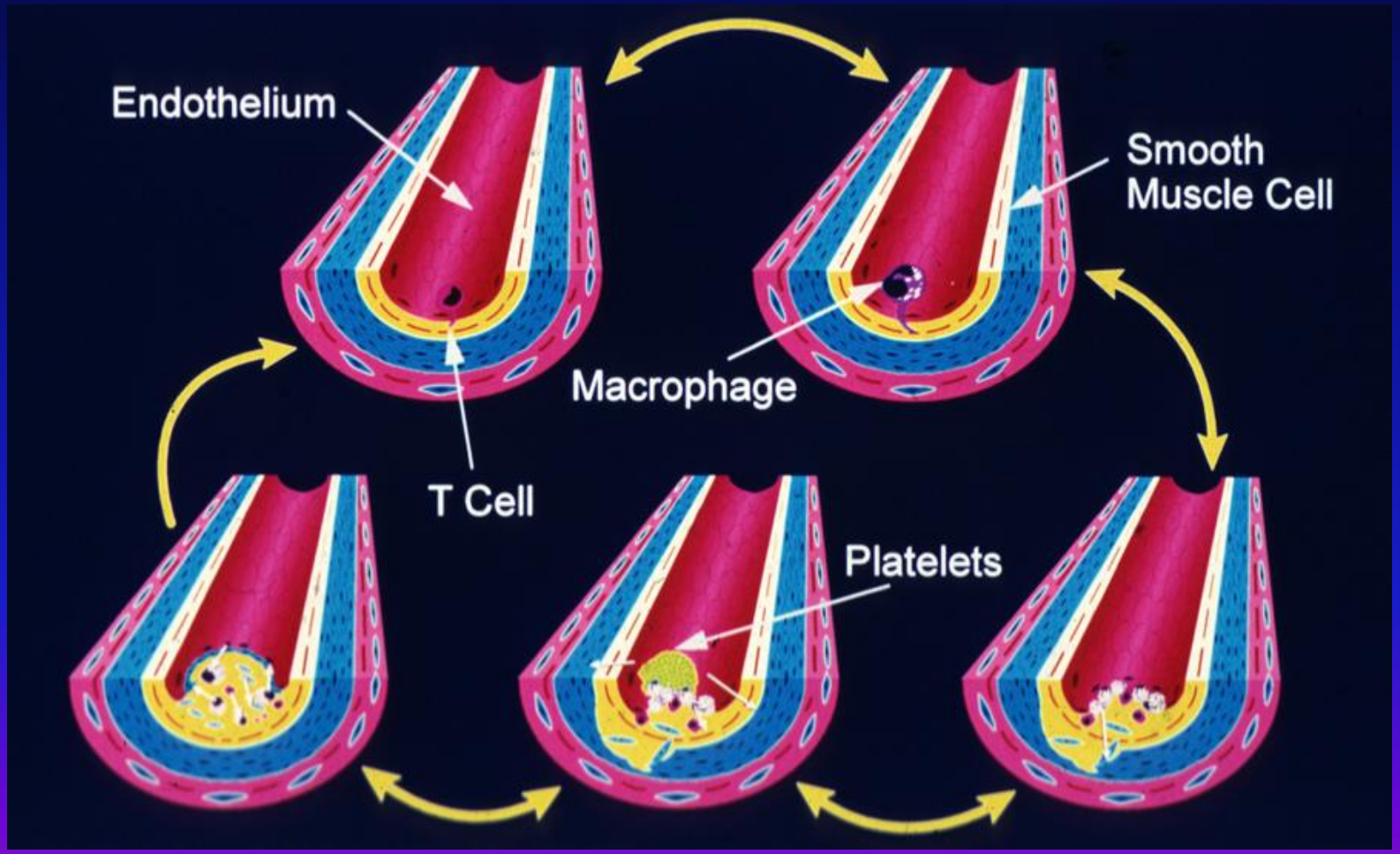
Physical Properties of Human Lipoproteins

Class	Density g/ml	Electrophoretic mobility	Diameter nm	Molecular weight
Chylomicron	0.93	Remains at origin	75-1,200	50-1,000 × 10^6
VLDL	0.93-1.006	Pre-β-lipoproteins	30-80	10-80 × 10^6
IDL	1.006-1.019	Slow pre-β-lipoproteins	25-35	5-10 × 10^6
LDL*	1.019-1.063	β-lipoproteins	18-25	2.3 × 10^6
HDL_2	1.063-1.125	α-lipoproteins	9-12	3.6 × 10^5
HDL_3	1.125-1.210	α-lipoproteins	5-9	1.75 × 10^5

Foam Cell Formation



Formation and Evolution
“Injury”



Ross. *Nature.* 1993;362:801.

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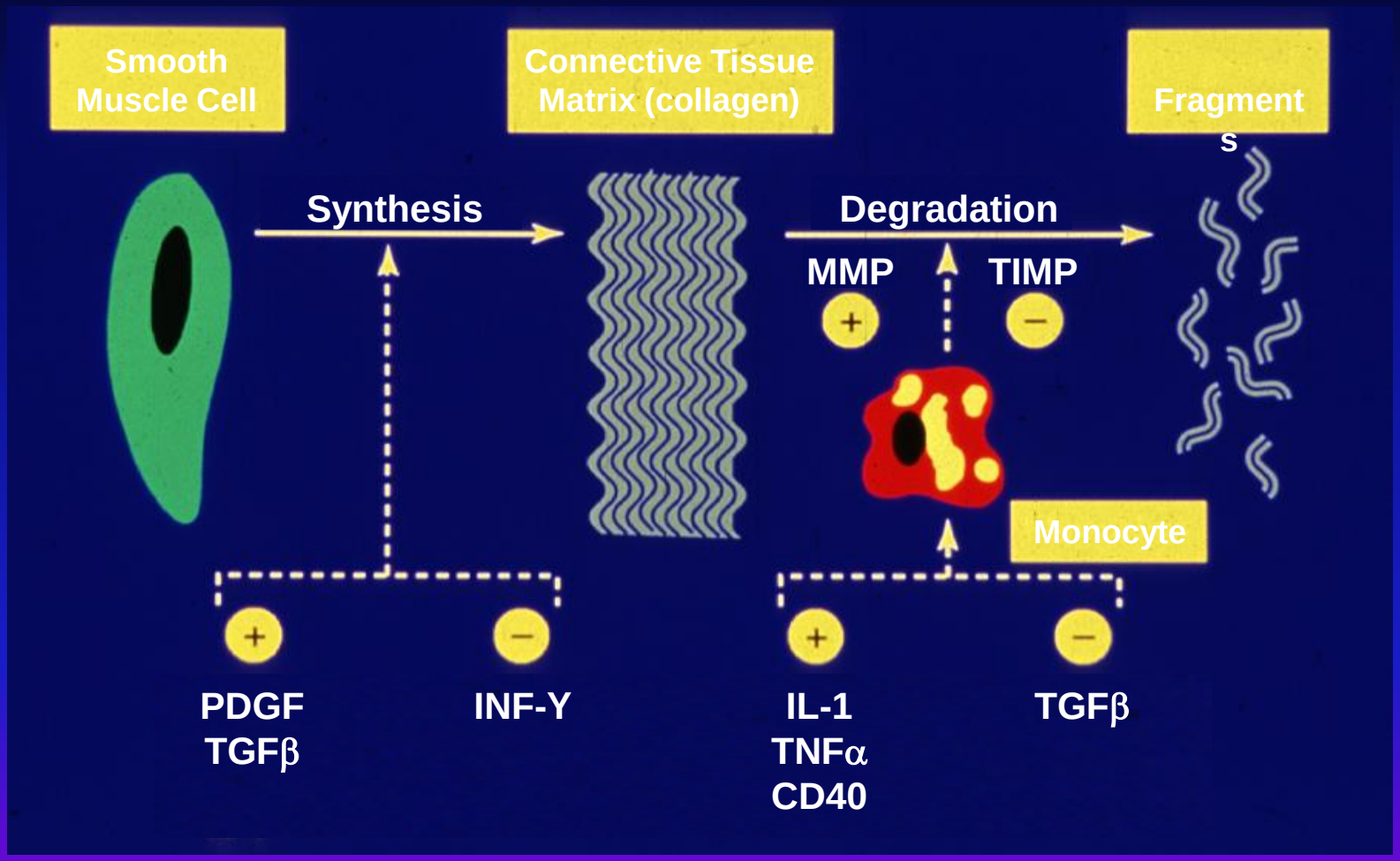
Plaque Cap Dynamics



Libby. *Circulation.* 1995;91:2844.

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Plaque Rupture

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Lipid Modification and Event Reduction Conclusions

- Major clinical trials with statins in various populations demonstrate ↓ risk of cardiovascular and cerebrovascular events
- Emerging evidence on the benefits of early, intensive therapy
- Advantages associated with statins may go beyond the beneficial effects on lipids

Nonpharmacological Management of Elevated Cholesterol

Diet Therapy

- Approximately 29% of adults in US require dietary intervention for elevated cholesterol
- Diet is first-line therapy
  - NCEP Step I and Step II diets
  - increased fiber intake
- Each 5% reduction in LDL-C on a population-wide basis would reduce the number of candidates for drug therapy by ~7 million

Sempos et al. *JAMA.* 1993;269:3009.

Effect of Dietary Factors on CHD

- Pathogenic dietary factors
  - saturated fat
  - dietary cholesterol
  - trans fatty acids
- Protective dietary factors
  - polyunsaturated fat
    - n–6 fatty acid-rich vegetable oils
    - n–3 fatty acids from fish and fish oils
  - monounsaturated fat
  - plant foods (fruit, vegetables, grains, and beans)
  - antioxidants (vitamin E)

Connor (editorial). *Am J Clin Nutr*. 1996;64:253.

Soluble Fiber and Blood Lipids

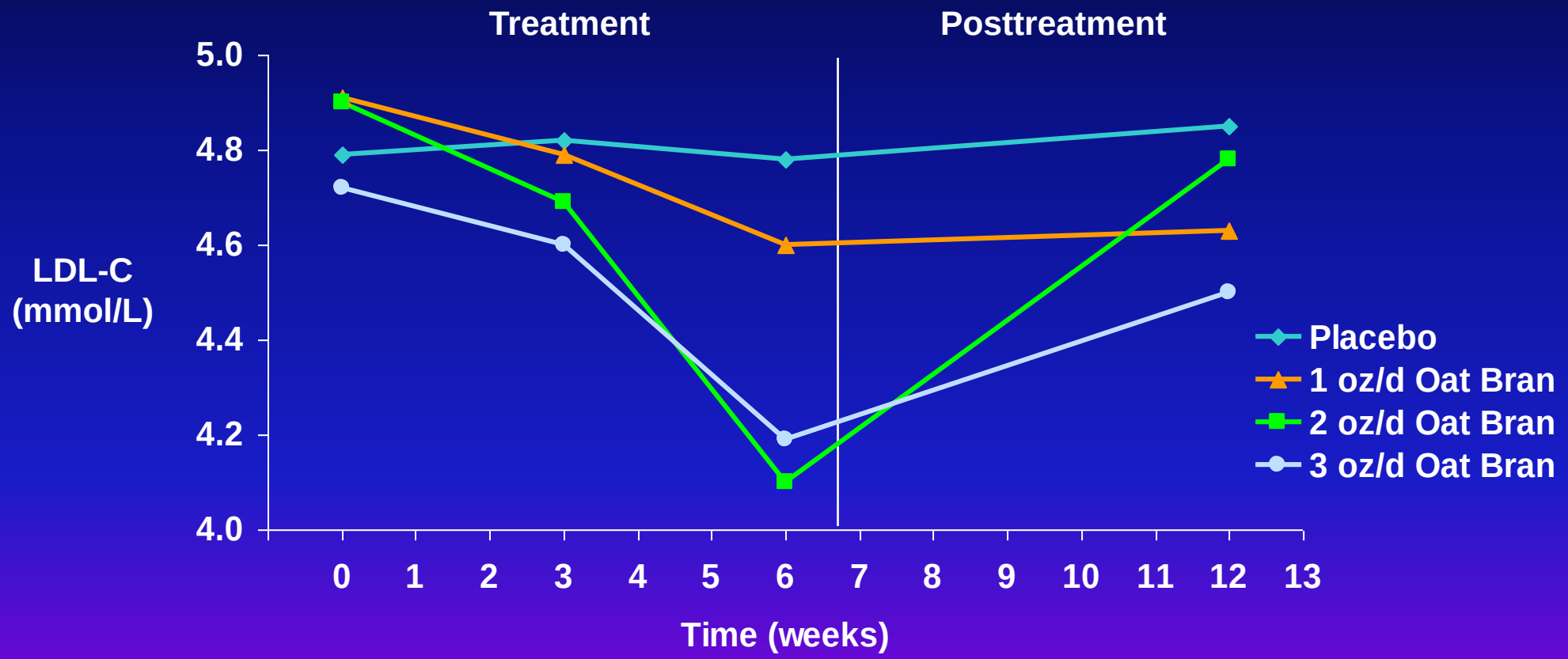
- Dietary fiber supplements lower LDL-C 5% to 15%
- Additive to influence of NCEP Step I diet
- Effects maintained at least 6 to 12 months
- FDA-approved health claims for psyllium and oat fiber

Lipid-Lowering and Non–Lipid-Lowering Fiber Sources

- Lipid-lowering
  - oat bran 25-100 g/d
  - oatmeal 57-140 g/d
  - psyllium 10-30 g/d
  - pectin 6-40 g/d
- Non–lipid-lowering
  - wheat
  - inulin
  - gum arabic/acacia gum

Brown et al. *Am J Clin Nutr.* 1999;69:30.
Glore et al. *J Am Diet Assoc.* 1994;94:425.

Short-Term Dose Effects of Oat Bran on LDL-C



Davidson et al. *JAMA.* 1991;265:1833.

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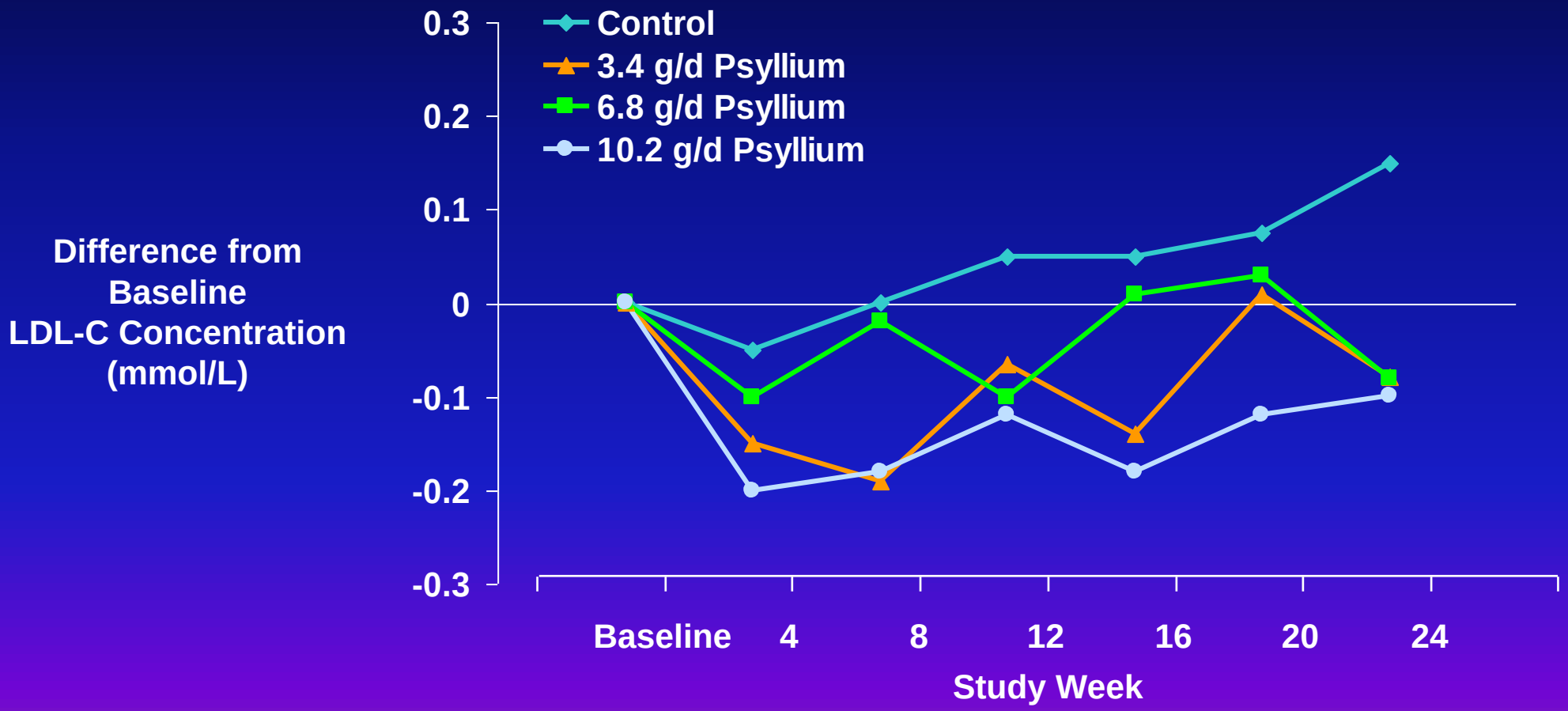
Long-Term Effects of Psyllium Food on LDL-C in Hypercholesterolemic Patients



Davidson et al. *Am J Clin Nutr.* 1998;67:367.

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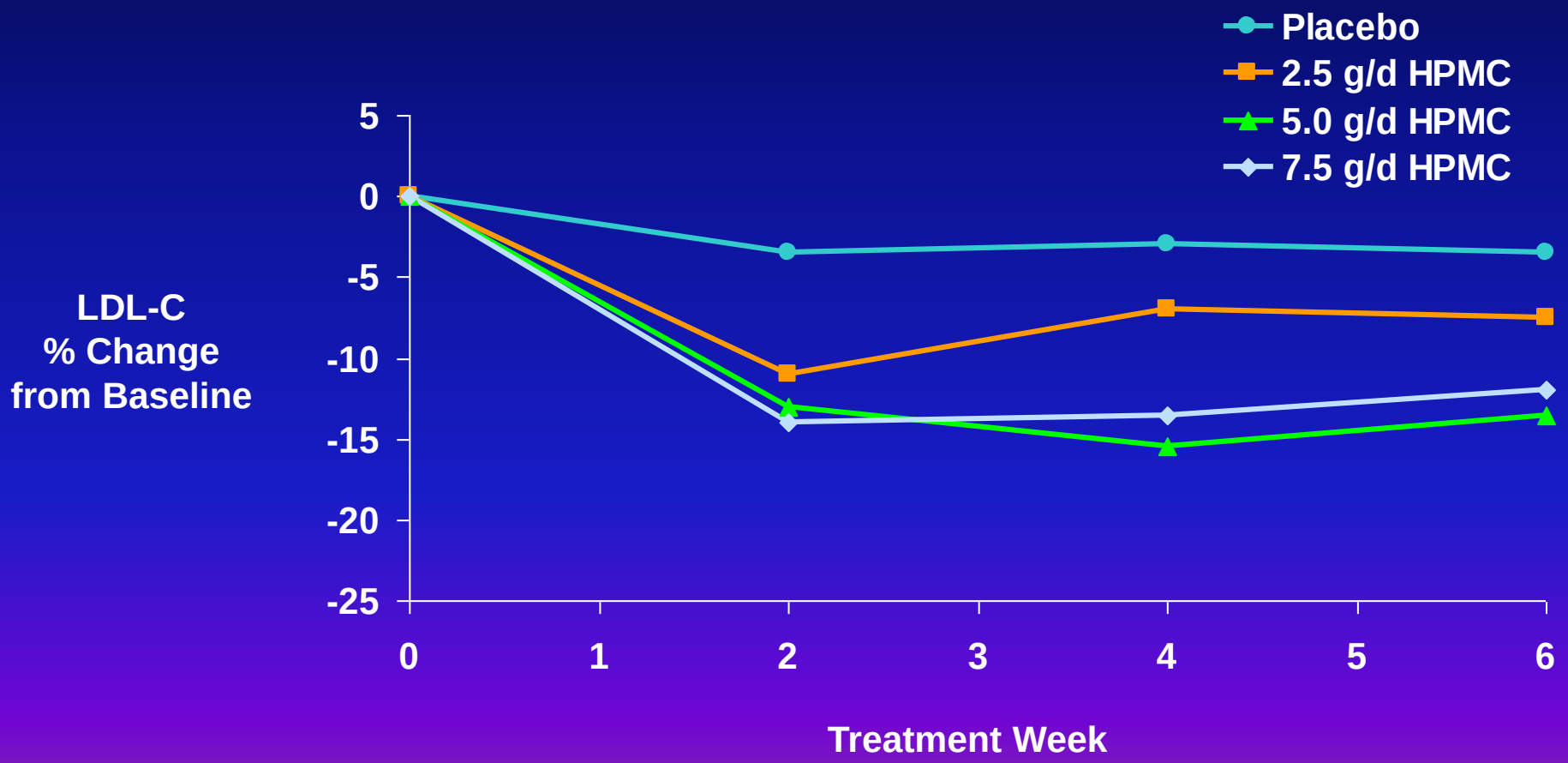
Effects of High-Viscosity Hydroxypropylmethylcellulose (HPMC) on LDL-C



Davidson et al. Unpublished data.

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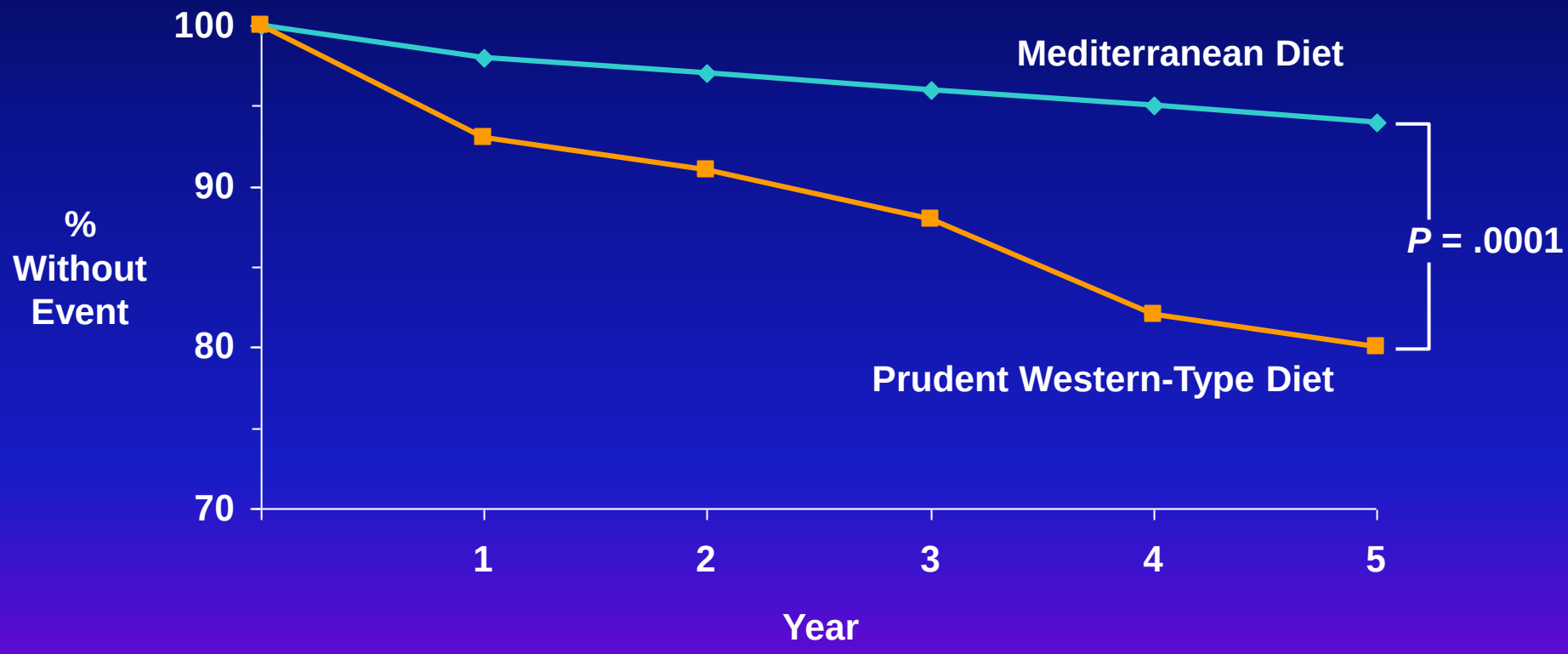
Cumulative Survival without Nonfatal MI

Lyon Diet Heart Study



de Lorgeril et al. *Circulation.* 1999;99:779.

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Efficacy of Garlic Treatment

- Garlic preparations have been reported to reduce levels of serum lipids
- Recent, rigorously designed controlled studies have not substantiated the efficacy of garlic

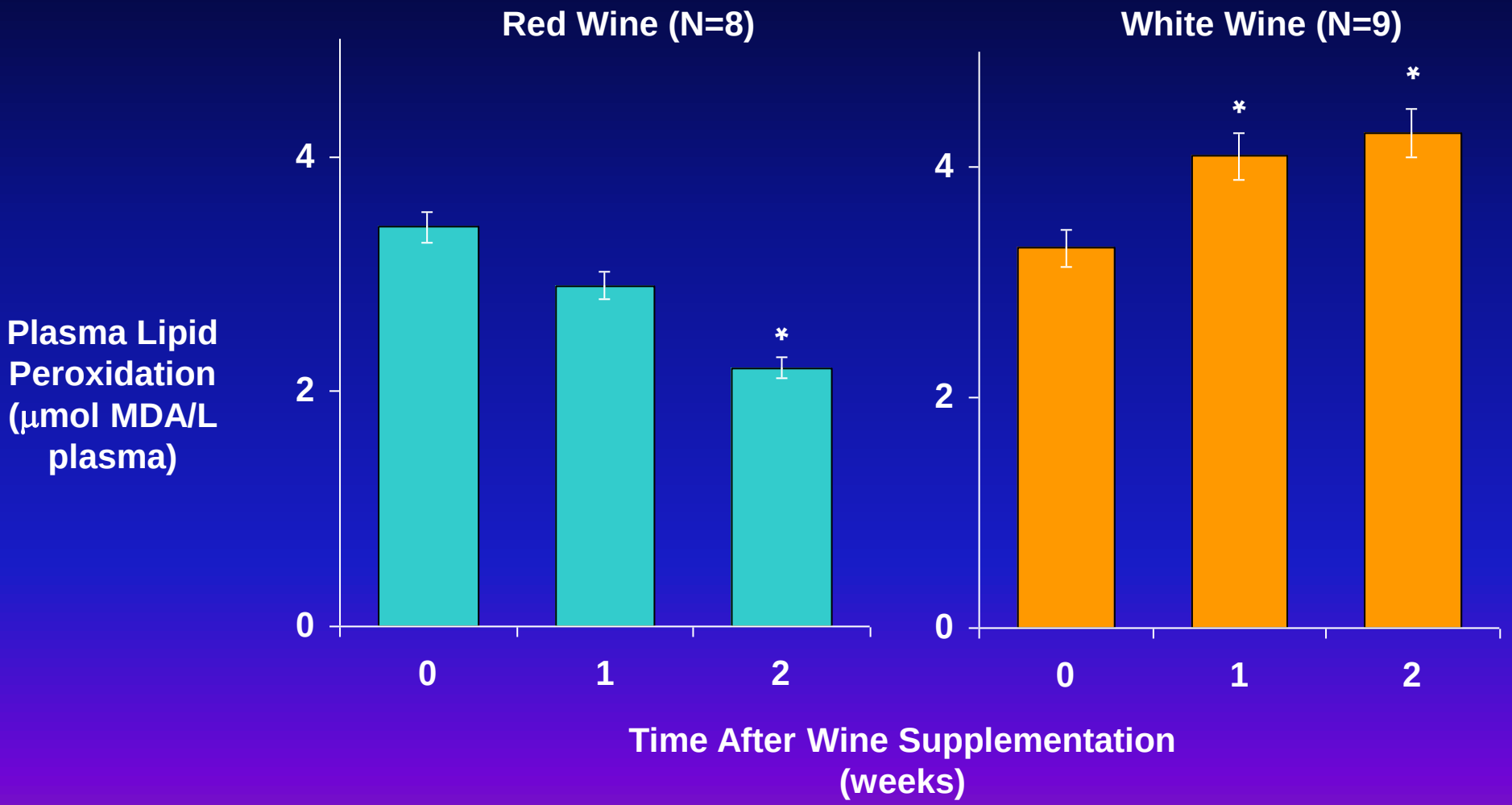
Berthold and Sudhop. *Curr Opin Lipidol.* 1998;9:565.
Jain et al. *Am J Med.* 1993;94:632.

Prospective Studies of Flavonol Intake and Cardiovascular Disease

Reference Study	Location	Follow-Up (y)	Number, Type of Event	RR
Hertog et al, 1993	Netherlands	5	43 CHD deaths	0.3
			38 first MI	0.5
Keli et al, 1996	Netherlands	15	42 strokes	0.3
Knekt et al, 1996	Finland	20	473 CHD deaths	0.7
Rimm et al, 1996	United States	6	486 nonfatal MI	1.1
			140 CHD deaths	0.8
Hertog et al, 1997	United Kingdom	10	186 CHD cases	1.0
		14	131 CHD deaths	1.6

Katan (editorial). *Am J Clin Nutr*. 1997;65:1542.

Plasma Lipid Peroxidation with Red or White Wine Consumption



* *P*<.01

Fuhrman et al. *Am J Clin Nutr.* 1995;61:549.

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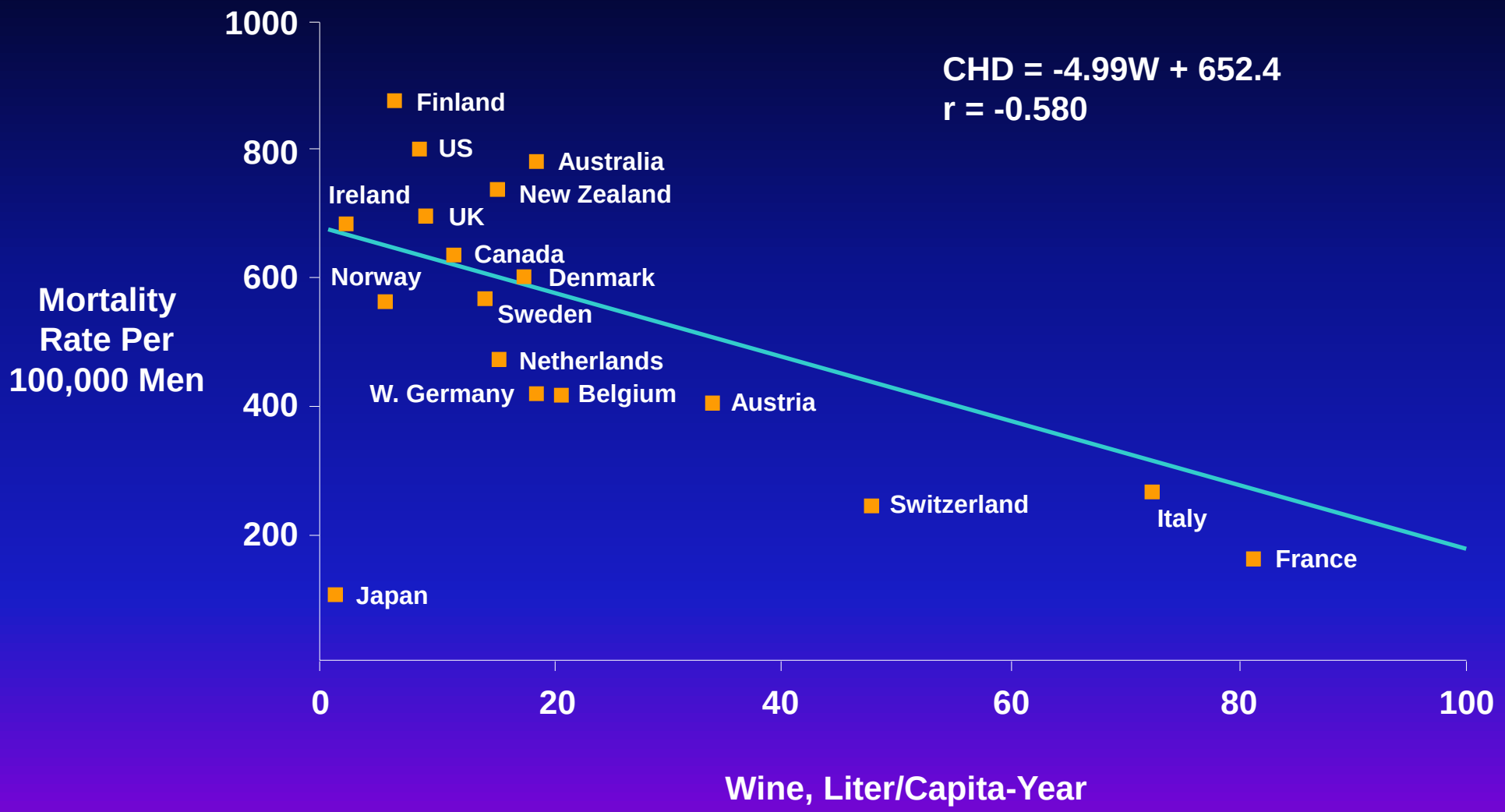
Wine Consumption and CHD



Hegsted and Ausman. *J Nutr.* 1988;118:1184.

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Theoretical Mechanisms for Cholesterol-Lowering Effect of Soy Protein

- Interrupts intestinal absorption of bile acids and dietary cholesterol
- Alters hepatic metabolism of cholesterol and/or lipoproteins
- Influences endocrine system

Potter. *Nutr Rev*. 1998;56:231.

Effect of Change in Fish Intake on Mortality and Reinfarction

- Randomized, controlled trial examined the effects of dietary intervention in 2033 men who had recovered from MI
- 29% reduction in 2-year all-cause mortality for men advised to eat fatty fish (2 or 3 portions/week) compared with those not so advised
- Modest intake of fatty fish reduced mortality in men after MI

Burr et al. *Lancet.* 1989;2:757.

Effects of Plant Stanol Esters on Serum LDL-C Levels

Population (study)	Baseline LDL-C (mg/dL)	Plant Stanol Intake (g/d)	Duration (wk)	Reduction In LDL-C (mg/dL)	(%)
Familial hypercholesterolemic children					
Gylling et al, 1995	211.6	3.0	6	31.7	15
Hypercholesterolemia					
Vanhanen et al, 1993	144.6	3.4	6	13	9
Vanhanen et al, 1994	129.2	3.2	6	19.6	15.2
Miettinen et al, 1994	131.1	0.8	9	9.2	7
Miettinen et al, 1995	160.9	2.6	26	18.2	11.3
Hypercholesterolemic NIDDM					
Gylling et al, 1994	148.1	3.0	6	13.8	9.3
Gylling et al, 1996	NR	3.0	7	23.2	14
Postmenopausal women					
Gylling et al, 1997	141.5	3.0	7	21.2	15

Mensink and Plat. *Postgrad Med.* 1998; Nov:27.

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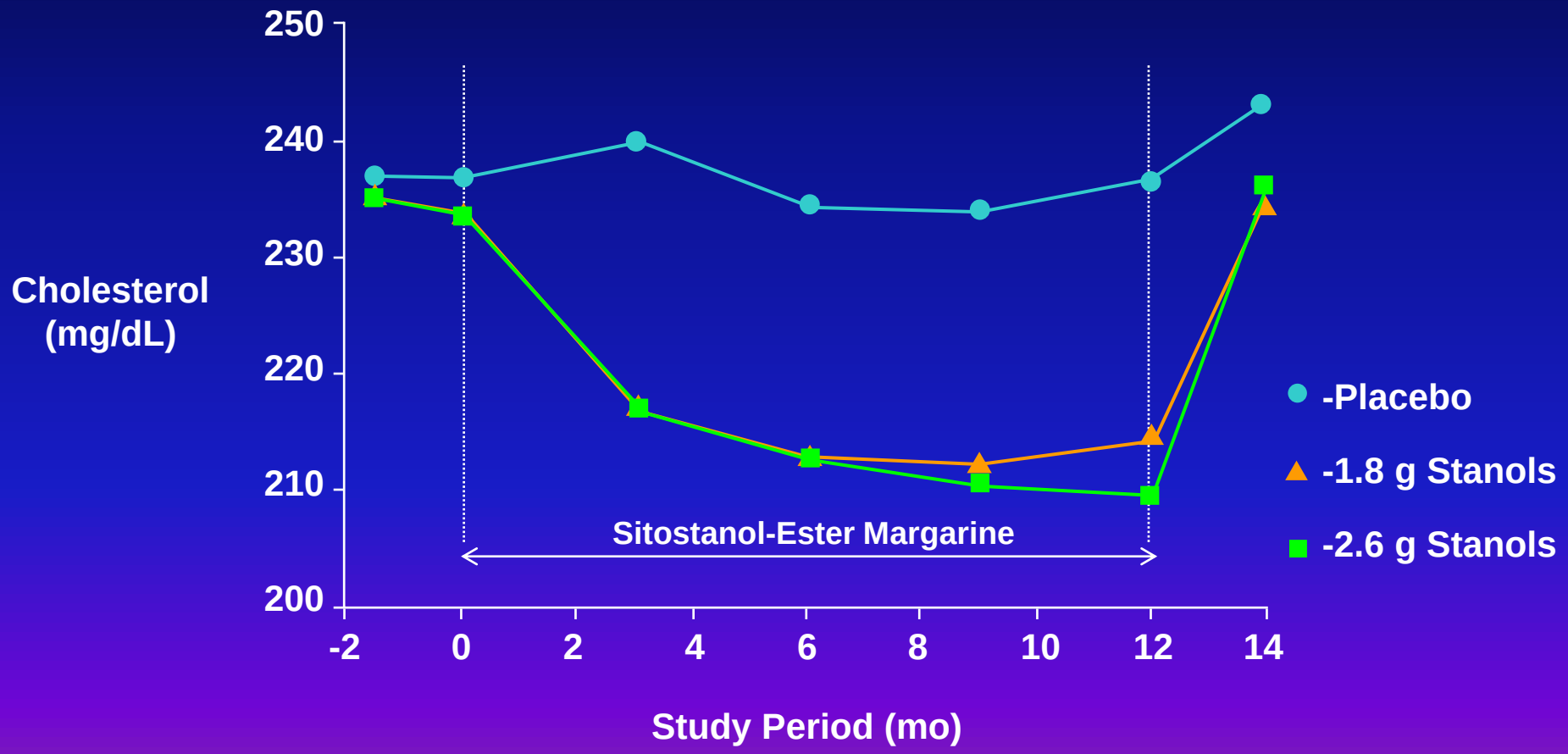
Serum Cholesterol Levels Before and After Consumption of Dietary Spread with and without Sitostanol Ester



Miettinen et al. *N Engl J Med.* 1995;333:1308.

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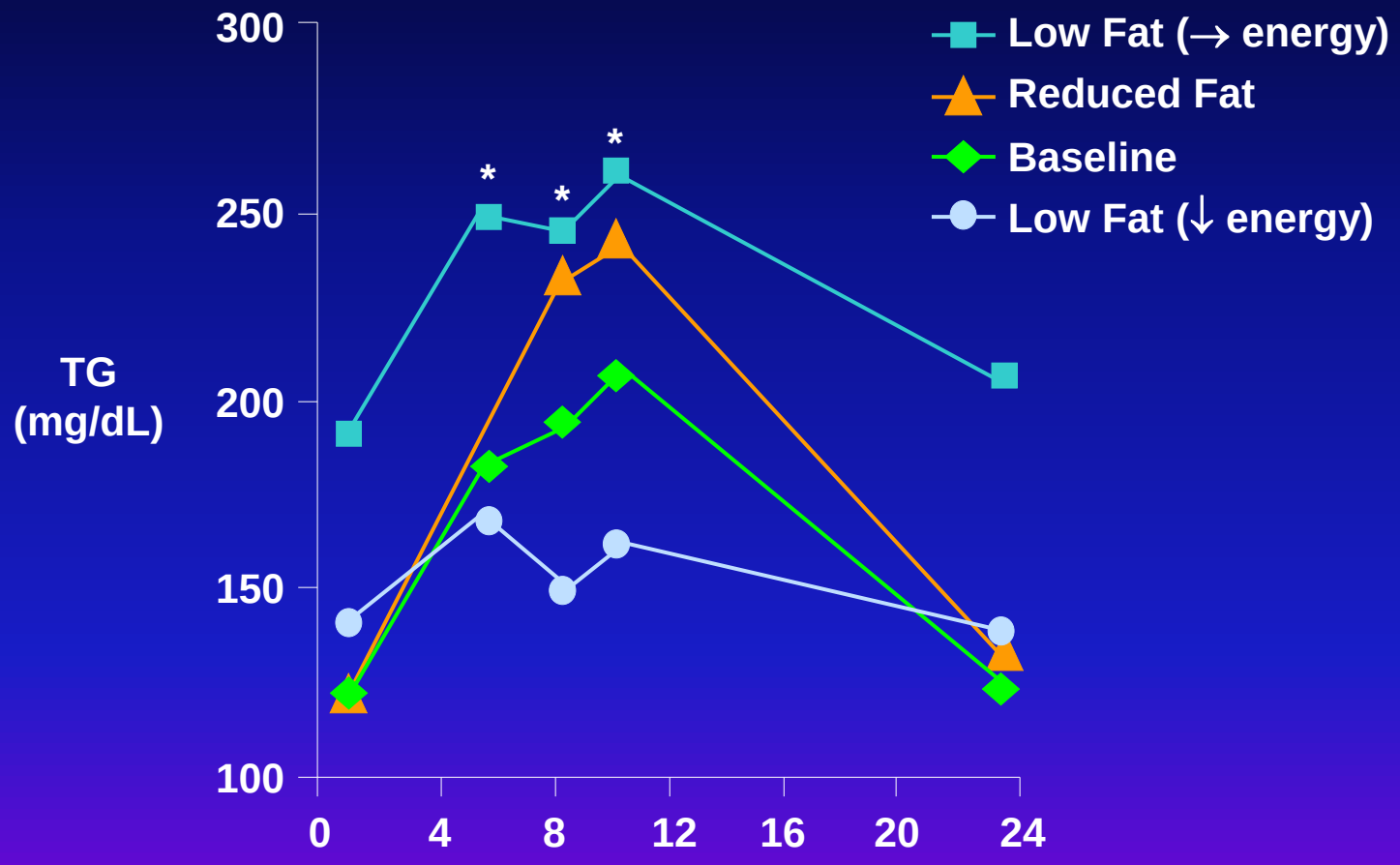
Impact on TG Following Dietary Restrictions



**P* <.05 at 5, 8, and 10 hours postprandial vs 0 and 24 hours.

Lichtenstein et al. *Arterioscler Thromb*. 1994;14:1751.

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Effect of Lifestyle Changes on Angiographic CHD

Study	N	Patient Type	Therapy	Duration (y)	% (Control-Treatment)* Progression	% (Control-Treatment)* Regression
Lifestyle	28	CAD	Diet, exercise, meditation	1	35	-40
STARS	90	CAD, high TC	Diet (including ↑ fiber)	3.2	35	-38
Heidelberg	113	CAD	Diet + exercise	1	25	-15

Superko and Krauss. *Circulation.* 1994;90:1056.
*% (Control-Treatment) = mean difference between control and treatment groups.

Summary: Nonpharmacological Management of Elevated Cholesterol

- ↓ Dietary fat to <30%
- ↓ Saturated fat to <10%
- ↑ Dietary fiber to ≥20 g/d
- Supplementation with oat bran or psyllium
- ↑ Consumption of soy protein
- ↑ Consumption of fatty fish to ≥2 x wk
- Addition of plant stanol esters

Pharmacological Intervention into Elevated Cholesterol

VA-HDL-C Intervention Trial
Study Design

- First HDL-C intervention trial
- Hypothesis: fibrate (gemfibrozil) Rx of low HDL-C with “desirable” LDL-C will ↓ 2° CHD events
- Subjects
  - 2531 male veterans ≤74 y (avg 64 y)
  - 2° prevention (MI, revasc, angina, + angio)
  - HDL-C ≤40, LDL-C ≤140, TG ≤300 mg/dL
- Treatment: gemfibrozil 600 mg BID
- End point: nonfatal MI and CHD death
- ***!!! NO TOTAL MORTALITY BENEFIT !!!***
- Follow-up: 5.1 y

Rubins et al. *Am J Cardiol*. 1993;71:45.
Rubins et al. *Am J Cardiol*. 1996;78:572.

VA-HDL-C Intervention Trial
Preliminary Results

- Gemfibrozil
  - ↑ HDL-C 8%
  - ↓ TG 25%
  - no change in LDL-C
  - MI in 17% vs 22% on placebo

Anon. *Med Lett Drugs Ther*. 1998;40:117.

VA-HDL-C Intervention Trial
Conclusions from Preliminary Results

- Provides first direct clinical trial evidence of ~beneficial effect of ↑ HDL-C in CHD patients with desirable LDL-C
- First major clinical trial to suggest clinical benefit from ↑ HDL-C and ↓ TG without ↓ LDL-C
- Why no total mortality benefit in this high-risk population???

Treatment of Low HDL-C Syndrome

- Nonpharmacologic treatment: manage secondary causes
  - weight loss if overweight
  - smoking cessation
  - exercise
  - manage diabetes mellitus, renal disease, etc
- Pharmacologic treatment
  - niacin
  - fibrates
  - estrogens
  - HMG-CoA reductase inhibitors (statins)
  - ethanol?
  - combinations

Kashyap. *Am J Cardiol*. 1998;82:42U.

Bezafibrate Infarct Prevention Trial [*Secondary* Prevention in Israel LDL<180; Tg<300; HDL<45]

- Bezafibrate in 3090 (!) CHD patients
  - ↑ HDL-C 18%
  - ↓ TG 21%
  - no change in LDL-C
  - fatal or nonfatal myocardial infarction or sudden death reduced by 7.3% (p=0.24)

The BIP Study Group *Circulation*. 2000;102:21

Lipid Abnormalities in Diabetes

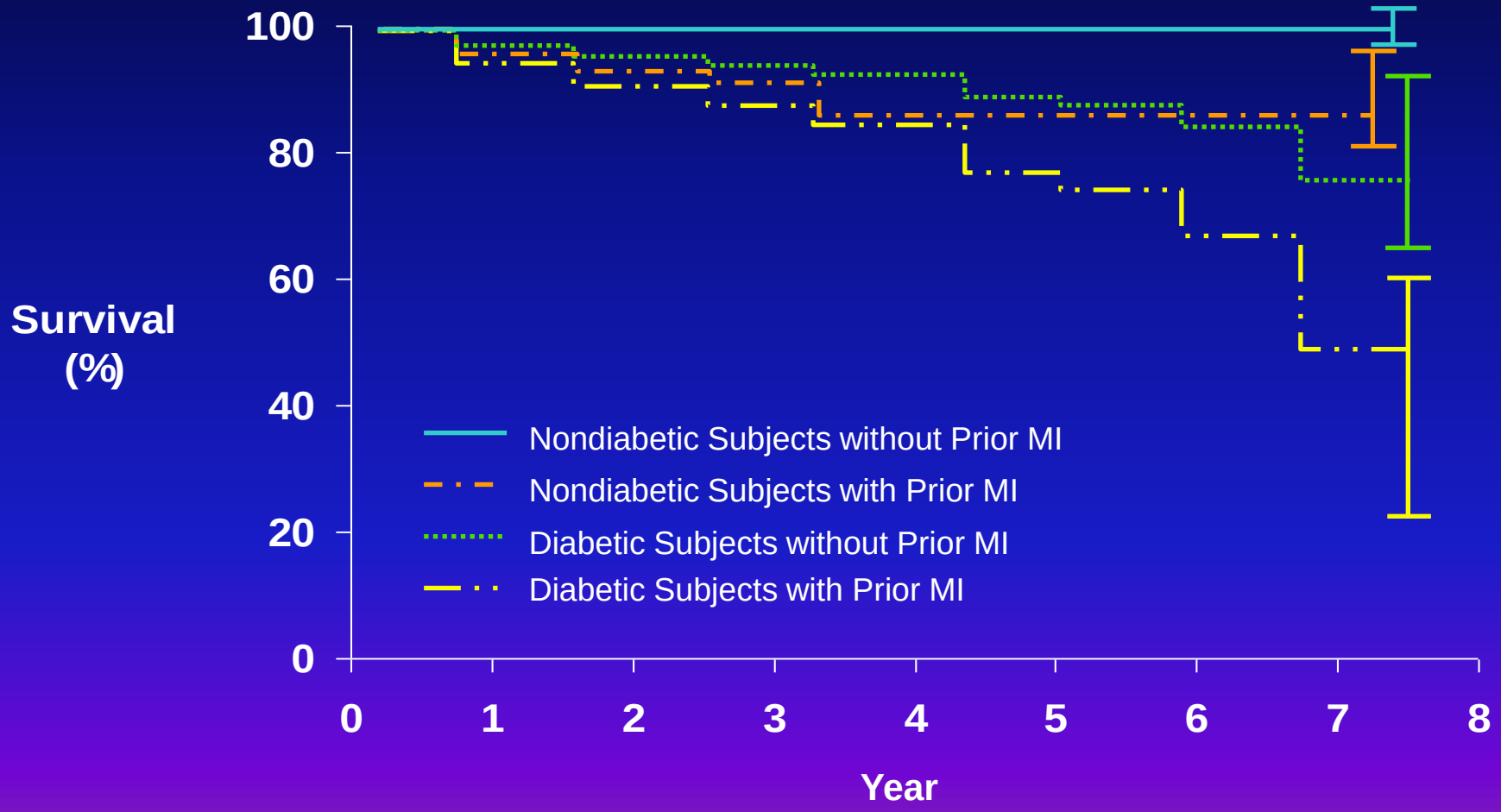
Lipid or Lipoprotein	Poor Glycemic Control	Good Control Type 1	Good Control Type 2
Total-C	↑	→	↑
TG	↑	→	↑
VLDL-C	↑	→	↑
LDL-C	↑	→	→
HDL-C	↓	↑	↓

↑ = increased; ↓ = decreased; → = normal.

McKenney and Hawkins, eds. *Handbook on the Management of Lipid Disorders*. Richmond, VA: National Pharmacy Cholesterol Council;1995.

Probability of Death from CHD

Patients with or without Diabetes (N=2437)



Haffner et al. *N Engl J Med.* 1998;339:229.

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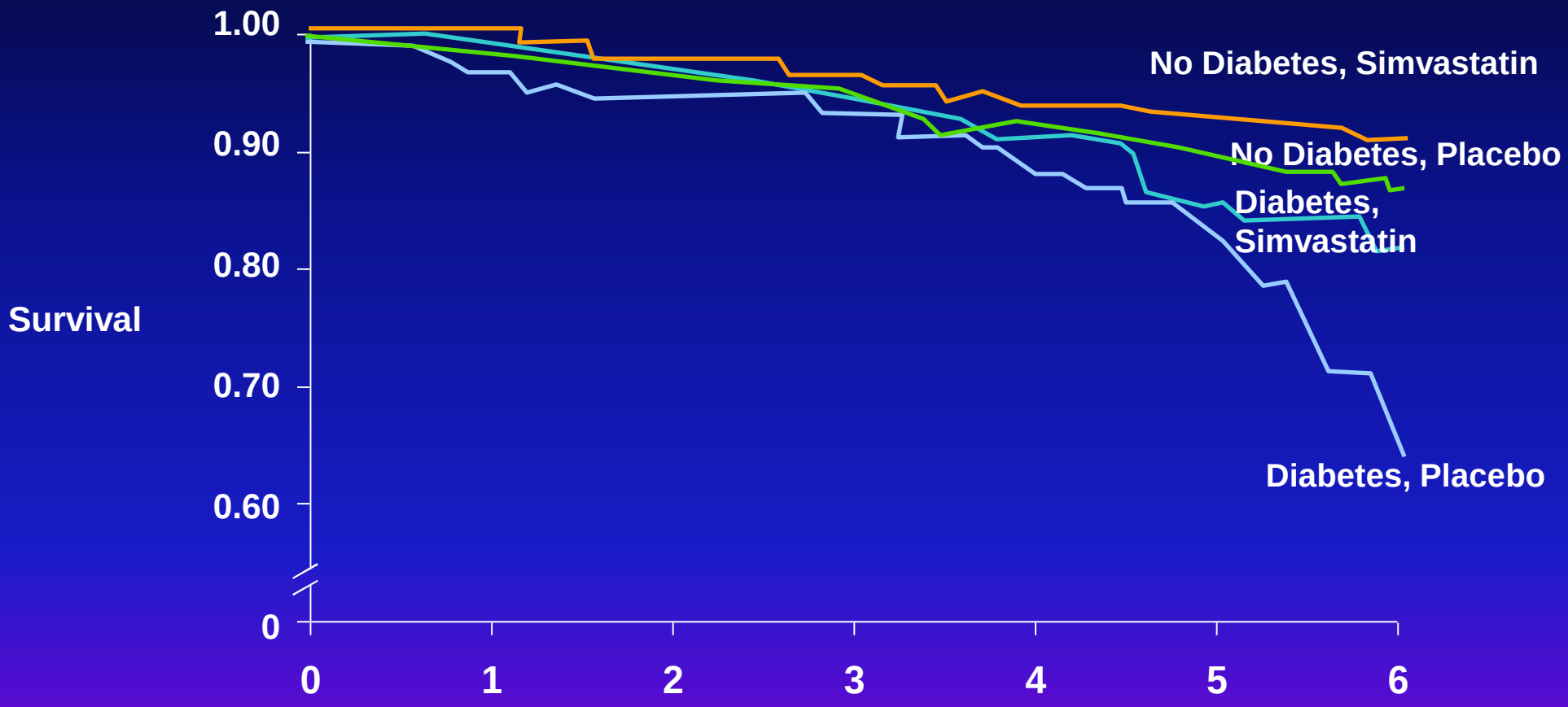
Reduction in Mortality in Subjects with or without Diabetes: 4S



Pyörälä et al. *Diabetes Care*. 1997;20:614.

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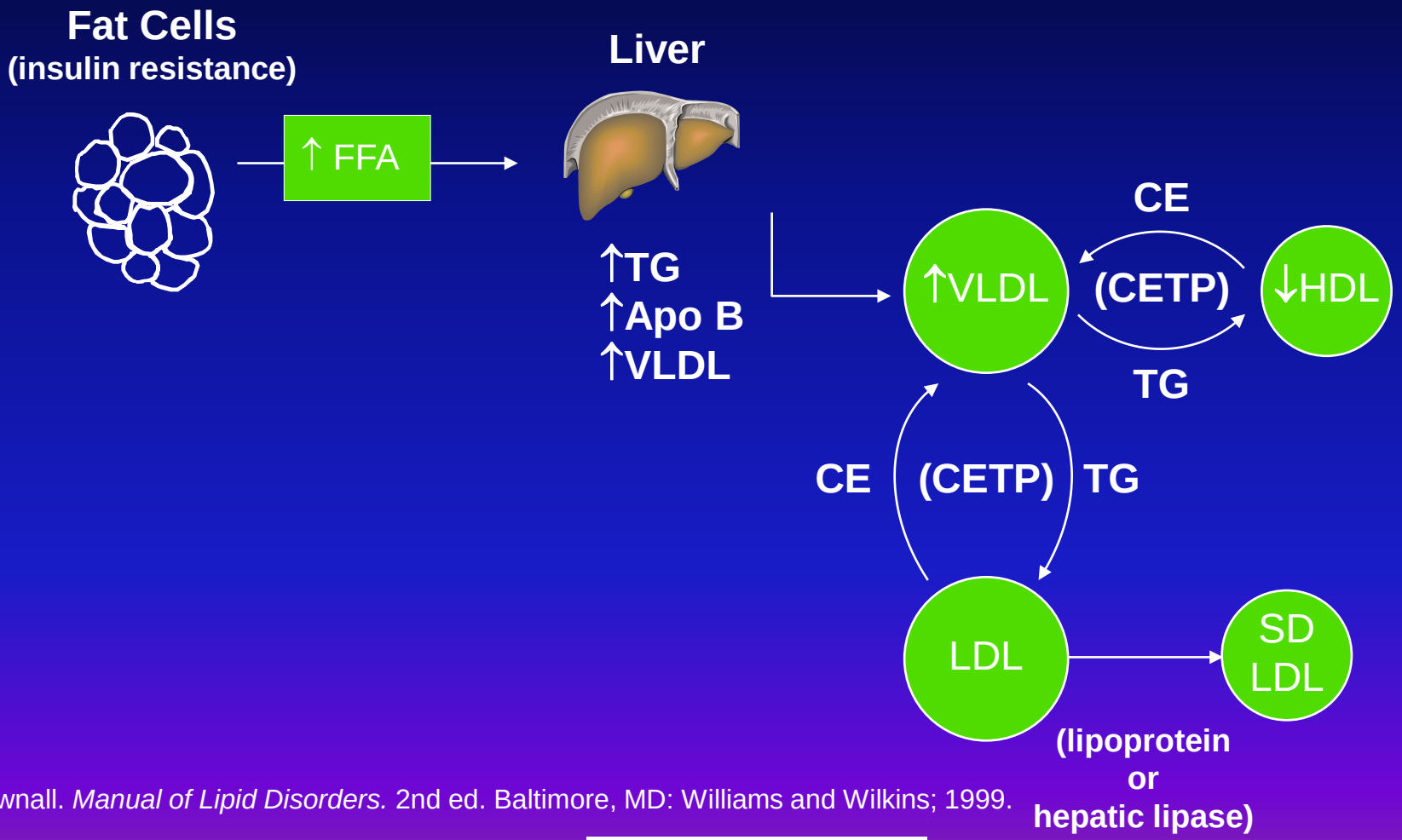
Common Lipid Abnormalities in Insulin Resistance

- Elevated TG (and VLDL)
- Reduced HDL-C
- LDL-C normal but particle size and composition altered

Taskinen. *Curr Opin Lipidol*. 1995;6:153.

Mechanisms Relating Insulin Resistance and Dyslipidemia



Gotto and Pownall. *Manual of Lipid Disorders.* 2nd ed. Baltimore, MD: Williams and Wilkins; 1999.

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CARE Trial Diabetes Subgroup Analysis

Event Reduction at 5 Years	Placebo (N=304)	Pravastatin (N=282)	RRR (%)
CHD death/nonfatal MI	62	50	13
CHD death	30	27	3
Fatal MI	14	7	46
Nonfatal MI	37	28	18
Expanded end point	112	81	25

RRR = relative reduction in risk.
Goldberg et al. *Circulation.* 1998;98:2513.

Pros and Cons of Treating Older Patients

Pros

- CHD leading cause of death/disability
- Aging population
- Considerable life expectancy
- High absolute risk
- Pathophysiology the same
- Equivalent treatment effects
- Stroke reduction

Cons

- Protected against CHD
- Reduced relative risk
- Poor prognosis
- Polypharmacy
- Cost of medication

Manolio et al. *Ann Epidemiol*. 1992;2:161.
McKenney and Hawkins, eds. *Handbook on the Management of Lipid Disorders*. Richmond, VA: National Pharmacy Cholesterol Council 1995.

Compliance

- Noncompliance is a major problem
- Treatment discontinuations, among all types of drugs including cholesterol-altering drugs, amount to ~50% at 1 year, and an additional ~35% at 2 years

NCPIE 1997.

Compliance (cont'd)

Drug discontinuations occur in pivotal statin trials for primary and secondary prevention of CHD with both high and average levels of LDL-C

Trial	Discontinuation Rate	Purpose
AFCAPS	29.0% in 5.2 y	Primary
WOSCOPS	29.6% in 4.9 y	Primary
CARE	6.0% in 5.0 y	Secondary
4S	10.4% in 5.4 y	Secondary
LIPID	12.0% in 4.0 y	Secondary

Downs et al. *JAMA*. 1998;279:1615.
Insull. *J Intern Med.* 1997;241:317.

Risk Factors for Noncompliance

- Number of daily doses
- Number of medications
- Occurrence and severity of side effects
- Incompatibility with patient's daily routine
- Inadequate physician-patient communication
- Cost

Russell. *Behavioral Counseling in Medicine: Strategies for Modifying At-Risk Behavior*. New York, NY: Oxford Press; 1986.

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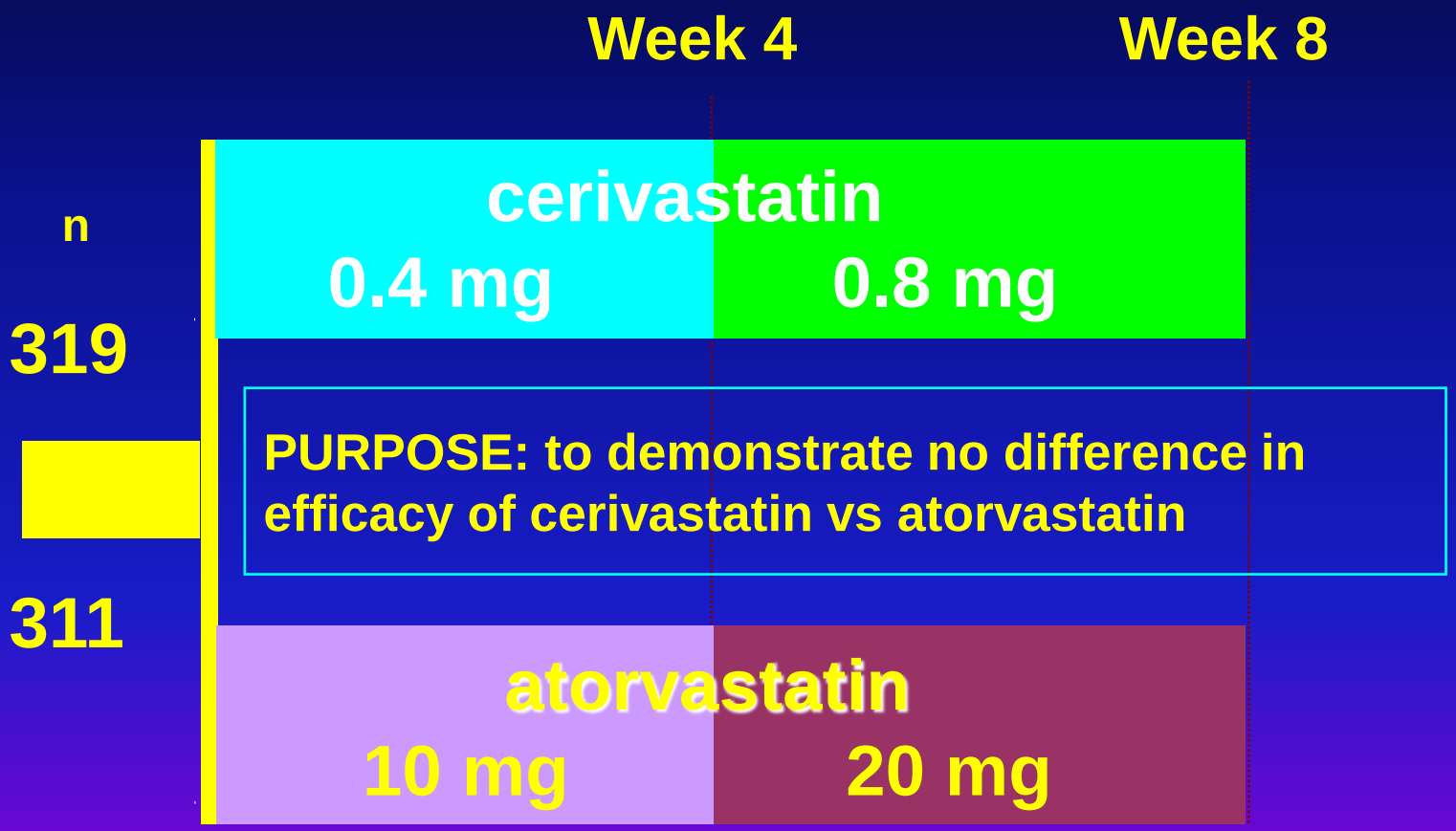
Cerivastatin vs Atorvastatin

Forced Titration



Bayer Study #71 (data on file)

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Cerivastatin vs Atorvastatin

Reasons for Premature Termination of Randomized Patients

	cerivastatin	atorvastatin
Patients entered	319	311
Discontinuations	4.1% (13)	5.5% (17)
-Adverse events	1.6% (5)	3.2% (10)
-Lost to follow-up	0.3% (1)	0.6% (2)
-Protocol violation	0.9% (3)	1.0% (3)
-Non-Compliance	0.3% (1)	0
-Consent withdrawn	0.6% (2)	0.6% (2)
-Death	0.3% (1)	0

Bayer Study #71 (data on file)

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Cerivastatin vs Atorvastatin

Patient Demographics‡

Variable	cerivastatin (n=313)	atorvastatin (n=305)
Age (yrs)	59	59
Males	54%	46%
BMI (kg/m^2)	26.3	25.9
Causasian	99%	100%
Non-drinkers	28%	30%
Family history of hyperlipidemia	32%	30%
Family history of CAD	49%	51%

Bayer Study #71 (data on file)

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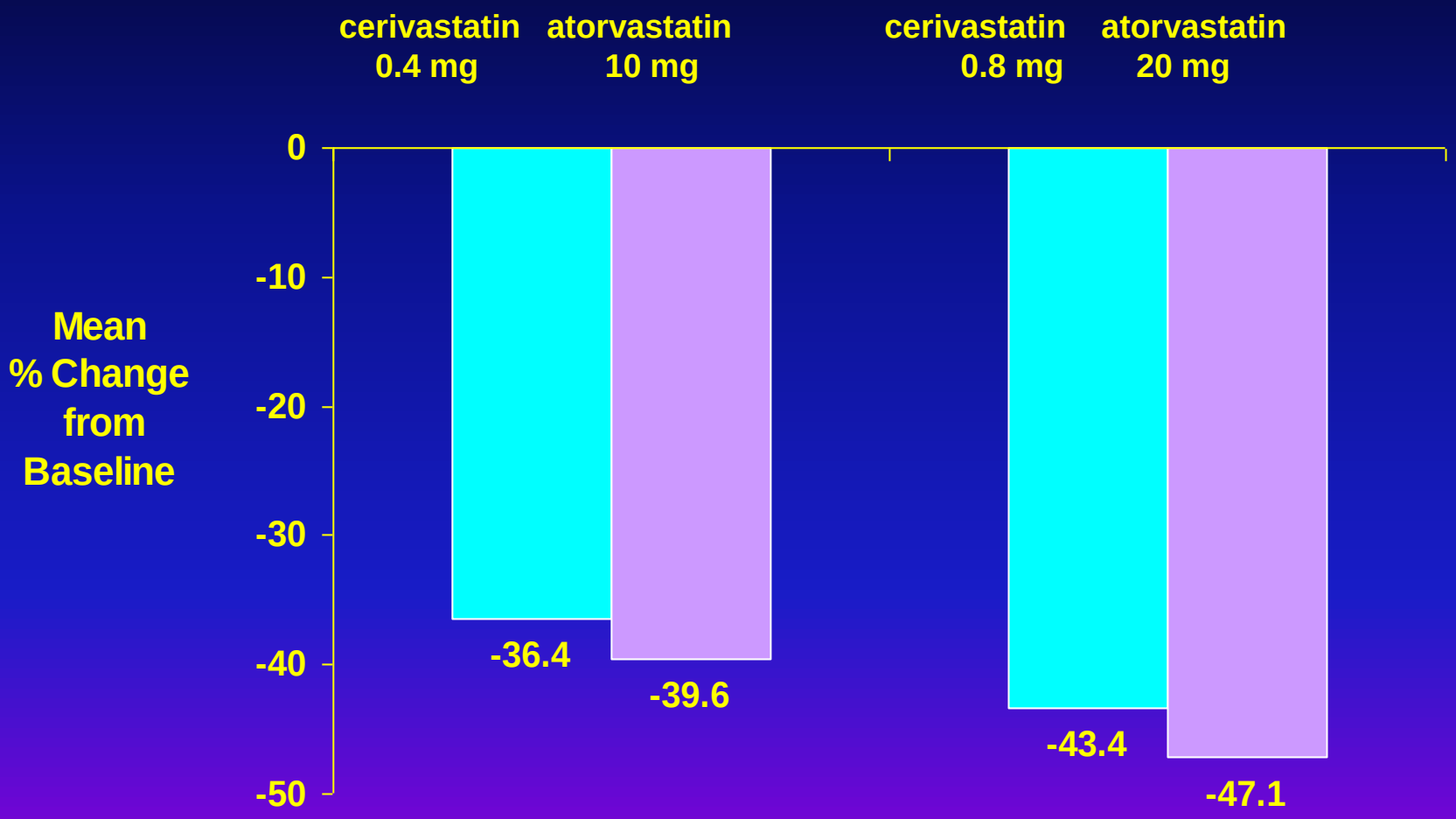
‡ Intent-to-Treat Population

Cerivastatin vs Atorvastatin

% LDL-C Reduction‡



Bayer Study #71 (data on file)

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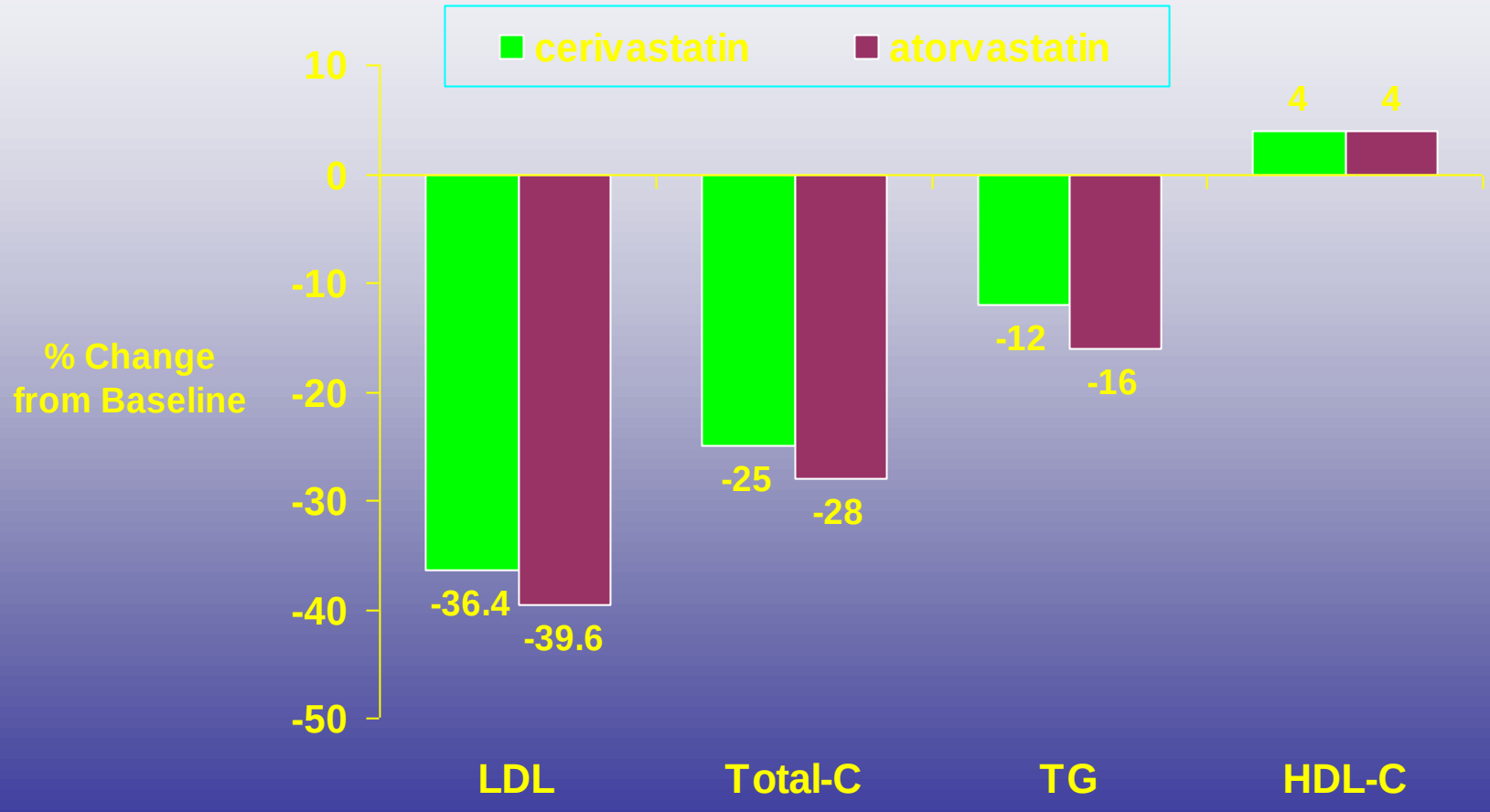
‡ Intent-to-Treat Population

Cerivastatin 0.4 vs Atorvastatin 10 mg

Lipid Parameters‡



Bayer Study #71 (data on file)

‡ Intent-to-Treat Population

Cerivastatin vs Atorvastatin

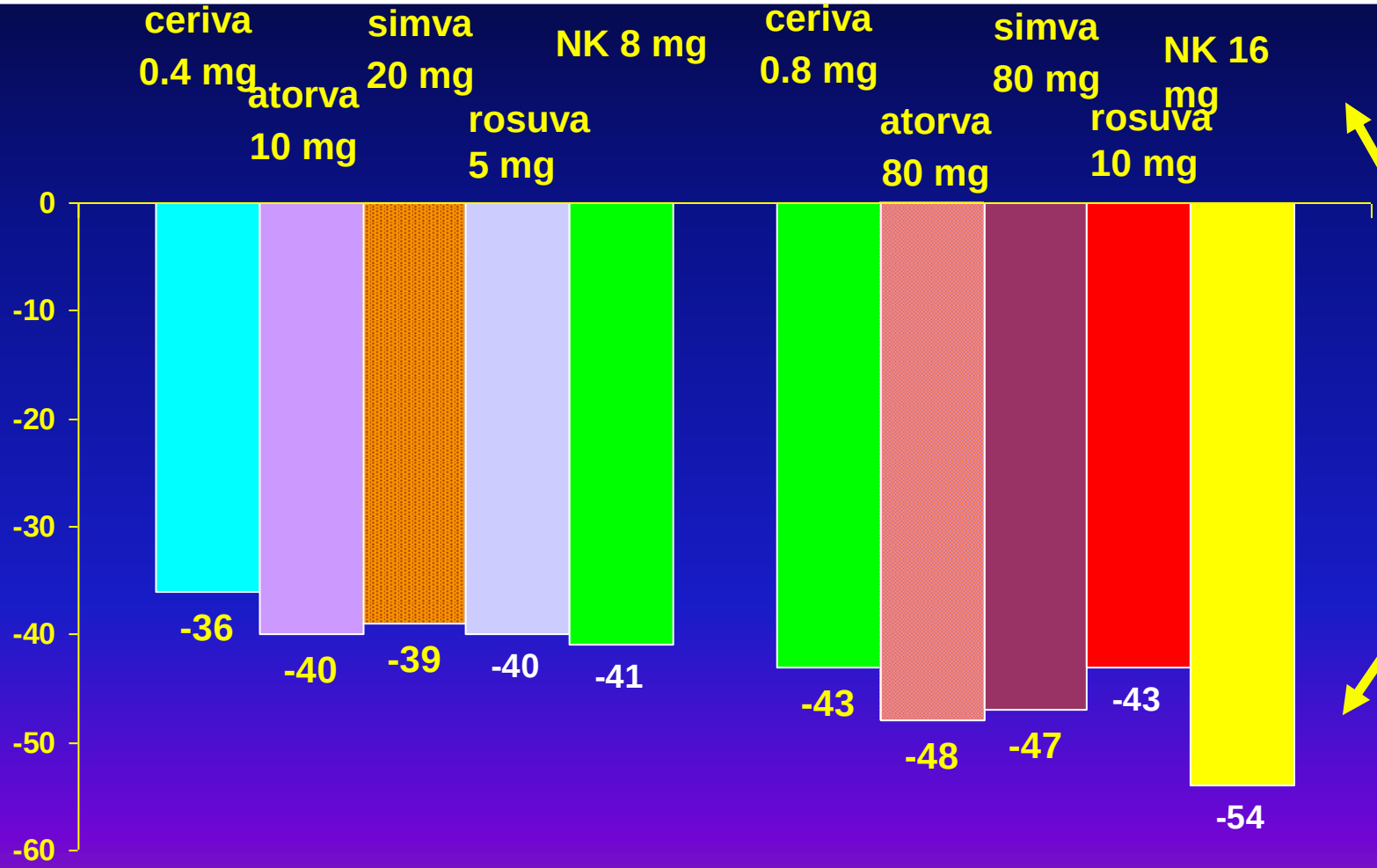
Most Common Adverse Events‡

Adverse event	cerivastatin (n=318)	atorvastatin (n=311)
Overall	25.2% (80)	25.1% (78)
CPK Increased	*3.1% (10)*	*1.0% (3)*
Myalgia	0.9% (3)	1.9% (6)
Rhinitis	1.6% (5)	1.0% (3)
Rash	1.6% (5)	1.3% (4)
Abdominal pain	1.3% (4)	1.6% (5)
Asthenia	1.3% (4)	1.3% (4)
Back Pain	1.3% (4)	1.6% (5)
Diarrhea	1.3% (4)	2.3% (7)
Insomnia	1.3% (4)	0.6% (2)
Accidental injury	0.9% (3)	1.3% (4)
Headache	0.9% (3)	1.9% (6)
Nausea	0.9% (3)	1.0% (3)
Arthralgia	0.6% (2)	1.9% (6)
Abnormal LFT	0.6% (2)	1.3% (4)

Bayer Study #71 (data on file)

‡ Patients Valid For Safety

Pitorvastatin vs Cerivastatin vs Atorvastatin vs Simvastatin vs Rosuvastatin % *LDL-C Reduction‡*



Bayer Studies #17 & #71 (data on file)

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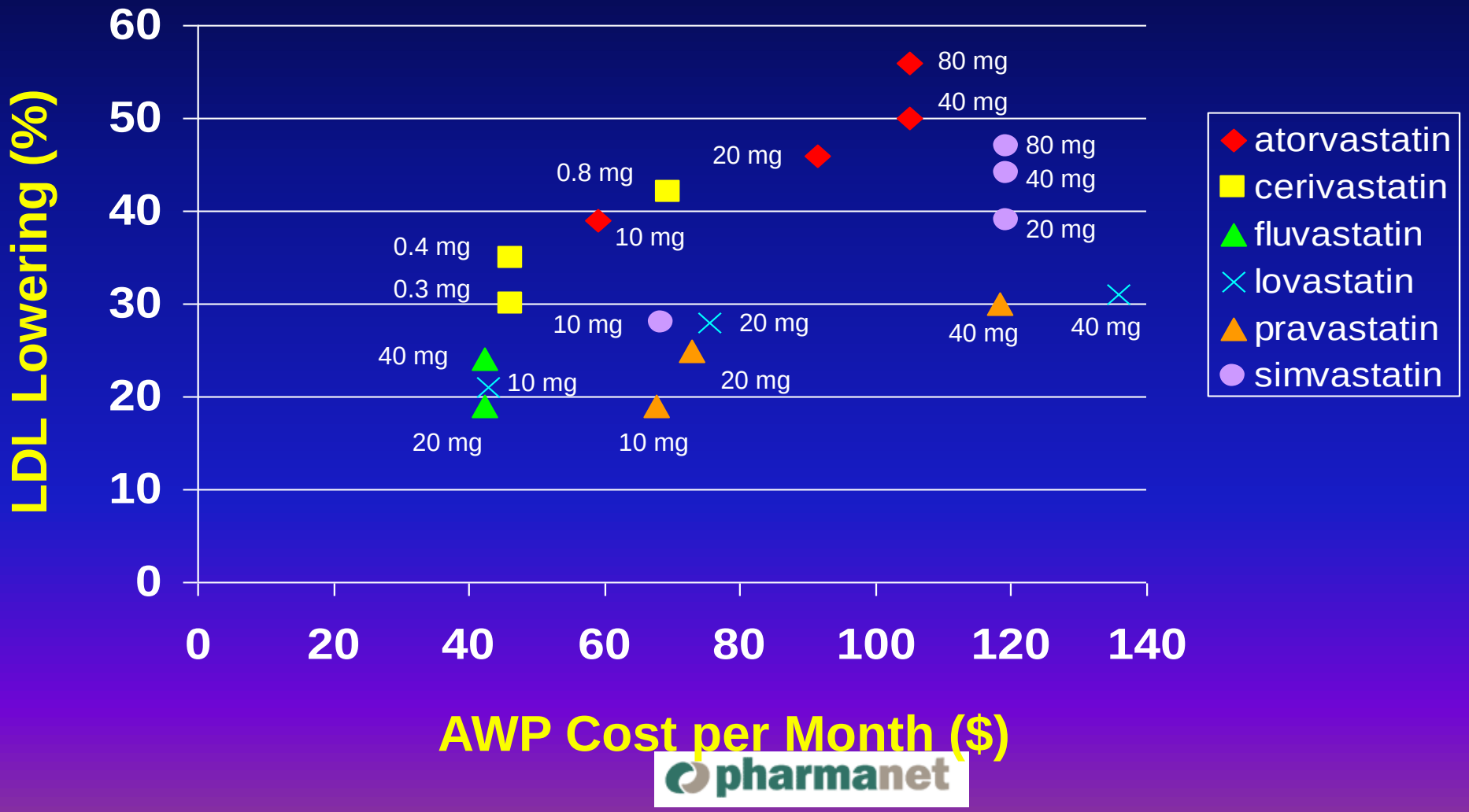
‡ Intent-to-Treat Population

Statin Cost Comparison



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-Protocol Review
--CRF Review
---Safety Considerations