Applied Clinical Lipidology

Advances in Dyslipidemia Diagnosis & Management:

A Short-course for Registered Dietitians & Nutritionists

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U.S. Indian Health Service, Albuquerque NM

Three part series

I. 7:45 – 10:00 a.m. Friday

II. 1:15 – 3:15 p.m. Friday

III. 10:45 – 12:45 a.m. Saturday

Course Curriculum

Lipids, Lipoproteins and Atherosclerosis

Diagnosis of dyslipidemia: essential diagnostic categories

Clinical Trials Overview

NCEP Guidelines overview

Nutrition and dietary management of dyslipidemia

Pharmacologic therapy

Physical activity intervention and dyslipidemia

Laboratory assessment of dyslipidemia

The Identification and Management of Cardiometabolic Risk

SCAN LIPID PROGRAM AGENDA

Introduction 15 min

The ACCL and BCCL certifications and competencies
Opportunities for RD's and nutritionists
Important Resources

Atherosclerosis, lipids and lipoproteins 30 min I

Diagnostic categories of dyslipidemia 30 min

Clinical Trials Overview 45 min

NCEP (ATP III/IV) Guidelines overview 15 min

NCEP dietary recommendations/nutrition and dyslipidemia 90 min II

Nutrient-drug interactions 15 min

Exercise and Dyslipidemia 20 min

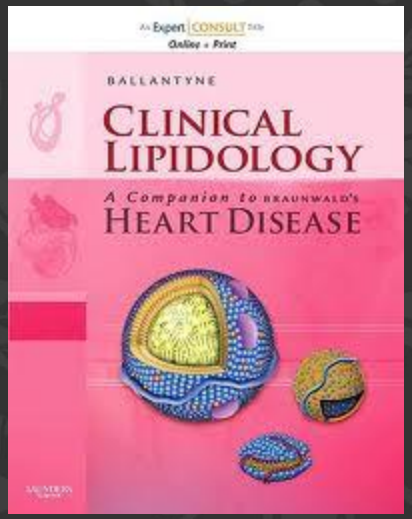
Pharmacologic Therapies and Treatment Targets 40 min

Laboratory assessment of lipids and lipoproteins 30 min III

Cardiometabolic Risk Assessment 15 min

Q & A and Wrap-Up 15 min

Total contact teaching hours for: 6.0 hours (three 2 hour segments)



The National Lipid Association defines “clinical lipidology" as a multidisciplinary branch of medicine focusing on lipid and lipoprotein metabolism and their associated disorders

There are two professional boards involved with credentialing those in clinical lipidology:

American Board of Clinical Lipidology (**ABCL**) *physicians*

Accreditation Council for Clinical Lipidology (**ACCL**) *nonphysicians*

Certification and Competency Exams

www.lipid.org

ABCL

American Board of Clinical Lipidology

ACCL

Accreditation Council for Clinical Lipidology

***CLS**

Clinical Lipid Specialist

BCCL

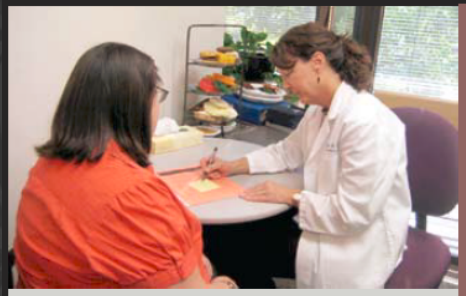
Basic Competency in Clinical Lipidology

- Lipid Academy (lipid mgmt train. Course)
- Four-volume SAP manuals

Accreditation Council for Clinical Lipidology

RDs Strive for Excellence

Demonstrate Your Expertise by Achieving Certification as a **Clinical Lipid Specialist**



"I was asked to join a multidisciplinary team focused on chronic disease management as the lipid specialist. Through this I gained a new level of respect from my teammates. Clinicians now consult me for the best lipid management tactics for their patients through which I have increased job security as I am the only registered dietitian certified as a Clinical Lipid Specialist in my state."

Julie Bolick, RD, MS, CD, CLS
Salt Lake City, Utah

The ACCL Offers Two Pathways to Recognition:

I. The **Clinical Lipid Specialist (CLS) Certification Program** is open to licensed RDs with advanced knowledge, experience and/or interest in specializing in lipid management.

II. The **Basic Competency in Clinical Lipidology (BCCL) Exam** is a *competency assessment and credentialing* pathway open to any healthcare professional with basic involvement in the lipid field.

Select a pathway that matches your professional goals. ACCL exams will evaluate and validate the specialized knowledge and training required to practice in the dynamic and multifaceted field of lipid management.

Demonstrate your professional commitment to the prevention of cardiovascular disease and document your expertise for patients, colleagues and employers.

ACCL
The Accreditation Council for Clinical Lipidology

Learn more at
www.lipidspecialist.org
Phone: 904.309.6250

NLA SAP Edition III

2012

Volume I: BASIC LIPOPROTEIN METABOLISM, DIAGNOSIS AND TREATMENT OF DYSLIPIDEMIAS
Volume II: MANAGEMENT OF CARDIOMETABOLIC RISK, BIOMARKERS OF ATHEROSCLEROSIS, EPIDEMIOLOGY AND STATISTICS, AND CLINICAL TRIALS
Volume III: COMPLEX CASE MANAGEMENT AND ADVANCED PHARMACOLOGY
Volume IV: VASCULAR BIOLOGY, ADVANCED LIPID METABOLISM AND LIPOPROTEIN BIOCHEMISTRY

Order at: (904) 998-0854 or e-mail CME@lipid.org.

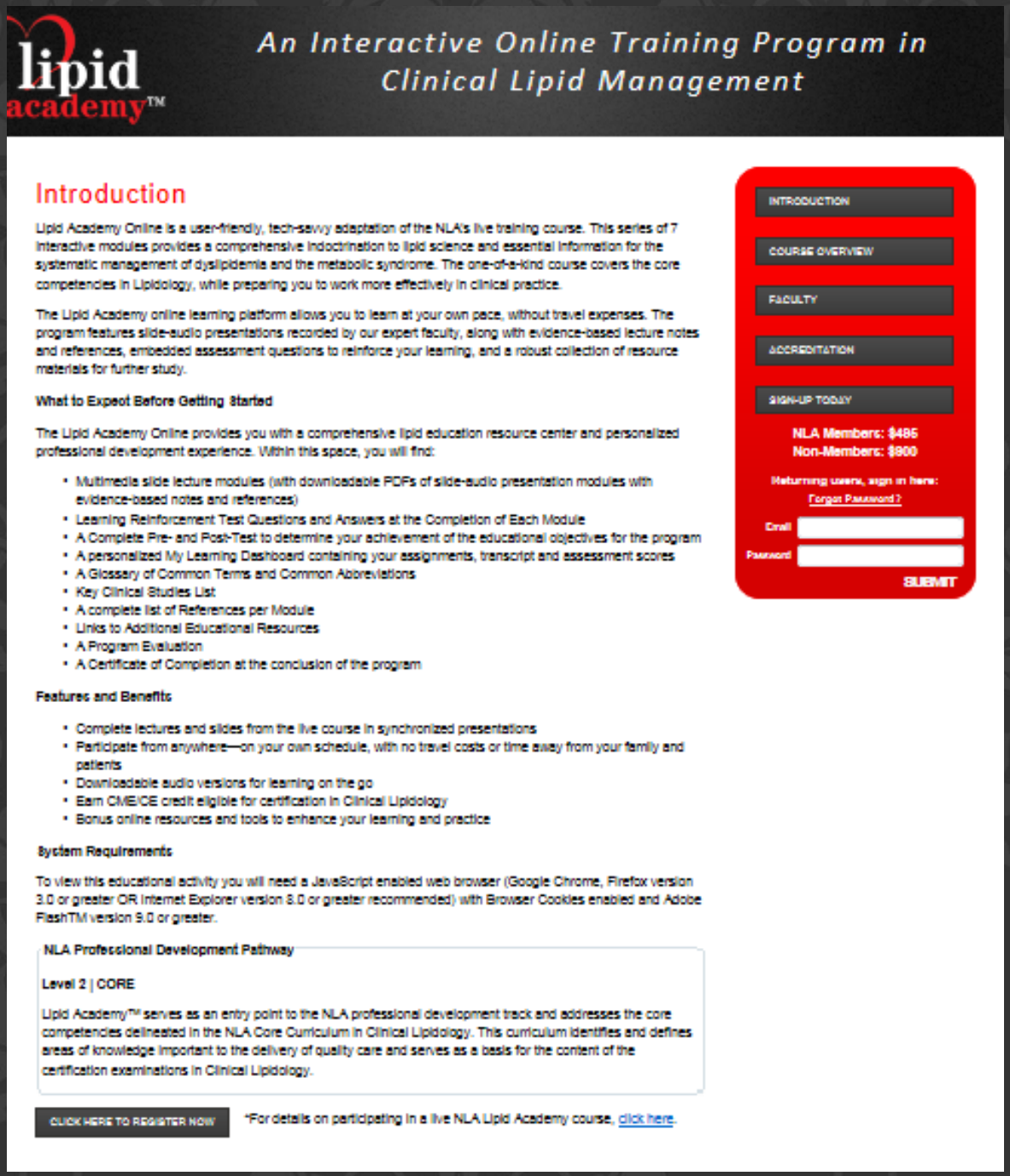
lipid academy™

This 1.5-day (12 hour) course provides a comprehensive indoctrination to lipid science and essential information for the systematic management of dyslipidemia and the metabolic syndrome. The curriculum covers basic competencies in Lipidology and sets the stage for effectively working in a lipid clinic setting. Elevate your knowledge of the fundamentals while preparing for more advanced training and/or a certification pathway such as the Certified Lipid Specialist or Basic Competency in Clinical Lipidology program.

Course Curriculum

- Lipids, Lipoproteins and Atherosclerosis
- Clinical Trials Overview
- Diagnosis, Clinical Appraisal and Treatment Targets
- Nonpharmacologic Therapies
- Pharmacologic Therapies and Treatment Guidelines
- Advanced Risk Assessment and Management of Residual Risk
- The Identification and Management of Cardiometabolic Risk

Web-based


lipid academy™
An Interactive Online Training Program in Clinical Lipid Management
Introduction
Lipid Academy Online is a user-friendly, tech-savvy adaptation of the NLA's live training course. This series of 7 interactive modules provides a comprehensive indoctrination to lipid science and essential information for the systematic management of dyslipidemia and the metabolic syndrome. The one-of-a-kind course covers the core competencies in Lipidology, while preparing you to work more effectively in clinical practice.
The Lipid Academy online learning platform allows you to learn at your own pace, without travel expenses. The program features slide-audio presentations recorded by our expert faculty, along with evidence-based lecture notes and references, embedded assessment questions to reinforce your learning, and a robust collection of resource materials for further study.
What to Expect Before Getting Started
The Lipid Academy Online provides you with a comprehensive lipid education resource center and personalized professional development experience. Within this space, you will find:
Multimedia slide lecture modules (with downloadable PDFs of slide-audio presentation modules with evidence-based notes and references)
Learning Reinforcement Test Questions and Answers at the Completion of Each Module
A Complete Pre- and Post-Test to determine your achievement of the educational objectives for the program
A personalized My Learning Dashboard containing your assignments, transcript and assessment scores
A Glossary of Common Terms and Common Abbreviations
Key Clinical Studies List
A complete list of References per Module
Links to Additional Educational Resources
A Program Evaluation
A Certificate of Completion at the conclusion of the program
Features and Benefits
Complete lectures and slides from the live course in synchronized presentations
Participate from anywhere—on your own schedule, with no travel costs or time away from your family and patients
Downloadable audio versions for learning on the go
Earn CME/CE credit eligible for certification in Clinical Lipidology
Bonus online resources and tools to enhance your learning and practice
System Requirements
To view this educational activity you will need a JavaScript enabled web browser (Google Chrome, Firefox version 3.0 or greater OR Internet Explorer version 8.0 or greater recommended) with Browser Cookies enabled and Adobe FlashTM version 9.0 or greater.
NLA Professional Development Pathway
Level 2 | CORE
Lipid Academy™ serves as an entry point to the NLA professional development track and addresses the core competencies delineated in the NLA Core Curriculum in Clinical Lipidology. This curriculum identifies and defines areas of knowledge important to the delivery of quality care and serves as a basis for the content of the certification examinations in Clinical Lipidology.
CLICK HERE TO REGISTER NOW
*For details on participating in a live NLA Lipid Academy course, click here.
INTRODUCTION
COURSE OVERVIEW
FACULTY
ACCREDITATION
SIGN-UP TODAY
NLA Members: $486
Non-Members: $900
Returning users, sign in here:
Forgot Password?
Email
Password
SUBMIT

Job Functions/Opportunities for RD Clinical Lipid Specialists

- Independent referrals from level 1 and 2 lipid clinics
- Lipid clinic staff member
- Specialization in dietary management of specialized lipid and lipoprotein disorders, e.g.,

  Familial hypercholesterolemia, PCOS, familial hypertriglyceridemia, mixed hyperlipidemia, hyperchylomicronemia, diabetic dyslipidemia
- Opportunity to incorporate anthropometric assessment and exercise recommendations into comprehensive lifestyle dyslipidemia management program

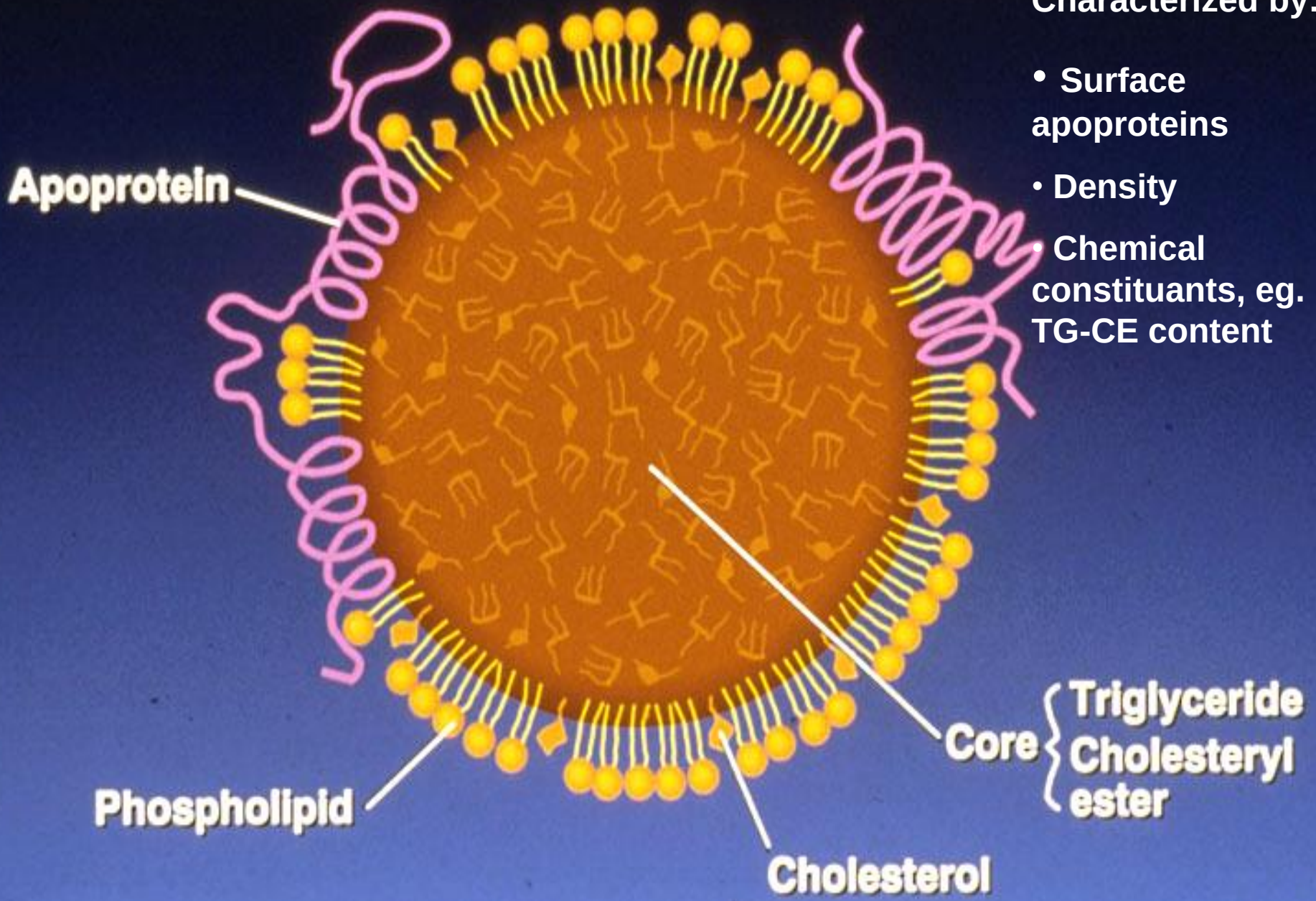
What are the key areas of lipidology that dietitians need to be familiar with ?

- Lipid and lipoprotein disorder categories
- Current NIH Guidelines
- Pharmacology
- Key clinical trials
- Lifestyle specifics
- Laboratory assessment
- Resources

Clinical Lipidology

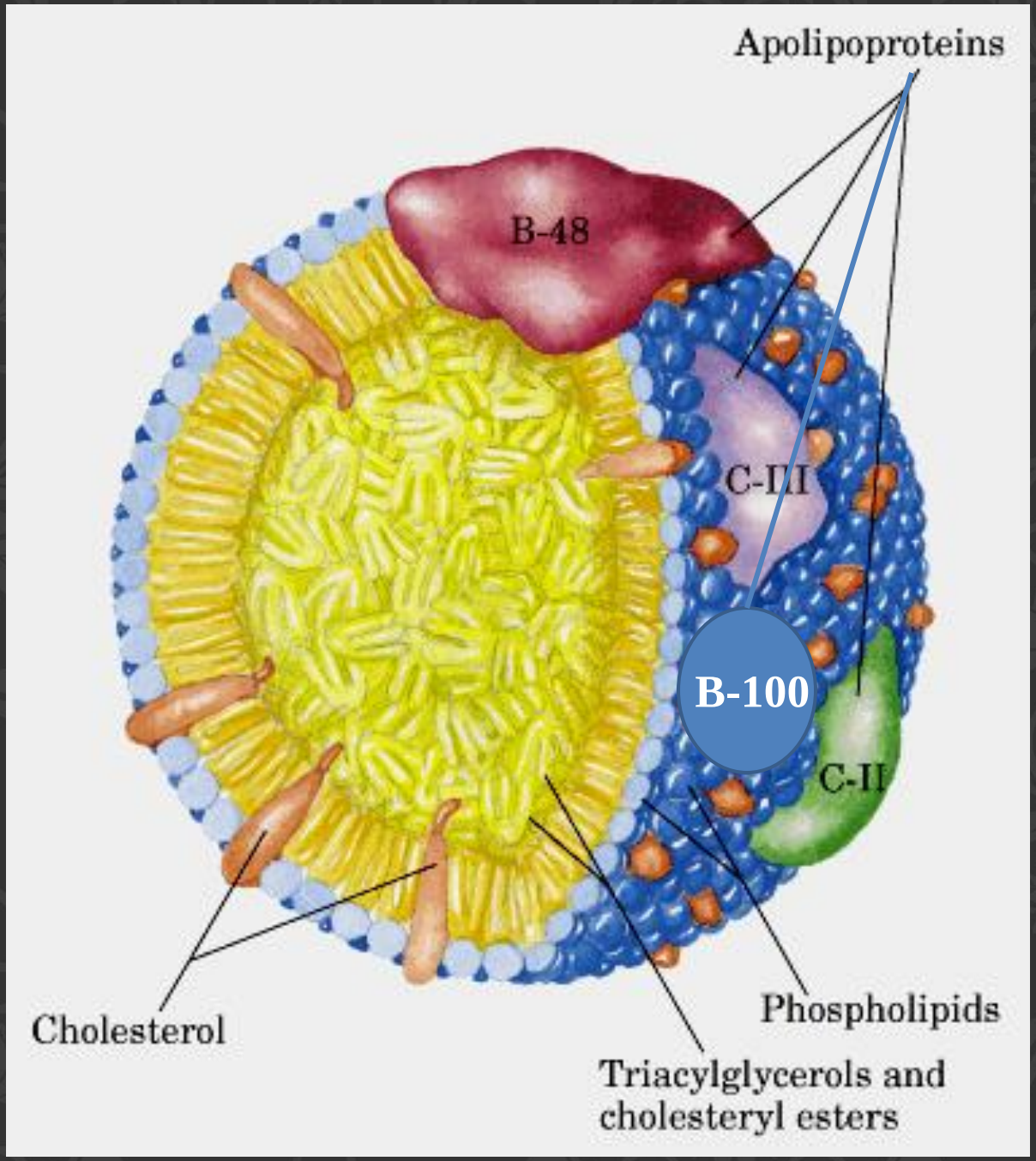
Bare Essentials

LIPOPROTEIN STRUCTURE



Characterized by:

- Surface apoproteins
- Density
- Chemical constituants, eg. TG-CE content

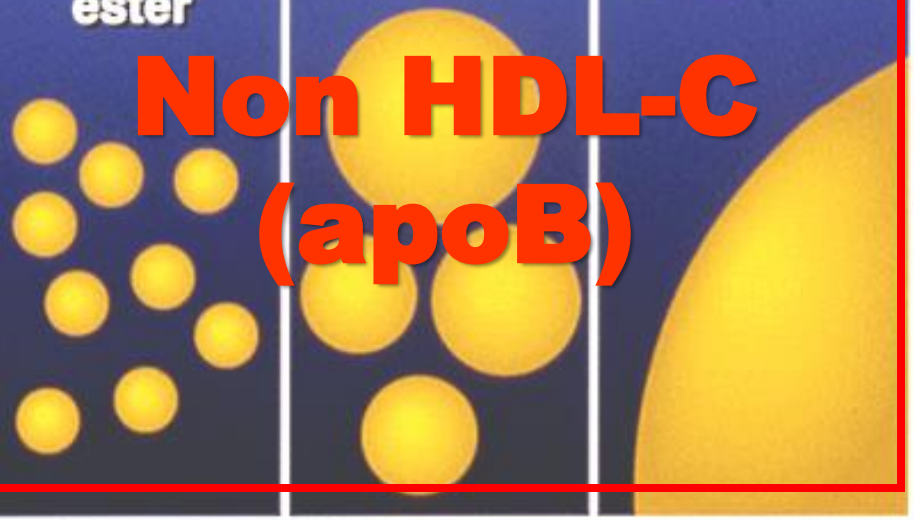


APOLIPOPROTEINS

- Structural support
- Enzymatic triggers
- Ligand for receptor binding (apo B, E, A-1)

FOUR MAJOR LIPOPROTEIN CLASSES

	High Density	Low Density	Very Low Density	Chylo-microns
Apolipo-proteins	A-I, A-II E, Cs	B-100	B-100, Cs, E	B-48, Cs, E, A-I, A-II
Major core lipids	Cholesteryl ester	Cholesteryl ester	Triglyceride	Triglyceride
Relative sizes	HDL_2 HDL_3			



Lipolytic Cascade for Lipoproteins

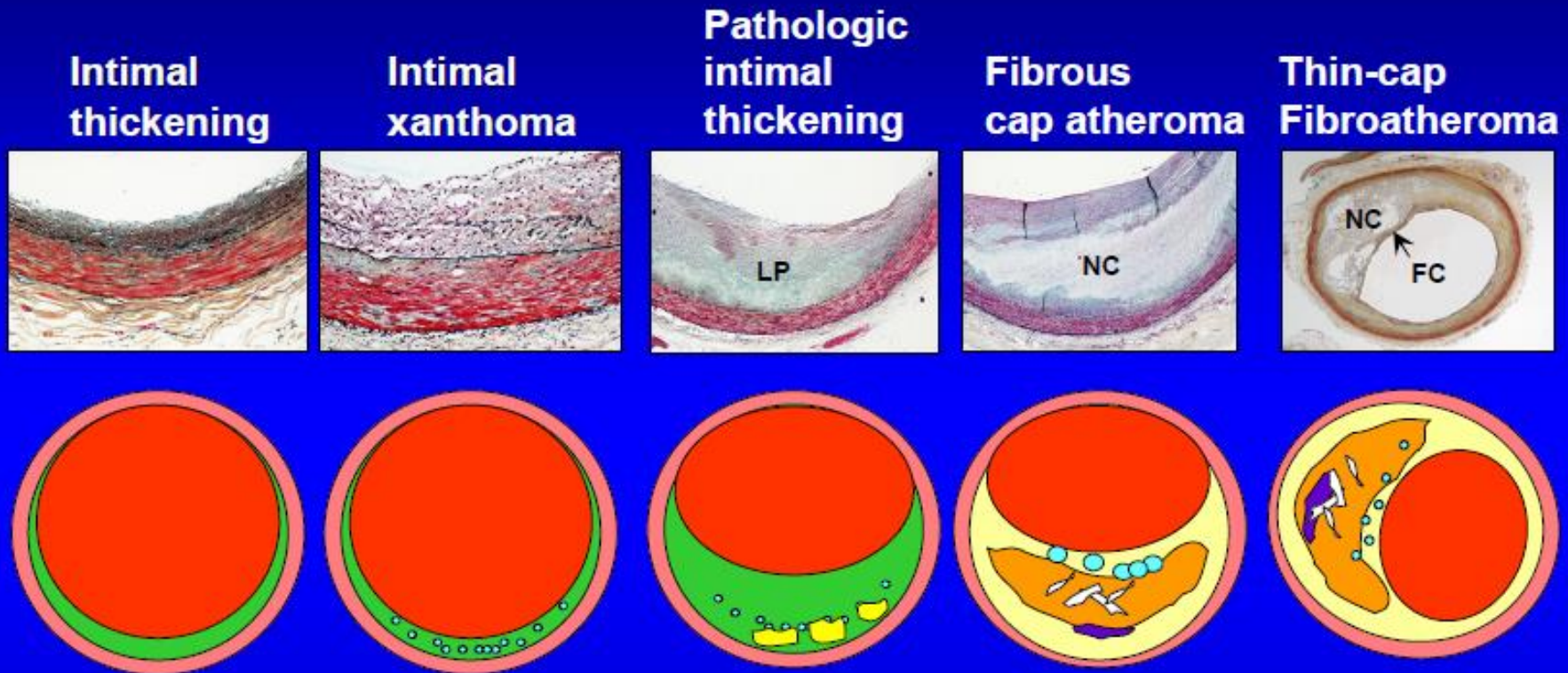
LPL lipoprotein lipase
HL hepatic lipase

Lipoproteins are quasi descrete structures. Interconversions of lipoprotein subfractions are a continuum that extends across the spectrum of intermediates that may begin for example with VLDL and end with a mature product LDL

Gotto A, 2002

Atherogenesis and Lipids

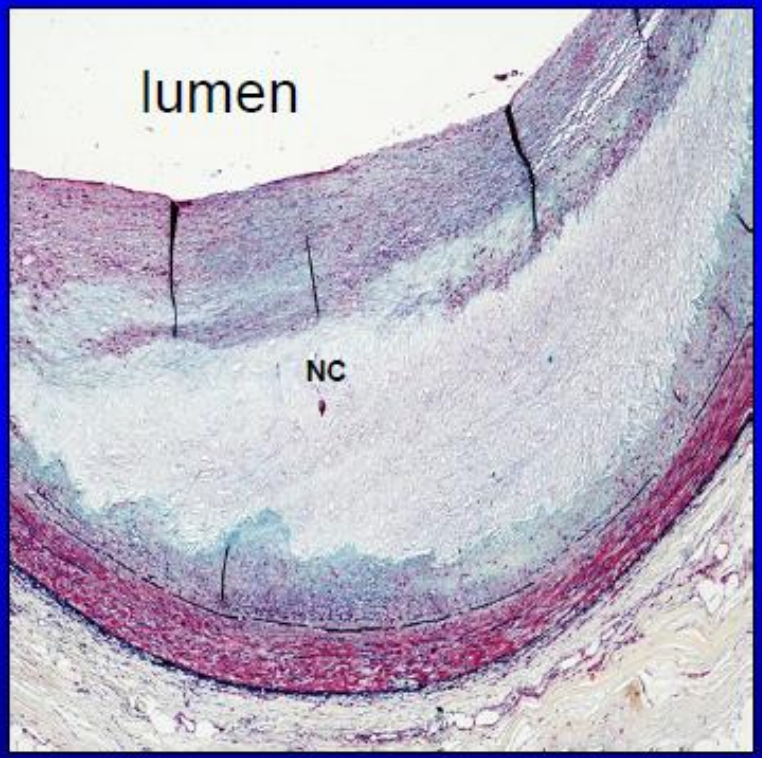
Development of Human Coronary Atherosclerosis



Ladich ER 2011

Fibrous cap atheroma

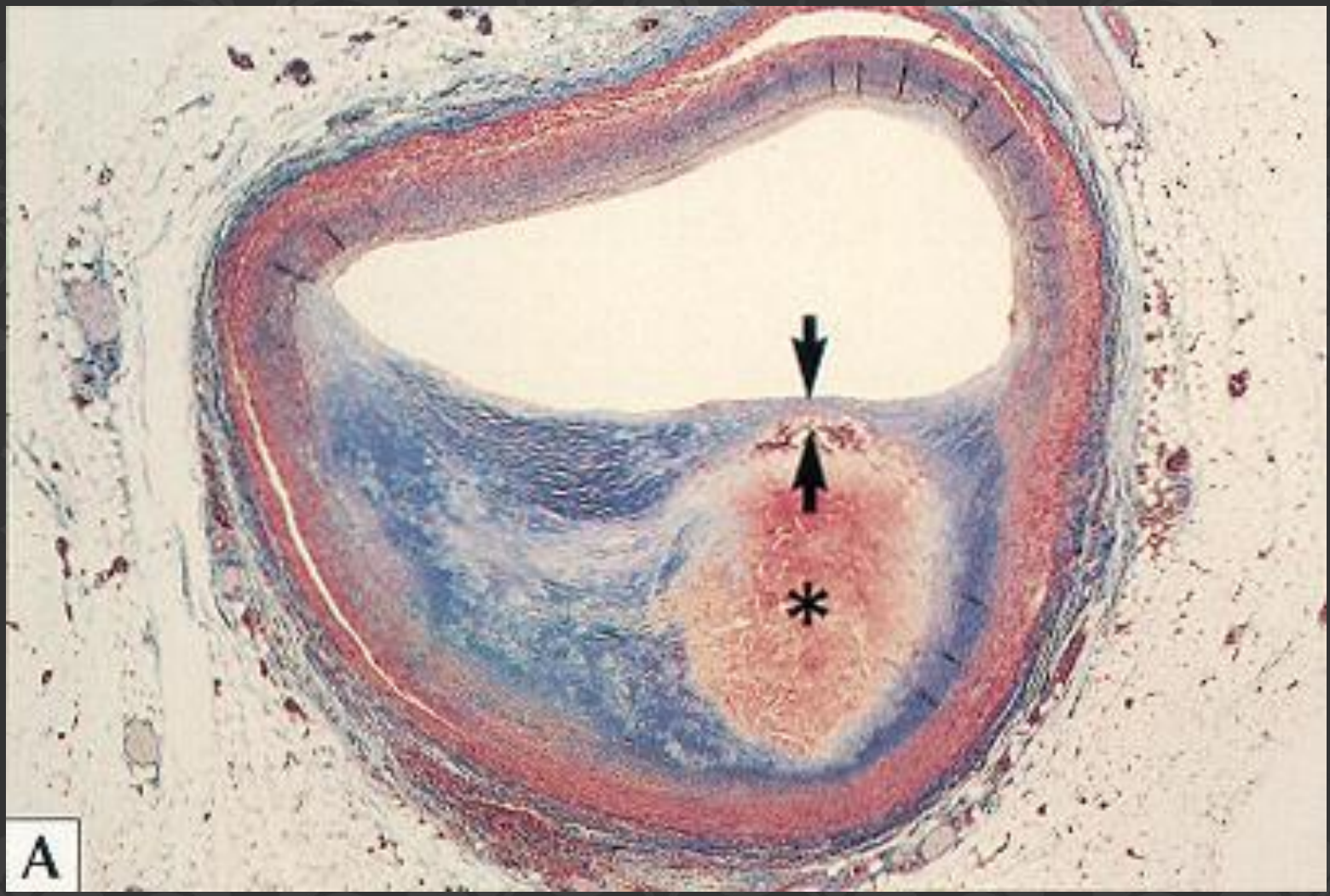
First advanced lesion atherosclerosis



Necrotic core contains cholesterol esters, free cholesterol, phospholipids, TG, necrotic debris
Fibrous cap consists of SMC in a proteoglycan collagen matrix

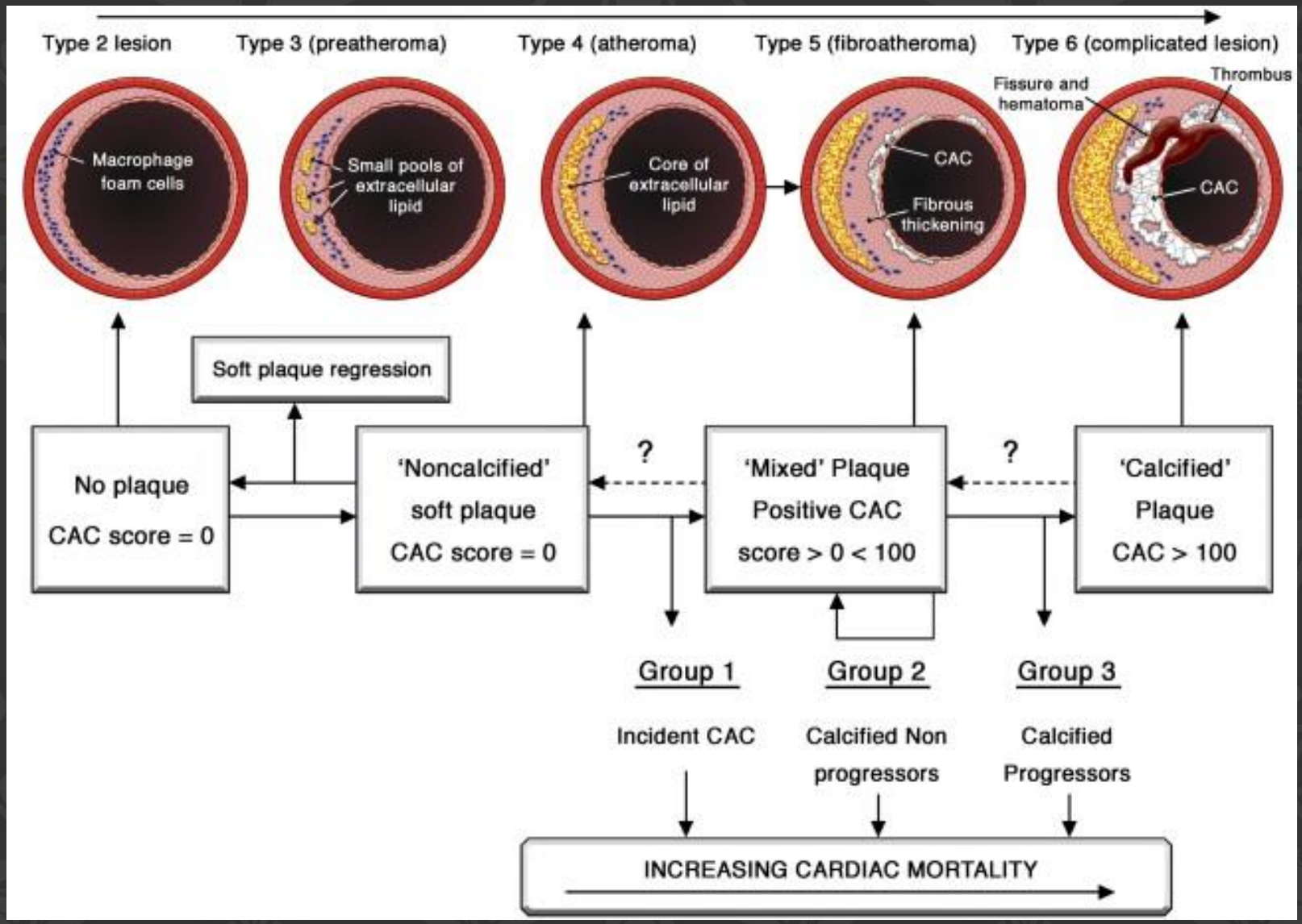
Ladich ER 2011

Consistency and vulnerability to rupture of coronary plaques

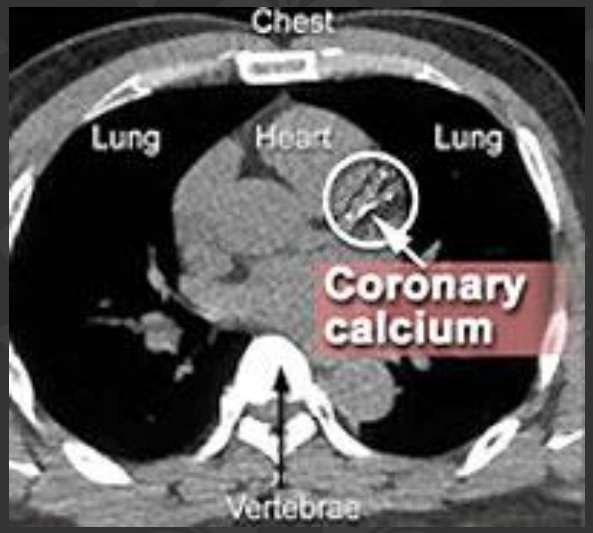


Braunwald 2007

Coronary Artery Calcium Progression: An Important Clinical Measurement?



McEvoy J et.al. JACC. 2010;56:1613 JHU



✓ Calcification is a good marker for plaque burden but correlation between plaque instability and absolute calcium score has not been demonstrated

✓ Aggressive management of lipids and/or lifestyle has also demonstrated no significant effect on CC although several have shown a trend for slowing progression of CC

Venkatesan S, 2011; McEvoy 2010

Lipid and Lipoprotein Targets

Important Dyslipidemias

Current Therapeutic Lipid Targets

NCEP ATP III

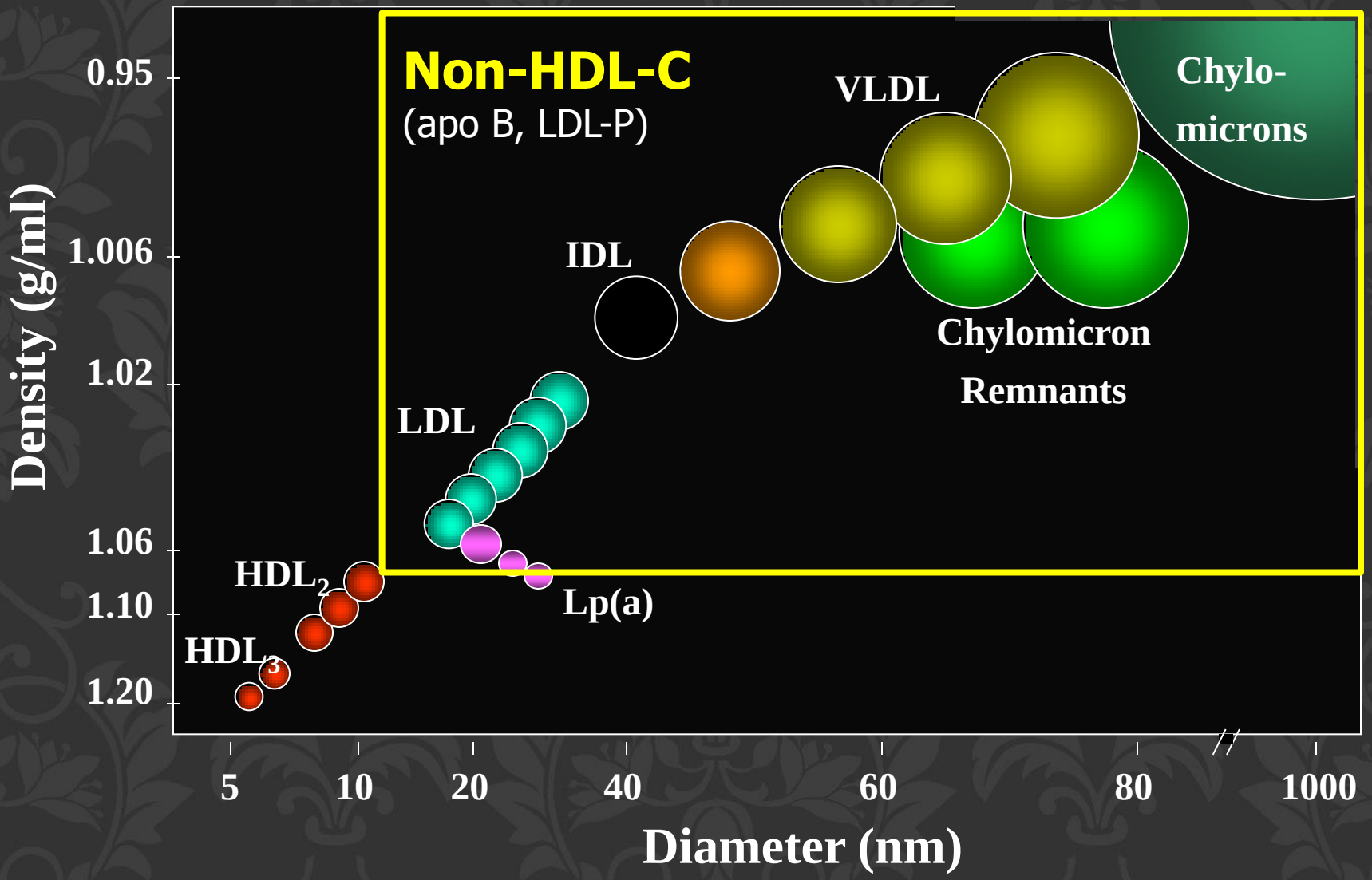
- **LDL Cholesterol**
- **HDL Cholesterol ***
- **Triglycerides**
- **Non HDL-C**

* Under scrutiny as target

- **LDL-P**
- **Apo B**
- **C-reactive protein**
- **Lp(a)**
- **LpPLA2**
- **Homocysteine**
- **Fibrinogen**
- **Oxidized LDL-C**
- **Calcium score, EBCT**
- **Apo protein isoforms**
- **Others**

Lipoprotein subclasses

Atherogenic Particle Focus



FREDRICKSON, LEVY, LEES CLASSIFICATION SCHEME FOR LIPID/LIPOPROTEIN DISORDERS

Phenotype	Lipid Elevation (primary)	Lipoprotein Elevation (primary)
Type I	Triglycerides	Chylomicrons
Type IIA	Cholesterol	LDL
Type IIB	Cholesterol & Triglycerides	LDL & VLDL
Type III	Cholesterol & Triglycerides	Beta-VLDL (VLDL & Chylomicron remnants)
Type IV	Triglycerides	VLDL
Type V	Triglycerides	Chylomicrons &VLDL

Chylomicrons present/predominant: Triglycerides >= 1500 mg/dL
Beta VLDL present: VLDL/Triglycerides > 0.30

Examples of Relatively Complex Dyslipidemias

1. Familial hypercholesterolemia
2. Familial hypertriglyceridemia
3. Familial combined hyperlipidemia
4. Chylomicronemia
5. Familial hypoalphalipoproteinemia
6. Familial dysbetalipoproteinemia
7. Hypobetalipoproteinemia
8. Lipoprotein lipase deficiency
9. Therapeutically resistant dyslipidemias

Diagnostic methods:

- Blood labs
- Cutaneous & opthamalogic expressions
- Genotype

Estimated Prevalence of Dyslipoproteinemias

Familial heterozygous hypercholesterolemia 1/300-500

Familial homozygous hypercholesterolemia 1/1,000,000

Familial defective apolipoprotein B-100 1/500

Polygenic hypercholesterolemia 1/10 - 1/20

Familial combined hyperlipidemia 1/150

Familial hypertriglyceridemia 1/100 - 1/300

Familial hypobetalipoproteinemia 1/500 heterozygotes

Familial lipoprotein lipase deficiency (type I, CmS) 1/100,000

Familial dysbetalipoproteinemia (type III) 1/5,000

Familial hypoalphalipoproteinemia 1/50

Excess lipoprotein (a) 1/3

Sitosterolemia 1/1,000,000

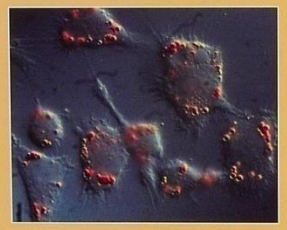
Homocysteinuria 1/100

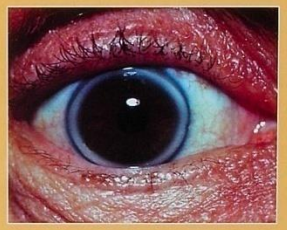
Gotto A Manual of Lipid Disorders 2009
Stone N & C Blum. Man of Lipids in Clin Pract, 2009
John Guyton, 2005
LaForge 2012

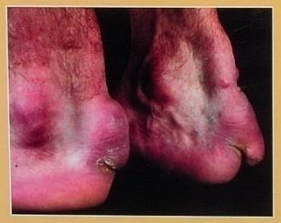
An Atlas of Investigation and Diagnosis

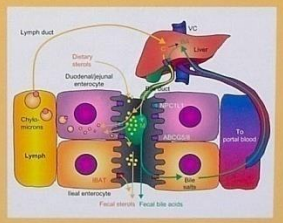
PRIMARY HYPERLIPIDEMIAS

J Davignon, R Dufour









CLINICAL PUBLISHING

Polygenic

vs

Complex Dyslipidemia

Polygenic hypercholesterolemia

(nonfamilial hypercholesterolemia, ICD-9 272.0; ICD-10 E78.0)

Susceptible genotype

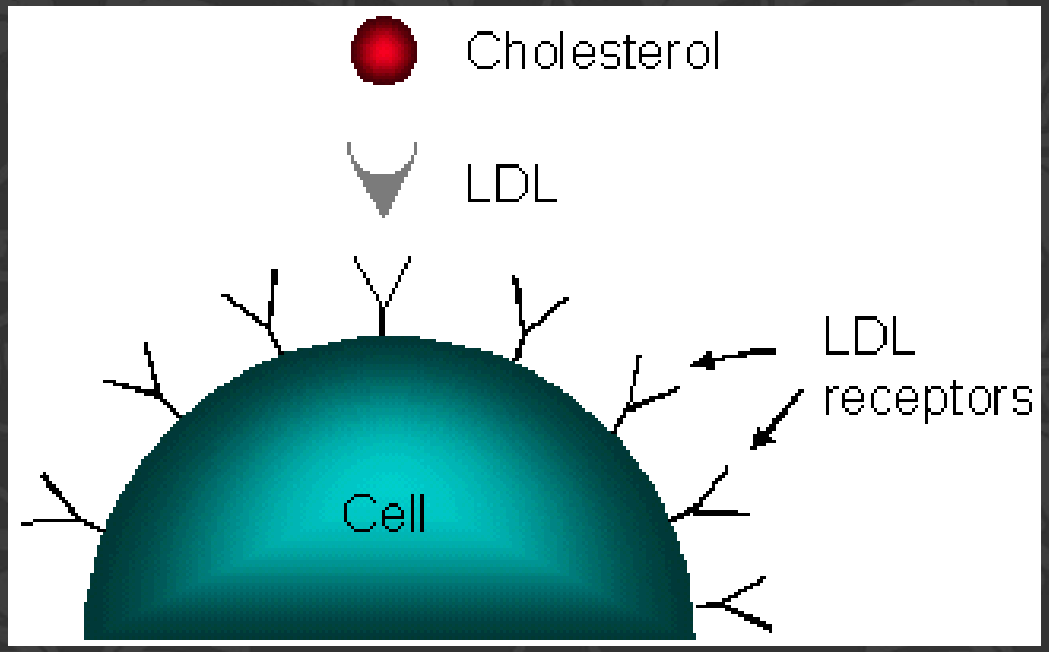
- Dietary trans and saturated fat, weight gain
- TC - 240-350 mg/dL
- LDL - >160
- TG nml
- no family history
- no xanthomas
- premature CAD

Complex hypercholesterolemia

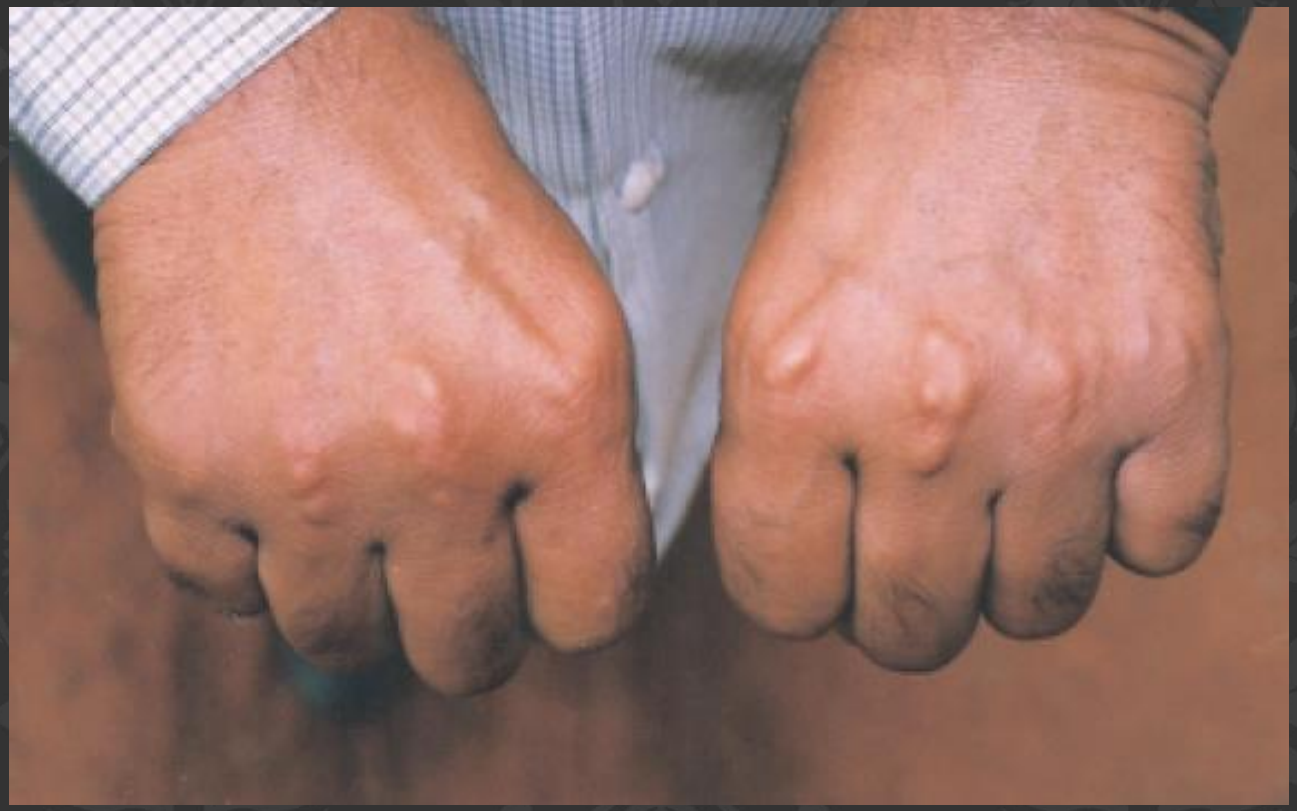
ICD 9 272.2-5; ICD 10 – E78.2-5

- Genetic defects, insulin resistance, metabolic syndrome, or combination
- Very high LDL-C, or
- Very high TG, or
- Combined dyslipidemia
- Very low HDL-C
- Xanthomas and/or corneal arcus
- Premature CAD

Familial Hypercholesterolemia

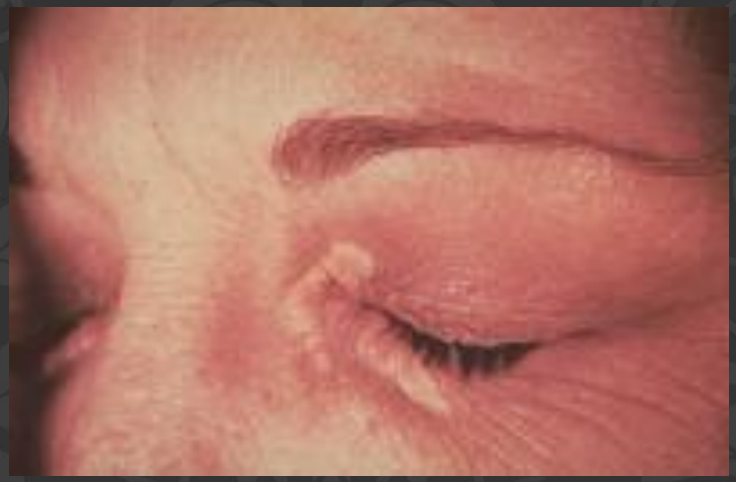


Heterozygous or
Homozygous

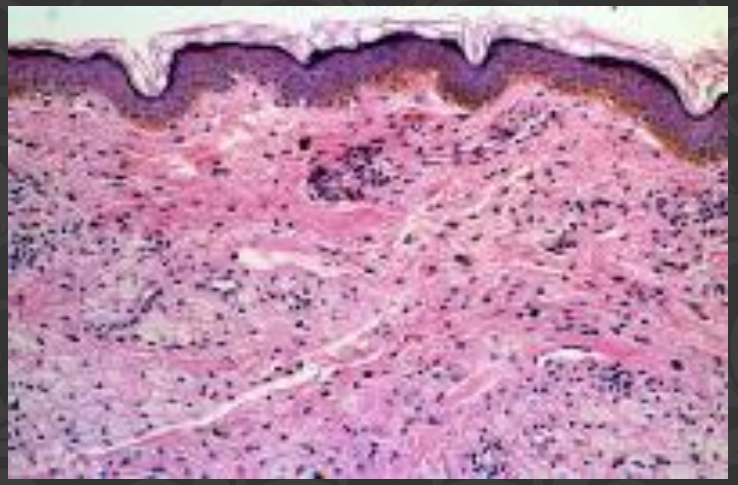


Tendonous xanthomas

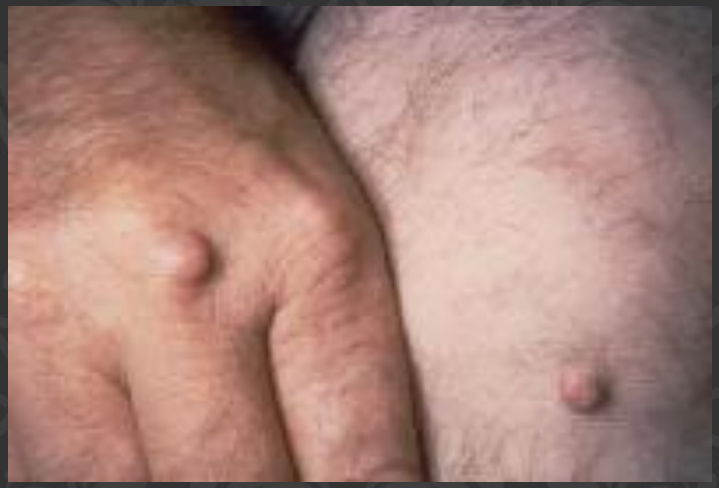
Male 40 yr FH LDL 490 mg/dL, TG 250



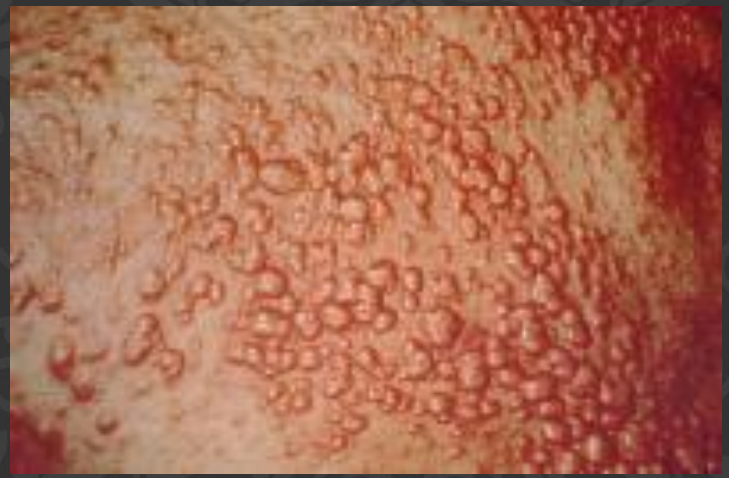
Xanthelasma (FH)



Microscopic view: xanthelasma
(lipid-laden macrophages)



Tuberous xanthomas (LDL++)



Eruptive xanthomas (TG++)

National Lipid Association Guidelines on Screening and Managing FH

The expert panel recommends universal screening for elevated cholesterol by 20 years of age and that FH should be suspected:

- **In adults** ≥20 years if they have LDL cholesterol >190 mg/dL or non-HDL cholesterol >220 mg/dL.
- **All children** aged 9 – 11 years should also be screened, with FH suspected in those with LDL cholesterol or non-HDL cholesterol >160 mg/dL and >190 mg/dL, respectively.
- Even children as young as two years should be screened for FH but only if there is a family history of premature cardiovascular disease or very high cholesterol levels suggesting FH in a parent.

Goldberg AC et.al. J Clin. Lipidol. 2011;5:133

Pediatric Cholesterol Levels

American Academy of Pediatrics

TC: <170 mg/dL
LDL: <110 mg/dL

TC borderline high: 170 - 199 mg/dL
LDL borderline high: 110 - 129 mg/dL

* It is considered high if total cholesterol is greater than 200 mg/dL and LDL is greater than 130 mg/dL. In addition, HDL should measure 35 mg/dL or higher and triglycerides less than 150 mg/dL.

HDL: ≥35 mg/dL
TG: <150 mg/dL.

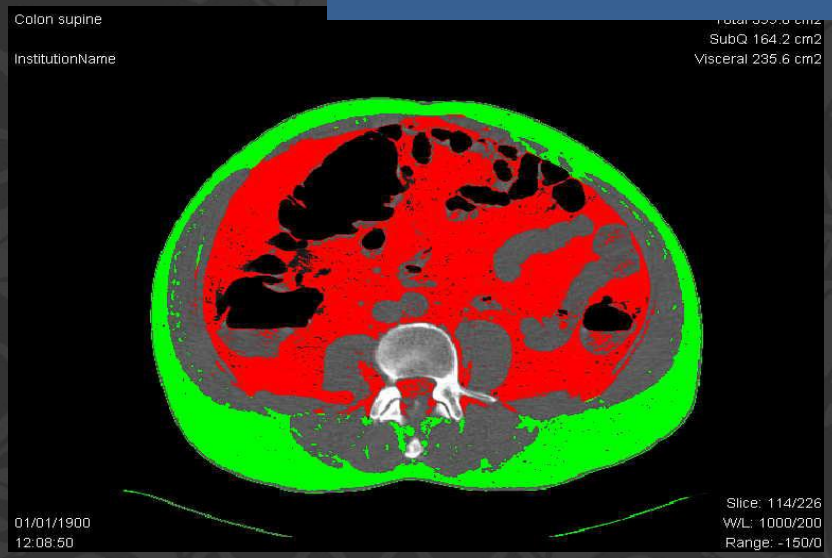
http://www.nhlbi.nih.gov/guidelines/cvd_ped/

Corneal Arcus

Sometimes a feature of
FH and *Familial Combined Hypercholesterolemia*

A ring of opacity in the peripheral part of the eye caused by a deposition of phospholipid and cholesterol in the corneal stroma

Familial combined Hyperlipidemia

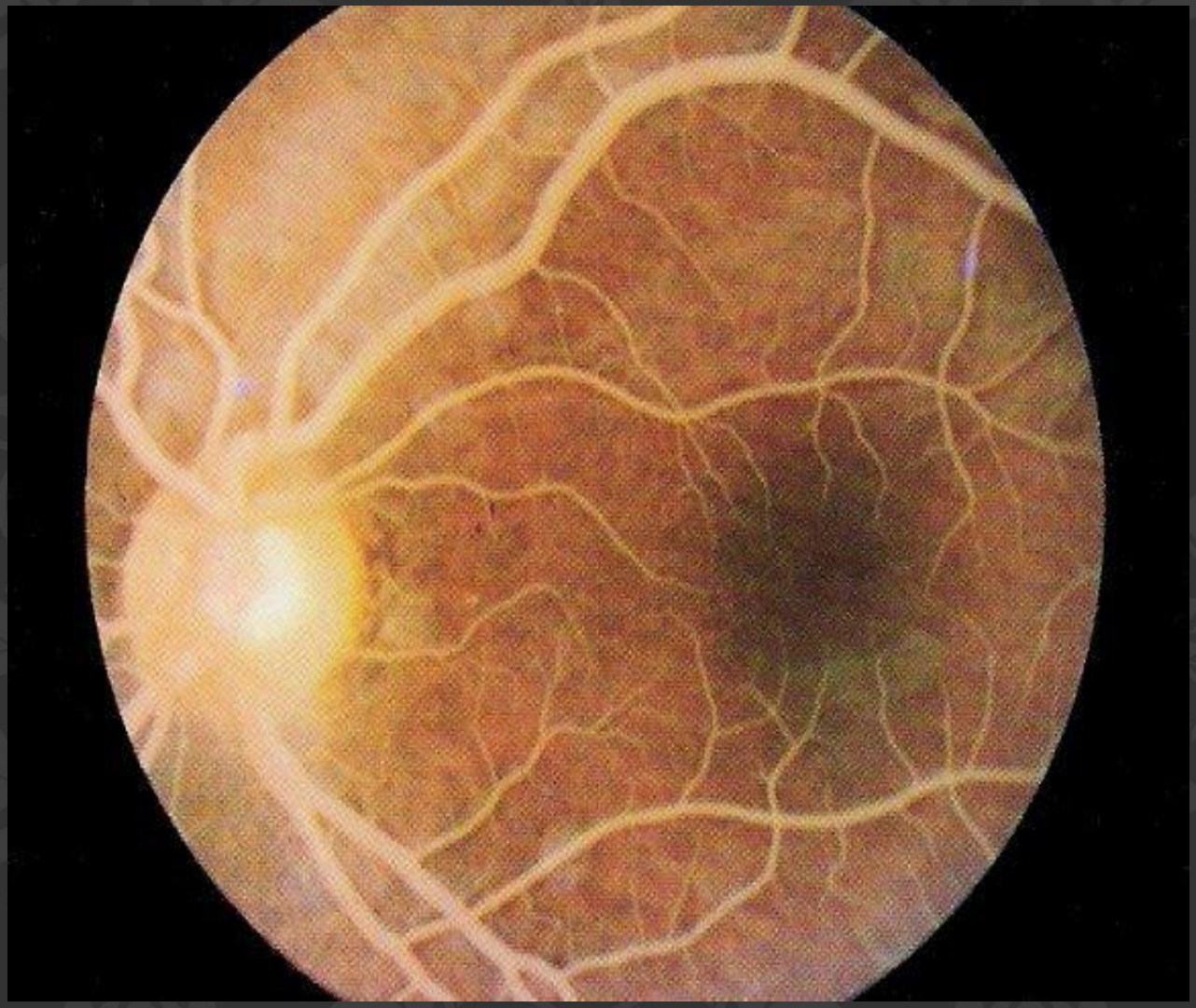


TG + TC

Excess central fat tends to be the most informative determinant of the expression of hypertriglyceridemia.

The data indicate that FCHL develops against a background of abdominal obesity.

Van der Kallen CJ et. Al. Ob Res. 2004;12:2054



Lipemia Retinalis

↑↑TG, VLDL, Chylomicrons

Hypoalphalipoproteinemia

(Isolated low HDL-C, e.g., <35 mg/dL)

25-35 mg/dL **Primary or familial HAL**

5-20 mg/dL **Apo A-1**milano

Apo A-1 Iowa

Apo A-1 deficiency

ABCA1 mutation (Tangiers disease)

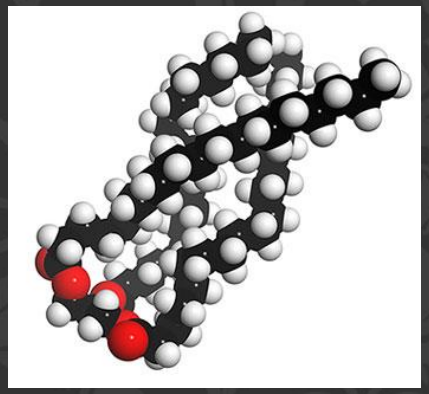
LCAT deficiency (fish eye disease)

LPL deficiency

Disappearing HDL syndrome (R, F, R+F)

Anabolic steroid use

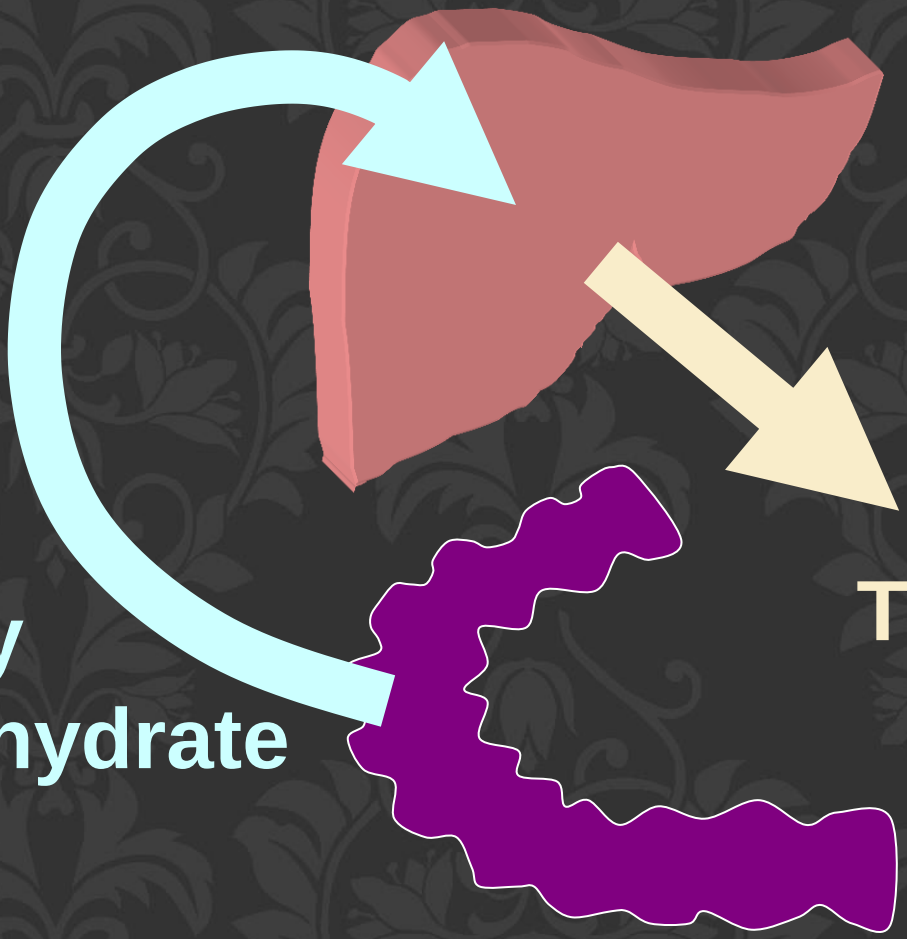
Hypertriglyceridemia



Why Elevated Fasting Triglycerides Can Be a Clinical Issue

- Likely to be an indicator of poor lifestyle habits
- The lipoprotein company they tend to keep (apoB, IDL, LDLp#)
- Frequently associated with decreased HDL-C
- Correlated with post prandial lipemia, arterial exposure to atherogenic TGRL's, and arterial endothelial dysfunction
- Positive relationship with the metabolic syndrome, CHD, and insulin resistance
- Effects clotting time at high levels
- Increases risk of pancreatitis

Dietary Carbohydrate Increases VLDL Production



Dietary Carbohydrate

Plasma Triglyceride (VLDL)

5 Minute Lesson in TG Management

TG 150 - 199 mg/dL

↓ CHO_{hg}, ex, wgt loss

TG 200 - 499 mg/dL

↓ CHO_{hg}, ex, wgt loss, ↑ n3, fib, niacin, statin

TG 500-2000 mg/dL

↓ Fat (avoid with Atkins), lifestyle changes, fibrates, n3, niacin

Drugs That Cause High TG

- **Large effects: oral contraceptives,** glucocorticoids, isotretinoin (Accutane), ketoconazole, cholestyramine, colestipol

- **Small effects:** postmenopausal estrogens, diuretics, beta blockers

Critical Triglyceride Level for Pancreatitis and Other Symptoms of Chylomicronemia

2,000 mg/dl

Risk begins to significantly increase
beginning at ~ 1000 mg/dL

Indicate with a true (T) or false (F) regarding which of the following nutrients or treatments usually raise serum triglyceride levels but also raise HDL Levels.

T A. Alcohol

B. Polyunsaturated fats

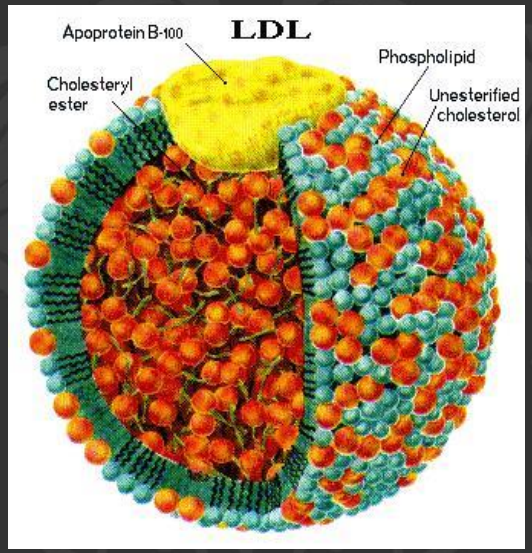
T C. Bile acid sequestrants

T D. Oral conjugated estrogens

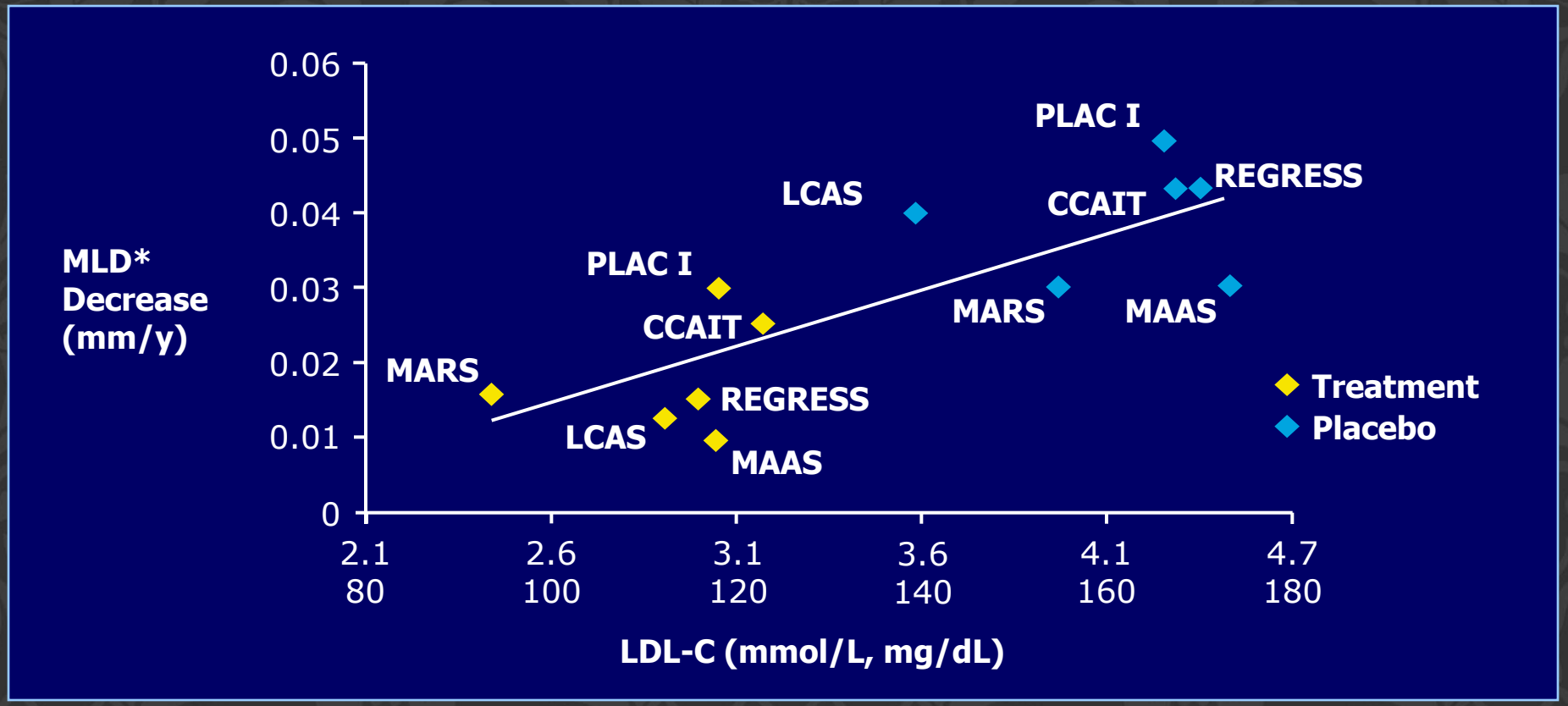
E. Carbohydrates

LDL-C

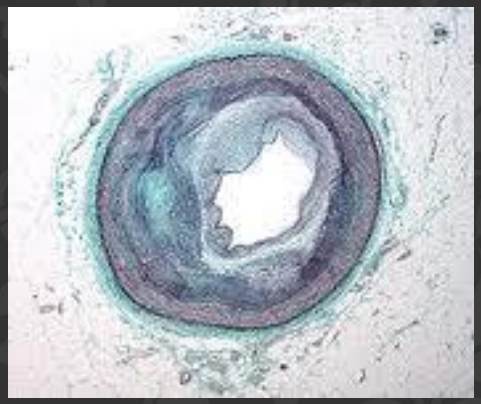
The most important therapeutic lipoprotein target



LDL-C Levels Correlate with Angiographic Progression of CAD



Ballantyne CM, et al. *Curr Opin Lipidol.* 1997;8:354–361.



LDL-C "thresholds" for atherosclerotic plaque volume changes

(projected from IVUS studies)

80 – 130 mg/dL	Slow progression
65 – 80 mg/dL	? Stop progression ?
<65 mg/dL	Regression

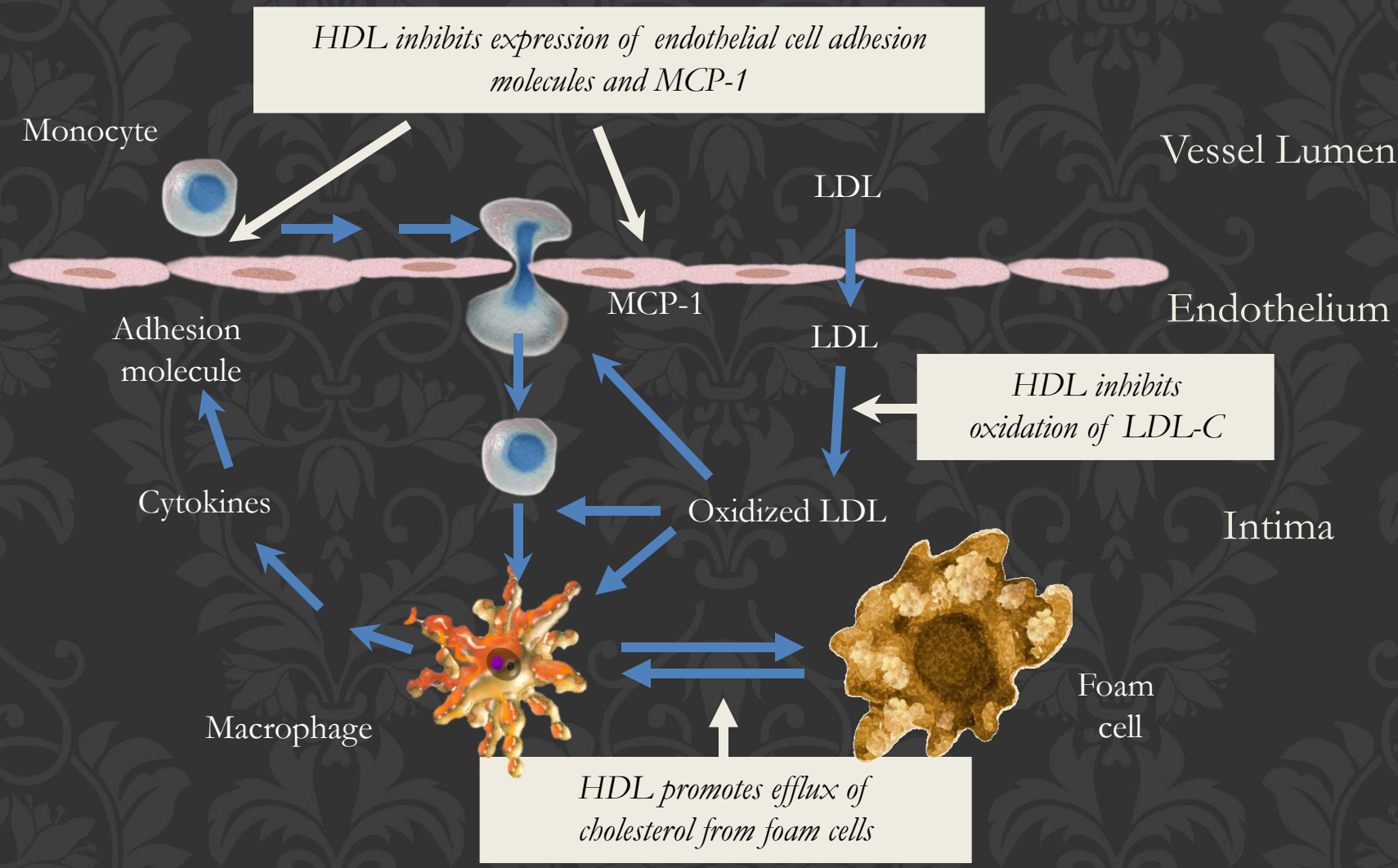
✓ However, ≥10-15% reduction in LDL-C can significantly reduce clinical events, e.g., MI and stroke

Nissen S 2010

HDL-C

High Density Lipoprotein

POTENTIAL ANTIATHEROGENIC ACTIONS OF HDL



MCP-1 = monocyte chemoattractant protein-1

Adapted from Barter PJ et al. *Circ Res*. 2004;95:764-772.

FUNCTIONAL AND COMPOSITIONAL ASSESSMENT OF HDL

Cholesterol efflux

Antioxidant activity

Anti-inflammatory activity

Proteomics/lipidomics

Note: these are research tools w/o known clinical relevance of application

Rosenson RS, Brewer HB Jr, Chapman MJ, Fazio S, Hussain MM, Kontush A, Krauss RM, Otvos JD, Remaley AT, Schaefer EJ. *Clin Chem.* 2011;57(3):392-410.

HDL-C RISK FACTOR VS RISK MARKER ?

Low HDL-C predicts high CVD Risk
High HDL-C predicts anti-atherogenic effects:

Anti-inflammatory
Antioxidant
Antithrombotic
Pro-endothelial

But clinical trials <u>have not</u> yet proven that:

HDL is a *causal factor* vs *biomarker* of risk, or
Raising HDL-C reduces CVD risk

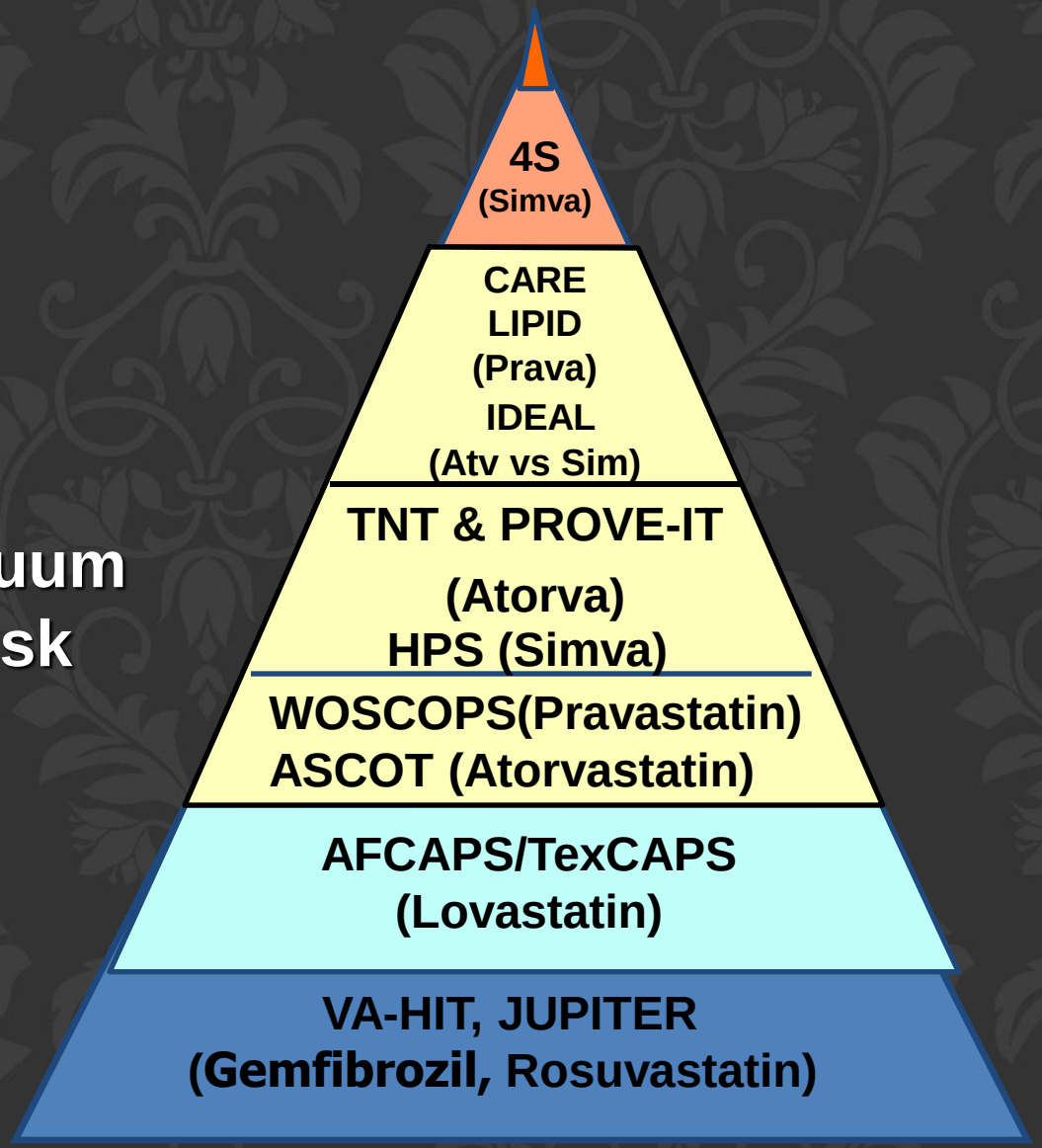
LIFESTYLE MODIFICATIONS TO RAISE HDL-C LEVELS

- **Smoking Cessation**
  - HDL-C levels are 7-20% lower in smokers, but return to normal 1-2 months after smoking cessation
- **Whole Food Plant Based Diet**
- **Weight Reduction**
  - For every 3 kg (7 lb) of weight loss, HDL-C levels increase about 1 mg/dL (~2-4% increase)
- **Exercise**
  - Aerobic exercise (40 min, 3-4 times weekly) increases HDL-C by about 2.5 mg/dL (~5-10% increase)

Rössner S et al. *Atherosclerosis.* 1987;64:125-130.
Wood PD et al. *N Engl J Med.* 1988;319:1173-1179.
Ornish D et al. *JAMA.* 1998;280:2001-2007.
Cullen P et al. *Eur Heart J.* 1998;19:1632-1641.
Kokkinos PF et al. *Arch Intern Med.* 1995;155:415-420.
Kodama S et al. *Arch Intern Med.* 2007;167:999-1008.

Key Clinical Trials

Landmark Clinical Event Trials: Relevance to Clinical Practice



Continuum of Risk

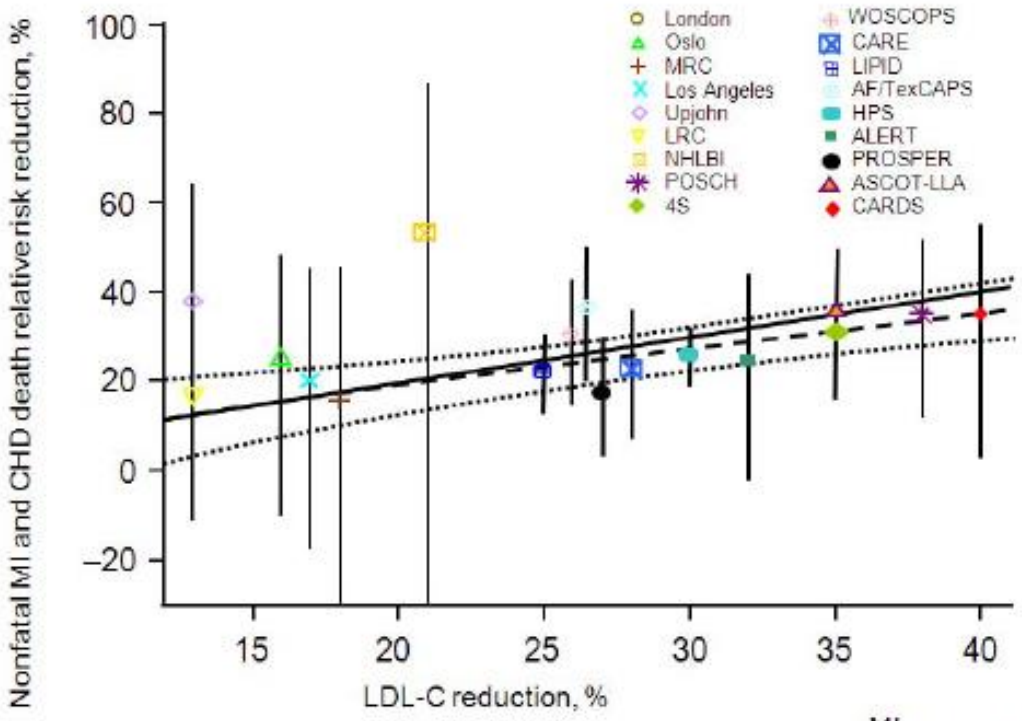
High-risk CHD patients

Majority of CHD patients at risk

Patients at high risk for CHD

Patients at low risk for CHD

Multiple Studies Showed a Relationship Between LDL-C Reduction and CHD Relative Risk

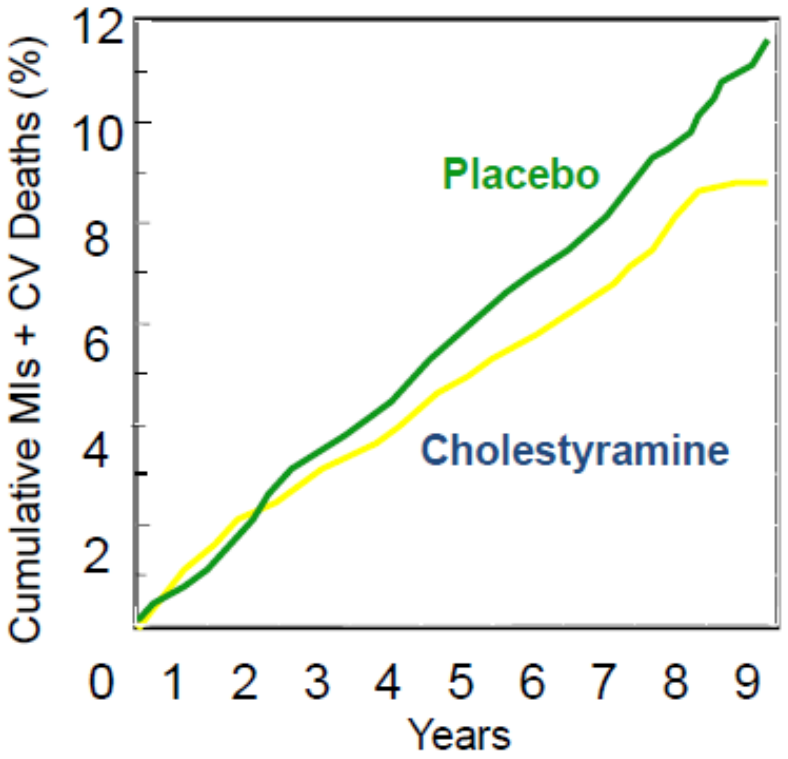


MI = myocardial infarction.

Adapted with permission from Robinson JG, et al. *J Am Coll Cardiol.* 2005;46:1855-1862.

Lipid Research Clinics Coronary Primary Prevention Trial

- 3806 men aged <60 yr with total cholesterol ≥265 mg/dL and high LDL-C, initially free of coronary disease
- Followed 7.4 yr
- Cholestyramine 24 g/day vs. placebo
- LDL-C –20.3%
  HDL-C +1.6%
- 19% reduction in CHD death and/or nonfatal MI



The Lipid Research Clinics Coronary Primary Prevention Trial results. *JAMA*. 1984;251:351-364.

Statins

&

LDL-C

SCANDINAVIAN SIMVASTATIN SURVIVAL STUDY (4S)

The Lancet, Vol 344, November 19, 1994

4S OBJECTIVES

Randomized trial of cholesterol lowering in 4,444 patients with CAD: The Scandinavian Simvastatin Survival Study.

To investigate whether long-term simvastatin therapy reduces total mortality and coronary events in post-MI and or angina patients with total cholesterol between 212-309 mg/dL. Mean LDL-C = 188 mg/dL

The Lancet, Vol 344, November 19, 1994

4S Treatment Schedule

Simvastatin 20 mg/day or matching placebo

↓

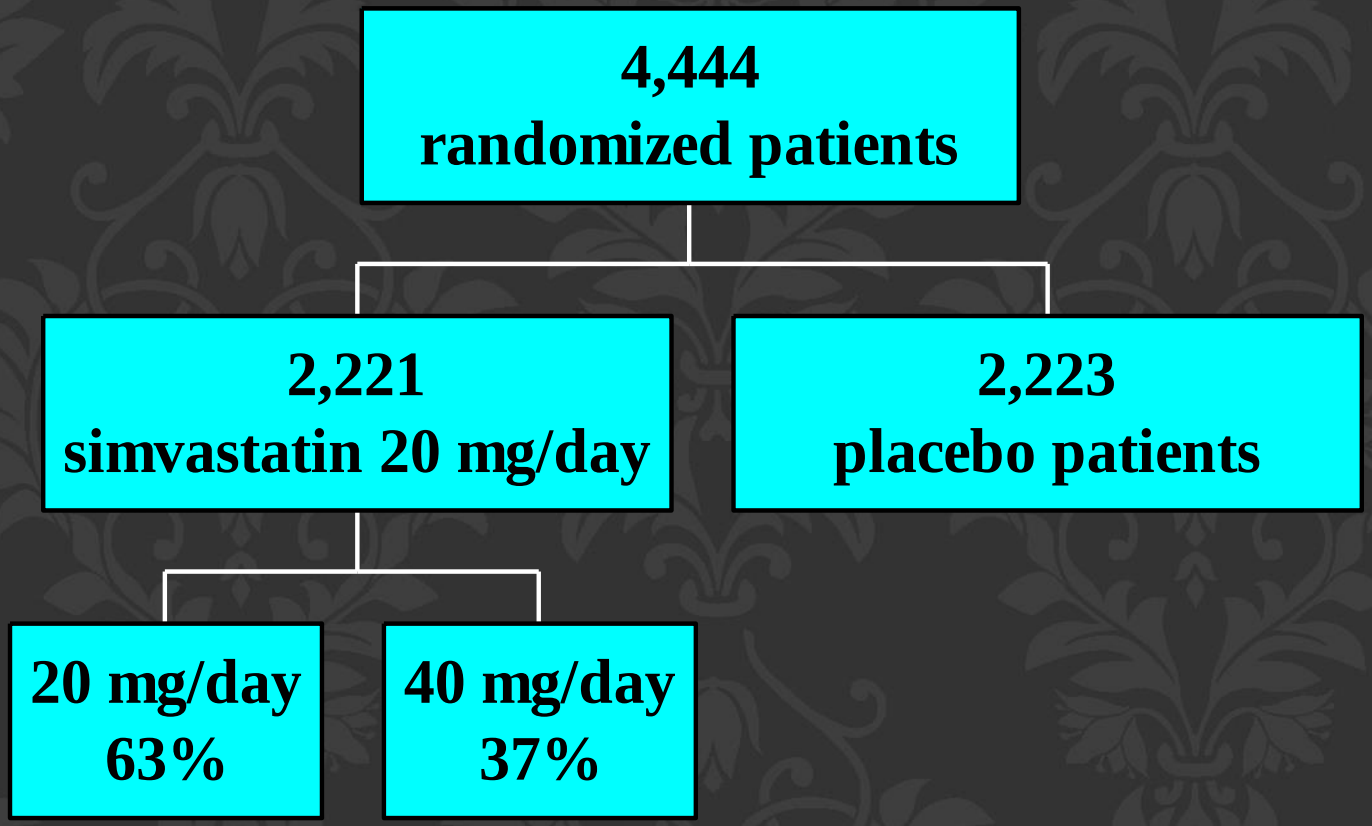
Increased to 40 mg/day if TC exceeded 200 mg/dL

↓

Study Goal:
TC 116-200 mg/dL

The Lancet, Vol 344, November 19, 1994

4S DOSAGE TITRATION



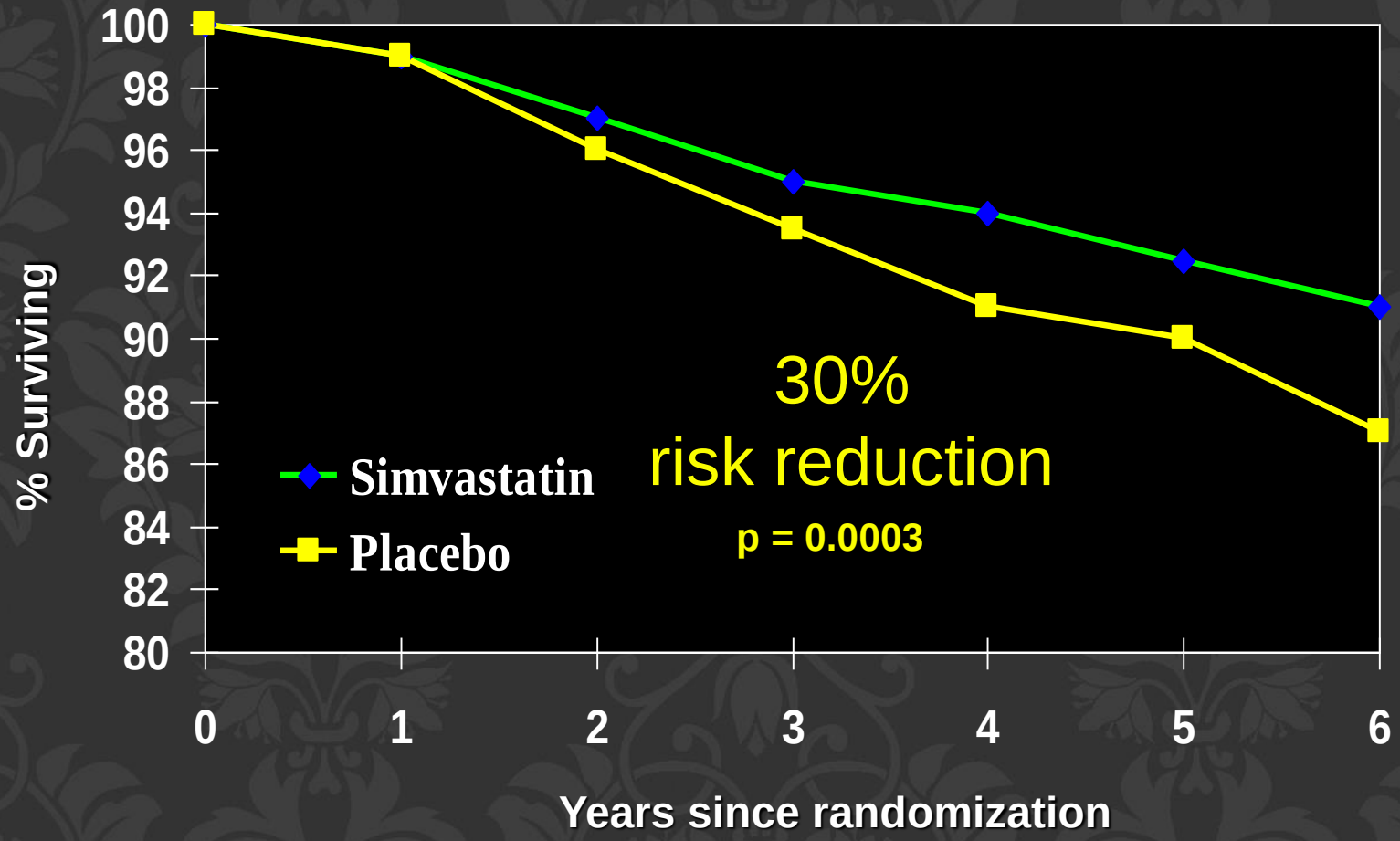
The Lancet, Vol 344, November 19, 1994

BASELINE CHARACTERISTICS 4S

	Placebo (n=2223)	Simvastatin (n=2221)
Mean age (years)-men	58.1	58.2
Mean age (years)-women	60.5	60.5
Angina only	21%	21%
MI only	62%	63%
Both angina and MI	17%	16%
Hypertension	26%	26%
Smoker	27%	24%
TC (mg/dL)	260	260
LDL (mg/dL)	180	180

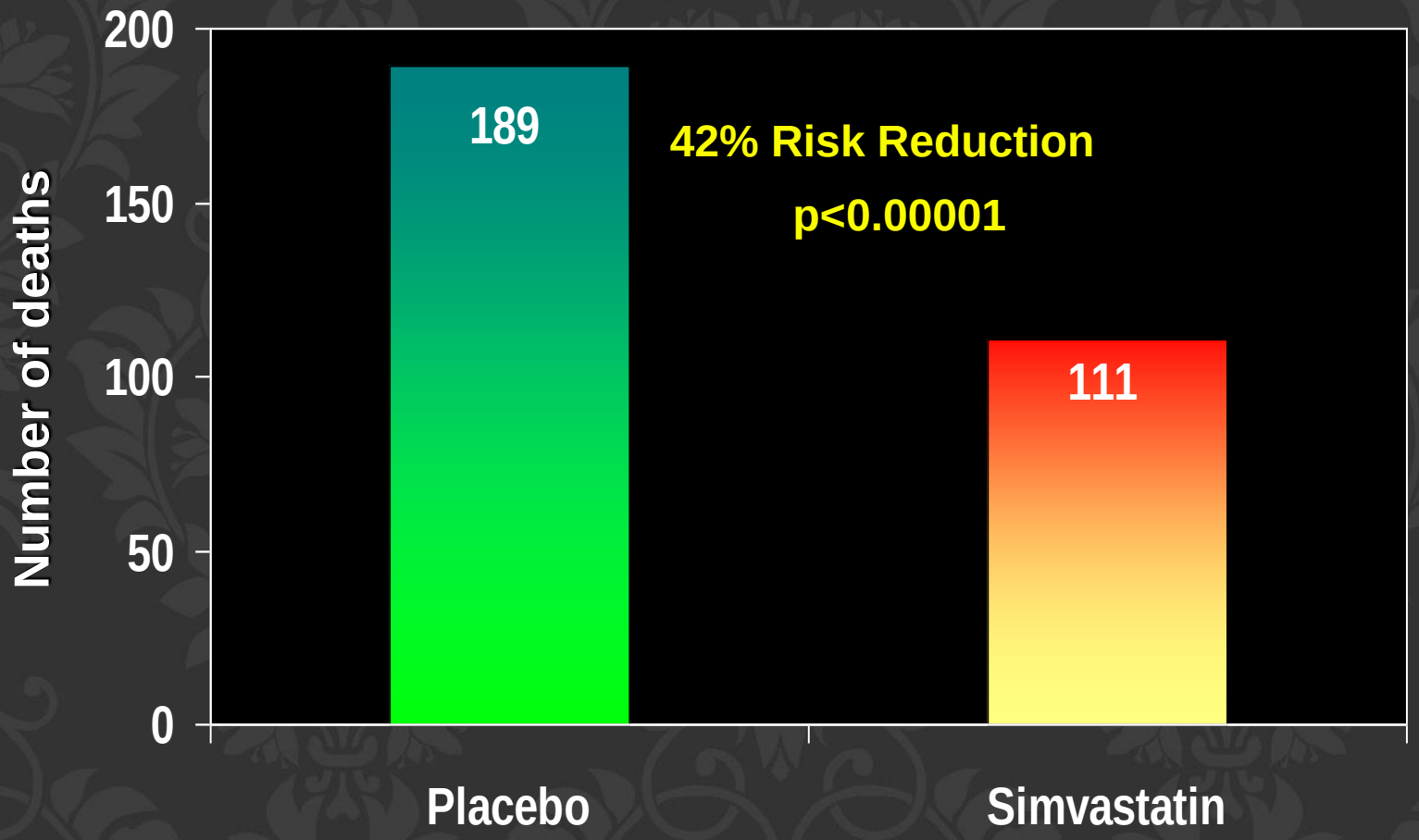
The Lancet, Vol 344, November 19, 1994

PRIMARY ENDPOINT: OVERALL SURVIVAL 4S



The Lancet, Vol 344, November 19, 1994

Coronary Mortality 4S



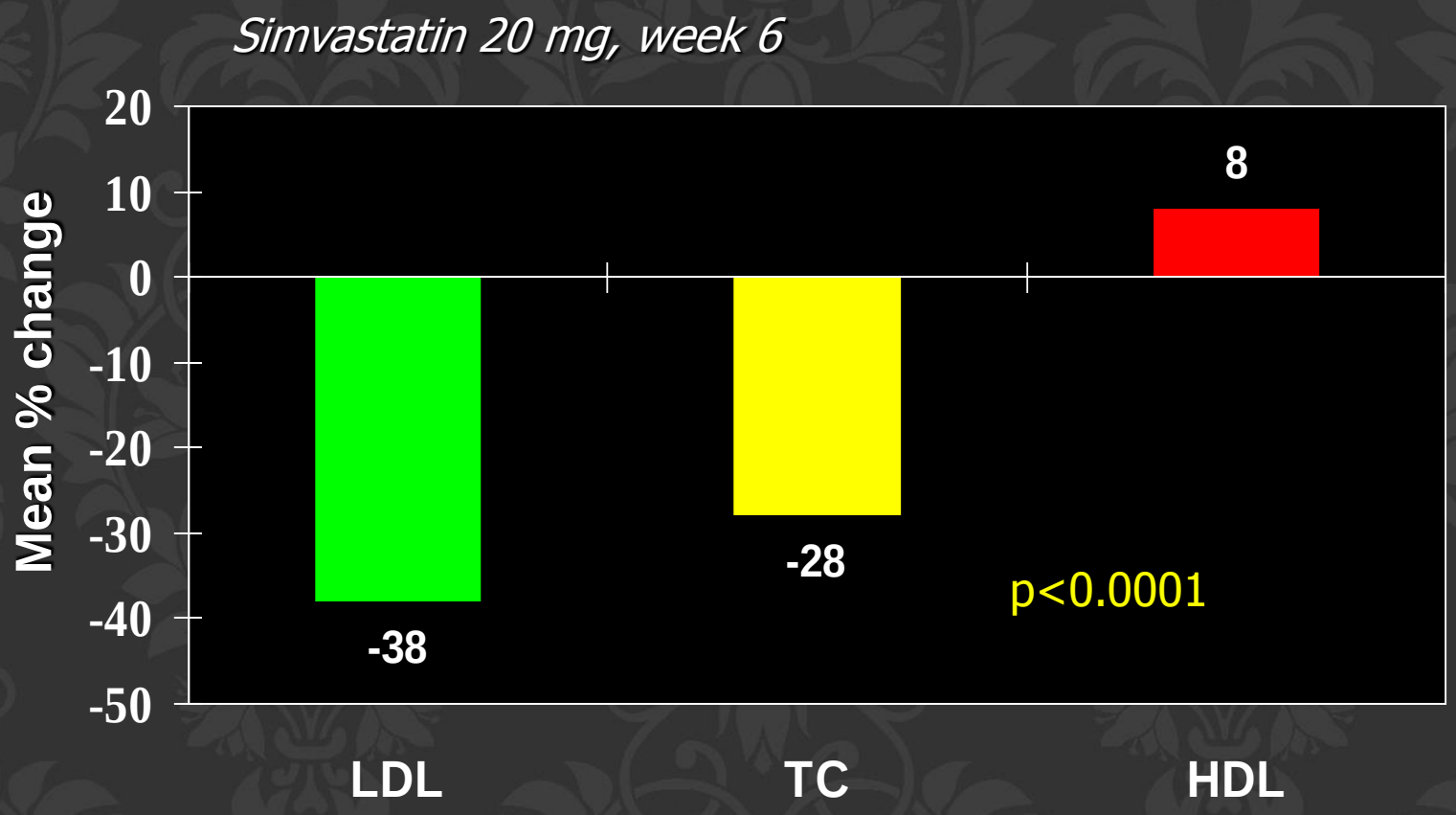
The Lancet, Vol 344, November 19, 1994

All-Cause Mortality 4S

Cause of death	Placebo (n=2223)	Simvastatin (n=2221)	Risk Reduction
Coronary	189	111	42%
Noncoronary vascular	18	25	
Non-cardiovascular	49	46	
-Cancer	35	33	
-Suicide	4	5	
-Trauma	3	1	
-Other	7	7	
All Deaths	**256**	**182**	**30%**

The Lancet, Vol 344, November 19, 1994

4S CHOLESTEROL PARAMETERS



The Lancet, Vol 344, November 19, 1994

Safety Profile 4S

# of patients with	Placebo (n=2223)	Simvastatin (n=2221)
Nonfatal cancer	61	57
AST 3x ULN	23	20
ALT 3x ULN	33	49
CPK 10x ULN	1	6
Rhabdomyolisis	0	1

The Lancet, Vol 344, November 19, 1994

4S Summary

Compared with Placebo, Simvastatin:

Improved survival

Reduced coronary mortality

Reduced major coronary events

Reduced need for PTCA and CABG Improved event-free survival

Substantially reduced TC and LDL

The Lancet, Vol 344, November 19, 1994

Collaborative Atorvastatin Diabetes Study (CARDS)

Colhoun HM et. al. University College Med. School, London

Lancet, August 21, 2004

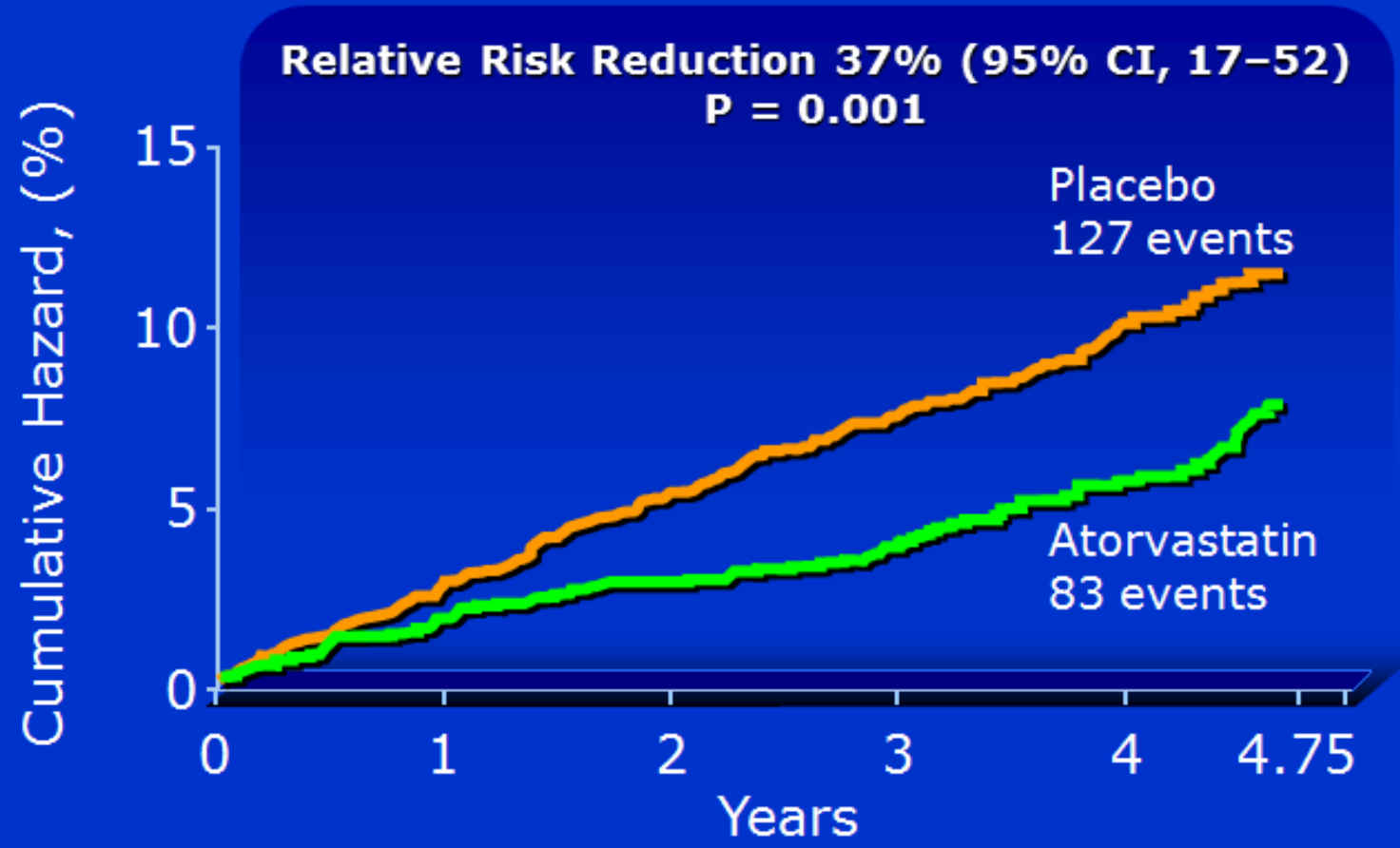
Double-blind, randomized, placebo controlled trial (Diabetes UK) of primary prevention of CVD in 2838 men and women with T2D with no previous CHD who do not have LDL-C > 160 mg/dL.
4-year F/U

Intervention: Fixed dose of atorvastatin (10 mg)

Primary end-points:

- Major CV events (fatal and nonfatal MI)
- CV procedures (CABG, PTCA..)
- Cerebrovascular disease death and nonfatal stroke

CARDS: Effect of Atorvastatin on the Primary Endpoint: Major CV Events Including Stroke



Placebo	1410	1351	1306	1022	651	305
Atorvastatin	1428	1392	1361	1074	694	328

Colhoun HM et al. *Lancet* 2004;364:685-696.

Slide Source:

CARDS: ADVERSE AND SERIOUS ADVERSE EVENTS

Type of Event	Patients (%) with Event	
	Placebo (n = 1410)	Atorvastatin 10 mg (n = 1428)
Serious adverse event possibly associated with study drug	20 (1.1%)	19 (1.1%)
Discontinued for AE	145 (10%)	122 (9%)
Rhabdomyolysis	0	0
Myopathy AE report	1 (0.1%)	1 (0.1%)
CPK $\geq 10 \times$ ULN	10 (0.7%)	2 (0.1%)
ALT $\geq 3 \times$ ULN	14 (1%)	17 (1%)
AST $\geq 3 \times$ ULN	4 (0.3%)	6 (0.4%)

Colhoun HM et al. *Lancet* 2004;364:685-696.

TNT: Effect of Lowering LDL Cholesterol Substantially Below Currently Recommended Levels in Patients With Coronary Heart Disease and Diabetes

The Treating to New Targets study

Shepherd J, Haffner, S et.al. Diabetes Care 2006;29:1220-1226

- **Atorva 80 vs 10 mg** in 1201 T2D+CHD pts with LDL <130 mg/dl

- Patients were followed for a median of 4.9 years.

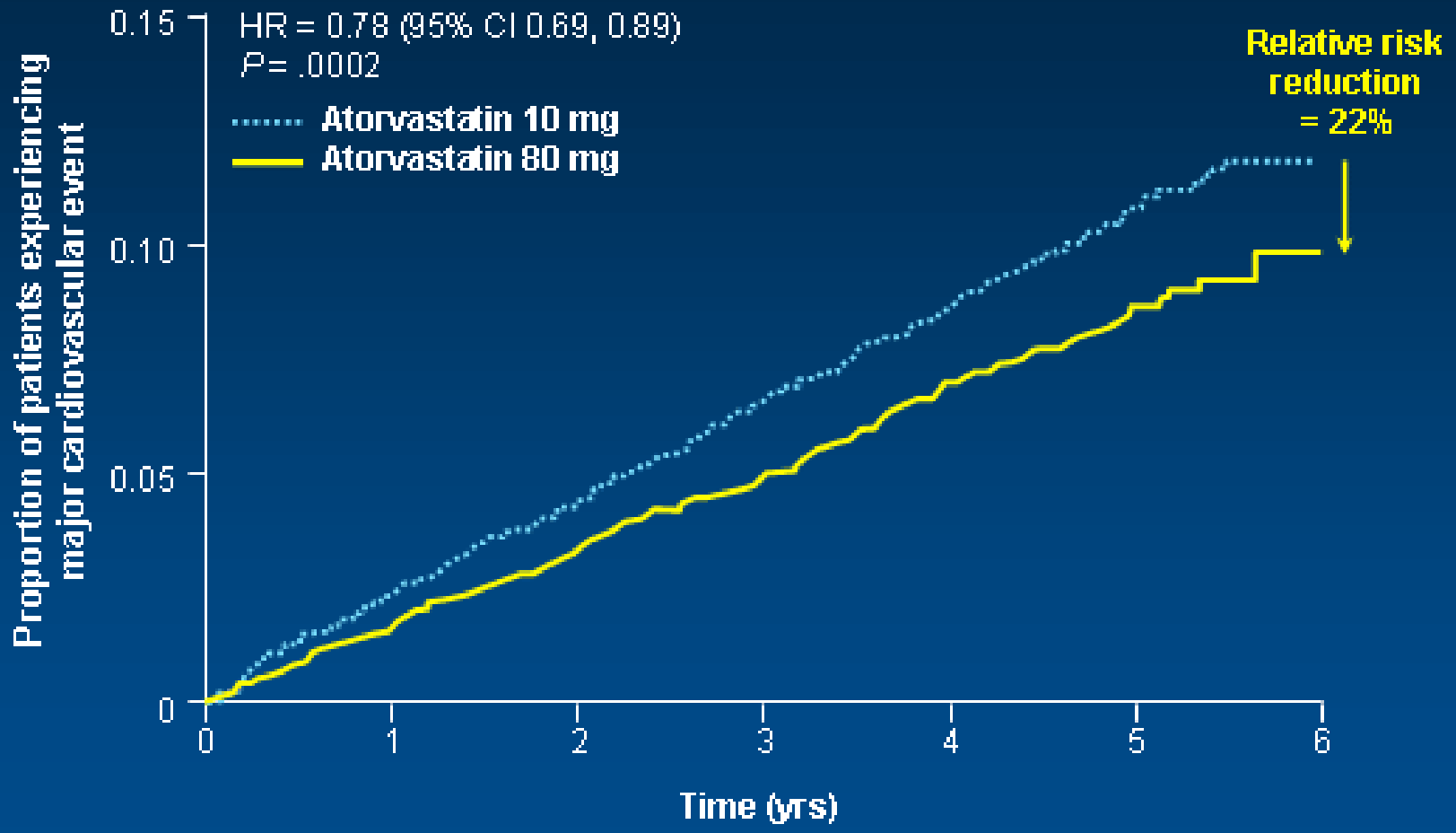
- Primary end point was the time to first major cardiovascular event

RESULTS— 5 yr follow-up. **Atorva 80: 77 mg/dL vs Atorva 10: 99 mg/dL**

- A primary event occurred in 135 patients (17.9%) receiving atorvastatin 10 mg, compared with 103 patients (13.8%) receiving atorvastatin 80 mg (**hazard ratio 0.75,** P = 0.026).

- Significant differences between the groups in favor of atorvastatin 80 mg were also observed for time to CBV event (0.69, P = 0.037) and any CVevent (0.85, P = 0.044).

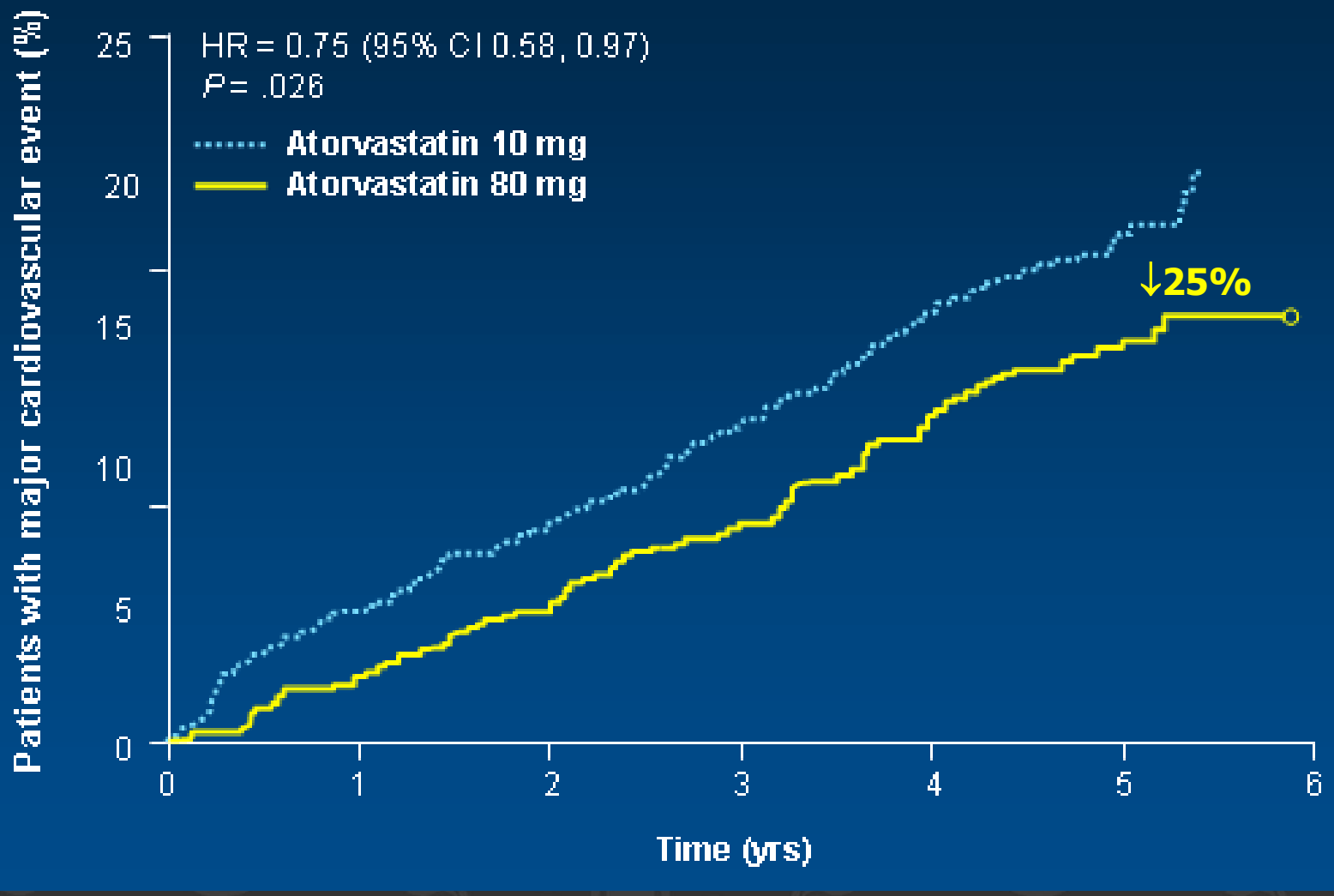
TNT



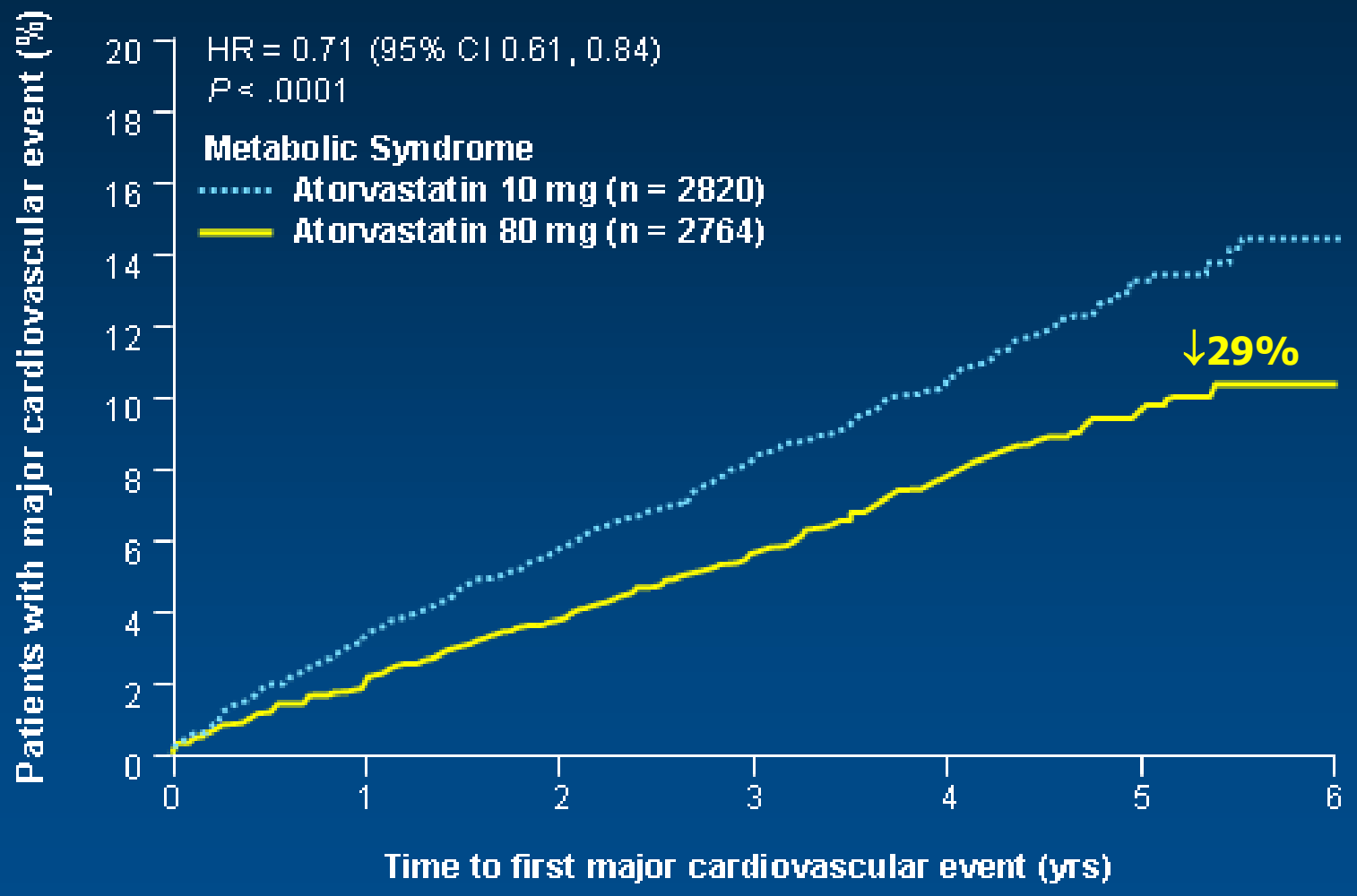
CHD death, nonfatal, nonprocedure-related MI, resuscitated cardiac arrest, fatal or nonfatal stroke

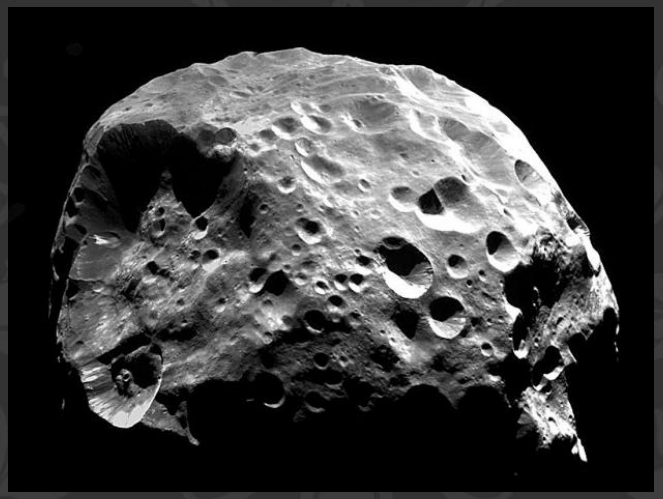
LaRosa JC, et al. *N Engl J Med.* 2005;352:1425-1435.

TNT - Diabetes



TNT – Metabolic Syndrome





ASTEROID

Intravascular ultrasound study

507 pts with at least single vessel disease

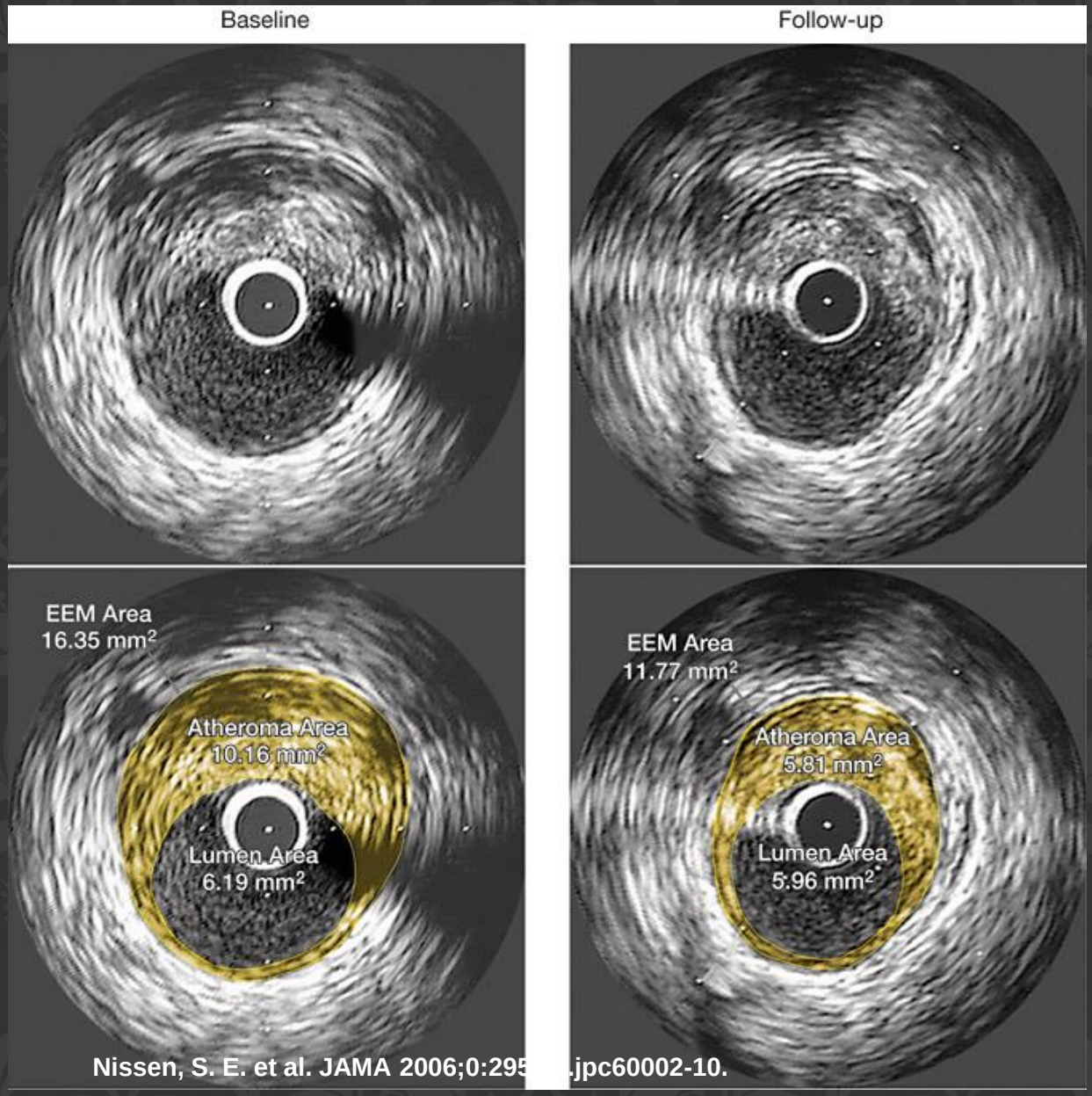
IVUS in non PTCA coronary artery

Rosuvastatin (Crestor) 40 for 24 months

LDL 130 $\rightarrow$ 61 mg/dL

HDL 43 $\rightarrow$ 49 mg/dL

Nissen SE et.al. JAMA 2006;295

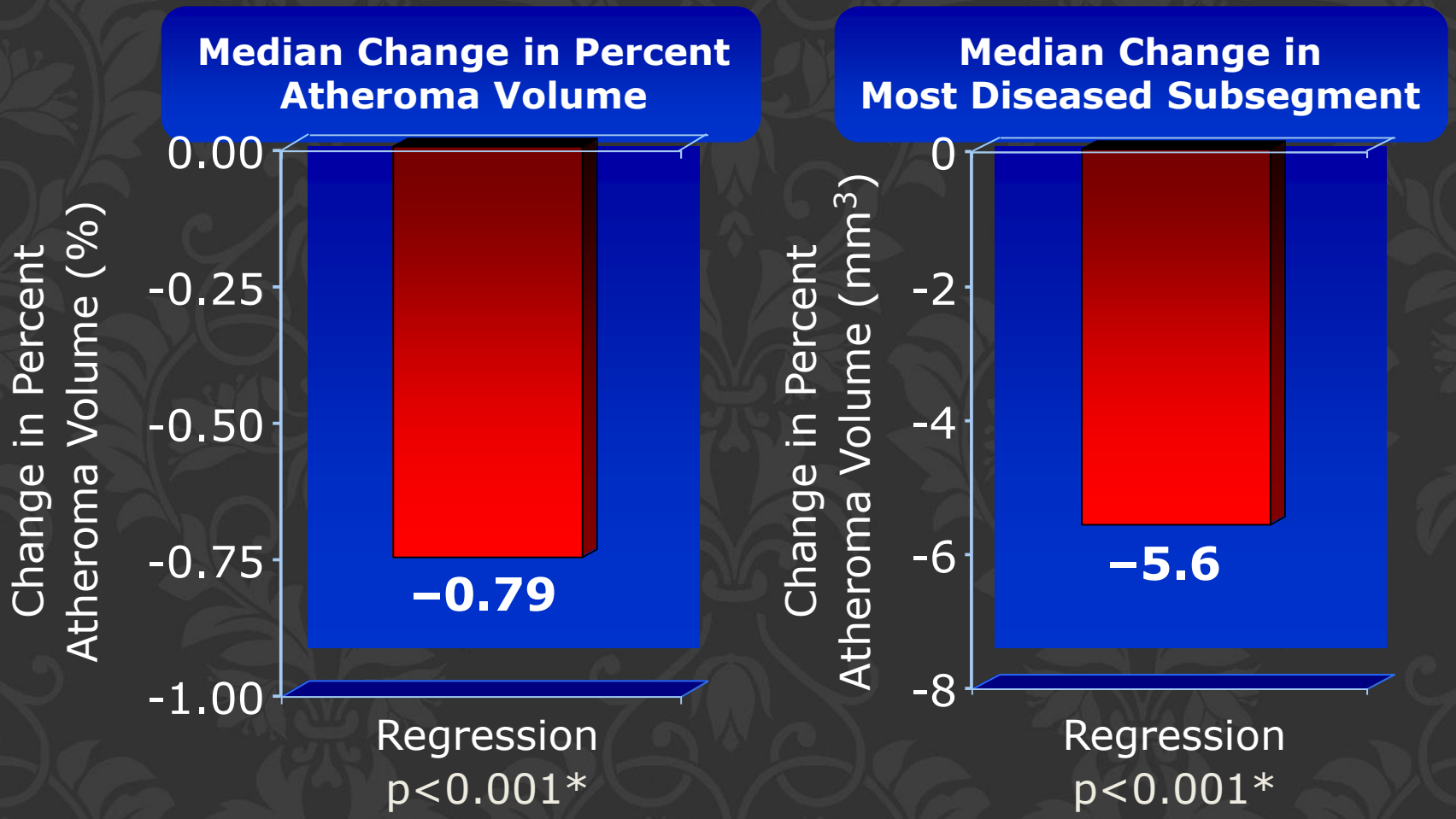


Nissen, S. E. et al. JAMA 2006;0:295[illegible].jpc60002-10.

Example of Regression of Atherosclerosis in a Patient in the Trial

JAMA

DUAL PRIMARY IVUS EFFICACY PARAMETERS



*Wilcoxon signed rank test for comparison with baseline

Nissen SE et al. *JAMA* 2006;295:1556-1565.

Progression-Regression “threshold”

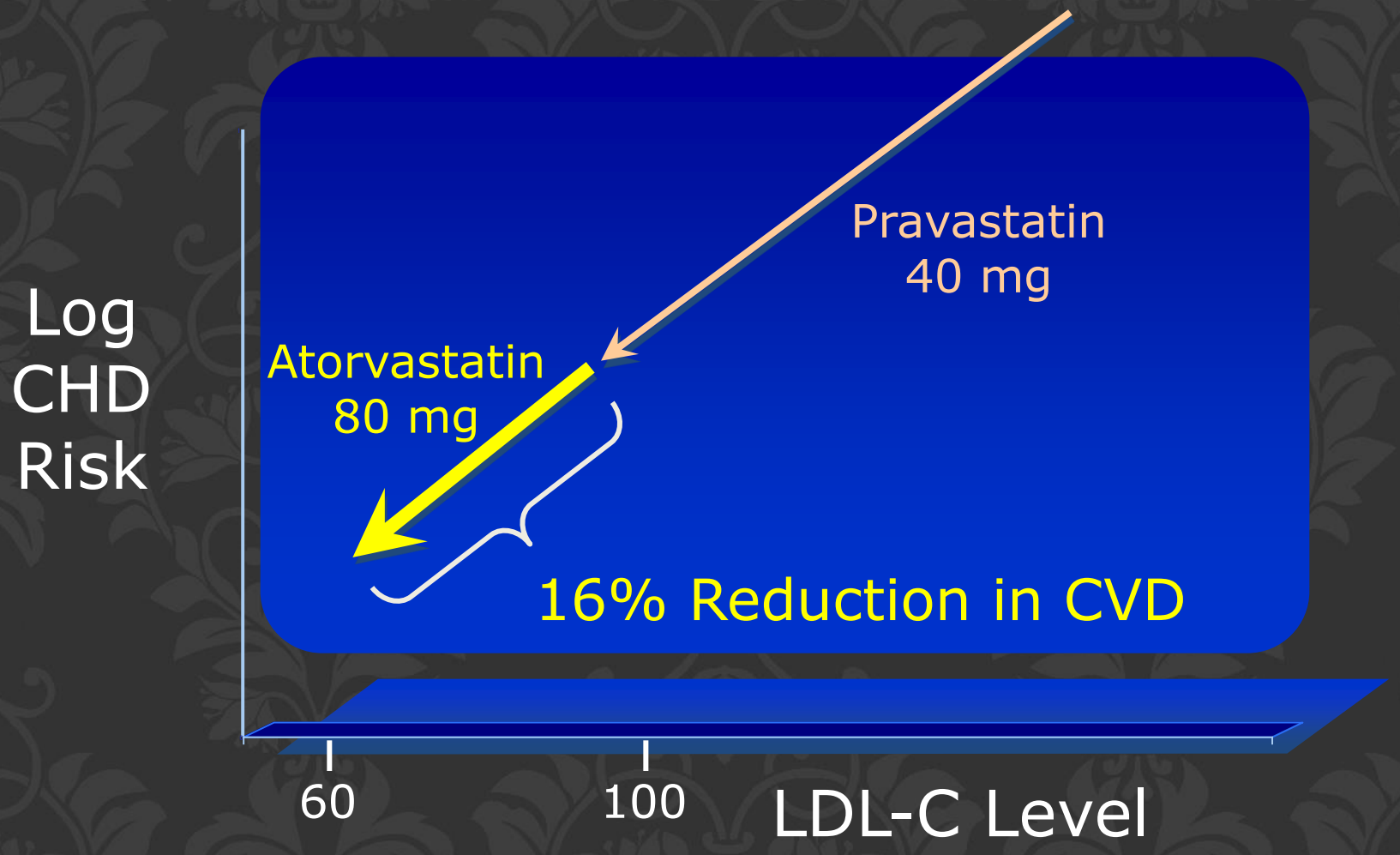
It appears that an LDL-C value of 76 mg/dL was the cutoff at which the linear regression analysis predicted no plaque increase: the transition from progression to regression. (Asteroid data)

This is in agreement with our finding in patients with documented coronary artery disease treated by usual care who underwent serial ultrasonic examinations of the left main coronary artery during at least 12 months of follow-up.

✓ We found that a mean LDL-C value of 75 mg/dL was the cutoff at which regression analysis predicted no plaque progression. (Clemens von Birgelen; Marc Hartmann 2007)

PROVE IT–TIMI 22 (2-YEAR TRIAL)

N=4,162 WITH ACUTE CORONARY SYNDROME



Cannon CP et al. *N Engl J Med* 2004;350:1495-1504.

✓ Lowering LDL-C with statins appears to reduce CVD risk in both Secondary prevention and Primary prevention studies

SECONDARY PREVENTION TRIALS OF LIPID-ALTERING THERAPY INCLUDING PATIENTS WITH DIABETES

Trial	Diabetic, n	Total N in Study	Lipid-Altering Drug, mg/d	CHD* Risk vs Placebo in Diabetic Patients, %
4S Reanalysis	202† 483‡	4,444	Simvastatin 20–40	–55 (p=.002) –42 (p=.001)
CARE	586†	4,159	Pravastatin 40	–25 (p=.05)
LIPID	1,077‡	9,014	Pravastatin 40	–19 (NS)
LIPS §	202†	1,677	Fluvastatin 80	–47 (p=.04)
HPS §	3,051†	13,386	Simvastatin 40	–18 (p=.002)
4D ¶	1,255†	1,255	Atorvastatin 20	–8 (NS)
VA-HIT	769‡	2,351	Gemfibrozil 1,200	–32 (p=.004)
DAIS ¶ ‖	418†	418	Fenofibrate 200	–23 (NS)

*Includes stroke in 4D and VA-HIT
†By history
‡By history or glucose ≥126 mg/dL

§ Type 1 or 2 diabetes
¶ Prospective trial in diabetic subjects; others are subgroup analyses
‖ Angiographic study

Bays H et al. *Future Cardiology* 2005;1:39-59. | Pyörälä K et al. *Diabetes Care* 1997;20:614-620. | Haffner SM et al. *Arch Intern Med* 1999;159:2661-2667. | Goldberg RB et al. *Circulation* 1998;98:2513-2519. | Keech A et al. *Diabetes* Care 2003;26:2713-2721. | Serruys PWJC et al. *JAMA* 2002;287:3215-3222. | HPS Collaborative Group. *Lancet* 2003;361:2005-2016. | Wanner C. Presented at ASN annual meeting, 2004. | Rubins HB et al. *Arch Intern Med* 2002;162:2597-2604. | DAIS Investigators. *Lancet* 2001;357:905-910.

PRIMARY PREVENTION TRIALS OF LIPID-ALTERING THERAPY INCLUDING PATIENTS WITH DIABETES

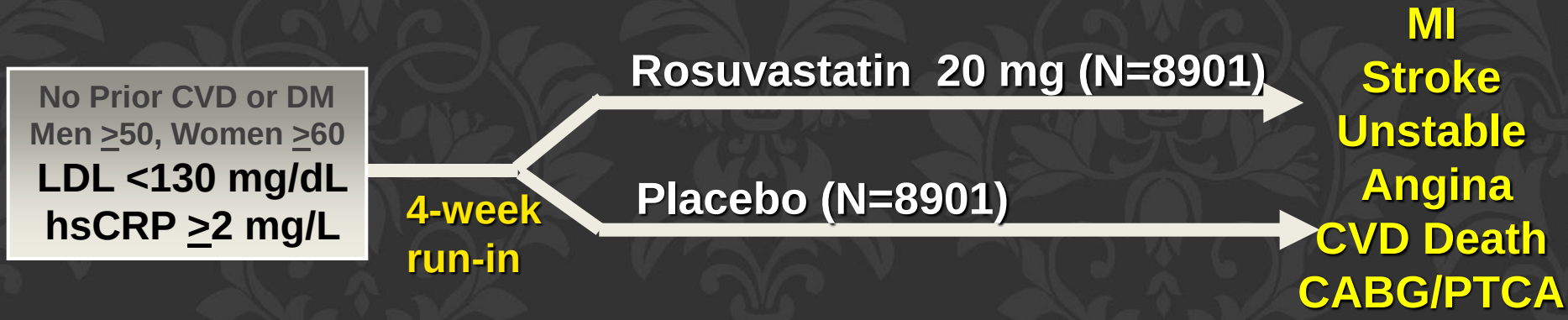
Trial	Diabetic,* n	Total N in Study	Lipid-Altering Drug, mg/d	CHD* Risk vs Placebo in Diabetic Patients, %
CARDS †	2,838	2,838	Atorvastatin 10	–37 (p=.001)
AFCAPS	155	6,605	Lovastatin 20–40 ‡	–44 (NS)
HPS §	2,912	7,150	Simvastatin 40	–33 (p=.0003)
ASCOT	2,532	10,305	Atorvastatin 10	–16 (NS)
PROSPER	623	5,804	Pravastatin 40	+27 (NS)
HHS	135	4,081	Gemfibrozil 1200	–68 (NS)

* By history
† Prospective trial in diabetic subjects; others are subgroup analyses
‡ Mean 30 mg/d
§ Type 1 or 2 diabetes

Bays H et al. *Future Cardiology* 2005;1:39-59. | Colhoun HM et al. *Lancet* 2004;364:685-696. | Downs JR et al. *JAMA* 1998;279:1615-1622. | HPS Collaborative Group. *Lancet* 2003;361:2005-2016. | Sever PS et al. *Lancet* 2003;361:1149-1158. | Shepherd J et al. *Lancet* 2002;360:1623-1630. | Koskinen P et al. *Diabetes Care* 1992;15:820-825.

JUPITER

Multi-National Randomized Double Blind Placebo Controlled Trial of Rosuvastatin in the Prevention of Cardiovascular Events Among Individuals With Low LDL and Elevated hsCRP



Argentina, Belgium, Brazil, Bulgaria, Canada, Chile, Colombia, Costa Rica, Denmark, El Salvador, Estonia, Germany, Israel, Mexico, Netherlands, Norway, Panama, Poland, Romania, Russia, South Africa, Switzerland, United Kingdom, Uruguay, United States, Venezuela

Ridker et al, Circulation 2003;108:2292-2297.

JUPITER
Baseline Blood Levels (median, interquartile range)

Ridker et al NEJM 2008

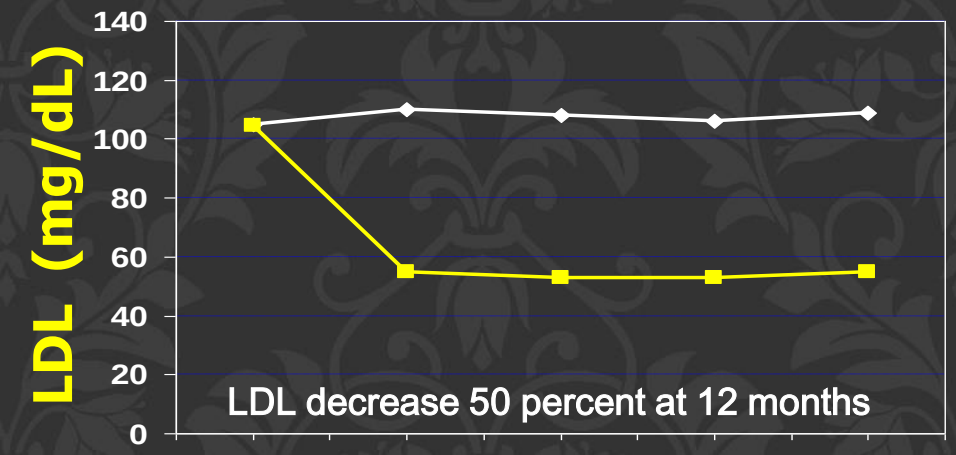
	Rosuvastatin (N = 8901)		Placebo (n = 8901)	
hsCRP, mg/L	4.2	(2.8 - 7.1)	4.3	(2.8 - 7.2)
LDL, mg/dL	108	(94 - 119)	108	(94 - 119)
HDL, mg/dL	49	(40 – 60)	49	(40 – 60)
Triglycerides, mg/L	118	(85 - 169)	118	(86 - 169)
Total Cholesterol, mg/dL	186	(168 - 200)	185	(169 - 199)
Glucose, mg/dL	94	(87 – 102)	94	(88 – 102)
HbA1c, %	5.7	(5.4 – 5.9)	5.7	(5.5 – 5.9)

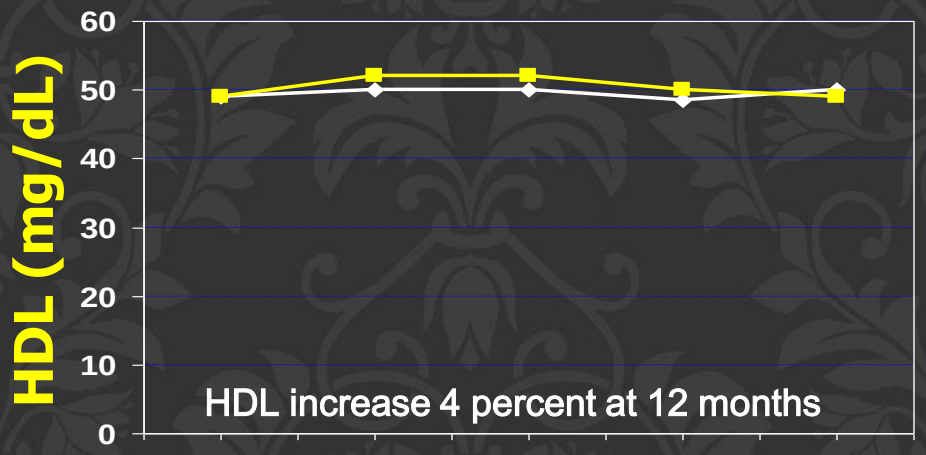
All values are median (interquartile range). [Mean LDL = 104 mg/dL]

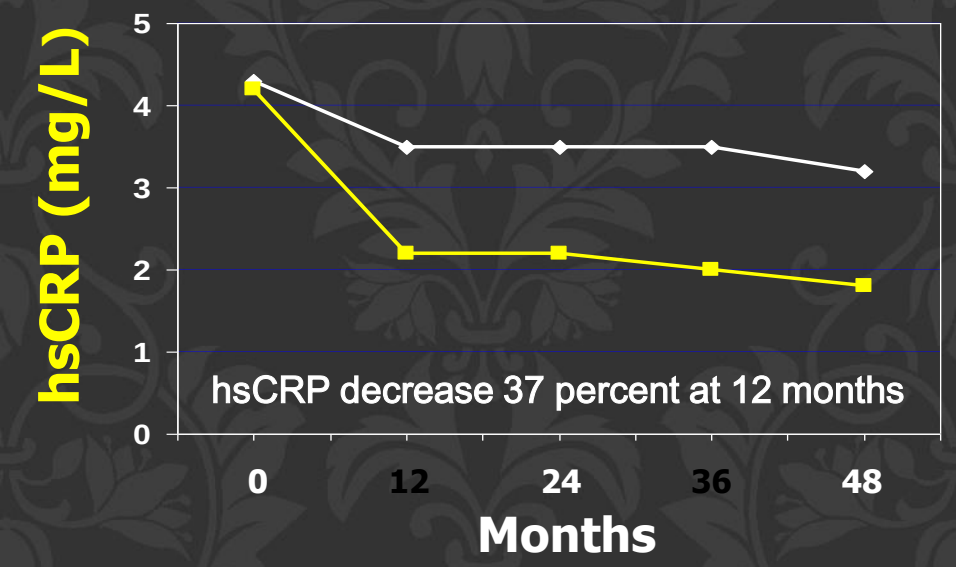
JUPITER

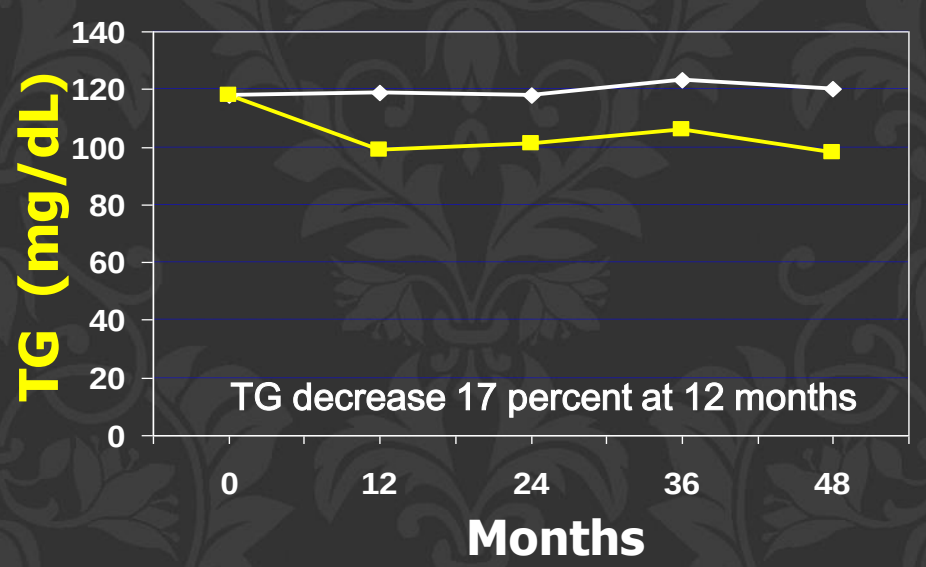
Effects of rosuvastatin 20 mg on LDL, HDL, TG, and hsCRP

Ridker et al NEJM 2008





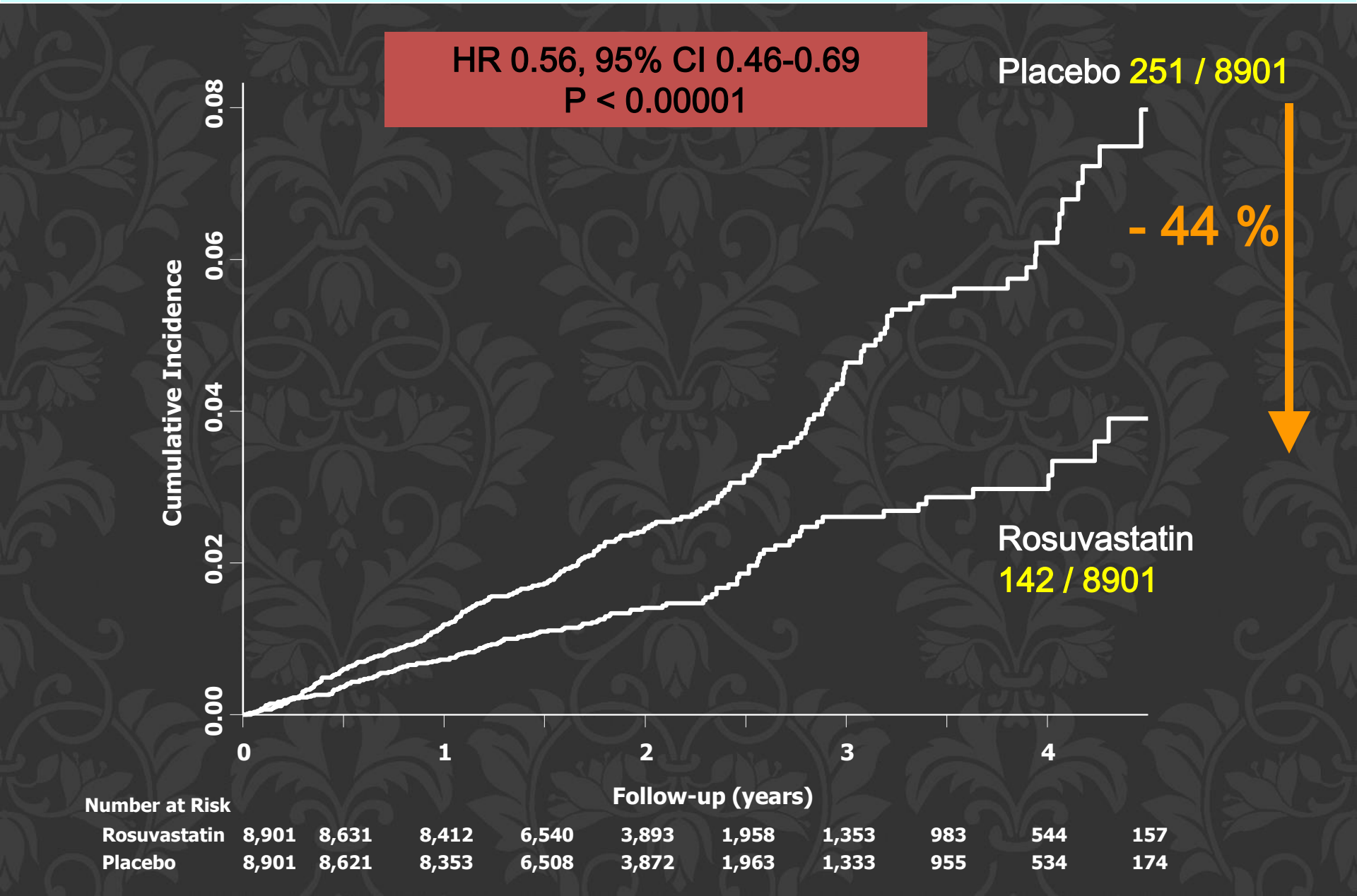




JUPITER

Ridker et al NEJM 2008

Primary Trial Endpoint：MI, Stroke, UA/Revascularization, CV Death



Cardiovascular Event Reduction and Adverse Events Among Subjects Attaining Low-Density Lipoprotein Cholesterol <50 mg/dl With Rosuvastatin: The JUPITER Trial

Judith Hsia, Ridker P et.al. Am Coll Cardiol, 2011; 57:1666-1675

In a post-hoc analysis, participants allocated to rosuvastatin were categorized as to whether or not they had a follow-up LDL-C level **<50 mg/dl**.

Results: During a median follow-up of 2 years (range up to 5 years), rates of the primary trial endpoint (MI, Stroke, UA/Revascularization, CV Death) were:

Placebo RRR +18%
LDL >50 mg/dL -14% (N=4,000)
LDL <50 mg/dL - 56% (N=4,154)

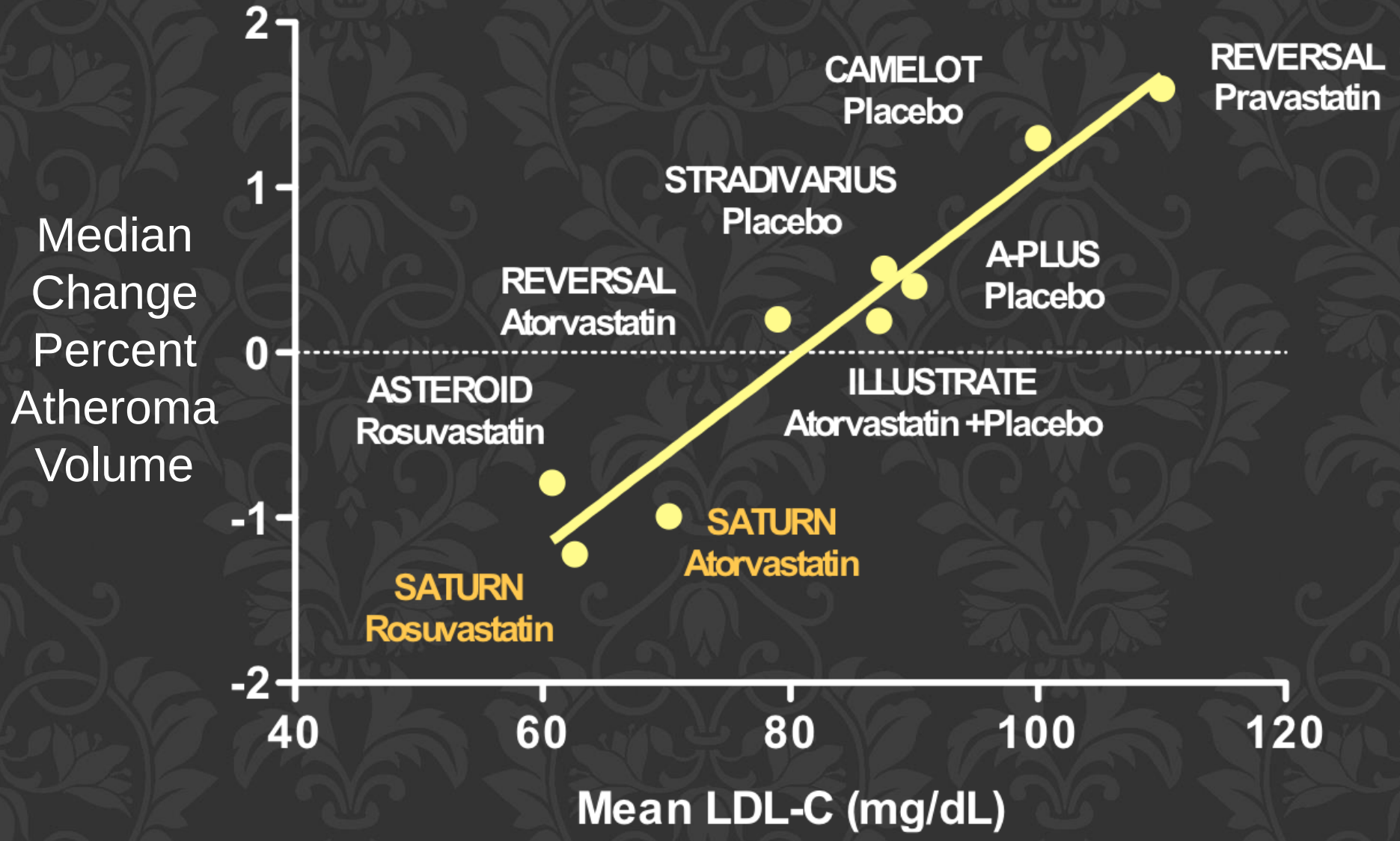
*1.18, 0.86, and 0.44 per 100 person-years

- Rates of myalgia, muscle weakness, neuropsychiatric conditions, cancer, and diabetes mellitus were not significantly different among rosuvastatin-allocated participants with and without LDL-C <50 mg/dl.

Conclusions: Among adults with LDL-C <130 mg/dl and high-sensitivity C-reactive protein 2 mg/l, rosuvastatin-allocated participants attaining LDL-C <50 mg/dl had a lower risk of cardiovascular events without a systematic increase in reported adverse events.

Hsia, Ridker 2011

LDL-C AND DISEASE PROGRESSION



LOOK AHEAD: STUDY DESIGN

Look Action for Health in Diabetes

N = 5145
45(55)-74 years with T2DM, BMI ≥25 kg/m² (≥27 kg/m² if taking insulin)

Usual medical care + diabetes support and education for 4 years	**Total follow-up 11.5 years**	**Usual medical care + lifestyle intervention* 4 years; maintenance counseling thereafter**

Primary endpoint: **CV death, nonfatal MI, nonfatal stroke**

***≥7% mean weight loss with hypocaloric diet ± pharmacologic therapy + ≥175 min/week moderate physical activity**

Diet = 1200-1500 kcal/day (<250 lbs) or 1500-1800 kcal/day (≥250 lbs)

Look AHEAD Research Group. *Control Clin Trials*. 2003;24:610-28; *Obesity*. 2006;14:737-52.

Look AHEAD *ExRx*

Physical activity goal: 175 minutes/wk of moderate intensity exercise

e.g., brisk walking and similar aerobic activity*

* ≥10 minutes duration

Plus, *Lifestyle Activity*

e.g., stairs, pedometer activity, etc.

Look AHEAD Research Group, OBESITY Vol. 14 No. 5 May 2006

LookAHEAD.halt12

The ILI group experienced significantly greater average improvements in all risk factors except LDL-C levels.

Weight loss: Year 1: 8.6% Year 11: 4.9%

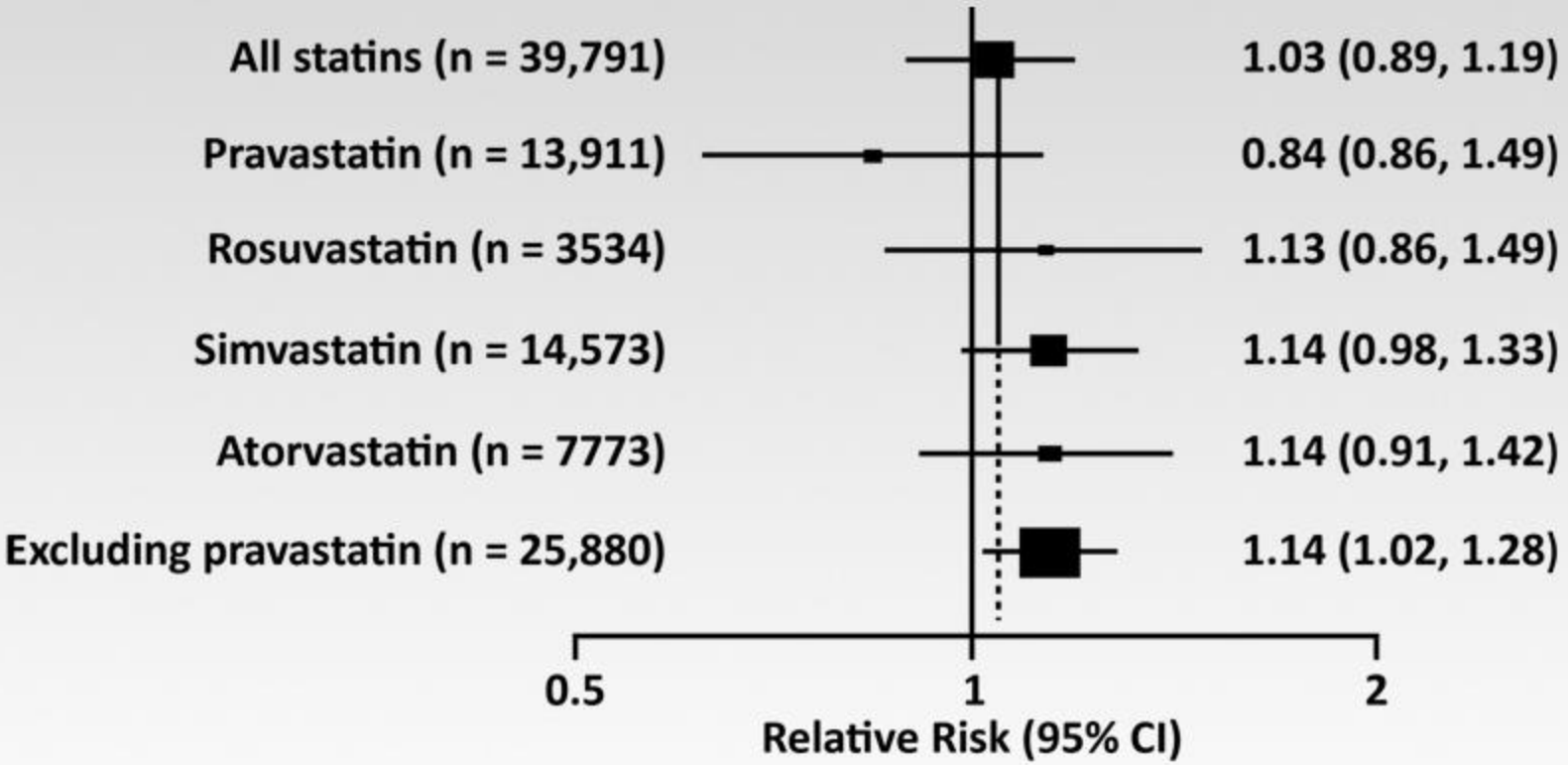
TG	**179**	**to**	**155 mg/dL**
HDL	**43**	**to**	**46 mg/dL**
LDL	**112**	**to**	**100 mg/dL**

Statistical significance criteria: Five thousand participants will provide a minimum of 80% power to detect an 18% relative decrease in the rate of the primary outcome in participants assigned to the Lifestyle Intervention.

✓ **PRIMARY OUTCOME**: ***rate of nonfat MI, nonfat stroke, death, or hosp. for angina***

Statins and Diabetes Risk

Meta-analysis of Statin Trials for New-Onset Type 2 Diabetes During Follow-up



Coleman CI, et al. *Curr Med Res Opin*. 2008;24:1359-1362.

Do Statins Alter Glucose/Insulin Metabolism?

Possible Mechanisms

- Improvement in pancreatic islet vasculature?
- Increase or decrease in insulin *secretion*?
- Decrease or increase in insulin *sensitivity*?
  - IRS-1/GLUT4 effects
  - Lipid-mediated effects
  - Adipokine effects
  - Anti-inflammatory effects
  - Other?
- Differential effects on diabetes vs pre-diabetes?

Class Effects vs Agent-Specific Effects

- Basic data mixed and very confusing
- Clinical trial data emerging

IRS-1 = insulin receptor substrate-1

Kostapanos MS, et al. *Curr Vasc Pharmacol.* 2010;8:612-631.

Niacin
(nicotinic acid)

&

HDL-C

Niacin raises HDL-C up to 30%

but also lowers LDL, LDL-P, and VLDL

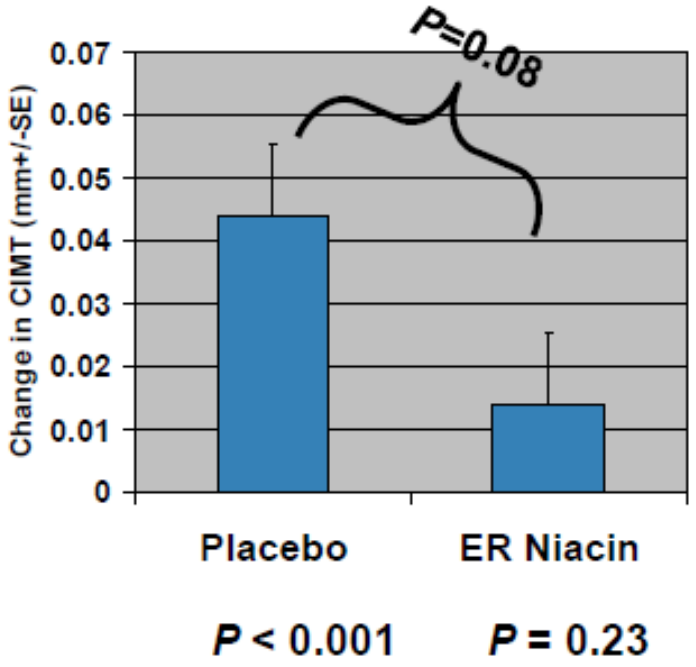
Fibrates raise HDL-C 5-20%

Statins raise HDL-C 3-15%

*CETP inhibitors (investigational) raise HDL-C 40-90%

ARBITER* 2: Effect of ER-Niacin 1000 mg hs Added to Statin on Carotid IMT in CAD Patients

- 167 patients with known CAD, mean age 67 yr
- Extended-release niacin 1000 mg hs (at bedtime) vs. placebo added to background statin Rx (all participants on statin at baseline, average duration 4.8 ± 4.3 y, most on simvastatin ≥20 mg)
- Primary endpoint: change in CIMT at 1 year
- HDL-C 40 mg/dL → 47 mg/dL
- Baseline CIMT: 0.868 mm (placebo), 0.893 mm (niacin)

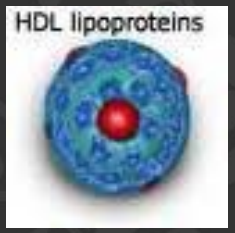


* Arterial Biology for Investigation of Treatment Effects of Reducing Cholesterol

Taylor AJ, et al. *Circulation*. 2004;110:3512-3517.

AIM-HIGH

Cholesterol Management Program



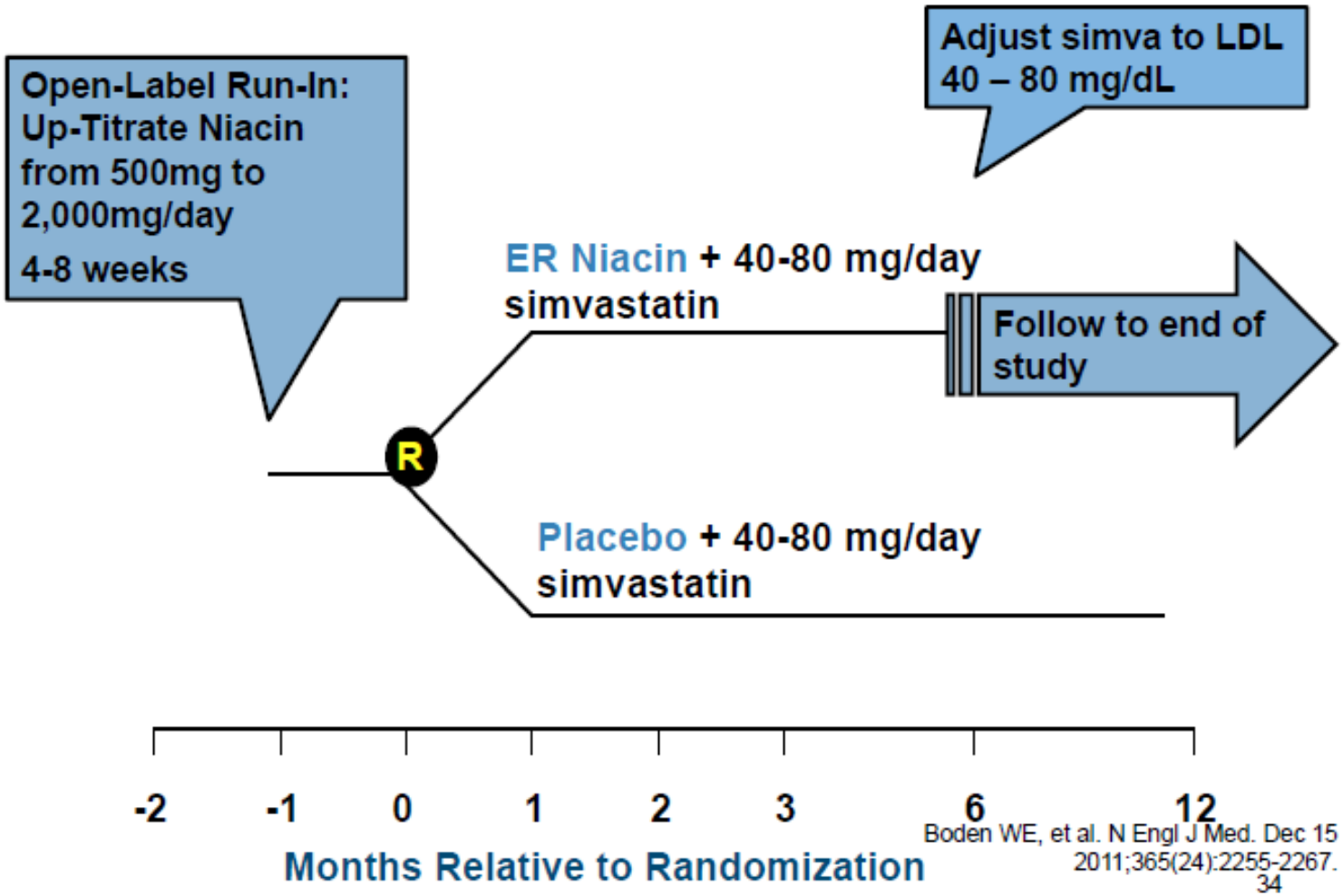
Statin
vs
Statin + Niasin

→

Coronary heart disease death, myocardial infarction, stroke, or high-risk acute coronary syndrome hospitalization

N=3400, Metsyn

Study Design



Boden WE, et al. N Engl J Med. Dec 15 2011;365(24):2255-2267.

AIM-HIGH: Results

	Baseline	At Year 3	
		Niacin	Placebo
LDL-C (mg/dL)	75.8	65.2	68.3
HDL-C (mg/dL)	35.3	44.1	39.1
Triglycerides (mg/dL)	162	120	152

- Incidence of Primary Endpoint
  - –Statin plus placebo: 16.2%
  - –Statin plus niacin: 16.4% p=0.80

N Engl J Med. 2011;365:2255-67.

New Study Looks at Niacin and Statin Combination Therapy for Atherosclerosis Regression, CVD Prevention: AIM-HIGH

Michos ED *Am Coll Cardiol* 2012; DOI:10.1016/j.jacc.2012 (April)

The reasons for the increase in HDL cholesterol in the placebo arm are unclear, but:

- **more patients in the placebo arm were taking higher doses of statins**, and this might have contributed to the increase.

- In addition, **to ensure blinding, placebo patients received a very low dose of niacin** to induce flushing, and even though the 200-mg extended-release niacin dose was well below the therapeutic dose of 1500 mg/day, it is impossible to know whether this was responsible for the increase in HDL cholesterol in the placebo arm.

- The vast majority of patients were treated with **simvastatin** in order to reduce LDL-cholesterol levels to less than 80 mg/dL, and these low LDL-cholesterol levels might have altered the composition of the atherosclerotic plaque.

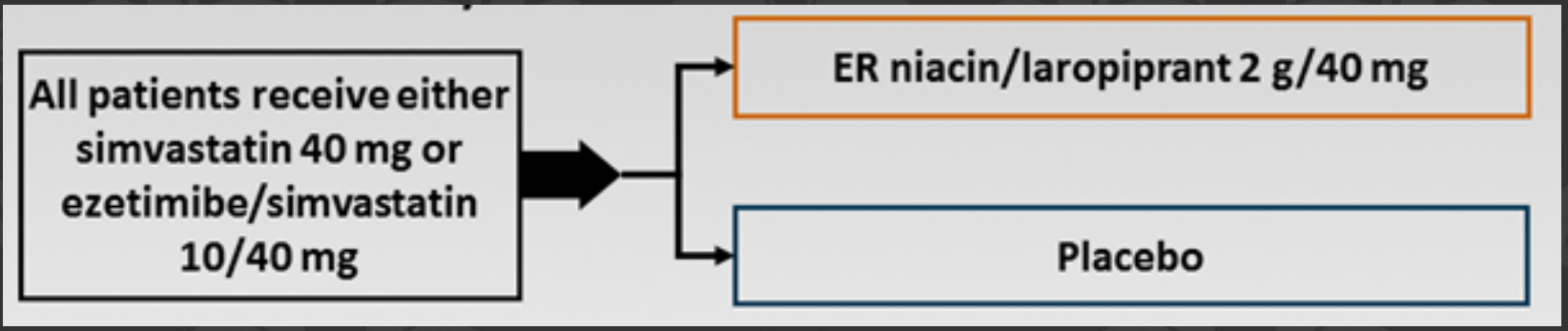
One argument why niacin did not significantly impact primary outcome of AIM HIGH:

- Niacin alters the composition of HDL not the total number of HDL-P (NMR).
- Niacin reduces the numbers of small HDL particles and increases the number of large HDL particles thus no net effect on HDL-P

Otvos J, JCL 2011

Statin or Statin + Niacin/Lrp

HPS2-THRIVE involved over 25,000 volunteers aged between 50 and 80 with a history of heart disease, stroke or other circulatory disease recruited from almost 250 hospitals in 6 countries (China, Denmark, Finland, Norway, Sweden and the United Kingdom).



Armitage J, et al ACC Mtg 2013

HPS-2 THRIVE Misses Primary End Point: No Benefit of Niacin/Laropiprant

12/20/12

✓ After nearly four years of follow-up, the combination of niacin with the antiflushing agent laropiprant **did not** significantly reduce the risk of the combination of *coronary deaths, nonfatal MI, strokes, or coronary revascularizations* compared with statin therapy.

✓ On average, baseline LDL-C was 63 mg/dL and non-HDL-C about 84 mg/dL, such that subjects were not in need of niacin for lowering these levels

✓ Among the subjects from Europe there was a clinically significant ~10% decrease in vascular events with ERNL, while among the 43% of subjects from China, there was a towards a ~3% increase in MVE (heterogeneity p=06). Thus, ERNL has a net harm in Chinese patients when added to simvastatin

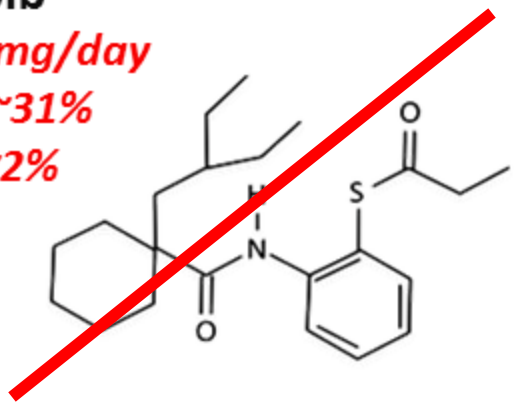
Comparison of CETP Inhibitors to raise HDL-C

Dalcetrapib

Dose: 600 mg/day

HDL-C: ↑ ~31%

LDL-C: ↓ ~2%

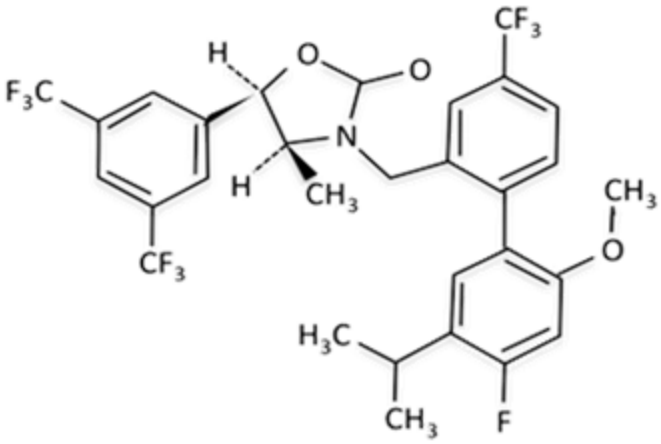


Anacetrapib

Dose: 100 mg/day

HDL-C: ↑ ~138%

LDL-C: ↓ ~40%

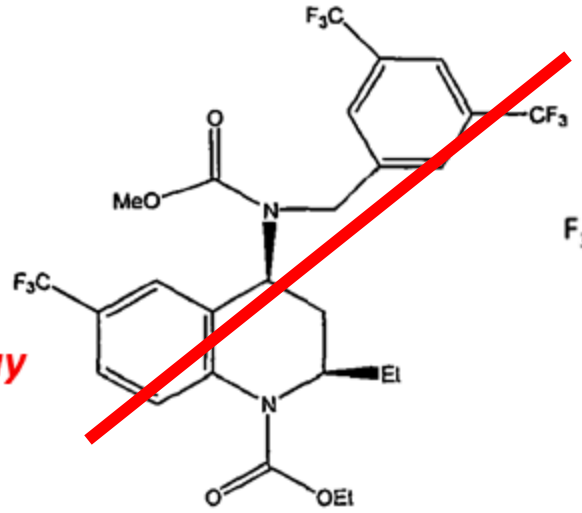


Torcetrapib

Dose: 60 mg/day

HDL-C: ↑ ~61%

LDL-C: ↓ ~24%

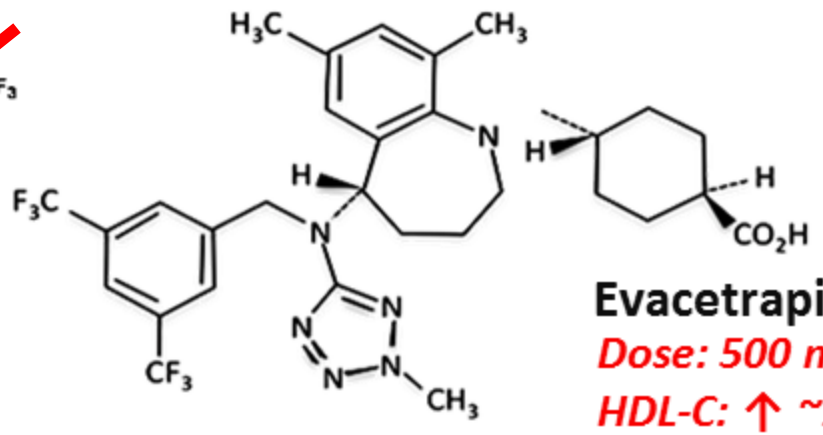


Evacetrapib

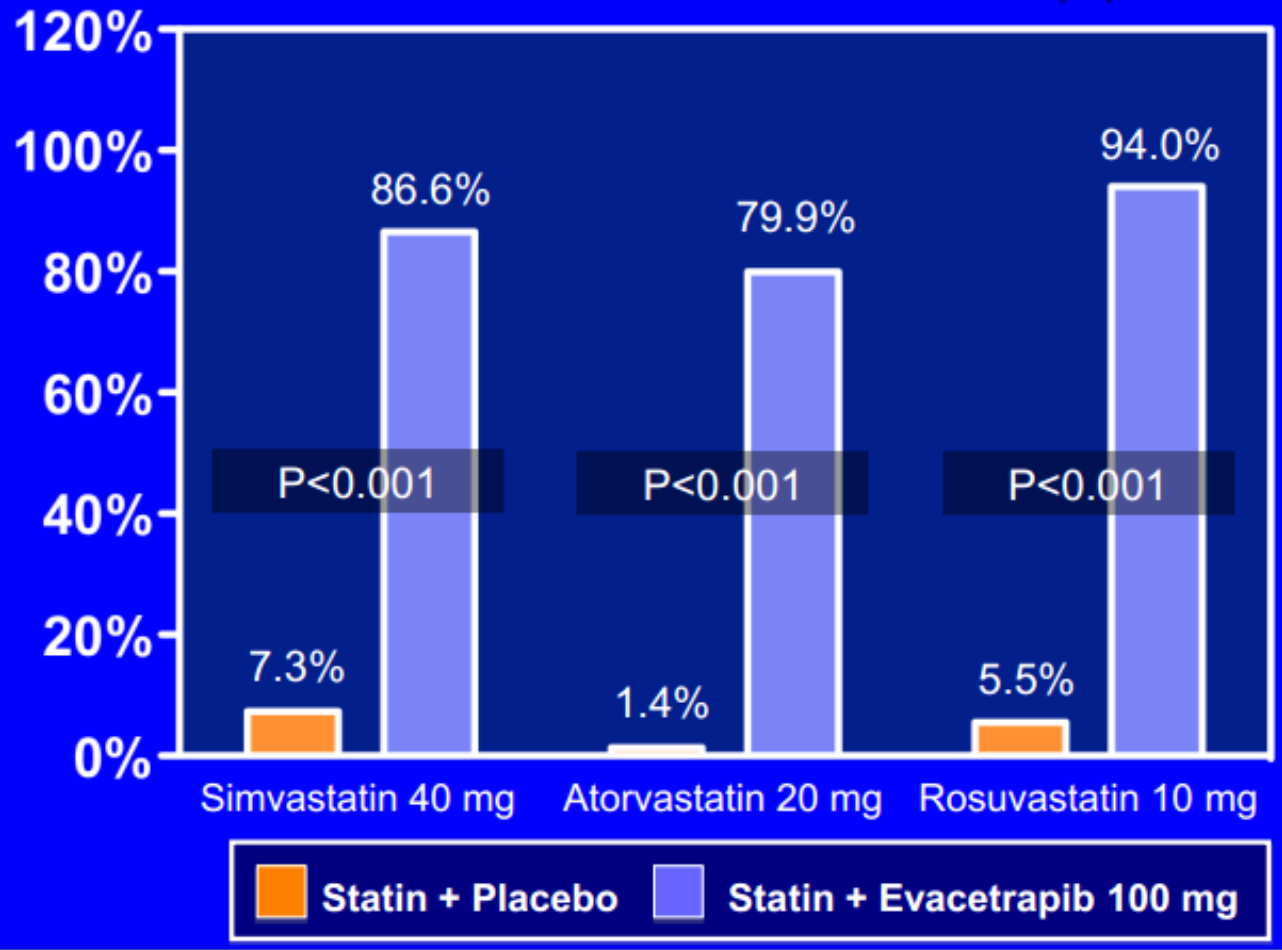
Dose: 500 mg/day

HDL-C: ↑ ~129%

LDL-C: ↓ ~36%



Percent Change HDL-C: Evacetrapib 100 mg Combined with Statin Therapy



12 weeks, N=393

Nicholls S, Nissen S, et.al. 2011

Cholesterol Transport Inhibitor

Ezetimibe
(Zetia)

Slows intestinal absorption of cholesterol

15-18% dec. in LDL-C
Rx: add to statin

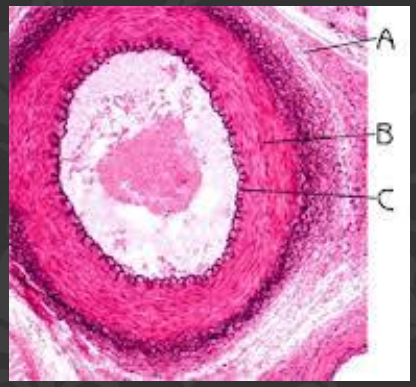
Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression (ENHANCE)

- 720 patients with familial hypercholesterolemia – most (81%) previously treated with statins randomly assigned to simvastatin 80 mg vs. simvastatin 80 mg + ezetimibe 10 mg for 2 years
- No difference in mean cIMT at the end of 2 years ($P = 0.64$)

Kastelein JP, et al. *N Engl J Med*. 2008;358:1431-1443

ENHANCE

Carotid Intimal Media Thickness



Primary endpoint

End point	Ezetimibe plus simvastatin	Simvastatin alone	p
Change in mean carotid IMT after 2-y treatment (mm)	0.0111	0.0058	0.29

Lipids

	Ezetimibe plus simvastatin	Simvastatin alone	p
Baseline LDL (mg/dL)	319	318	NS
Reduction after 2-y treatment (%)	58	41	<0.01

IMPROVE IT

IMProved Reduction of Outcomes: Vytorin (Simva+Ez) Efficacy International Trial

Patients stabilized post Acute Coronary Syndrome < 10 days
LDL ≤ 125 mg/dL (or ≤ 100 mg/dL if prior statin)

Double-blind

ASA + Standard Medical Therapy

n~18,000

Simvastatin 40 mg

Eze / Simva 10/40 mg

Follow-Up Visit Day 30, Every 4 Months

Duration: Minimum 2 1/2 year follow-up (>2955 events)

Primary Endpoint: CV Death, MI, Hospital Admission for UA, revascularization (> 30 days after randomization), or Stroke

Is LDL-C Passed Its Prime? The Emerging Role of Non-HDL, LDL-P, and ApoB in CHD Risk Assessment

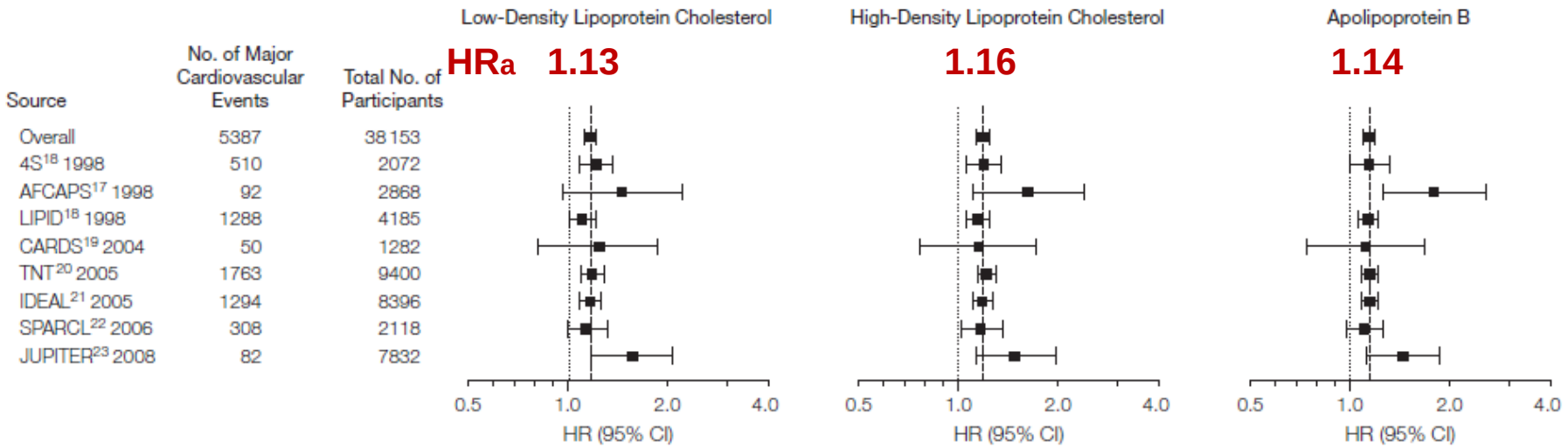
Michael H. Davidson

✓ An LDL-C focus has worked well in the past, but to address residual CV risk on statin therapy, the recent trials support a more significant role for non-HDL, apoB, and LDL-P

Arterioscler Thromb Vasc Biol. 2008;28:1582-1583

Association of LDL Cholesterol, Non–HDL Cholesterol, and Apolipoprotein B Levels With Risk of Cardiovascular Events Among Patients Treated With Statins: A Meta-analysis

Figure 2. Association Between on-Statin Lipid or Apolipoprotein Levels and Risk of Major Cardiovascular Events Stratified by Study



N=38,153

✓ Among statin-treated patients, levels of LDL-C, non– HDL-C, and apoB were each strongly associated with the risk of major cardiovascular events, but non-HDL-C was more strongly associated than LDL-C and apoB.

Boekholdt SM et.al. JAMA. 2012;307(12):1302-1309

Key Take-Away Messages: Clinical Trials

- CV event reduction (e.g., MI, stroke) is bottom line with LDL-C therapy with or without plaque regression
- Over time, lowering LDL-C reaps great benefits in terms of reduction of cardiovascular events.
- When LDL-C is lowered to optimal levels raising HDL-C probably does not matter in terms of further risk reduction
- Non-HDL-C is looming to be a slightly better CV risk predictor than LDL-C
- Clinical trials provide hope that novel therapies may provide additional benefits beyond LDL-C lowering.