Атеросклероз
Дислипидемии

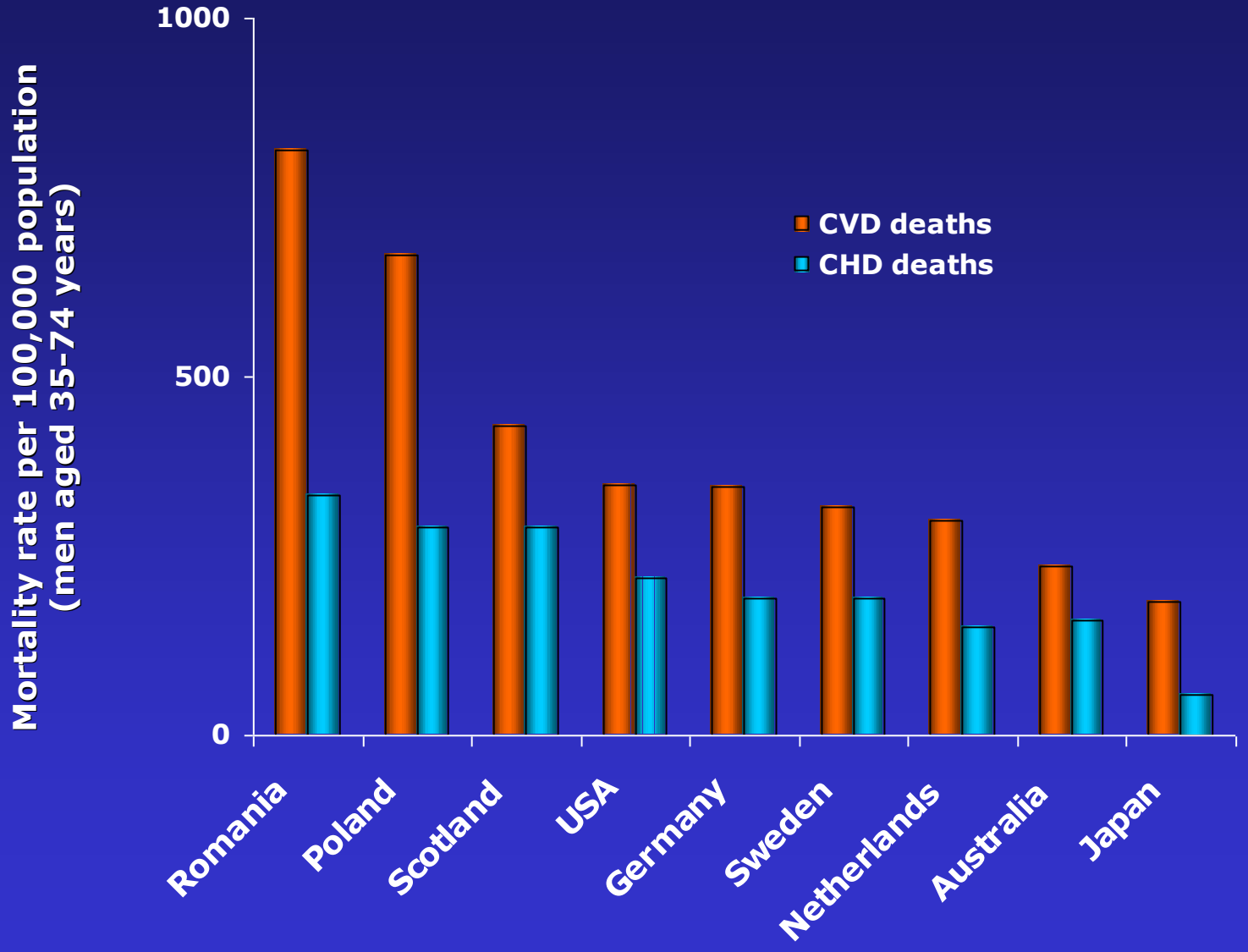
Атеросклероз. Дислипидемии. Атеросклероз.

- Определение
- Епидимиология и факторы риска
- Класификация дислипидемий и патогенез атеросклероза
- Липопротеины и липидный метаболизм

Определение

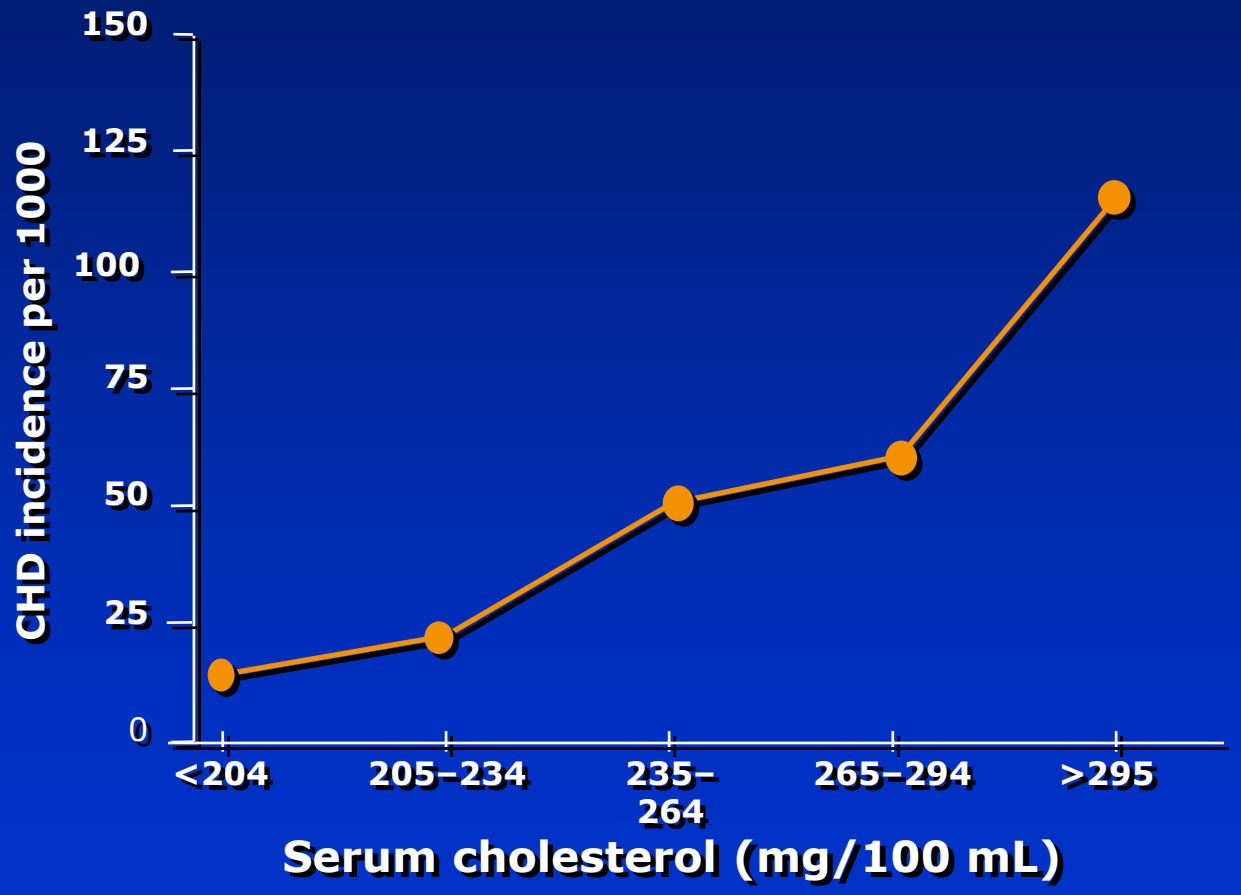
Епидимиология и факторы риска

Mortality from CVD and CHD in Selected Countries



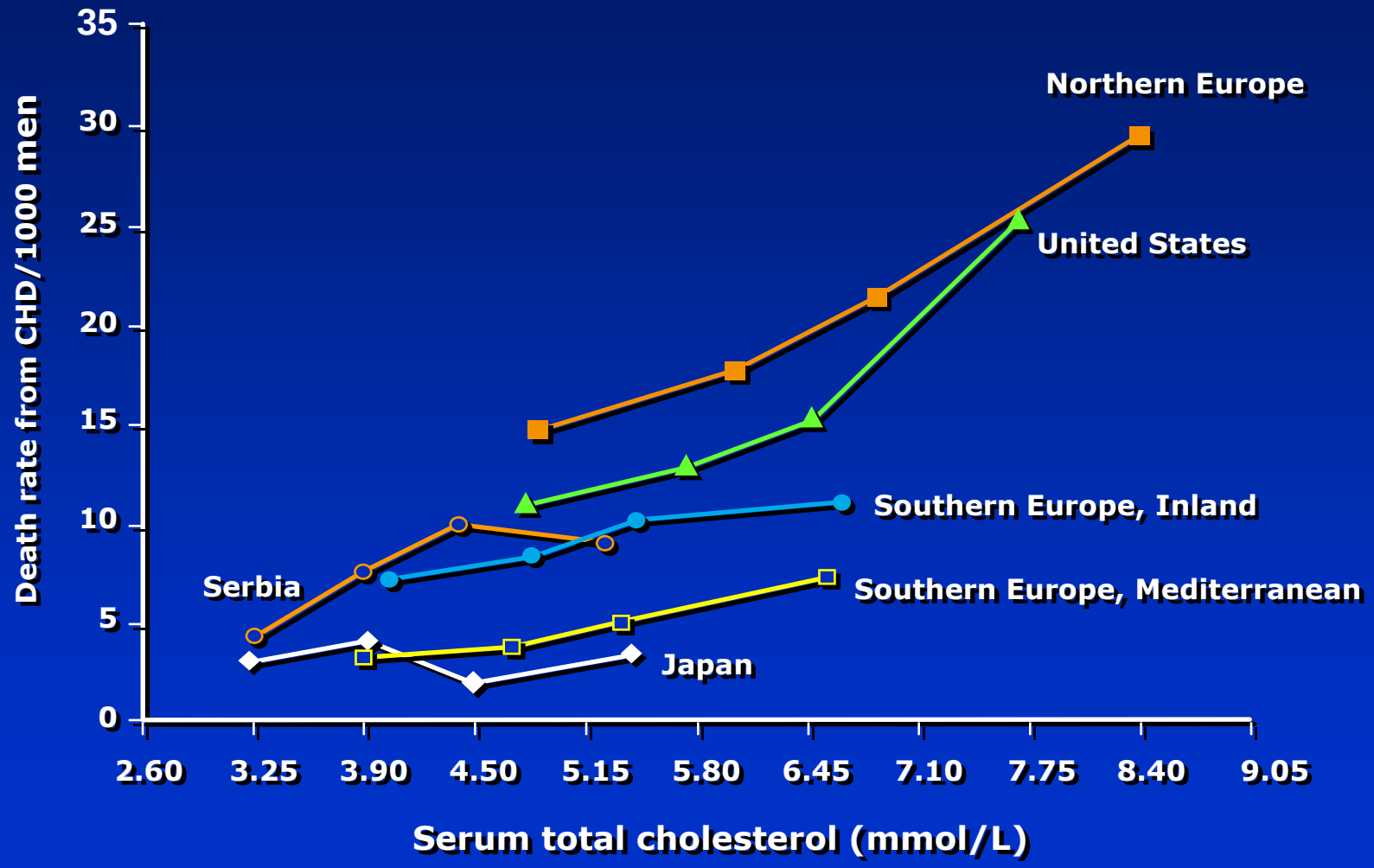
Adapted from International Cardiovascular Disease Statistics 2003; American Heart Association

The Framingham Study: Relationship Between Cholesterol and CHD Risk



Adapted from Castelli WP. *Am J Med* 1984;**76**:4–12

Seven Countries Study: Relationship of Serum Cholesterol to Mortality



Adapted from Verschuren WM *et al. J Am Med Assoc* 1995;**274(2)**:131–136

Cholesterol: A Modifiable Risk Factor

- In the USA, 37% (102 million) have elevated total cholesterol (>200 mg/dL, 5.2 mmol/L)[1]
- In EUROASPIRE II, 58% of patients with established CHD had elevated cholesterol (≥5 mmol/L, 190 mg/dL)[2]
- 10% reduction in total cholesterol results in:
  - 15% reduction in CHD mortality ($p<0.001$)
  - 11% reduction in total mortality ($p<0.001$)[3]
- LDL-cholesterol is the primary target to prevent CHD

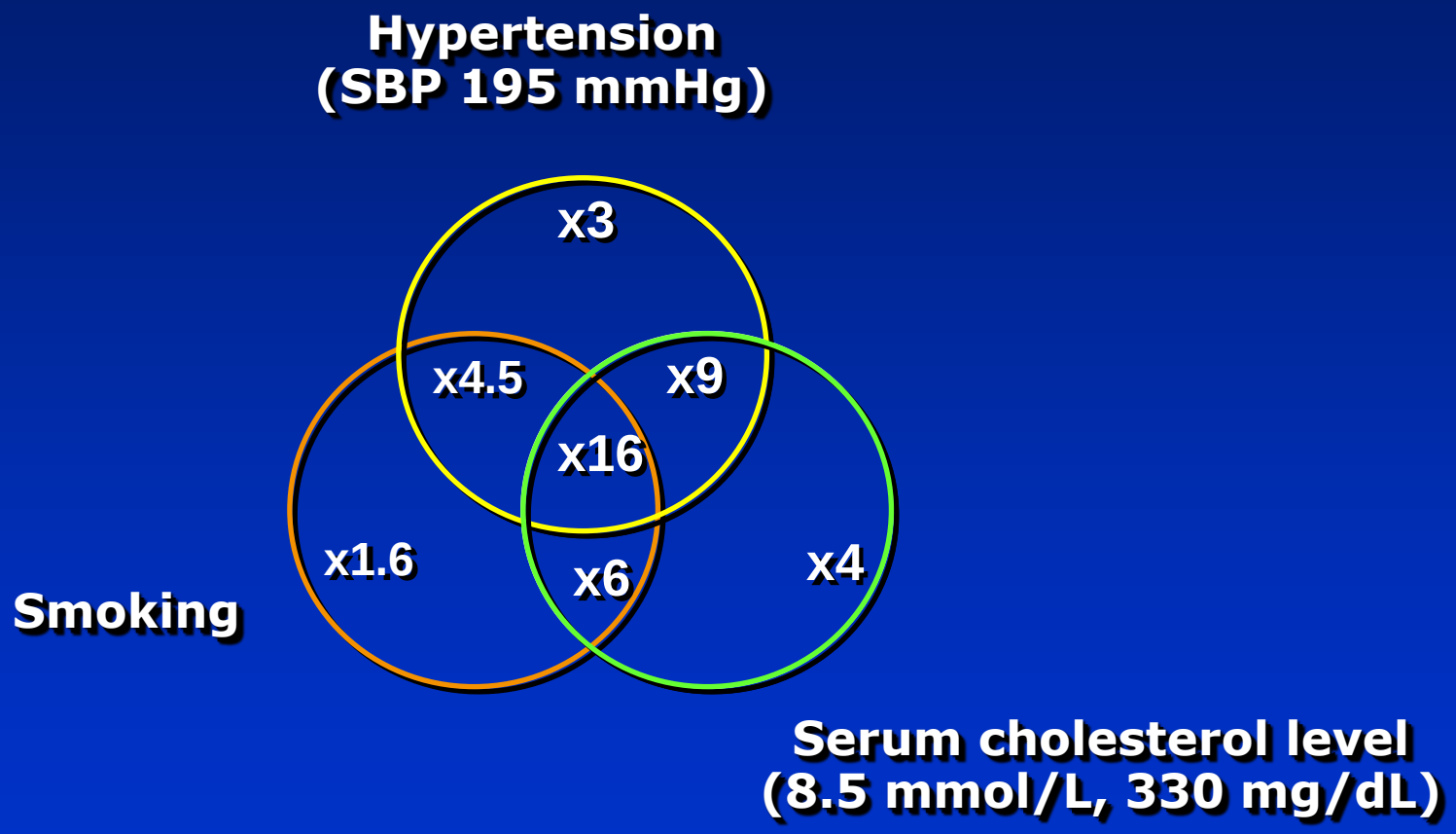
Adapted from: 1. American Heart Association. Heart and Stroke Statistical Update; 2002; 2. EUROASPIRE II Study Group. *Eur Heart J* 2001;**22**:554–572; 3. Gould AL *et al. Circulation* 1998;**97**:946–952

Risk Factors for Cardiovascular Disease

- Modifiable
  - Smoking
  - Dyslipidaemia
    - Raised LDL-cholesterol
    - Low HDL-cholesterol
    - Raised triglycerides
  - Raised blood pressure
  - Diabetes mellitus
  - Obesity
  - Dietary factors
  - Thrombogenic factors
  - Lack of exercise
  - Excess alcohol consumption
- Non-modifiable
  - Personal history of CHD
  - Family history of CHD
  - Age
  - Gender

Adapted from: Pyörälä K *et al. Eur Heart J* 1994;**15**:1300–1331

Levels of Risk Associated with Smoking, Hypertension and Hypercholesterolaemia



Adapted from Poulter N *et al.*, 1993

Класификация дислипидемий и патогенез атеросклероза

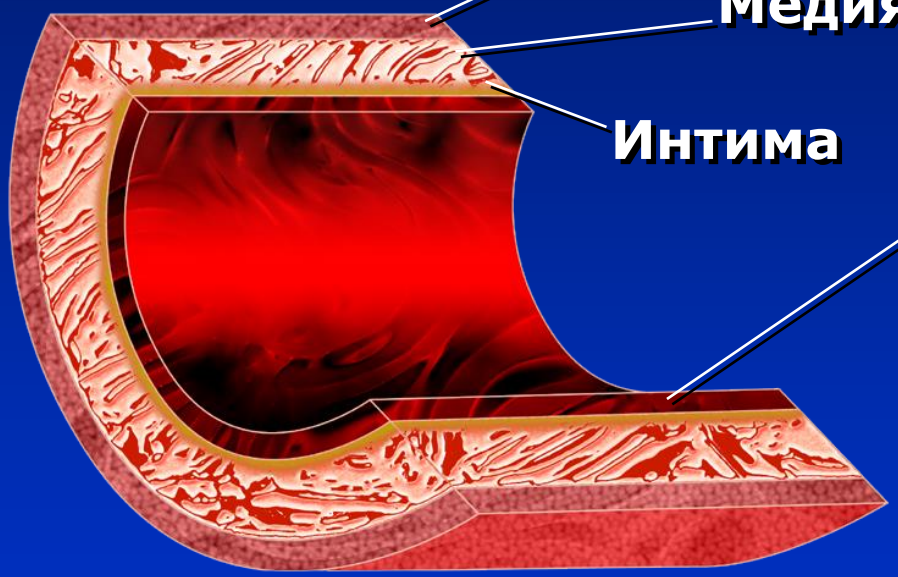
Classification of Dyslipidaemias: Fredrickson (WHO) Classification

Phenotype	Lipoprotein elevated	Serum cholesterol	Serum triglyceride	Atherogenicity	Prevalence
I	Chylomicrons	Normal to ↑	↑↑↑↑	None seen	Rare
IIa	LDL	↑↑	Normal	+++	Common
IIb	LDL and VLDL	↑↑	↑↑	+++	Common
III	IDL	↑↑	↑↑↑	+++	Intermediate
IV	VLDL	Normal to ↑	↑↑	+	Common
V	VLDL and chylomicrons	Normal to ↑	↑↑↑↑	+	Rare

LDL – low-density lipoprotein; IDL – intermediate-density lipoprotein; VLDL – very low-density lipoprotein. (High-density lipoprotein (HDL) cholesterol levels are not considered in the Fredrickson classification.)

Adapted from Yeshurun D, Gotto AM. *Southern Med J* 1995;**88(4)**:379–391

Нормальная артериальная стенка



Adapted from Weissberg PL. *Eur Heart J Supplements* 1999:**1**:T13–18

Патогенез атеросклеротической бляшки

повреждение эндотелия

↓

Защитная реакция в результате чего в производятся молекулы клеточной адгезии

↓

Моноциты и Т-лимфоциты прикрепляются к «Липкой» поверхности эндотелиальных клеток

↓

Миграция через стенки артерий в субэндотелиальное пространство

↓

Макрофаги занимают окисленные ЛНП-холестерина

↓

Пенистые клетки богатые липидами

↓

Жирные полосы и атеромная бляшка

"Активированный" Эндотелий

активирование эндотелия

- Цитокины (IL-1, TNF-α)
- Хемокины (MCP-1, IL-8)
- Фактор роста (PDGF, FGF)

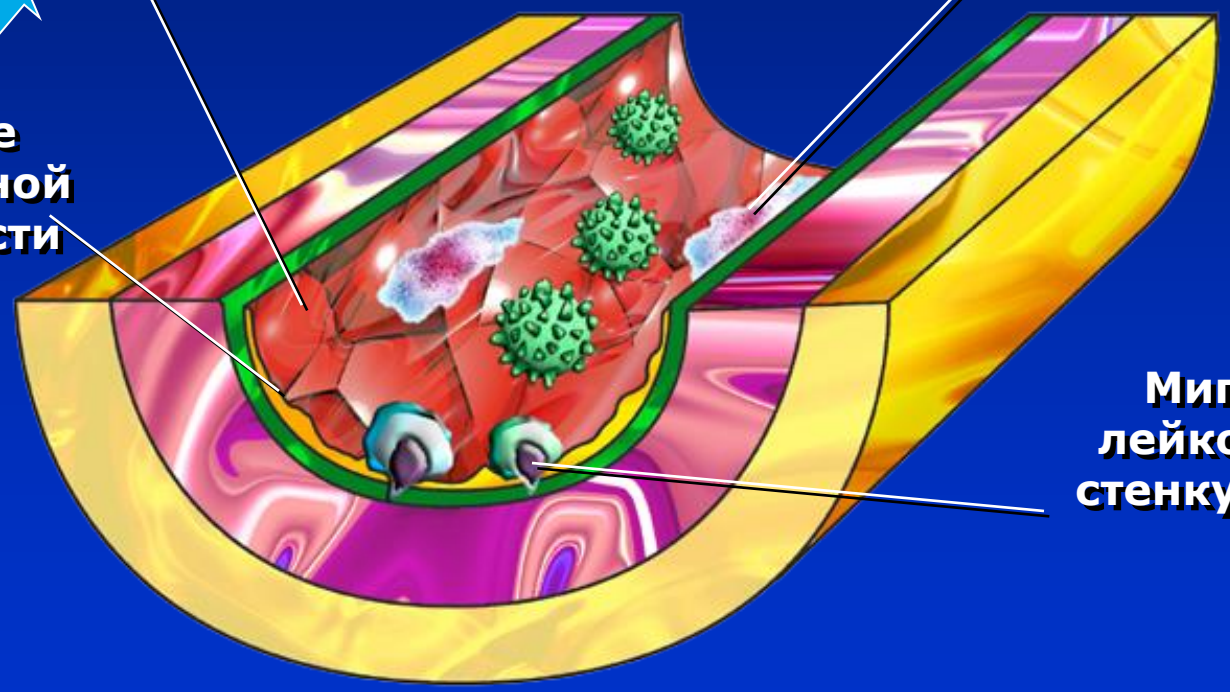
} **МОЛЕКУЛЫ КЛЕТОЧНОЙ АДГЕЗИИ**

привлекает моноциты и Т-лимфоциты которые приклепляются к эндотелиальным клеткам

индуцирует пролиферацию клеток и протромботическое состоянии

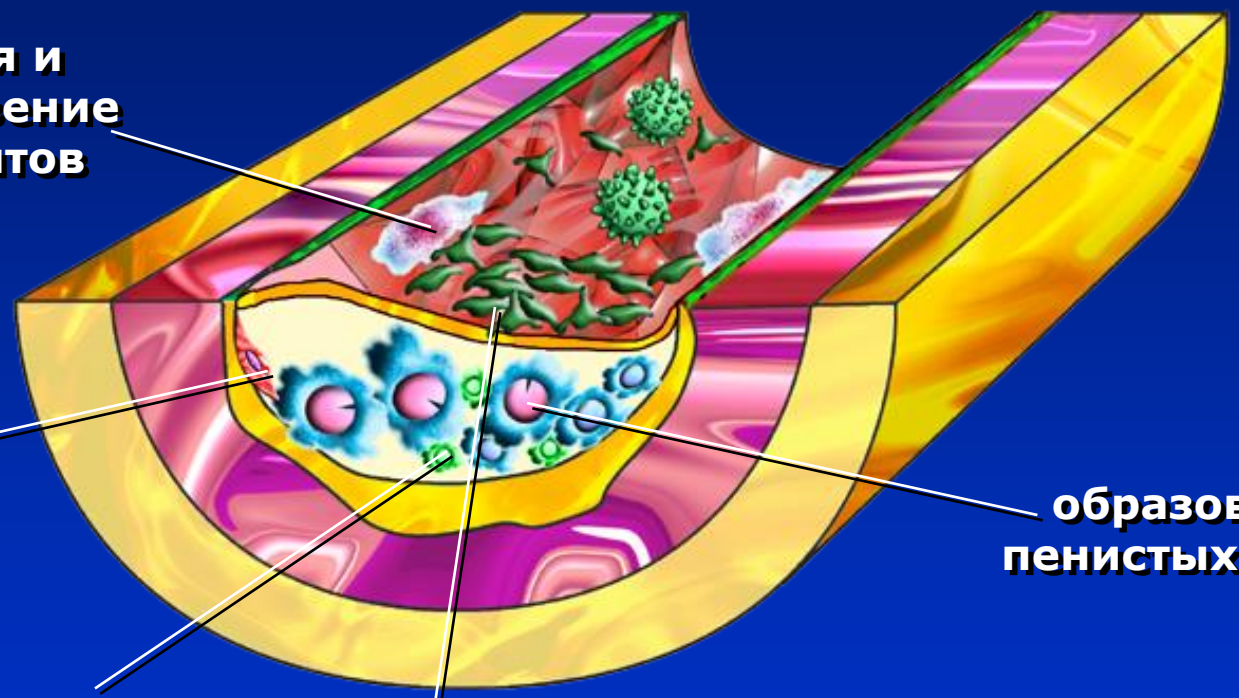
Adapted from Koenig W. *Eur Heart J* 1999;**1**(Suppl T);T19–26

Эндотелиальная дисфункции при атеросклерозе



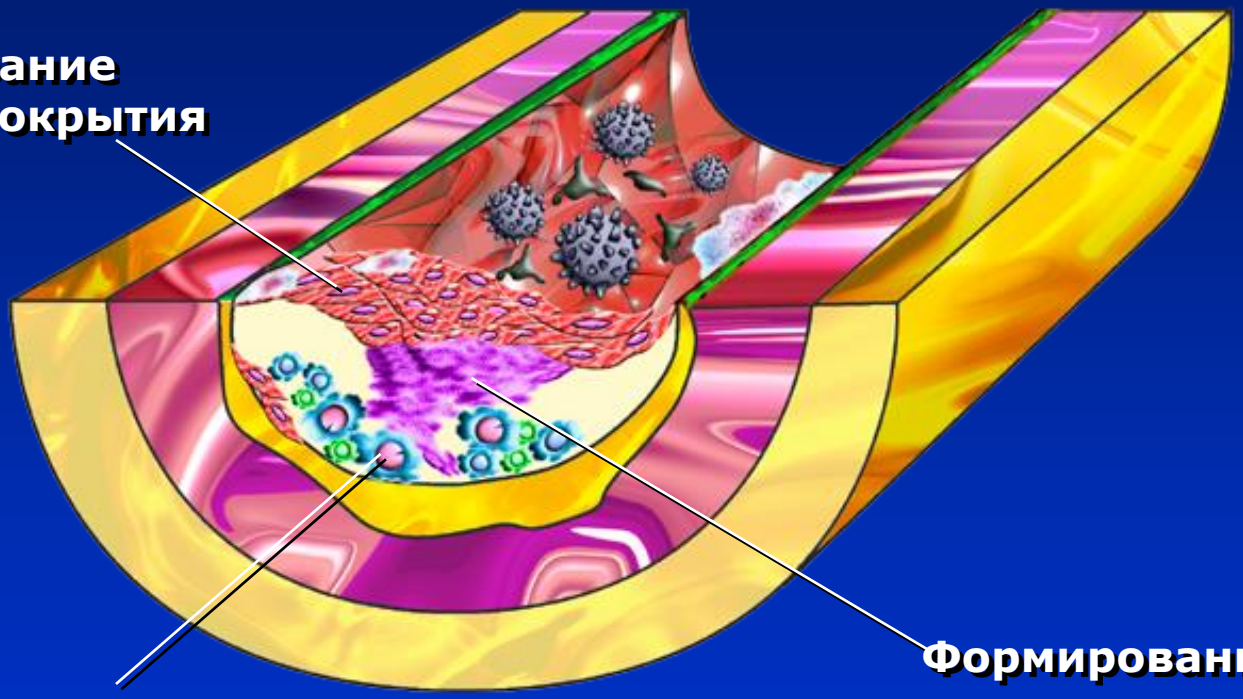
Adapted from Ross R. *N Engl J Med* 1999;**362**:115–126

Формирование жирных полос при атеросклерозе



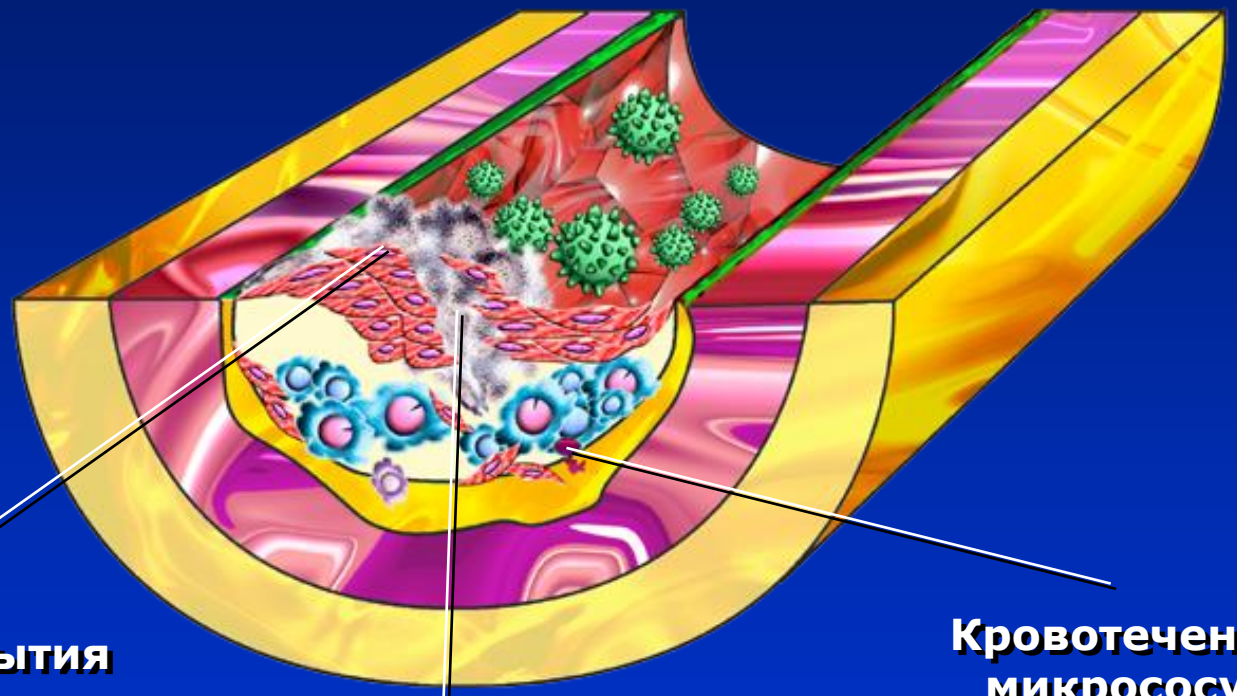
Adapted from Ross R. *N Engl J Med* 1999;**362**:115–126

Формирования осложнённой атеросклеротической бляшки



Adapted from Ross R. *N Engl J Med* 1999;**362**:115–126

Нестабильная атеросклеротической бляшки



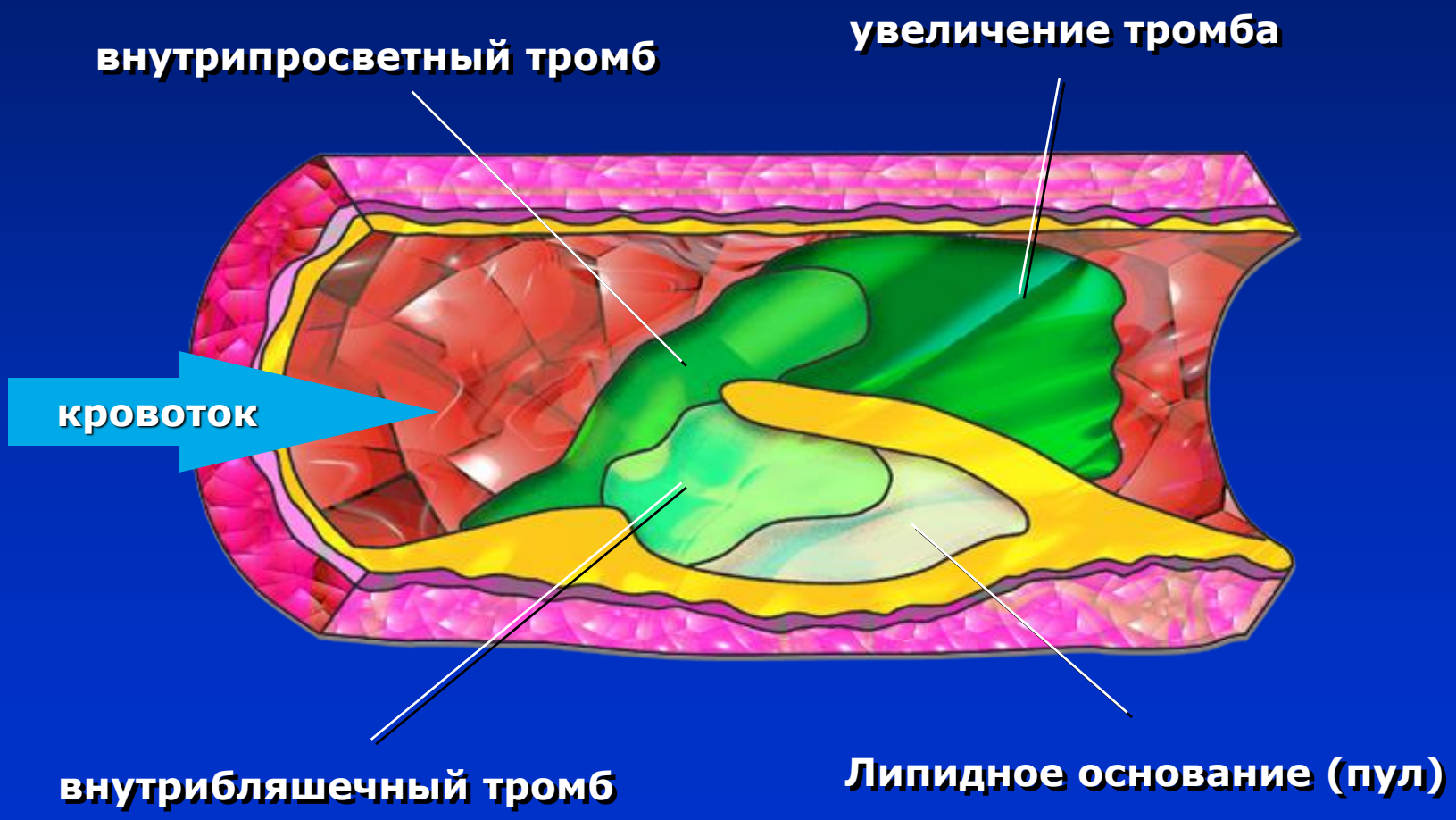
Истончение фиброзного покрытия

Разрыв фиброзного покрытия

Кровотечение из микрососудов бляшки

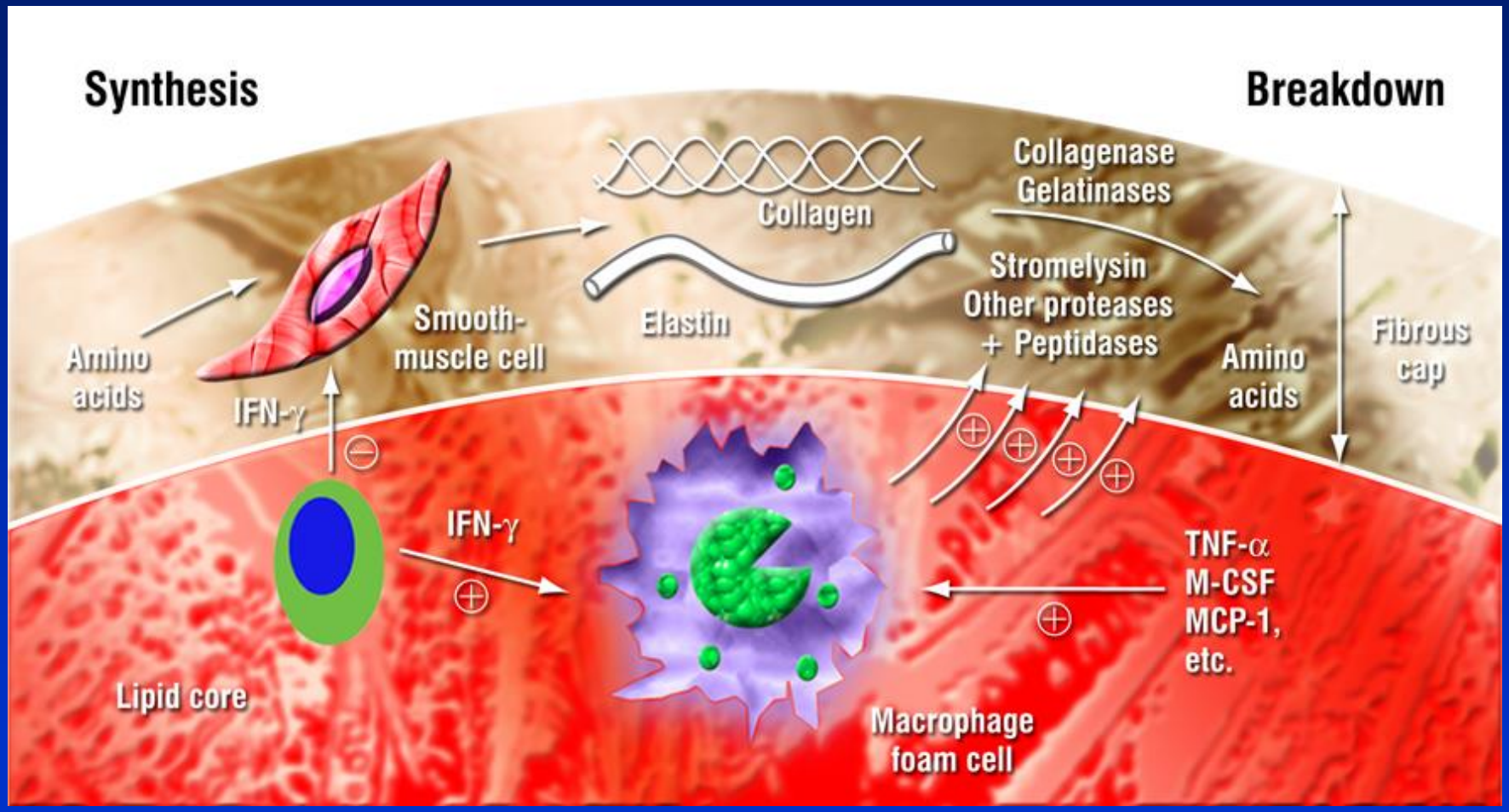
Adapted from Ross R. *N Engl J Med* 1999;**362**:115–126

Разрыв атеросклеротической бляшки и образование тромба



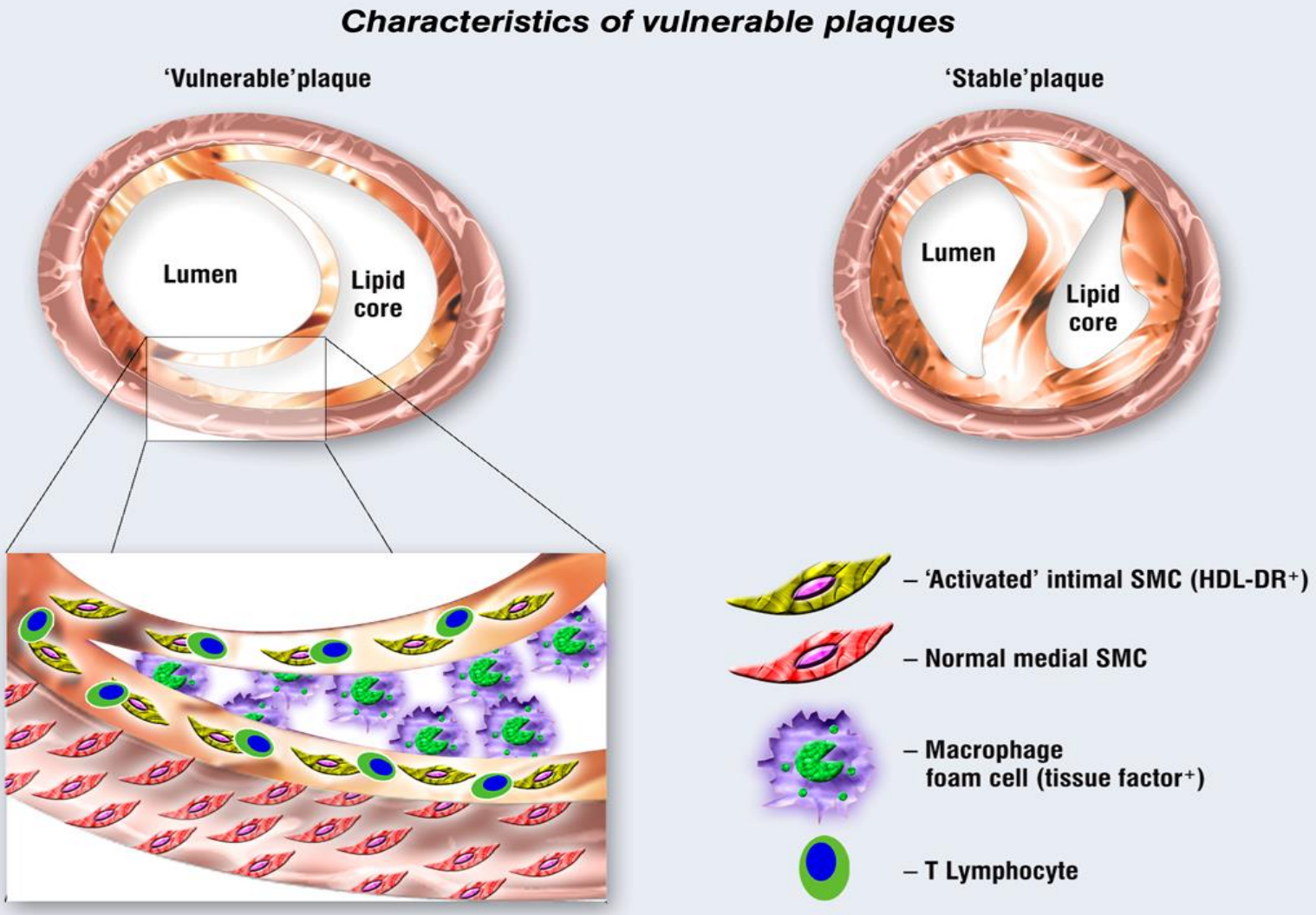
Adapted from Weissberg PL. *Eur Heart J Supplements* 1999;**1**:T13–18

Синтез и распад атеросклеротические бляшки



Adapted from Libby P. *Circulation* 1995;**91**:2844–2850

Уязвимая атеросклеротическая бляшка



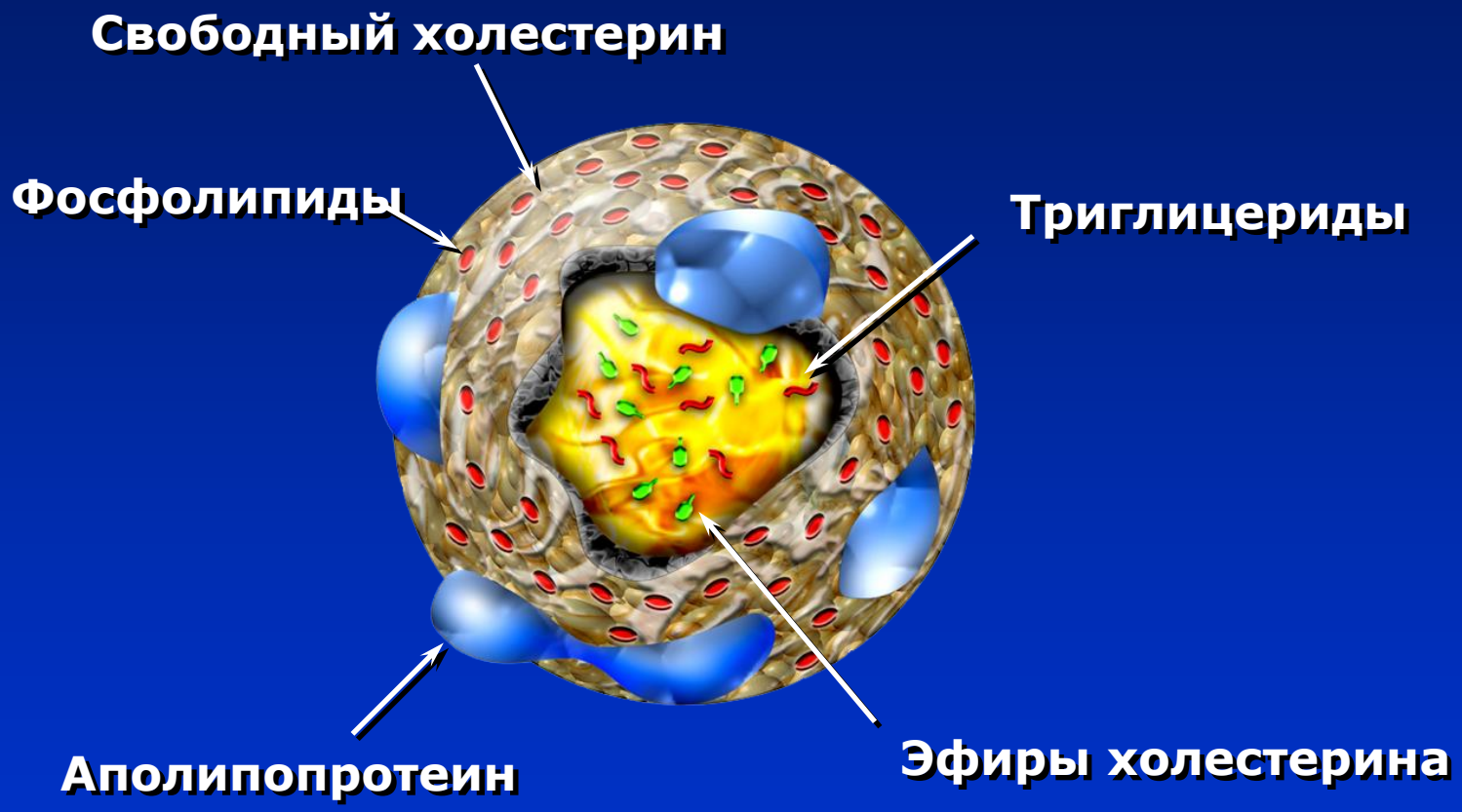
Adapted from Libby P. *Circulation* 1995;**91**:2844–2850

Клинические проявления атеросклероза

- Ишемическая болезнь сердца
  - Стенокардия, инфаркт миокарда, внезапная сердечная смерть
- Цереброваскулярные болезни
  - Транзиторное ишемическое нарушение
  - Инсульт
- Периферические заболевания сосудов
  - Перемежающаяся хромота
  - Гангрена

Липопротеины и липидный обмен

Структура липопротеины



Классификация липопротеинов

По плотности:

- Хиломикроны
- Липопротеины очень низкой плотности (ЛПОНП)
- Липопротеины промежуточной плотности (ЛППП)
- Липопротеины низкой плотности (ЛПНП)
- Липопротеины высокой плотности (ЛПВП)

Холестерин ЛПНП

- Связанный с развитием атеросклероза и Ишемической Болезнью Сердца
- Увеличение на 10% приводит к 20% увеличению риск ИБС
- Риск, связанный с ЛПНП увеличивается из за других факторов риска:
  - низкий уровень холестерина ЛПВП
    - курение
    - гипертензия
    - диабет

Триглицериды

- Связан с повышенным риском развития ИБС из за
  - низкий уровень HDL
  - очень атерогенными формами LDL-холестерина
  - гиперинсулинемия / резистентность к инсулину
  - прокоагулянтное состоянием
  - гипертензиия
  - абдоминальное ожирение
- Может сопровождать дислипидемию
- Нормальный уровень триглицеридов < 1,7 мг / дл
- высокий уровень увеличенивает риск панкреатита

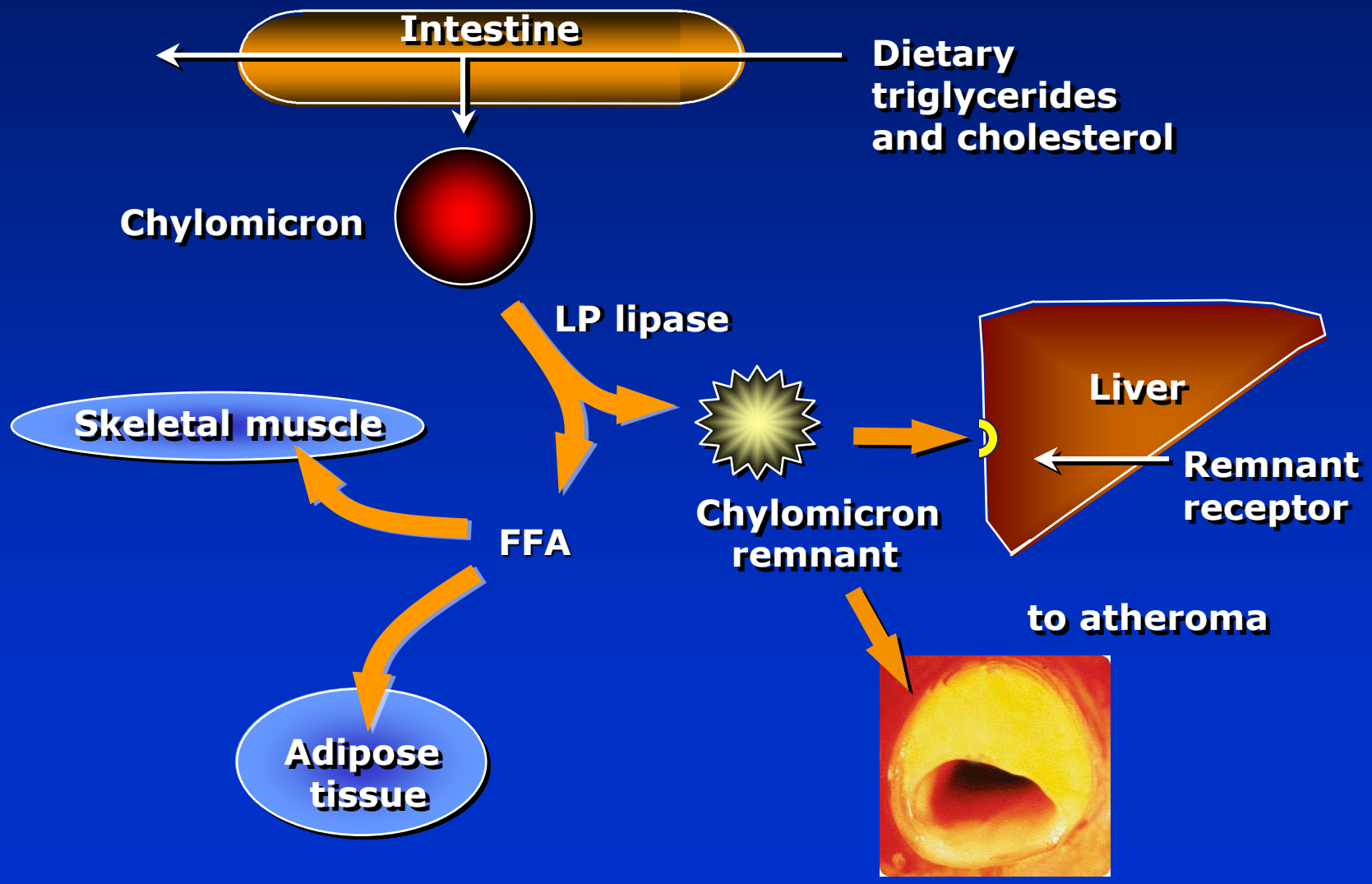
HDL- Холестерин

- HDL-холестерин, оказывает защитное действие снижает риск развития атеросклероза и ИБС
- Чем ниже уровень ЛПВП-холестерина, тем выше риск развития атеросклероза и ИБС
- нормальный уровень ЛПИП
  - М – ≥1.0 mmol/l
  - Ж - ≥1,2 mmol/l
- HDL-холестерин имеет тенденцию к снижению триглицеридов, когда последние высокие
- HDL-холестерина снижает
  - курение
  - ожирение
  - физическая инертность

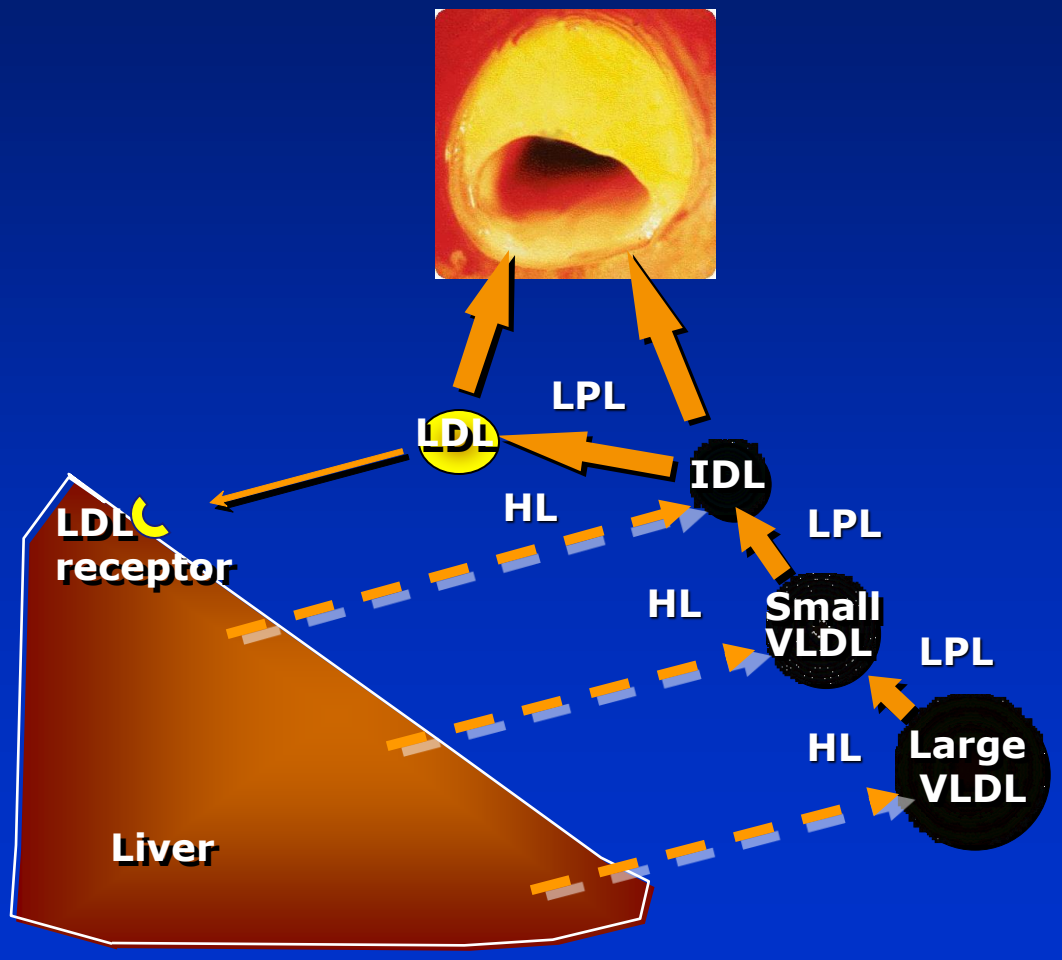
Аполипопротеины

- Основное содержимое липопротеидов
- Функции:
  - Содействие транспорта липидов
  - Активация метаболизма липидов
    - лецитина холестерин ацилтрансферазы (LCAT)
    - липопротеинлипазы (LPL)
    - печеночных триглицеридов липазы (HTGL)
- Связывание с рецепторами на поверхности клеток

Exogenous Pathway of Lipid Metabolism



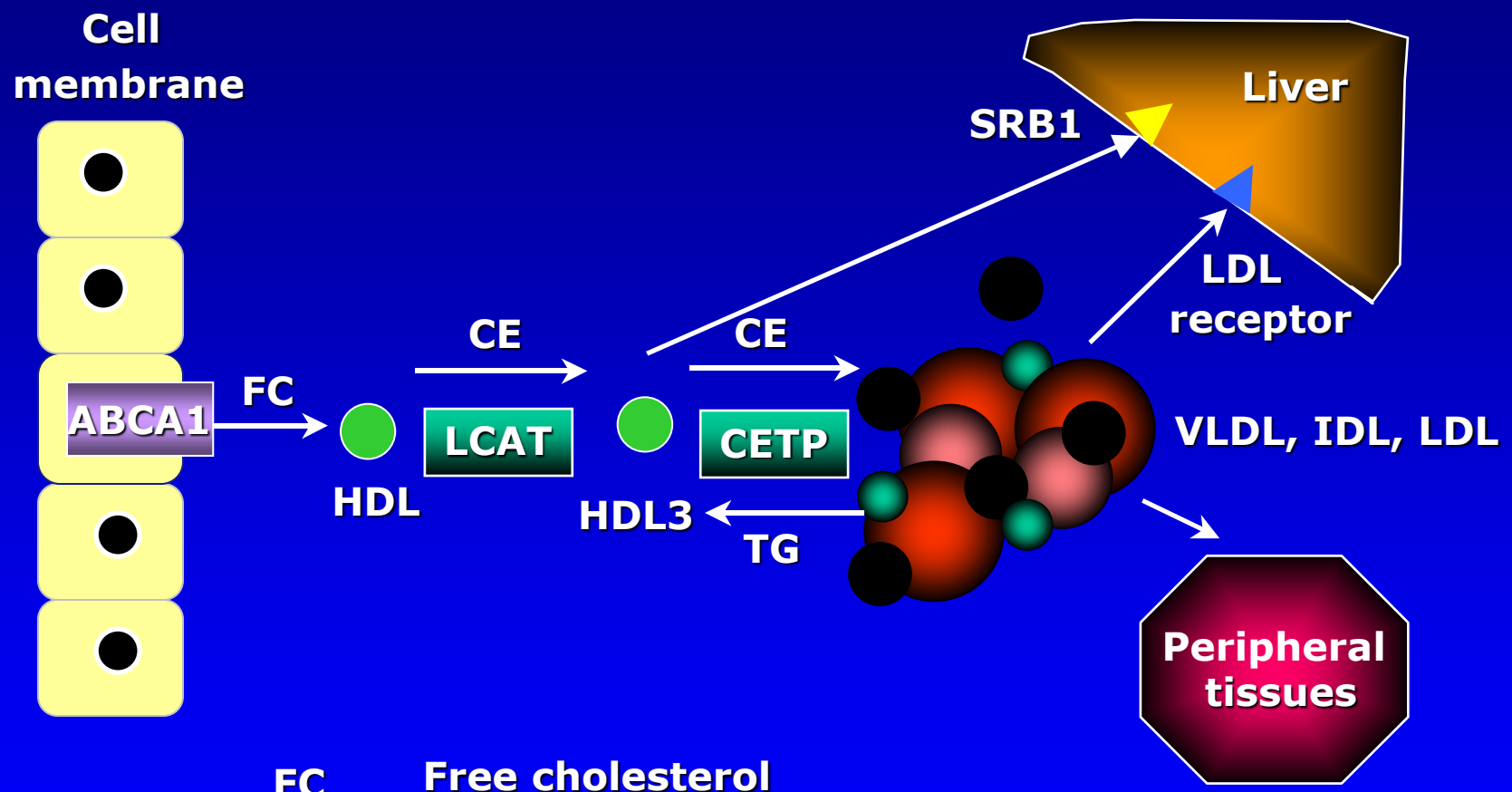
Endogenous Pathway of Lipid Metabolism



LPL Lipoprotein lipase

HL Hepatic lipase

Reverse Cholesterol Transport



FC	Free cholesterol
TG	Triglycerides
CE	Cholesterol esters
LCAT	Lecithin cholesterol acyl transferase
CETP	Cholesteryl ester transfer protein

Section 4

Guidelines and Unmet Need

Joint European Guidelines: ESC, EAS, ESH, ISBM, ESGP/FM, EHN

Estimate absolute CV risk using chart and initial TC value

Absolute CHD risk <20% over 10 years, TC ≥5 mmol/L

↓

Lifestyle advice
Aim: TC<5 mmol/L and LDL-C <3.0 mmol/L
Follow-up at 5-year intervals

Absolute CHD risk ≥20% over 10 years

↓

Measure fasting lipids, give lifestyle advice, with repeat lipids after 3 months

TC <5 mmol/L and LDL-C <3.0 mmol/L
Maintain lifestyle advice with annual follow-up

TC ≥5 mmol/L and/or LDL-C ≥3 mmol/L
Maintain lifestyle advice with drug therapy

Adapted from Wood D *et al. Atherosclerosis* 1998;**140**:199–270

NCEP ATP III: Focus on Multiple Risk factors

- Uses Framingham projections of 10-year absolute CHD risk to identify certain patients with ≥2 risk factors for more intensive treatment
- Raises persons with diabetes without CHD to the level of CHD risk equivalent
- Identifies persons with multiple metabolic risk factors (metabolic syndrome) as candidates for intensified TLC*

***TLC: therapeutic lifestyle changes**

National Cholesterol Education Program, Adult Treatment Panel III, 2001. *JAMA* 2001:**285**;2486–2497

NCEP ATP III: Modifications of Lipid Classification

- Identifies LDL-cholesterol <100 mg/dL (2.6 mmol/L) as optimal
- Raises categorical low HDL-cholesterol from <35 to <40 mg/dL (<0.9 to <1 mmol/L)
- Lowers TG cutpoints to:
  - normal: <150 mg/dL (<1.7 mmol/L)
  - borderline high: 150–199 mg/dL (1.7–2.2 mmol/L)
  - high: 200–499 mg/dL (2.2–5.6 mmol/L)
  - very high: ≥500 mg/dL (≥5.6 mmol/L)

National Cholesterol Education Program, Adult Treatment Panel III, 2001. *JAMA* 2001:**285**;2486–2497

NCEP ATP III Guidelines

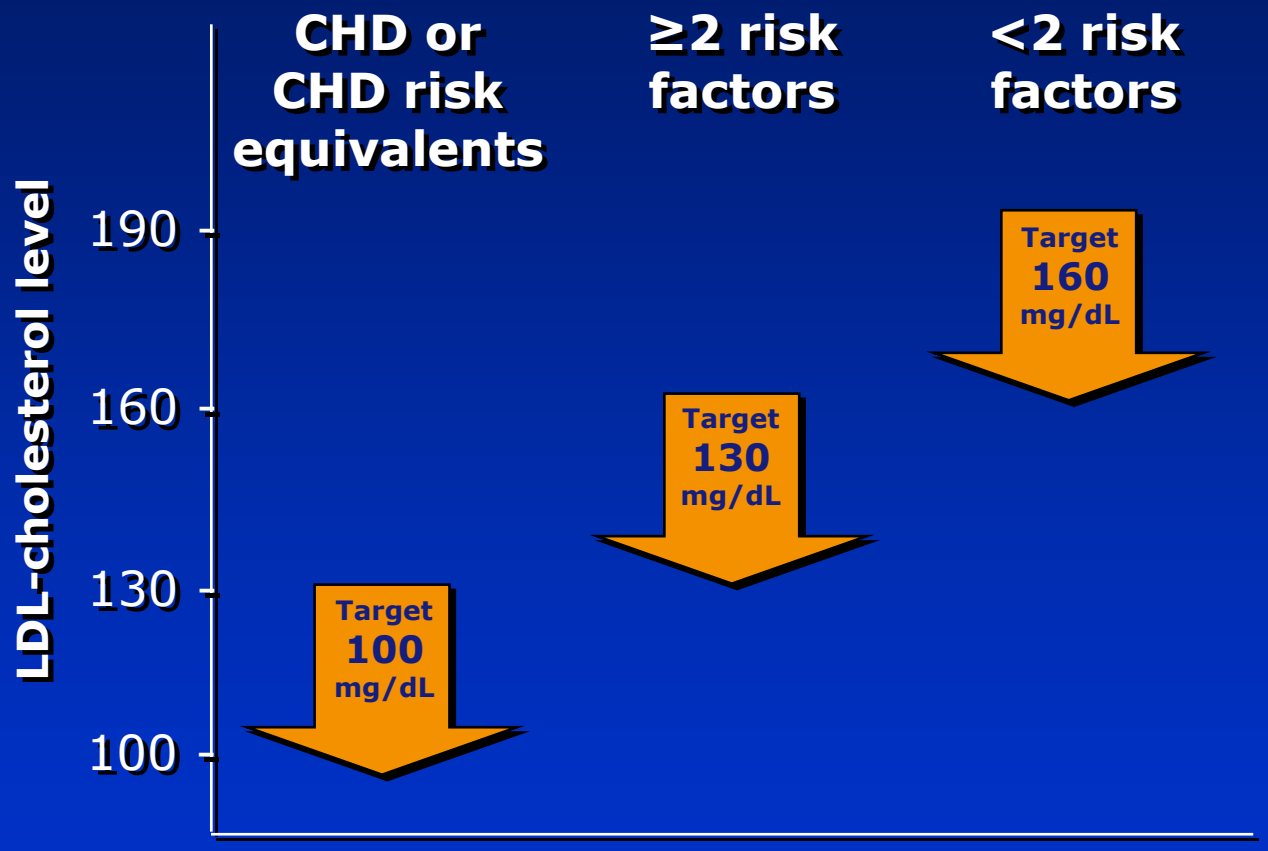
Patients with	Initiate TLC* if LDL-C	Drug therapy considered if LDL-C	LDL-C treatment goal
0-1 risk factors	≥ 160 mg/dL†	≥190 mg/dL (160 –189 mg/dL: drug optional)	<160 mg/dL†
≥2 risk factors (10-year risk ≤ 20%)	≥ 130 mg/dL†	10-year risk 10–20%: ≥130 mg/dL 10-year risk <10%: ≥ 160 mg/dL	<130 mg/dL†
CHD and CHD risk equivalents (10-year risk >20%)	≥ 100 mg/dL†	≥ 130 mg/dL (100–129 mg/dL: drug optional)	<100 mg/dL†

† 100 mg/dL = 2.6 mmol/L; 130 mg/dL = 3.4 mmol/L; 160 mg/dL = 4.1 mmol/L

* TLC: therapeutic lifestyle changes

National Cholesterol Education Program, Adult Treatment Panel III. *JAMA* 2001;**285**:2486–2497

NCEP ATP III: LDL-Cholesterol Goals



100 mg/dL = 2.6 mmol/L; 130 mg/dL = 3.4 mmol/L; 160 mg/dL = 4.1 mmol/L

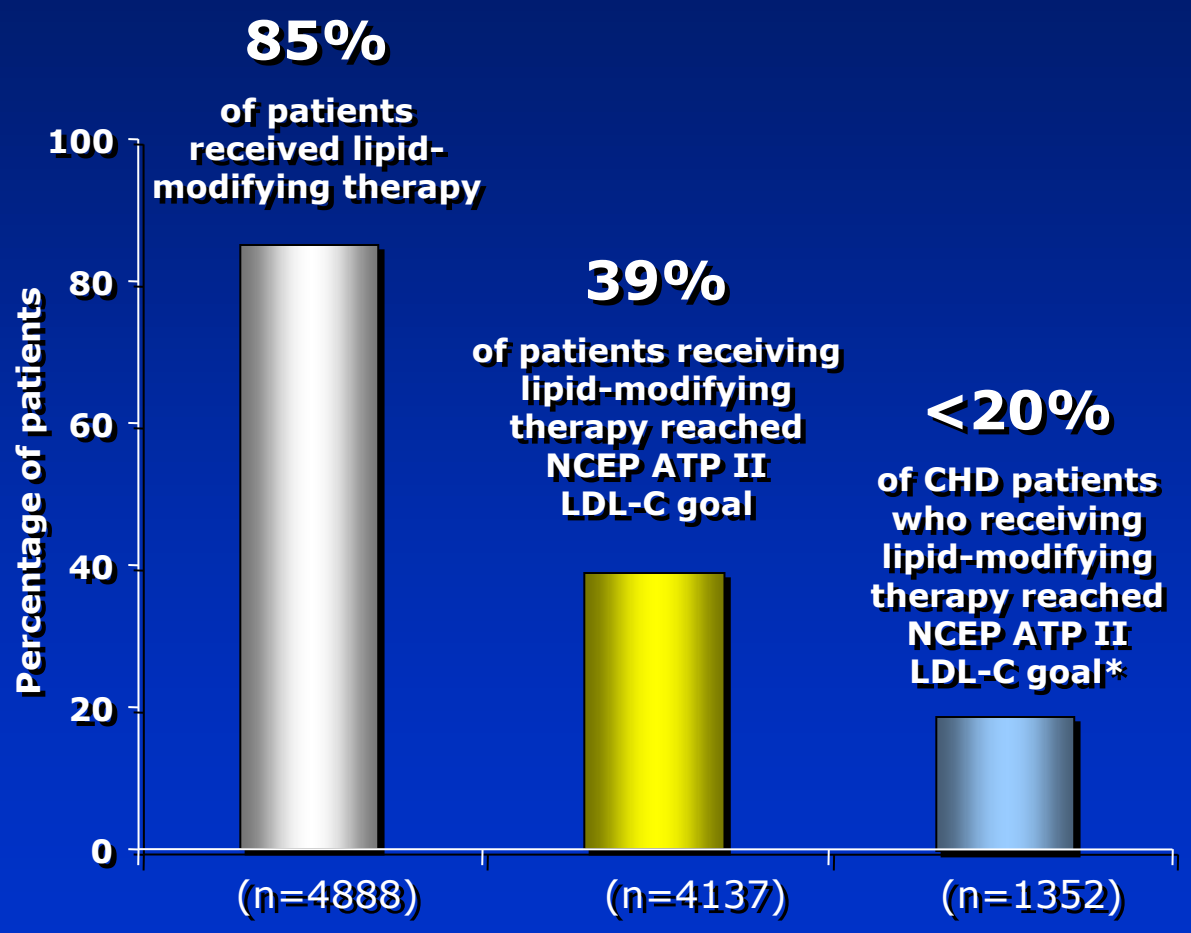
National Cholesterol Education Program, Adult Treatment Panel III, 2001. *JAMA* 2001:**285**;2486–2497

NCEP ATP III Guidelines Increase the Number of Patients Eligible for Treatment

Risk	NCEP ATP II	NCEP ATP III	% increase in drug-eligible patients
High	**8,612**	**14,713**	**71**
Moderate	**19,555**	**23,663**	**21**
Low	**1,264**	**1,264**	**0**
Total	**29,431**	**39,640**	**35**

Adapted from Davidson MH. *Am J Cardiol* 2002;**89**(Suppl 5A):1C–2C

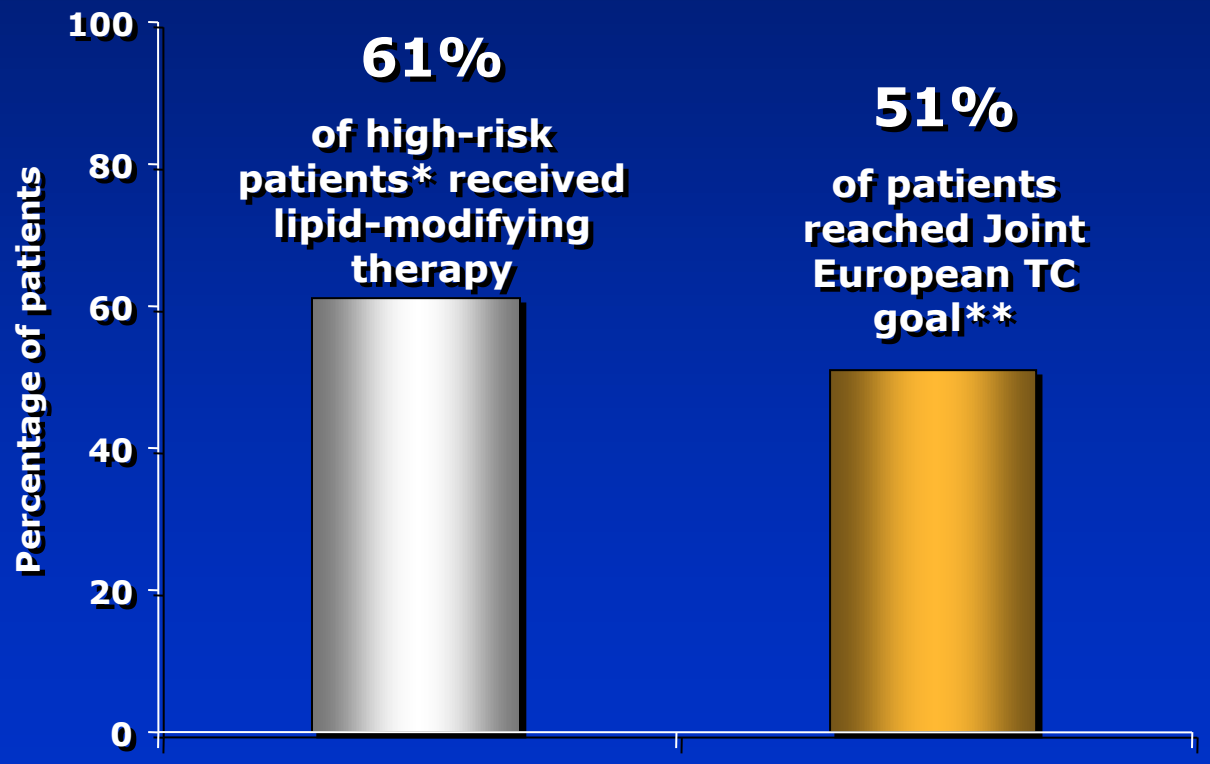
L-TAP: Achieving NCEP ATP II Goal on Lipid-modifying Therapy



* LDL-C ≤100 mg/dL

Adapted from Pearson TA *et al*. *Arch Intern Med* 2000;**160**:459–467

EUROASPIRE II: Achieving Joint European TC Goal



*CABG, PTCA, MI or ischaemia, ** TC <5 mmol/L

Adapted from EUROASPIRE II. *Euro Heart J* 2001;**22**:554–772

Section 5

Statins and Lipid-modifying Therapies

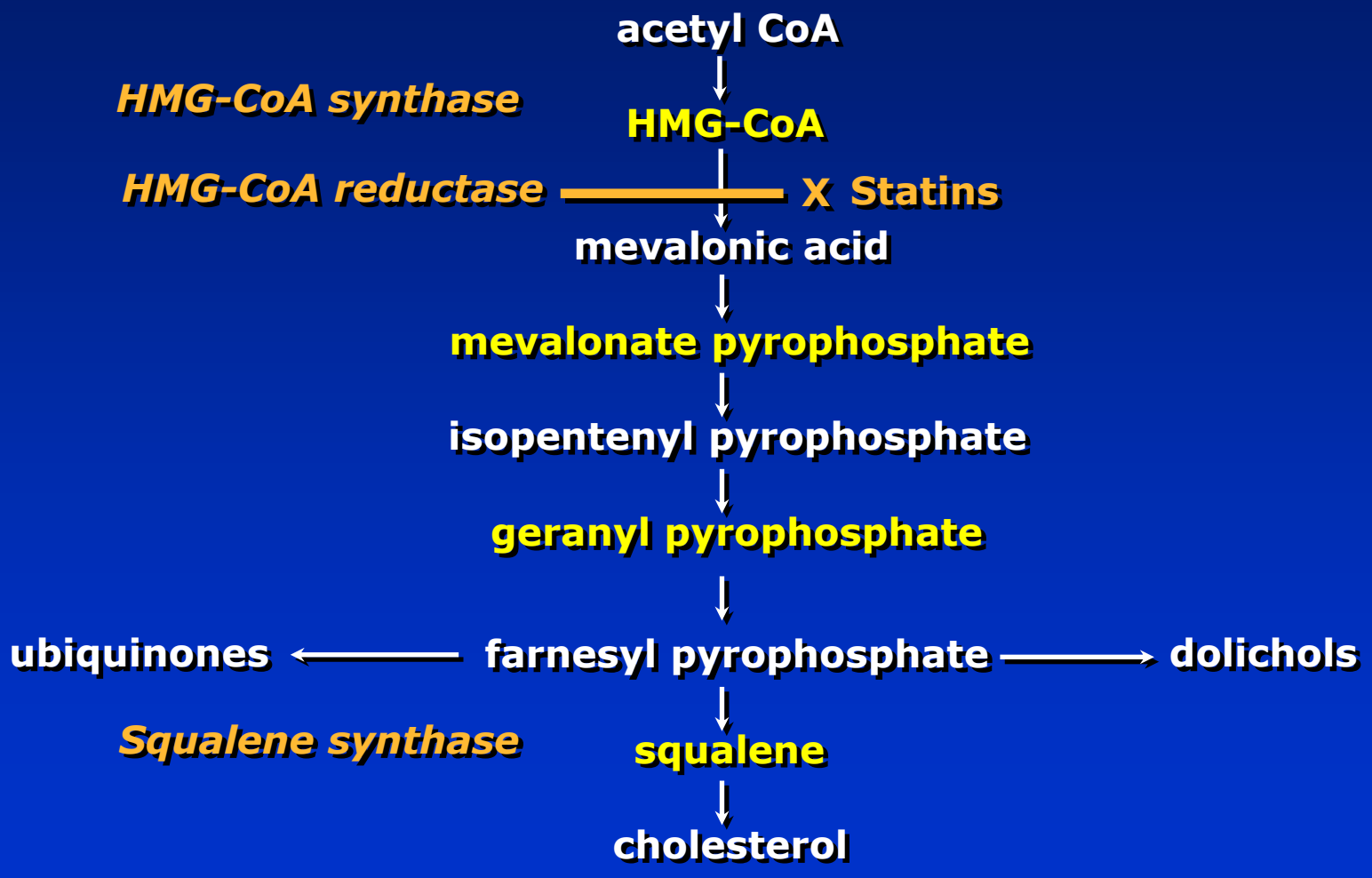
Effect of lipid-modifying therapies on lipids

Therapy	TC	LDL	HDL	TG	Patient tolerability
Bile acid sequestrants	Down 20%	Down 15–30%	Up 3–5%	Neutral or up	Poor
Nicotinic acid	Down 25%	Down 25%	Up 15–30%	Down 20–50%	Poor to reasonable
Fibrates (gemfibrozil)	Down 15%	Down 5–15%	Up 20%	Down 20–50%	Good
Probucol	Down 25%	Down 10–15%	Down 20–30%	Neutral	Reasonable
Statins*	Down 15–30%	Down 24–50%	Up 6–12%	Down 10–29%	Good
Ezetimibe		Down 15–20%	Up 4–9%		Good

TC–total cholesterol, LDL–low density lipoprotein, HDL–high density lipoprotein, TG–triglyceride. * Daily dose of 40mg of each drug, excluding rosuvastatin.

Adapted from Yeshurun D, Gotto AM. *Southern Med J* 1995;**88(4)**:379–391, Knopp RH. *N Engl J Med* 1999;**341**:498–511, Gupta EK, Ito MK. *Heart Dis* 2002;**4**:399–409

Mechanism of Action of Statins: Cholesterol Synthesis Pathway



Pharmacokinetics of Statins

Statin	Metabolised by CYP450	Protein binding (%)	Lipophilic	Half-life (h)
rosuvastatin	No	~90%	No	~19
atorvastatin	Yes	>98%	Yes	~15
simvastatin	Yes	95–8%	Yes	~3
pravastatin	No	~50%	No	~2
fluvastatin	Yes	>98%	No	~3

Adapted from Horsmans Y. *Eur Heart J Supplements* 1999;**1**(Suppl T):T7–12, Vaughan CJ *et al. J Am Coll Cardiol* 2000;**35**:1–10. Rosuvastatin data from Core Data Sheet

Effects of Statins on Lipids

	LDL-C % change	HDL-C % change	TG % change
rosuvastatin (10 mg)	-52	+14	-10
atorvastatin (10 mg)	-39	+6	-19
simvastatin (20 mg)	-38	+8	-19
pravastatin (20 mg)	-32	+2	-11
fluvastatin (20 mg)	-22	+3	-12

Adapted from Product Data Sheets.

Pleiotropic Effects of Statins

- Improving or restoring endothelial function
- Enhancing the stability of atherosclerotic plaques
- Decreasing oxidative stress
- Decreasing vascular inflammation
- Anti-thrombotic effects

Adapted from Takemoto M, Liao JK. *Arterioscler Thromb Vasc Biol* 2001;**21**:1712–1719

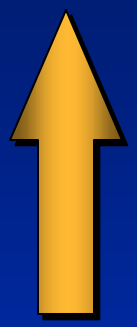
Section 6

Key Statin Trials

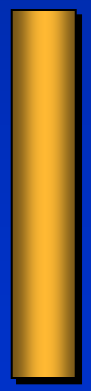
Design of Key Statin Trials

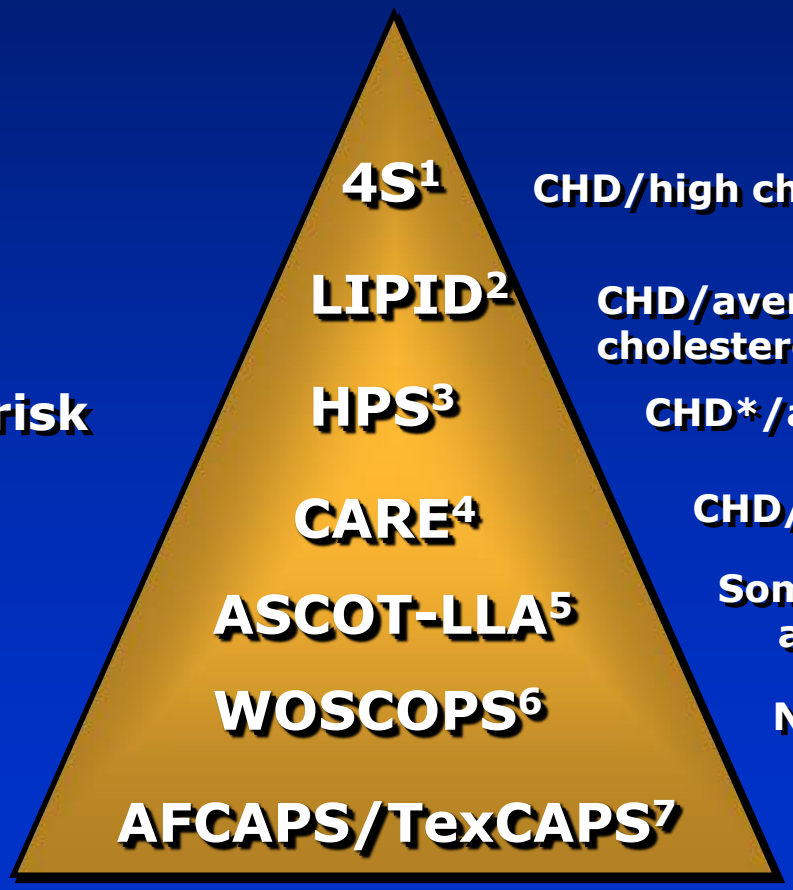
Study	Statin	Existing CHD	Patients	Cholesterol	Follow-up (years)
4S[1]	simvastatin 20 mg od	Yes	4444 male and female, aged 35–70	Raised Mean LDL-C 4.87 mmol/L, 188 mg/dL	5.4
WOSCOPS[2]	pravastatin 40 mg od	No MI, angina (5%)	6595 male, aged 45–64	Raised Mean LDL-C 4.97 mmol/L, 192 mg/dL	4.9
CARE[3]	pravastatin 40 mg od	Yes	4159 male and female, aged 21–75	Average Mean LDL-C 3.59 mmol/L, 139 mg/dL	5.0
LIPID[4]	pravastatin 40 mg od	Yes	9014 male and female, aged 31–75	Average Mean LDL-C 3.80 mmol/L, 147 mg/dL	6.1
AFCAPS/ TexCAPS[5]	lovastatin 40 mg od	No	6605 male and female, aged 45–73	Average Mean LDL-C 3.89 mmol/L, 150 mg/dL	5.2
HPS[6]	simvastatin 40 mg od	Yes	20536 male and female, aged 40–80	Low/average Mean LDL-C 3.4 mmol/L, 130 mg/dL	5.0
ASCOT-LLA[7]	atorvastatin 10 mg od	In some patients	10305 male and female, aged 40–79	Low/average Mean LDL-C 3.4 mmol/L, 130 mg/dL	3.3

Key Statin Trials and Spectrum of Risk



Increasing absolute CHD risk





CHD/high cholesterol

CHD/average to high cholesterol

CHD*/average to high cholesterol

CHD/average cholesterol

Some patients with CHD/ average cholesterol

No MI/high cholesterol

No CHD/average cholesterol

*CHD or CHD risk equivalent, e.g. diabetes

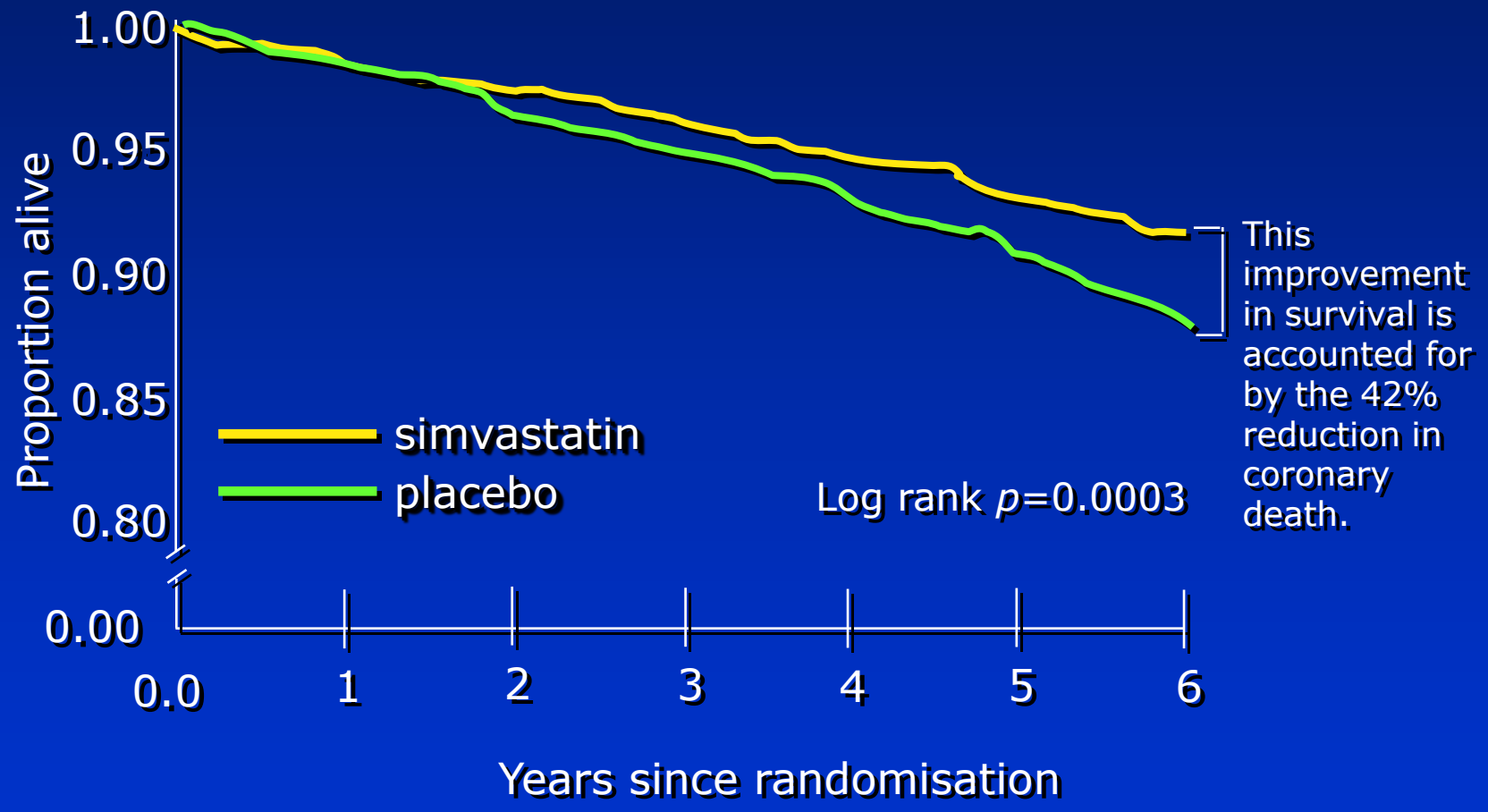
4S Cardiovascular Endpoints
Post-MI or Angina Patients with Raised Cholesterol

Outcomes	Number of events			
	placebo (*n=2223*)	simvastatin (*n=2221*)	Risk reduction (%)	*p*-value
Total mortality*	256	182	30	<0.001
Coronary death	189	111	42	<0.001
Major coronary events	622	431	34	<0.001
PCTA/CABG	383	252	37	<0.001

* primary endpoint

The Scandinavian Simvastatin Survival Study Group. *Lancet* 1994;**344**:1383–1389

4S: Total Mortality



The Scandinavian Simvastatin Survival Study Group. *Lancet* 1994;**344**:1383–1389

WOSCOPS: Cardiovascular Endpoints

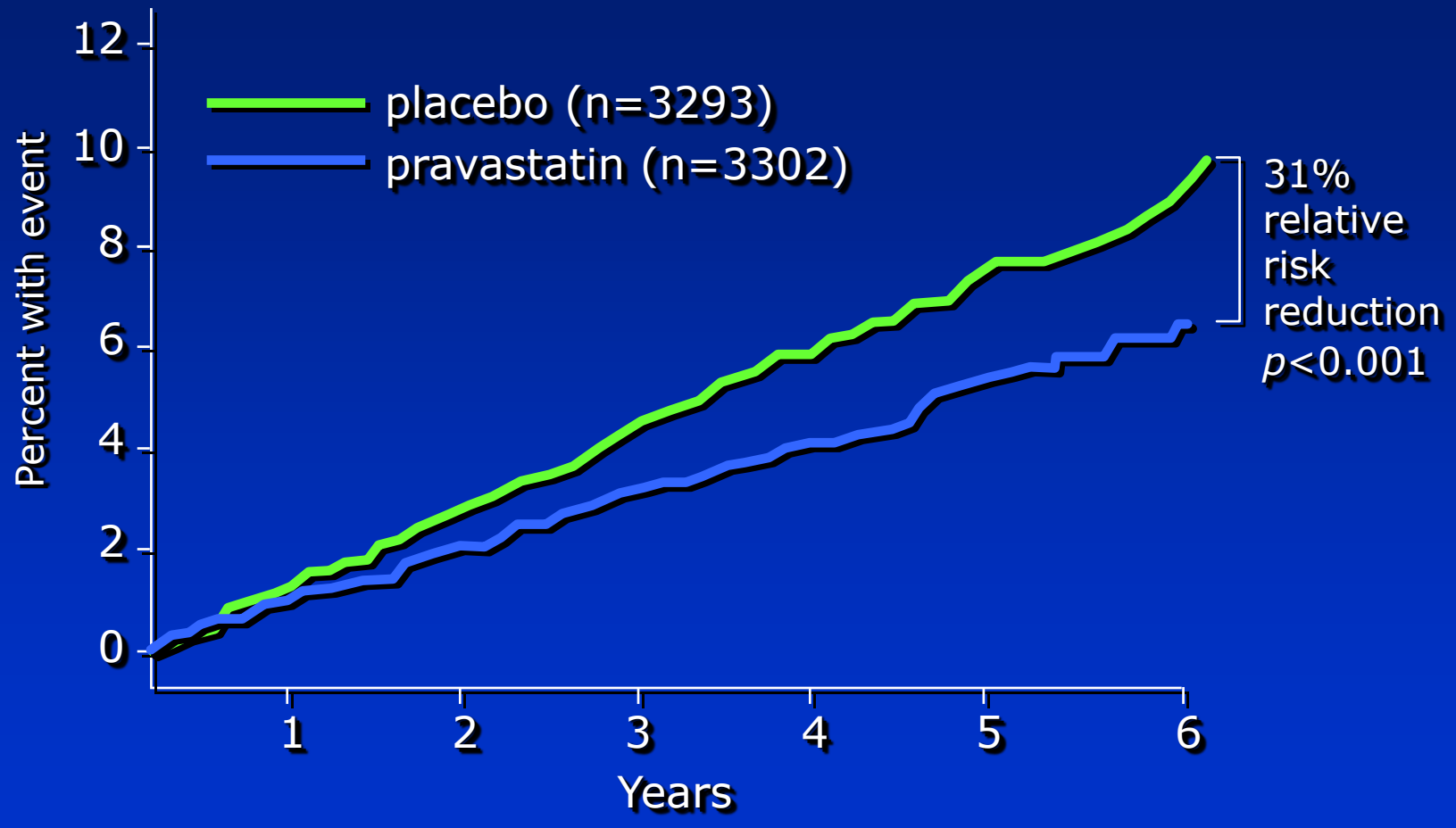
Subjects with No Previous MI but Raised Cholesterol

Outcomes	Number of events			
	placebo (*n=3293*)	pravastatin (*n=3302*)	Risk reduction (%)	*p*-value
Non-fatal MI/CHD death*	248	174	31	<0.001
CHD death	52	38	28	ns
Non-fatal MI	204	143	31	<0.001
PCTA/CABG	80	51	37	0.009
Stroke	51	46	0	ns
All cardiovascular deaths	73	50	32	0.033
Total mortality#	135	106	22	0.051

* primary endpoint
# study not powered to detect differences in this endpoint

Shepherd J *et al. N Engl J Med* 1995;**333**:1301–1307

WOSCOPS: Non-fatal MI and CHD Death



Shepherd J *et al. N Engl J Med* 1995;**333**:1301–1307

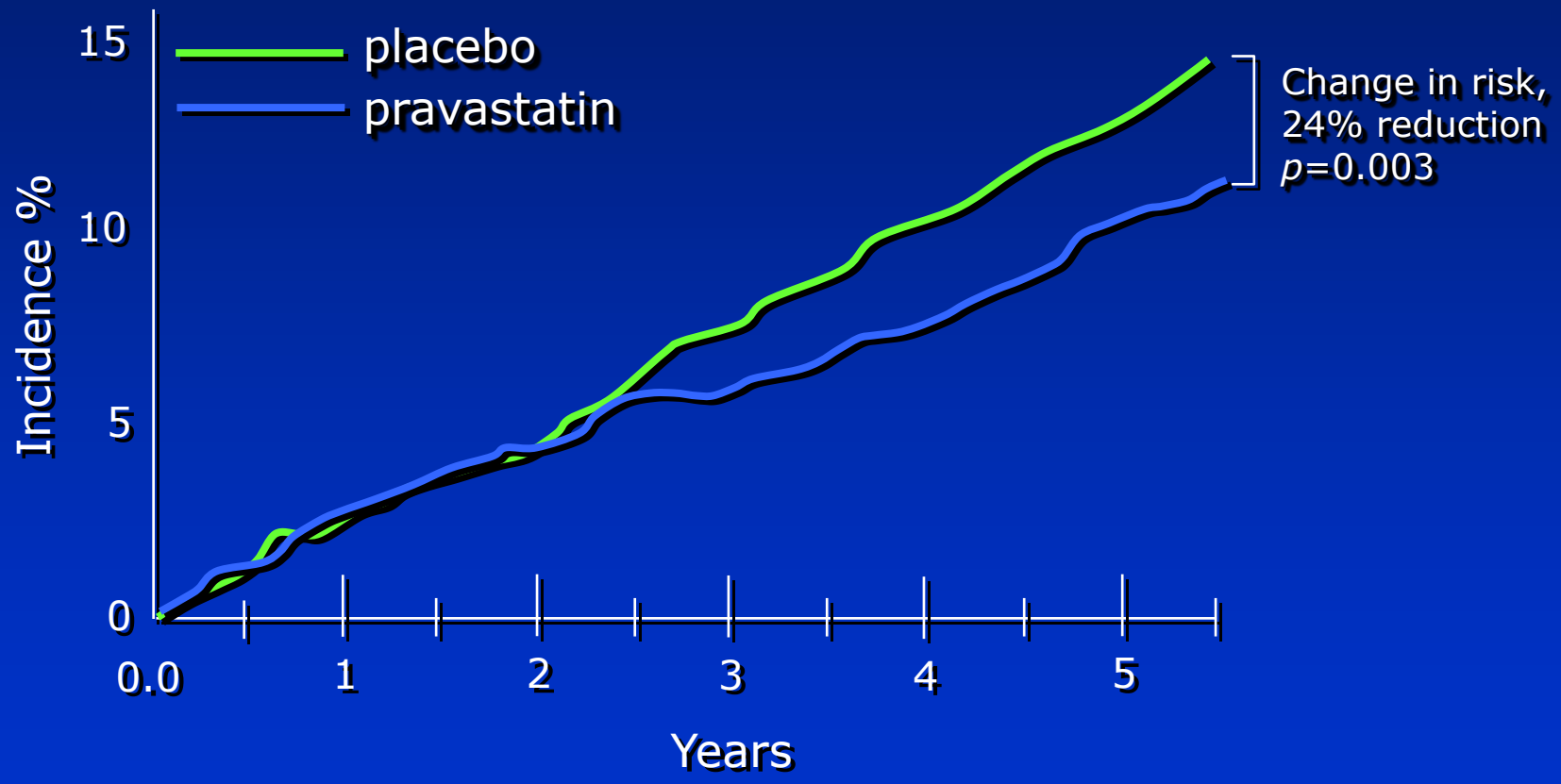
CARE: Cardiovascular Endpoints
Post-MI Patients with Average Cholesterol

Outcomes	Number of events			
	placebo (*n=2078*)	pravastatin (*n=2081*)	Risk reduction (%)	*p*-value
Non-fatal MI/CHD death*	274	212	24	0.003
CHD death	119	96	20	ns
Non-fatal MI	173	135	23	0.02
PCTA/CABG	391	294	27	0.009
Unstable angina	359	317	13	0.07
Stroke	78	54	31	0.03

* primary endpoint

Sacks FM *et al. N Engl J Med* 1996;**335**:1001–1009

CARE: Non-fatal MI or CHD Death



Sacks FM *et al. N Engl J Med* 1996;**335**:1001–1009

LIPID: Cardiovascular Endpoints

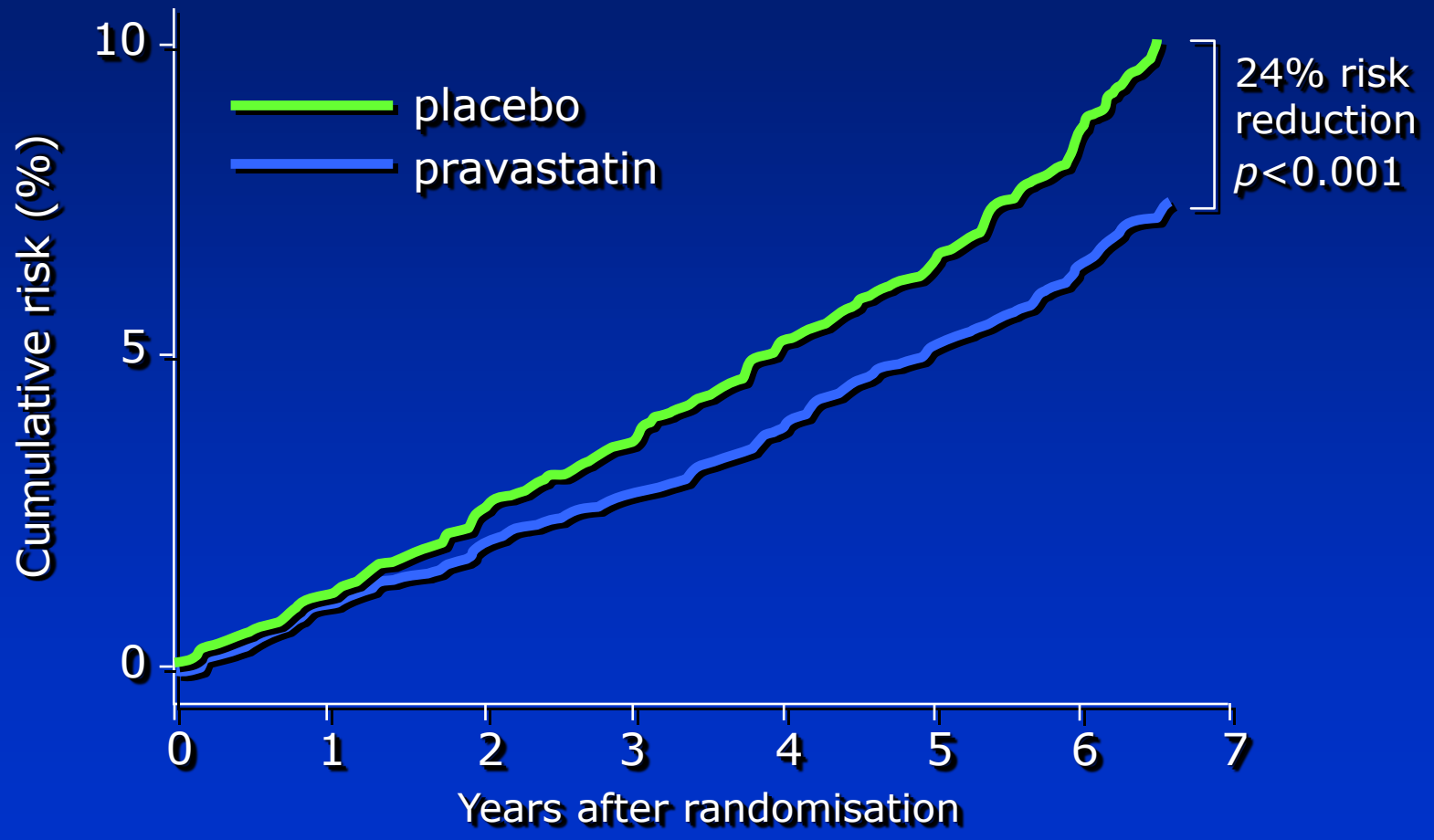
Post-MI or Unstable Angina Patients with Average/raised Cholesterol

Outcomes	Number of events			
	placebo (*n=4502*)	pravastatin (*n=4512*)	Risk reduction (%)	*p*-value
CHD death*	373	287	24	<0.001
CVD death	433	331	25	<0.001
All-cause mortality	633	498	22	<0.001
CHD death or non-fatal MI	715	557	24	<0.001
Any MI	463	336	29	<0.001
PCTA or CABG	708	585	20	<0.001
Hosp. for unstable angina	1106	1005	12	0.005
Stroke	204	169	19	0.048

* primary endpoint

LIPID. *N Engl J Med* 1998;**339**:1349–1357

LIPID: Cumulative Risk of Death from CHD



LIPID. *N Engl J Med* 1998;**339**:1349–1357

AFCAPS/TexCAPS: Cardiovascular Endpoints

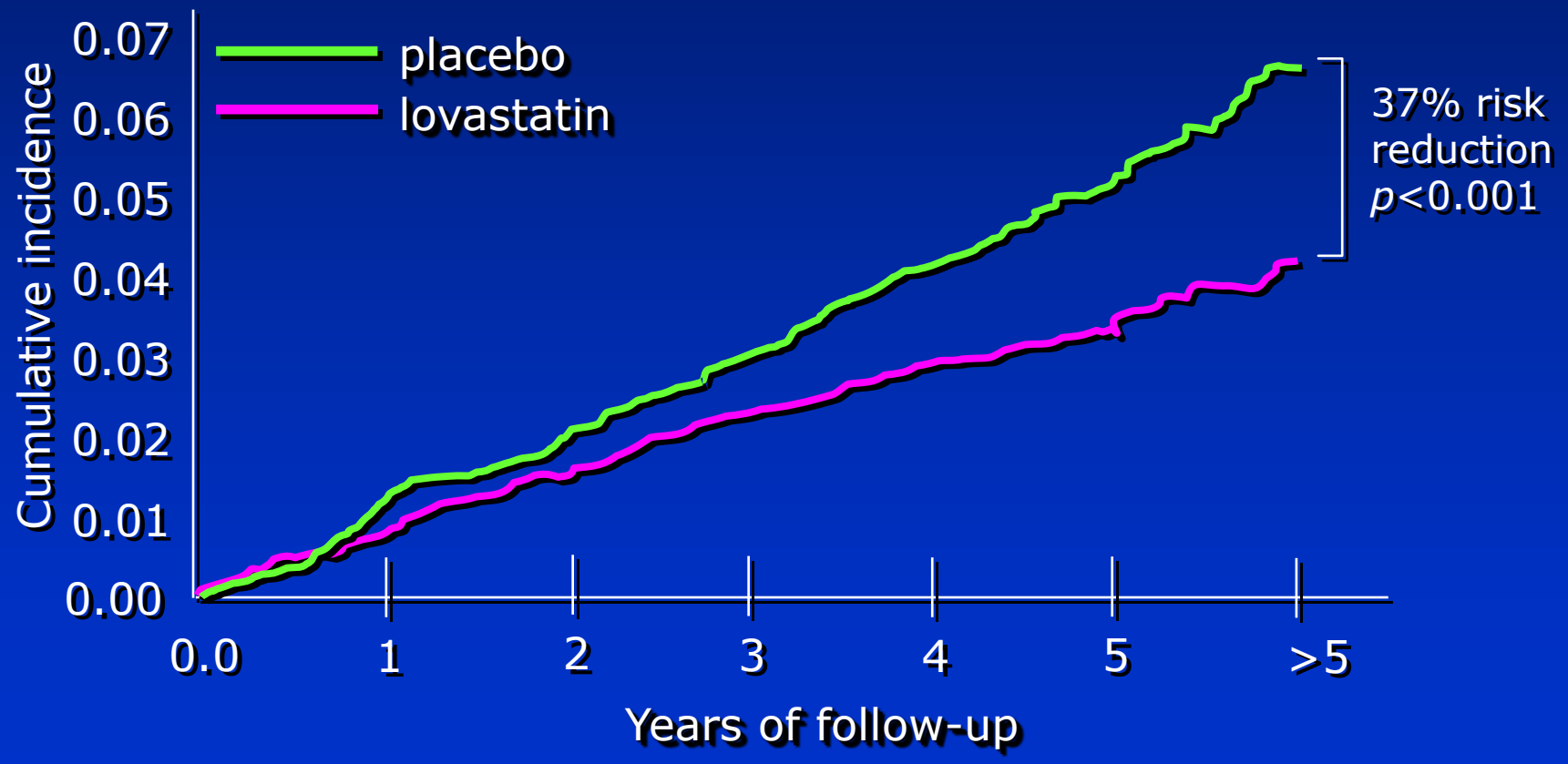
Subjects with No History of CHD and Average Cholesterol

Outcomes	Number of events			
	placebo (*n=3301*)	lovastatin (*n=3304*)	Risk reduction (%)	*p*-value
Fatal or non-fatal MI + unstable angina + sudden cardiac death*	**183**	116	37	<0.001
Revascularisations	**157**	106	33	<0.001
Fatal and non-fatal MI	**95**	57	40	0.002
Unstable angina	**87**	60	32	0.02

* primary endpoint

Downs JR *et al. J Am Med Assoc* 1998;**279**:1615–1622

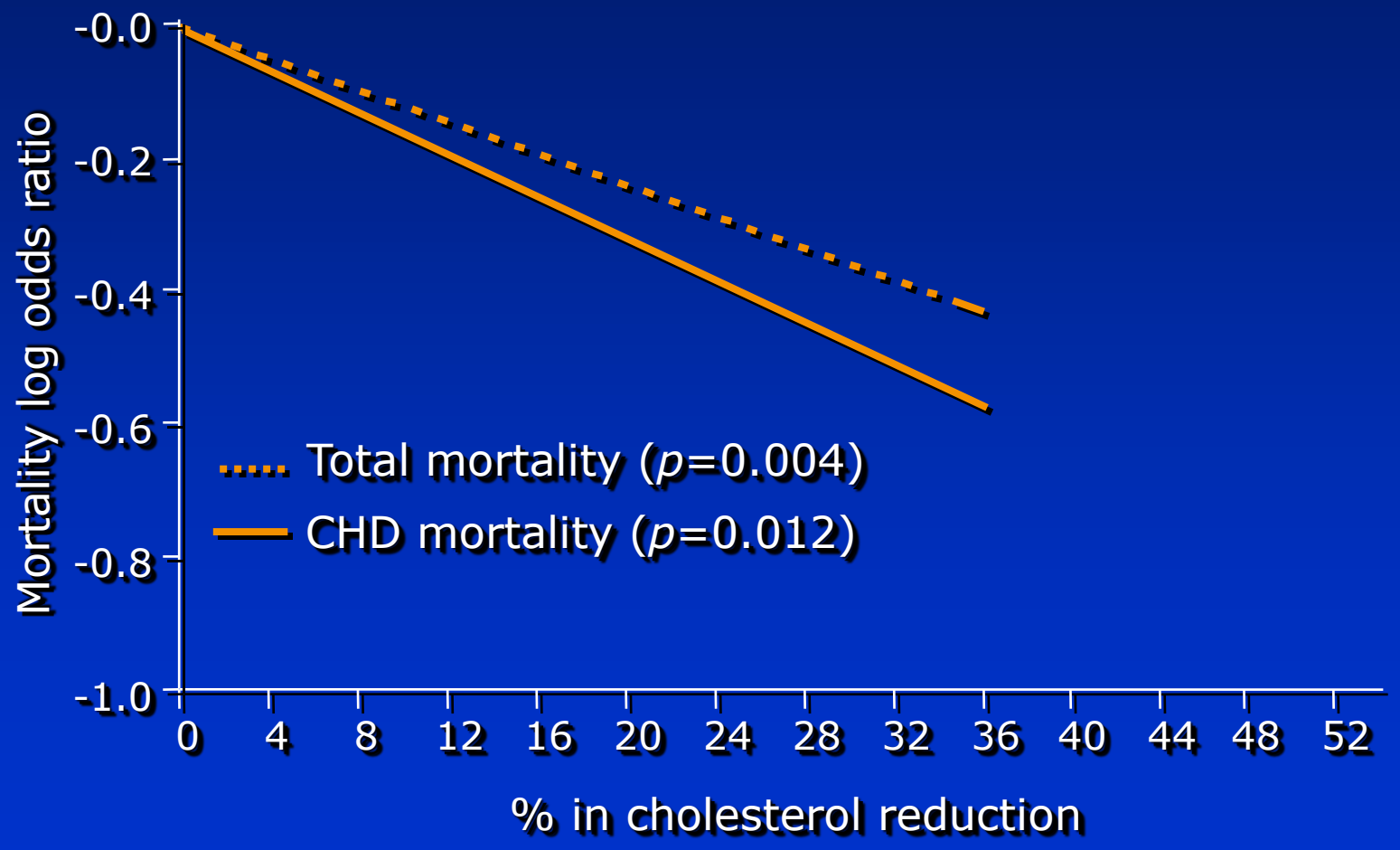
AFCAPS/TexCAPS: Fatal/Non-fatal MI, Sudden Cardiac Death, Unstable Angina



Downs JR *et al. J Am Med Assoc* 1998;**279**:1615–1622

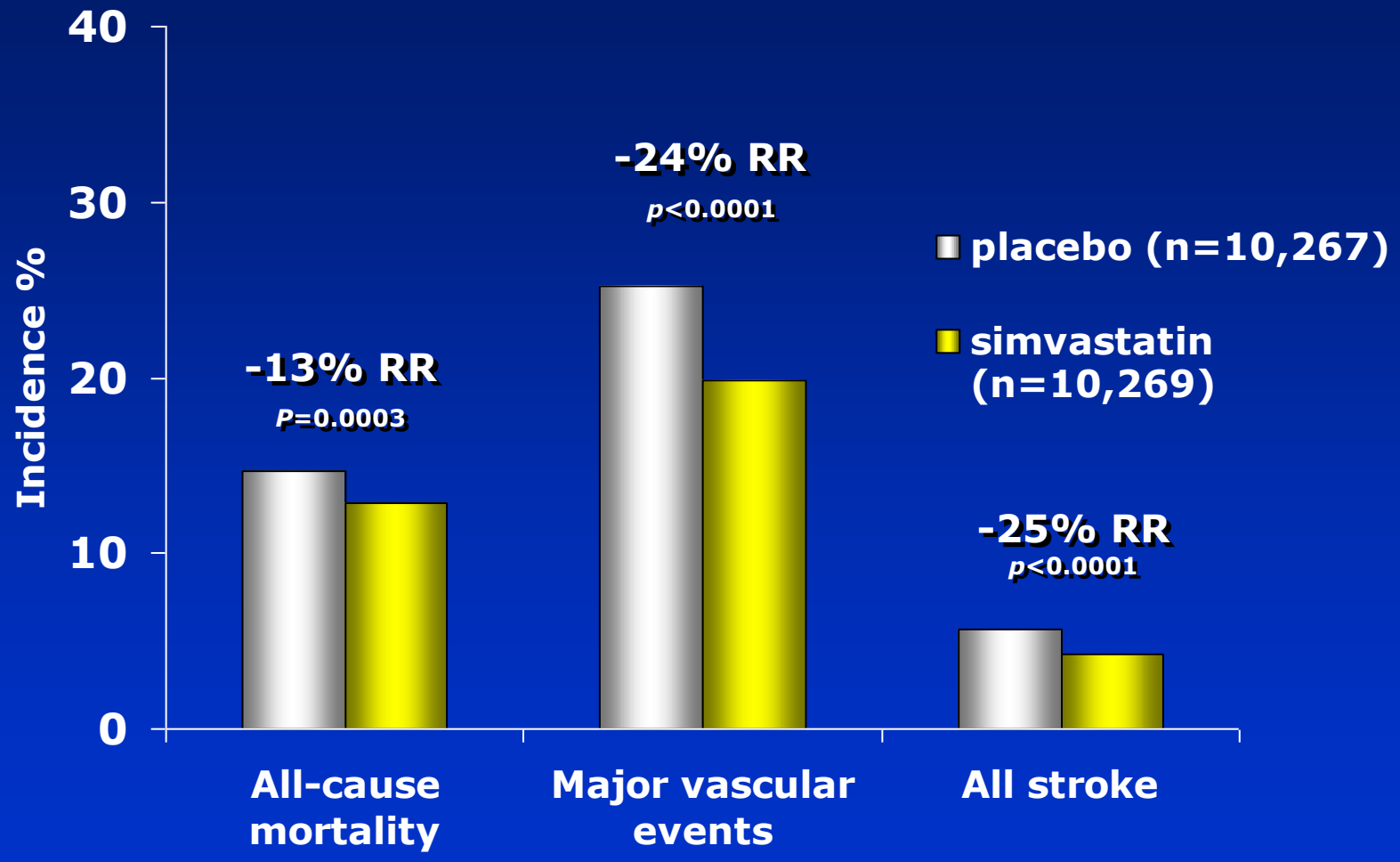
Benefits of Cholesterol Lowering

Meta-analysis of 38 primary and secondary intervention trials



Adapted from Gould AL *et al. Circulation.* 1998;**97**:946–952

HPS: Statin Benefits Patients with Low Baseline Cholesterol Levels



RR - relative reduction *vs.* placebo

Adapted from HPS Collaborative Group, *Lancet* 2002;**360**:7–22

ASCOT-LLA: Statin Benefits Hypertensive Patients with Average or Low Baseline Cholesterol Levels

Outcomes	Number of events			
	placebo (*n=5137*)	atorvastatin (*n=5168*)	Hazard ratio	*p*-value
Non-fatal MI# plus fatal CHD*	154	100	0.64	0.0005
Total CV events and procedures	486	389	0.79	0.0005
Total coronary events	247	178	0.71	0.0005
Non-fatal MI∞ plus fatal CHD	137	86	0.62	0.0005
Fatal and non-fatal stroke	121	89	0.73	0.0236

* primary endpoint, # includes silent MI, ∞ excludes silent MI

Adapted from Sever PS et al. *Lancet* 2003;**361**:1149–1158

Section 7

Diabetes: a Risk Factor for CHD?

Diabetes Mellitus

- One of the most common non-communicable diseases
- Fourth or fifth leading cause of death in most developed countries
- More than 177 million people with diabetes worldwide
- Incidence of diabetes is increasing – estimated to rise to 300 million by 2025
  - expected to triple in Africa, the Eastern Mediterranean and Middle East, and South-East Asia
  - to double in the Americas
  - to almost double in Europe

Adapted from: International Diabetes Federation website

The Chronic Complications of Diabetes Mellitus

Macrovascular complications:

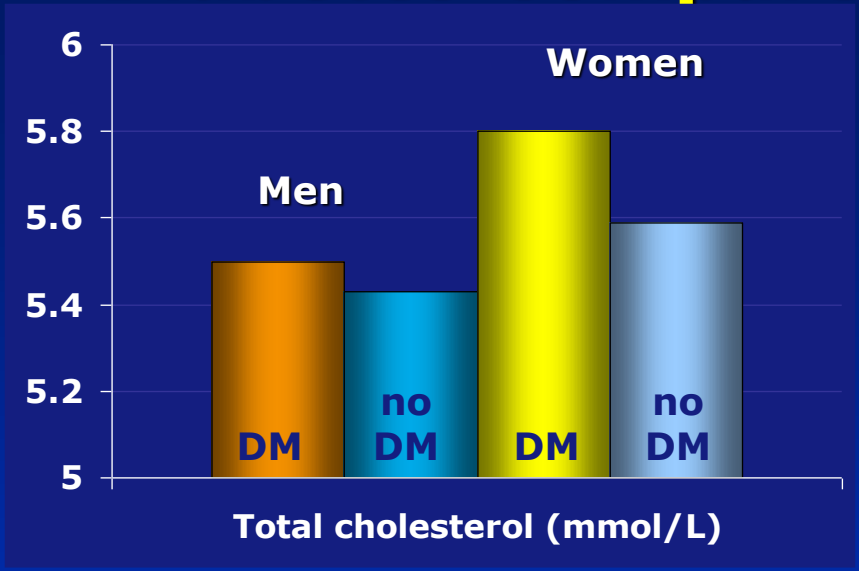
- Heart disease
  - Leading cause of diabetes related deaths (increases mortality and stroke by 2 to 4 times)

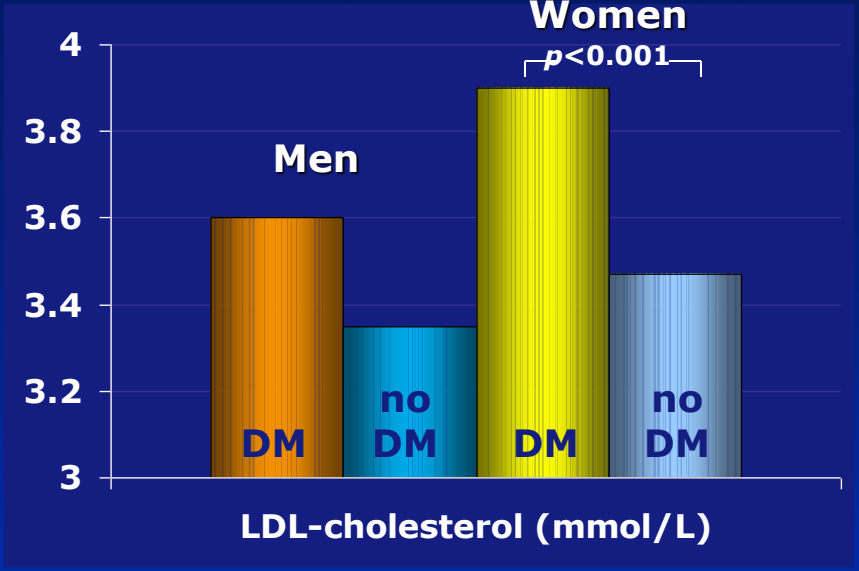
Microvascular complications:

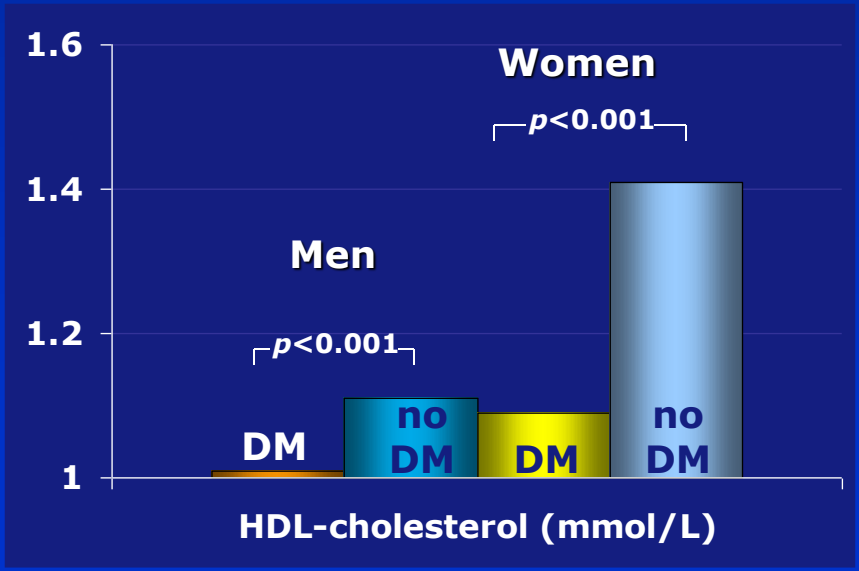
- Retinopathy
  - Leading cause of adult blindness
- Nephropathy
  - Accounts for 43% of new cases of ESRD
- Neuropathy
  - 60–70% of patients with diabetes have nervous system damage

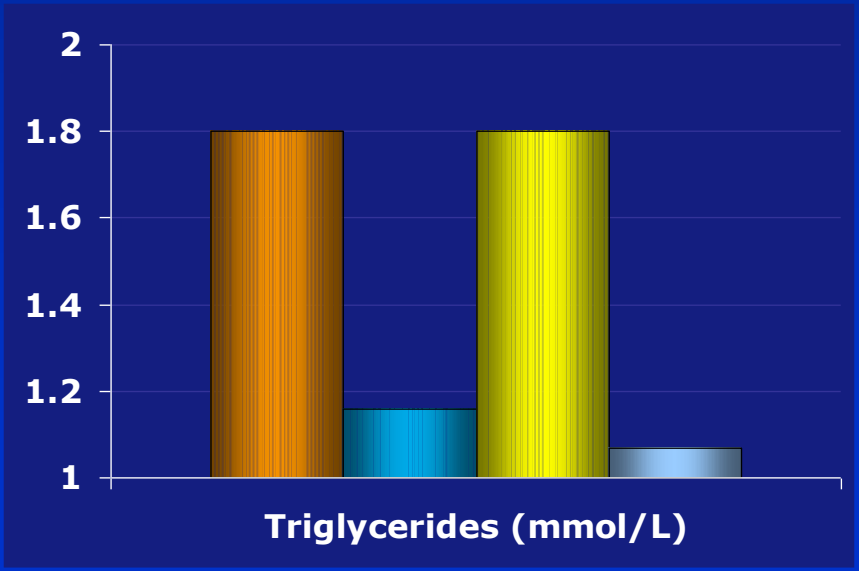
Adapted from National Diabetes Statistics US 2000

UKPDS: Typical Lipid Profile in Patients with Diabetes Compared with No Diabetes



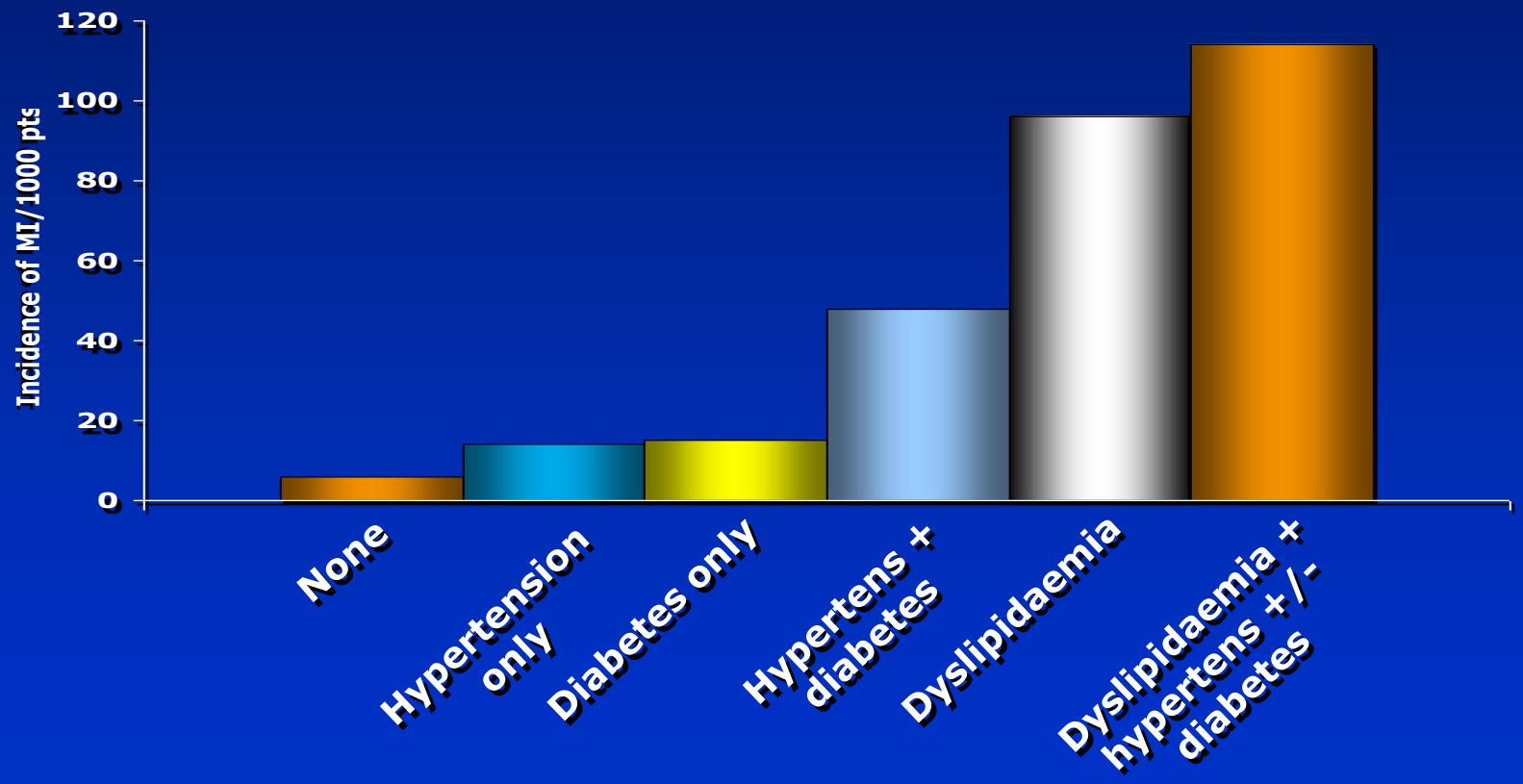






Adapted from UKPDS. *Diabetes Care* 1997;**20:**1683–1687

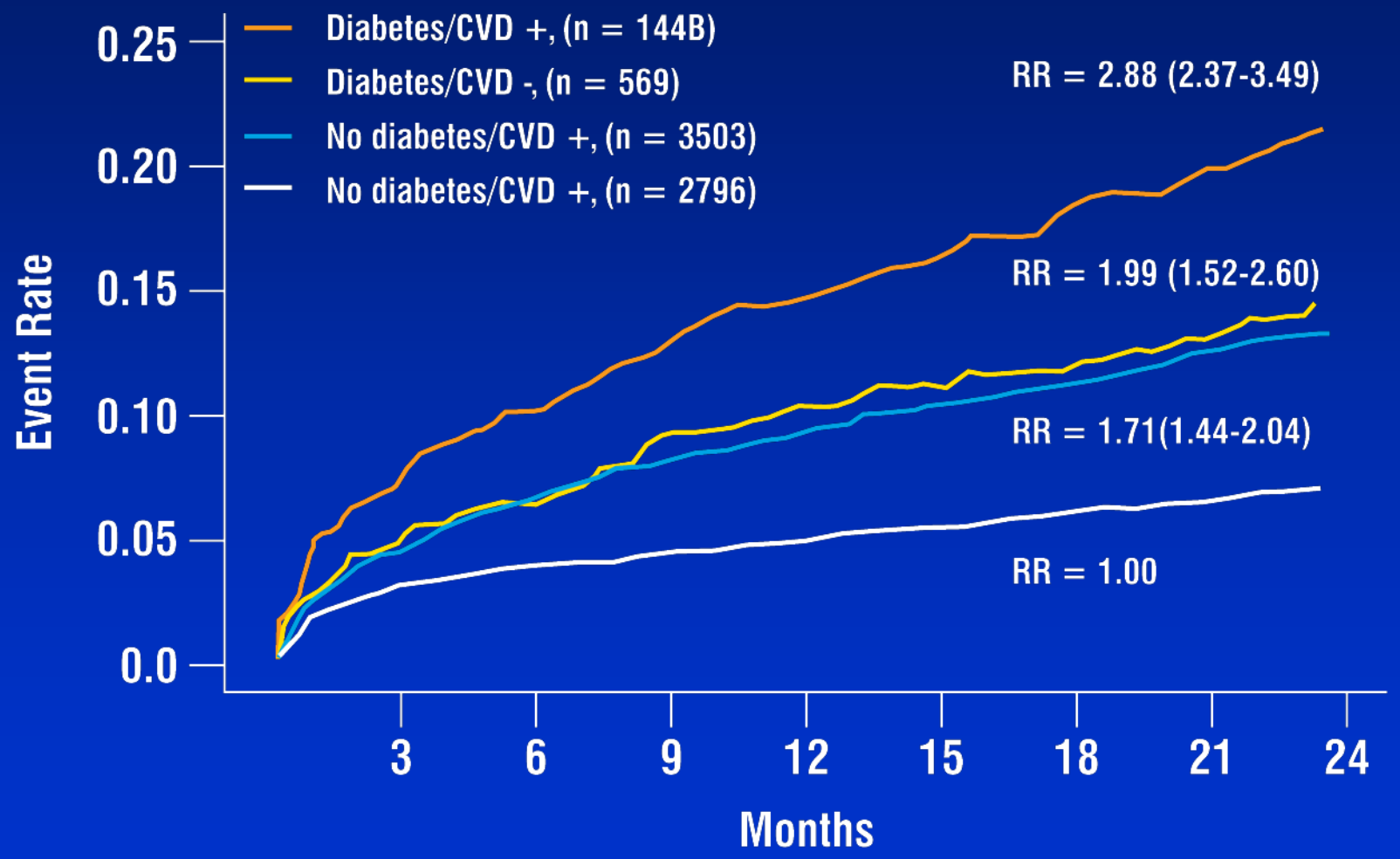
PROCAM: Combination of Risk Factors Increases Risk of MI



Prevalence (%):	**54.9**	**22.9**	**2.6**	**2.3**	**9.4**	**8.0**

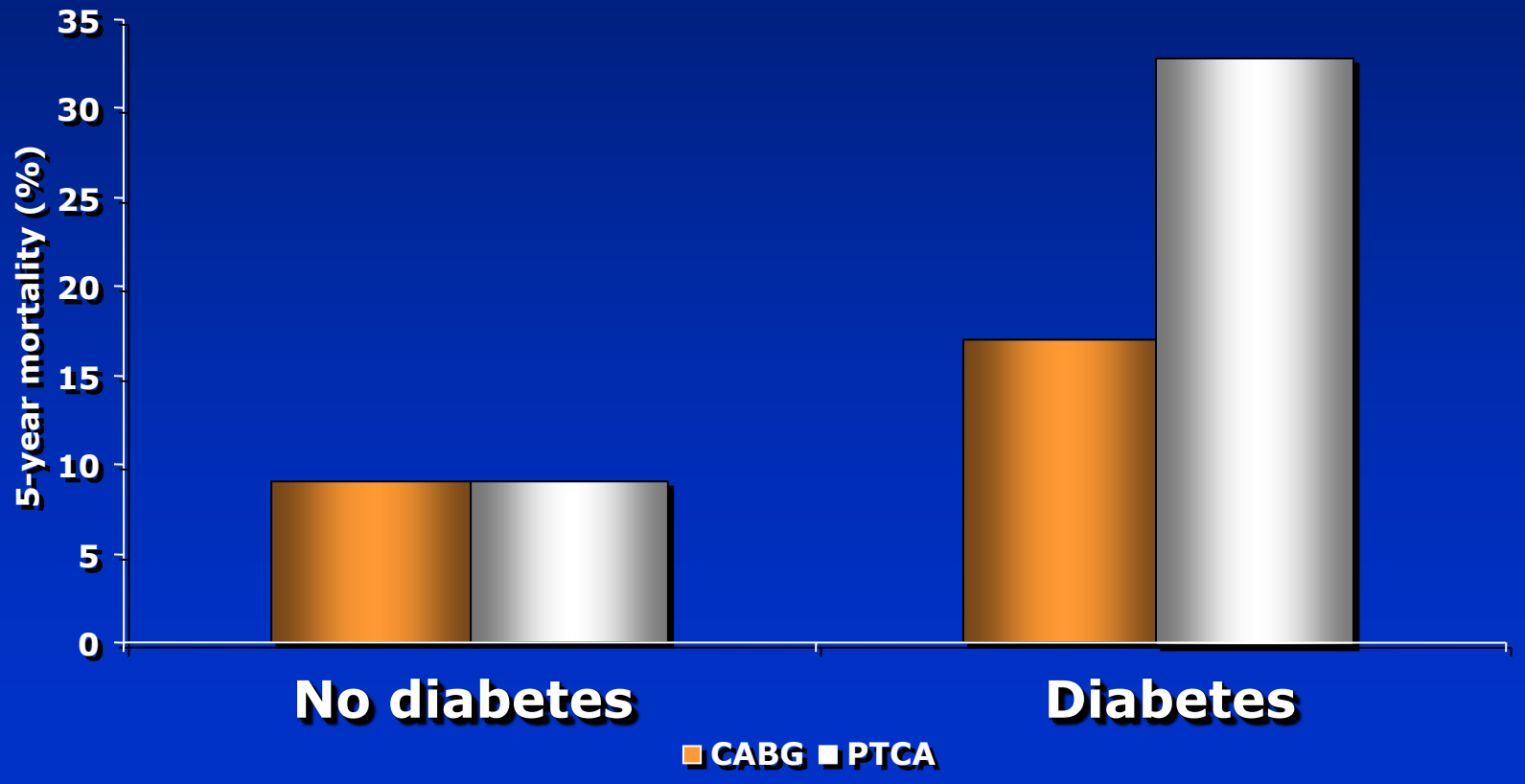
Adapted from Assman G, Schulte H. *Am Heart J* 1988;**116**:1713–1724

OASIS: Patients with Diabetes at Similar Risk to No Diabetes with CVD



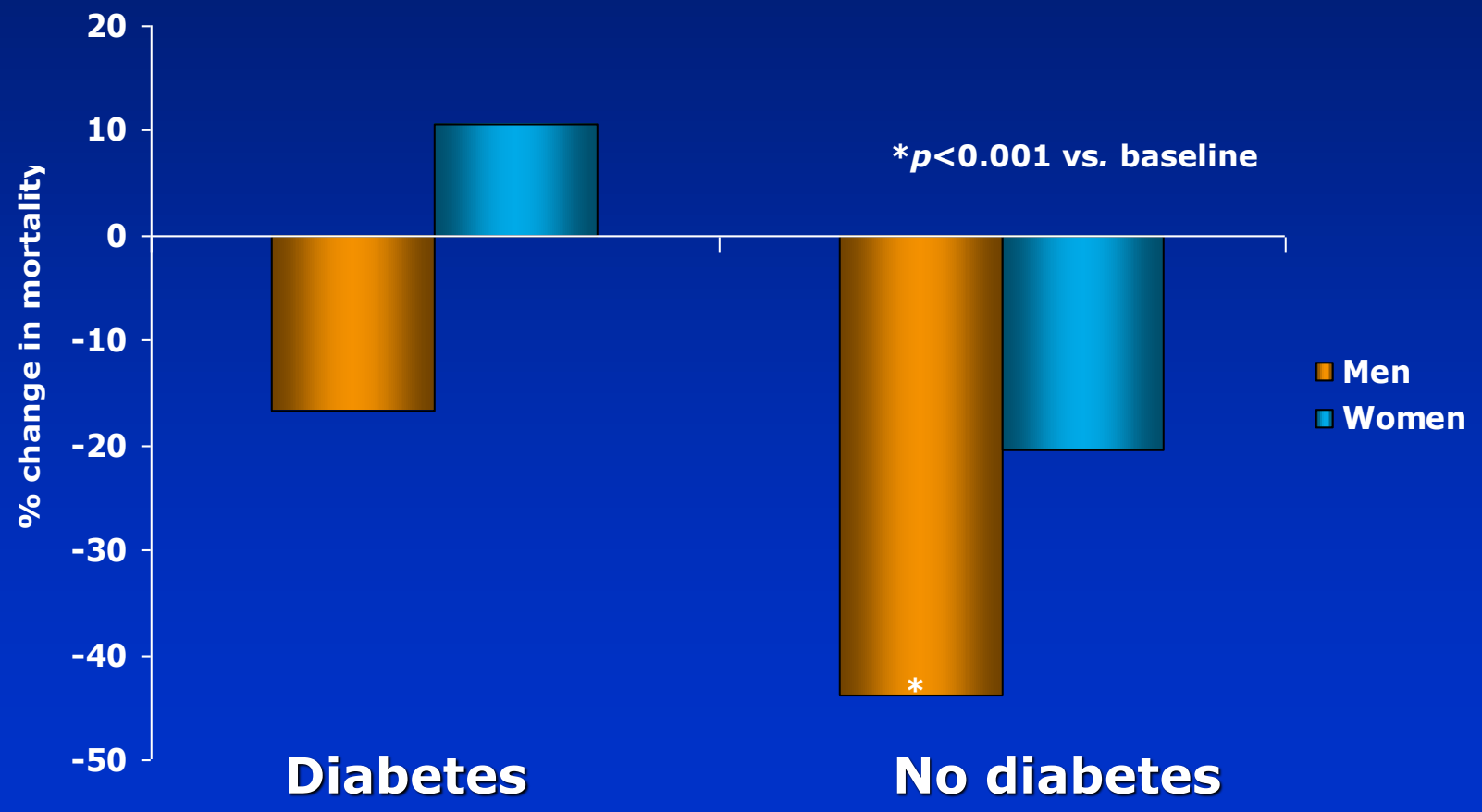
Adapted from Malmberg K *et al. Circulation* 2000;**102**:1014–1019

BARI: Diabetes Results in Less Favourable Outcome After Angioplasty Than No Diabetes



Adapted from BARI Investigators. *N Engl J Med* 1996:**335**:217–225

NHANES: Smaller Changes in CAD Mortality Rates in Patients with Diabetes than No Diabetes Over Time



Adapted from Gu K *et al. JAMA*; **281**:1291–1297

Section 8

The Metabolic Syndrome

The Metabolic Syndrome and Associated CVD Risk Factors

Insulin Resistance

Hypertension

Abdominal obesity

Hyperinsulinaemia

Diabetes

Hypercoagulability

Dyslipidaemia
- high TGs
- small dense LDL
- low HDL-C

Atherosclerosis

Endothelial Dysfunction

NCEP ATP III: The Metabolic Syndrome

Diagnosis is established when ≥3 of these risk factors are present

Risk Factor	Defining Level
Abdominal obesity **(Waist circumference)**	
Men	>102 cm (>40 in)
Women	>88 cm (>35 in)
TG	≥150 mg/dL (1.7 mmol/L)
HDL-C	
Men	<40 mg/dL (1.0 mmol/L)
Women	<50 mg/dL (1.3 mmol/L)
Blood pressure	≥130/≥85 mm Hg
Fasting glucose	≥110 mg/dL (6.0 mmol/L)

National Cholesterol Education Program, Adult Treatment Panel III, 2001. *JAMA* 2001:**285**;2486–2497

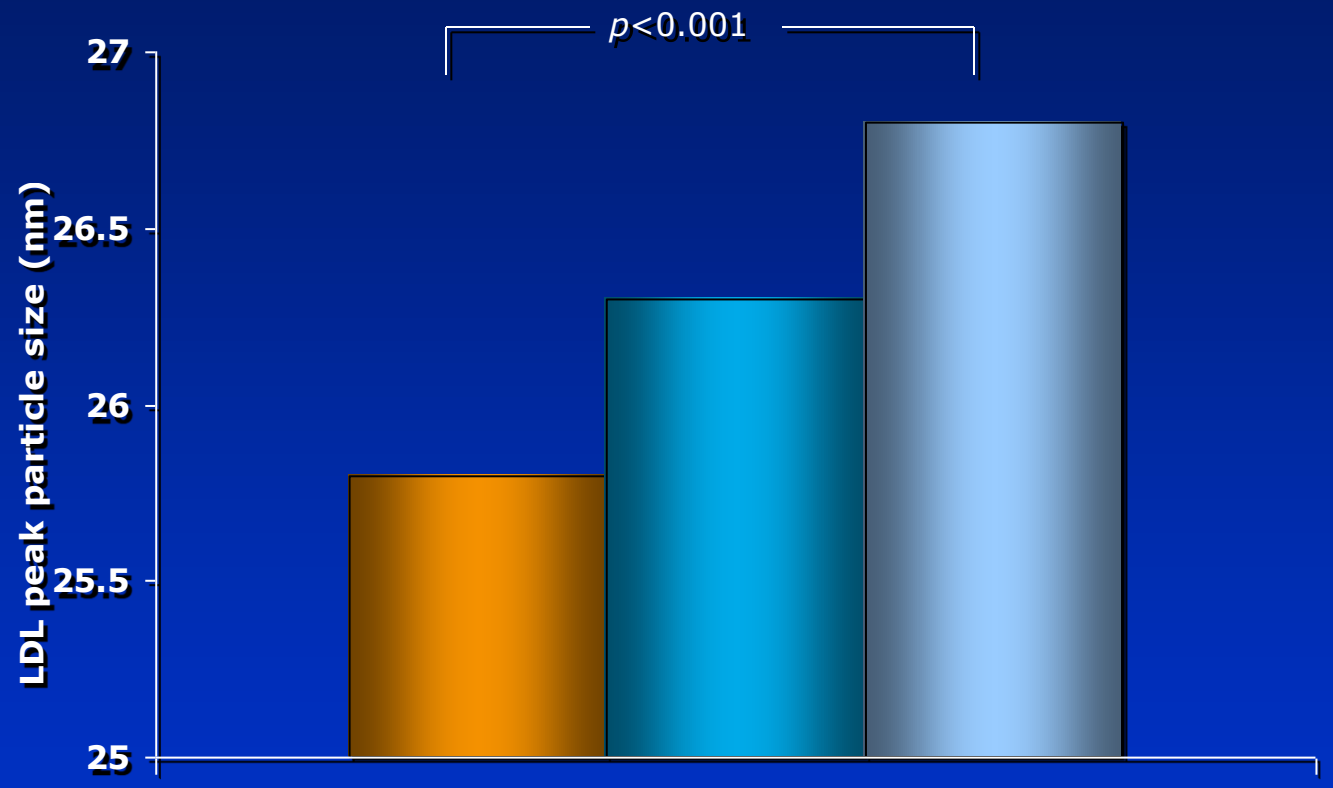
WHO: The Metabolic Syndrome

A working definition is glucose intolerance, IGT or diabetes mellitus and/or insulin resistance together with two or more of the following:

- Impaired glucose regulation or diabetes
- Insulin resistance
- Raised arterial pressure ≥160/90 mmHg
- Raised plasma triglycerides (≥1.7 mmol/L, 150 mg/dL) and/or low HDL-C (men <0.9 mmol/L, 35 mg/dl; women <1.0 mmol/L, 39 mg/dL)
- Central obesity
- Microalbuminuria (UAER ≤20 μg/min or albumin: creatinine ratio ≥20 mg/g)

Alberti KGMM, Zimmet PZ for the WHO. *Diabet Med* 1998:**15**;539–553

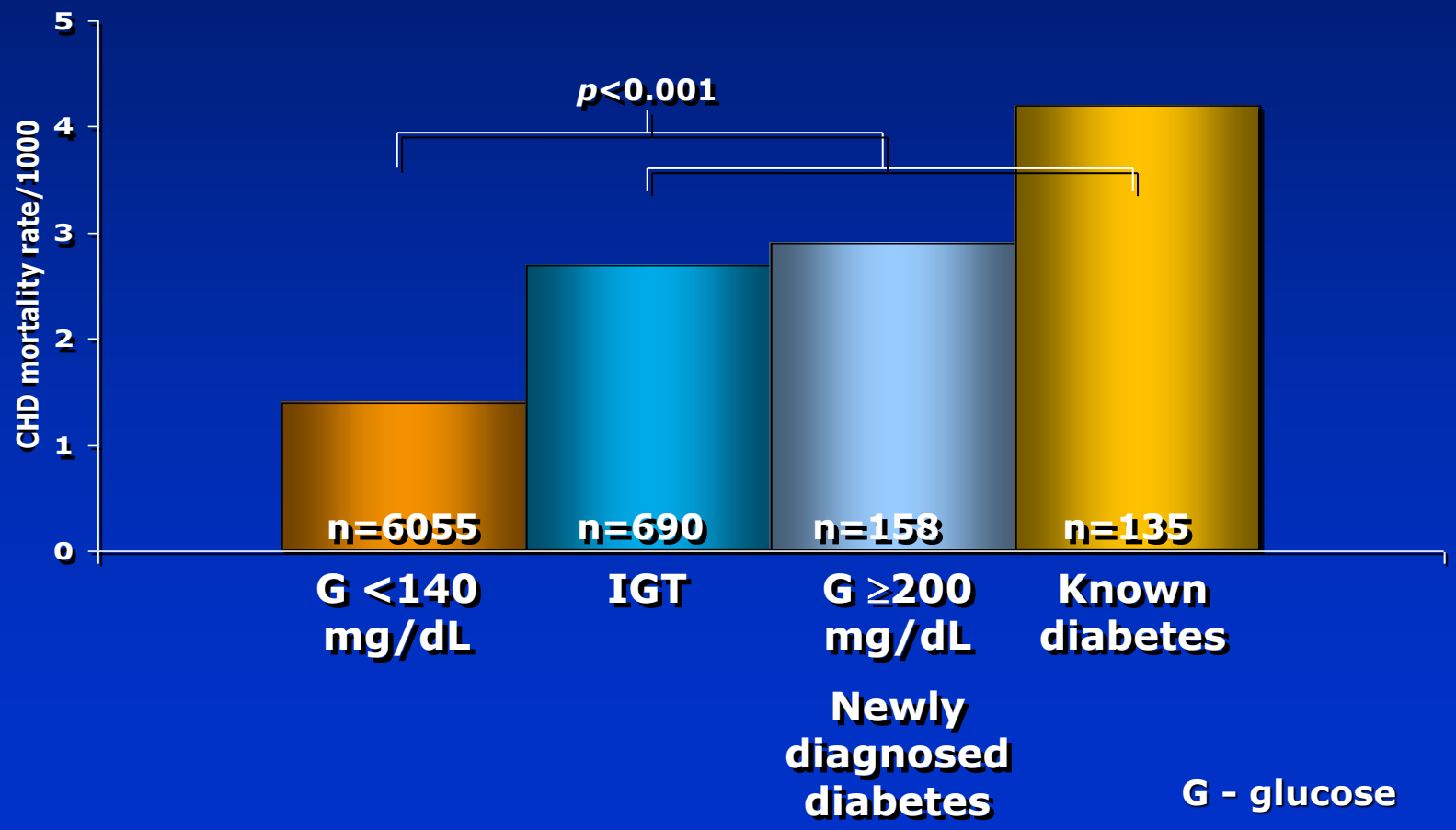
AIR: LDL Particle Size is Related to the Metabolic Syndrome



- Metabolic Syndrome (n=62)
- No Metabolic syndrome but 1 or more risk factors (n=252)
- No risk factors (n=77)

Adapted from Hulthe J *et al. Arterioscler Thromb Vasc Biol* 2000;**20**:2140–2147

PARIS: CHD Mortality Increases with Increased Impaired Glucose Tolerance



Adapted from Eschwege E *et al. Horm Metab Res* 1995;**17**(Suppl):41–46

Section 9

Outcome Trials in Diabetes

Trials with Fibrates in Patients with Diabetes

Study	Effect	*p*-value	Comment
Helsinki Heart Study *(gemfibrozil)*	**75% events** ↓	**ns**	**Primary prevention; post-hoc subgroup analysis**
SENDCAP *(bezafibrate)*	**65% events** ↓	**0.01**	**Specifically conducted in Type 2 diabetes; post-hoc analysis for IHD**
VA-HIT *(gemfibrozil)*	**24% events** ↓	**0.05**	**Secondary intervention; pre-planned subgroup analysis**
DAIS *(fenofibrate)*	**40-42% focal angio changes** ↓	**0.02**	**Specifically conducted in Type 2 diabetes; mixed primary and secondary intervention; angio study**

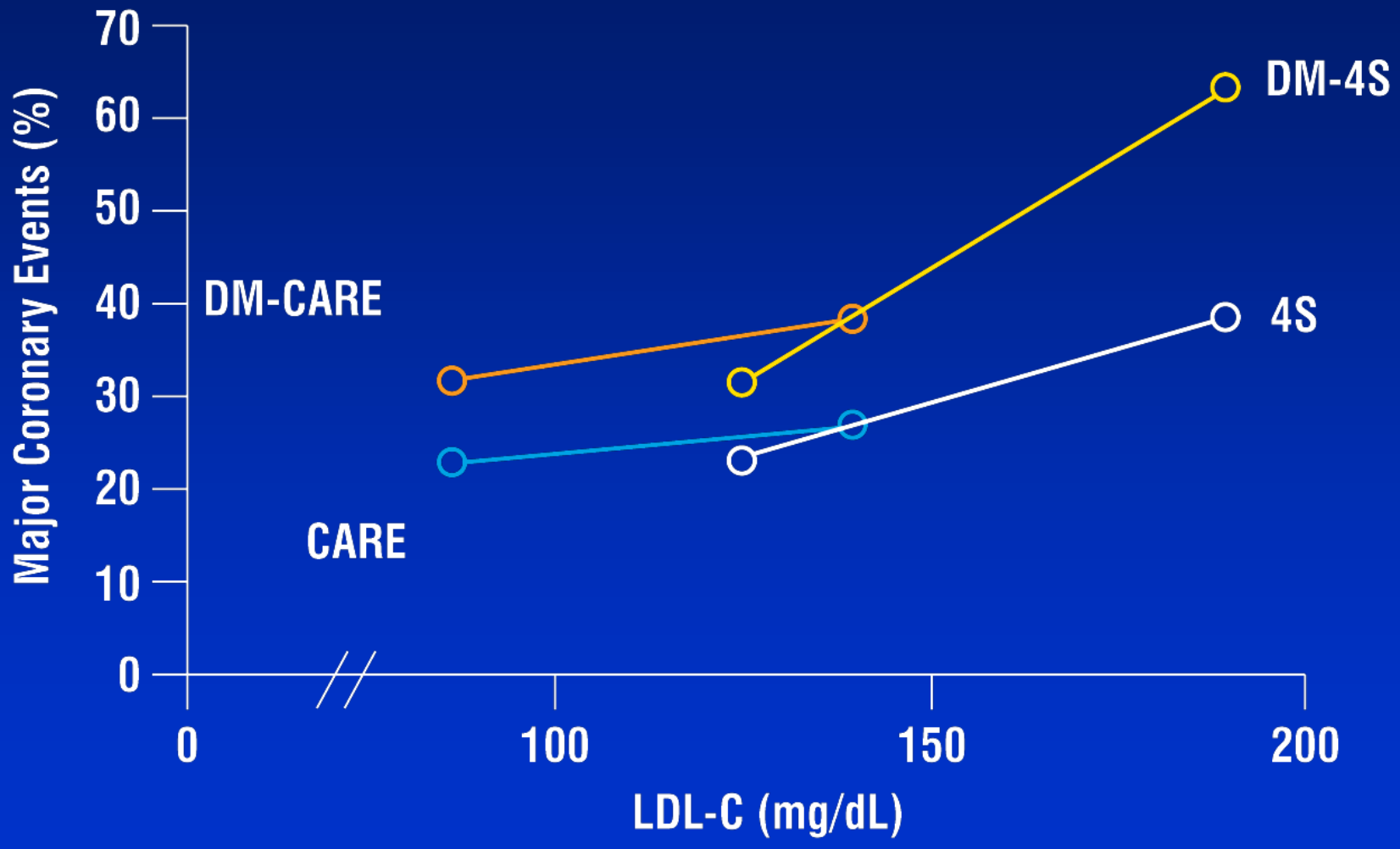
Frick MH *et al. N Engl J Med* 1987;**317**:1237–1245, Koskinen P *et al. Diabetes Care* 1992;**15**:820–825, Elkeles RS, Diamond JR, Poulter C *et al. Diabetes Care* 1998;**21(4)**:641–648, Rubins HB *et al. N Engl J Med* 1999;**341**:410–418, DAIS Investigators. *Lancet* 2001;**357**:905–910

Statins Reduce CHD Risk in Patients with Diabetes

Study	% LDL-C lowering	% CHD risk reduction (overall)	% CHD risk reduction (diabetes)
Primary prevention			
AFCAPS/TexCAPS[1] (lovastatin; n=239)	25	37 ($p<0.001$)	43
Secondary prevention			
CARE[2] (pravastatin; n=586)	28	23 ($p<0.001$)	25 ($p=0.05$)
4S[3] (simvastatin; n=202)	36	32 ($p<0.001$)	55 ($p=0.002$)
LIPID[4] (pravastatin; n=782)	25*	25	19

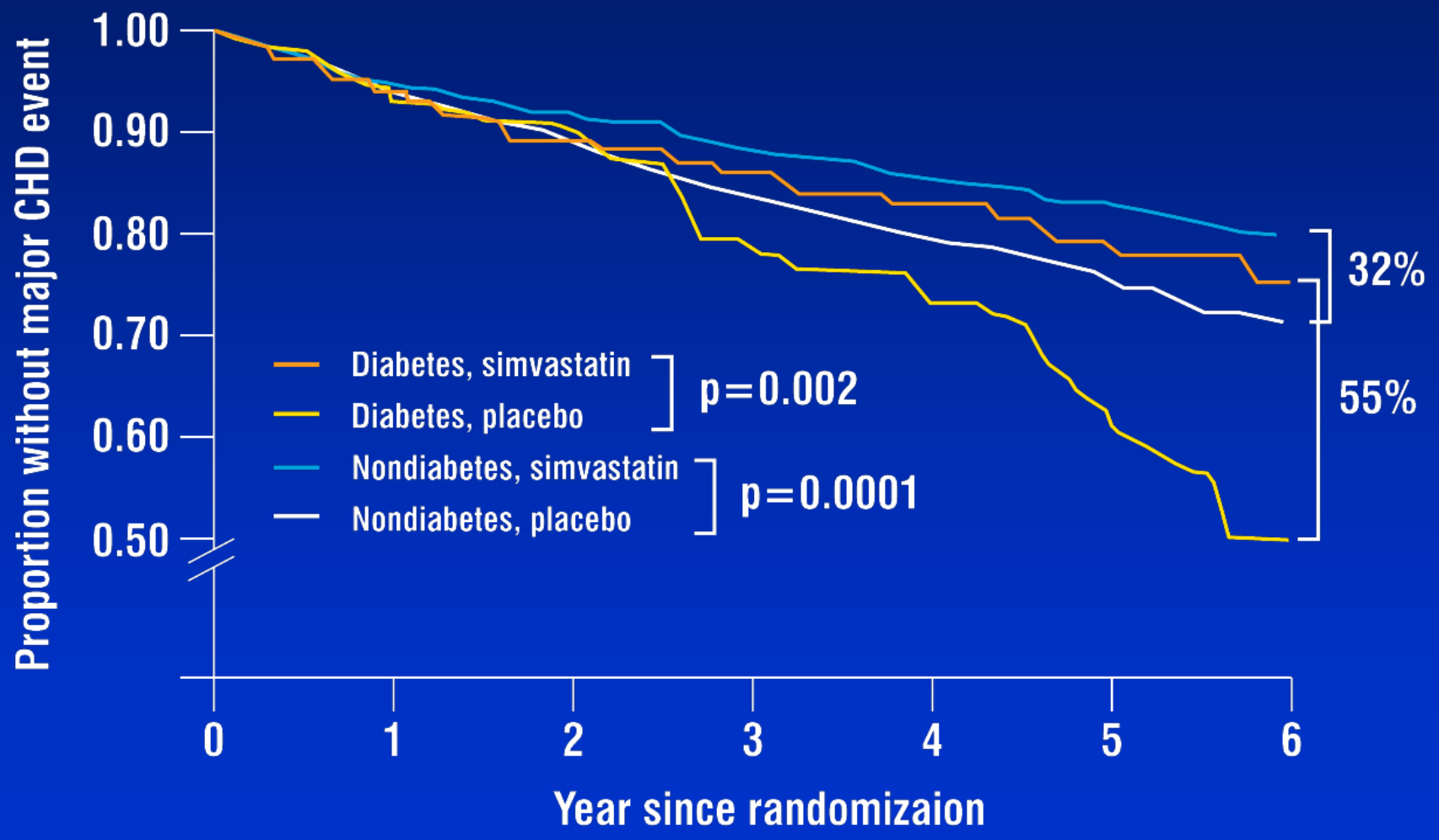
* value for overall group

4S/CARE: LDL Lowering in Patients with Diabetes



Adapted from Kreisberg RA. *Am J Cardiol* 1998;**82**:67U–73U

4S: CHD Event Reduction in Patients with Diabetes



Adapted from Pyörälä K *et al. Diabetes Care* 1997;**20**:614–620

WOSCOPS: Statin Treatment Protects Against Development of Diabetes

Total number of patients	Patients developing diabetes	% risk reduction	*p*-value
5974	139	30	0.042

Adapted from Freeman DJ *et al. Circulation* 2001;**103**:357–362