ΙΑΤΡΙΚΗ ΧΗΜΕΙΑ

ΠΑΝΕΠΙΣΤΗΜΙΟ ΙΩΑΝΝΙΝΩΝ
ΣΧΟΛΕΣ ΘΕΤΙΚΩΝ ΕΠΙΣΤΗΜΩΝ – ΕΠΙΣΤΗΜΩΝ ΥΓΕΙΑΣ
ΤΜΗΜΑΤΑ ΧΗΜΕΙΑΣ– ΙΑΤΡΙΚΗΣ-ΒΙΟΛΟΓΙΚΩΝ ΕΦΑΡΜΟΓΩΝ ΚΑΙ ΤΕΧΝΟΛΟΓΙΩΝ
ΔΠΜΣ«ΙΑΤΡΙΚΗ ΧΗΜΕΙΑ»
Τηλ.: 26510-07194, 26510-07225, 26510-08365, Fax: 26510-07006, E-mail: gramchem@cc.uoi.gr

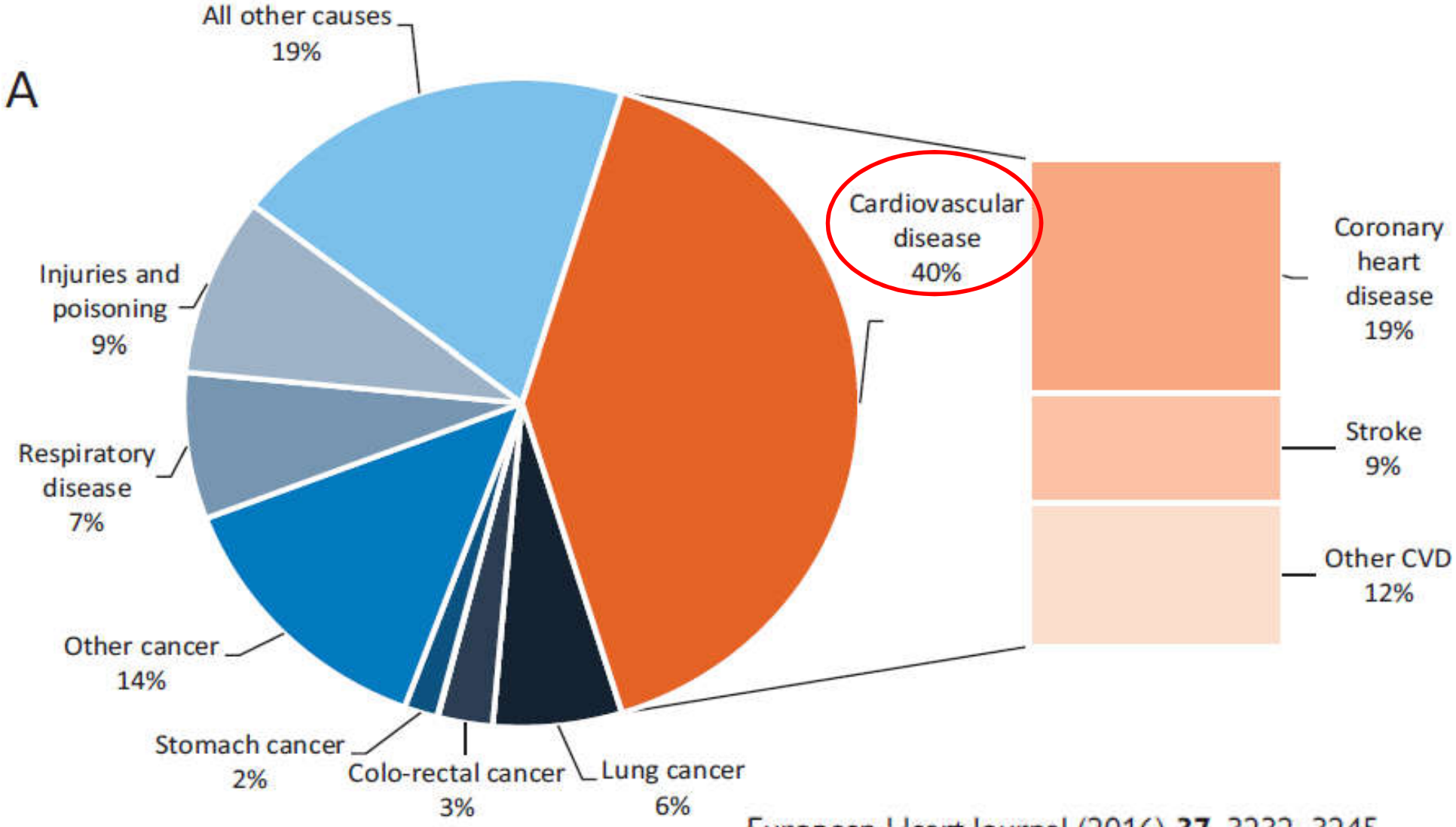
ΠΟΣΟΤΙΚΕΣ ΚΑΙ ΠΟΙΟΤΙΚΕΣ ΔΙΑΤΑΡΑΧΕΣ ΤΩΝ ΛΙΠΟΠΡΩΤΕΪΝΩΝ ΚΑΙ ΑΘΗΡΩΜΑΤΙΚΗ ΝΟΣΟΣ

Ευάγγελος Λυμπερόπουλος

Επίκουρος Καθηγητής Παθολογίας Ιατρικής Σχολής Παν/μίου Ιωαννίνων
www.bpath.gr & www.atherosclerosis.gr

ΕΙΣΑΓΩΓΗ

Cardiovascular disease in Europe: epidemiological update 2016

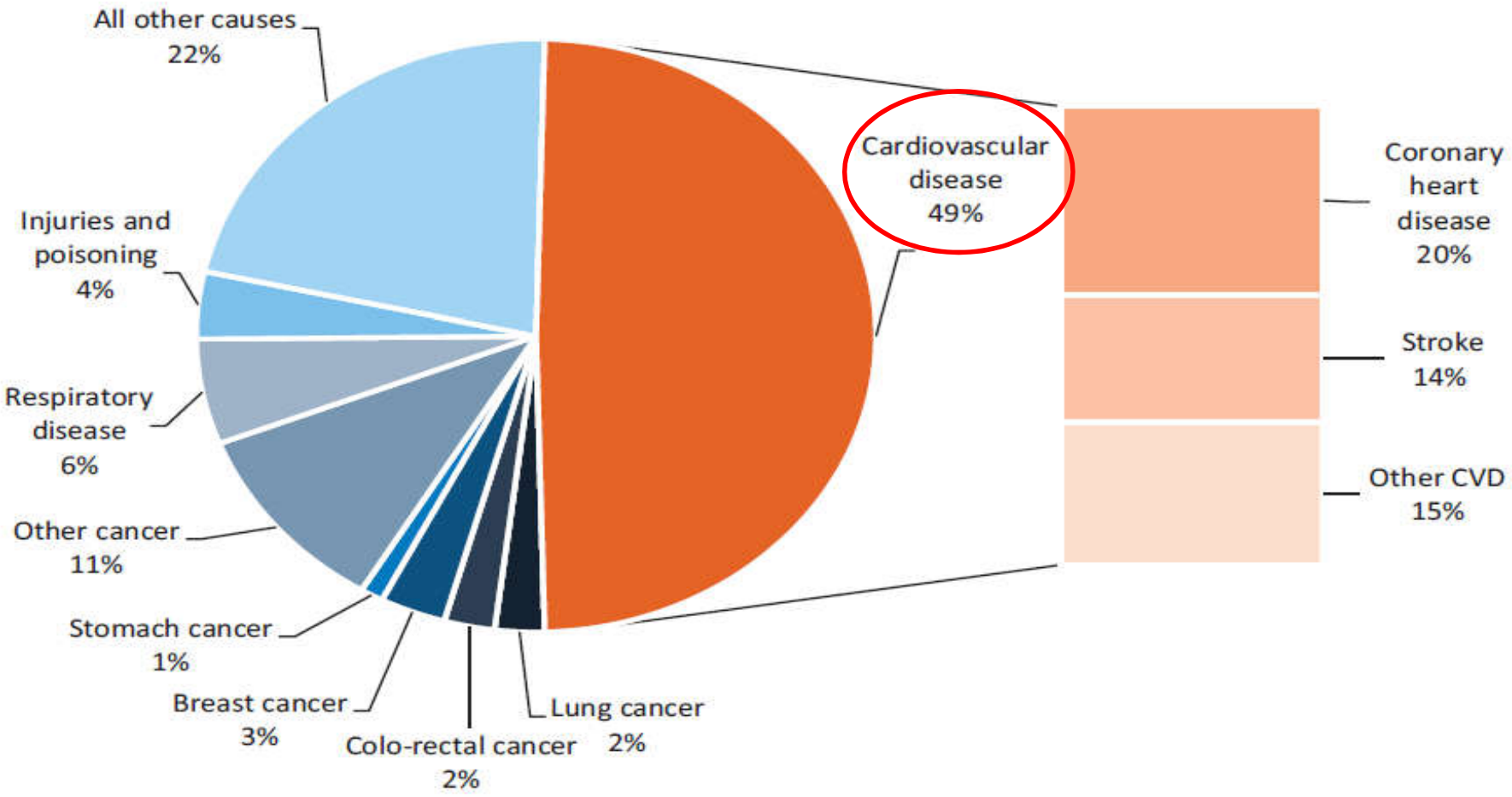


European Heart Journal (2016) **37**, 3232–3245

Figure 1 Proportion of all deaths due to major causes in Europe, latest available year, among men (A)

Cardiovascular disease in Europe: epidemiological update 2016

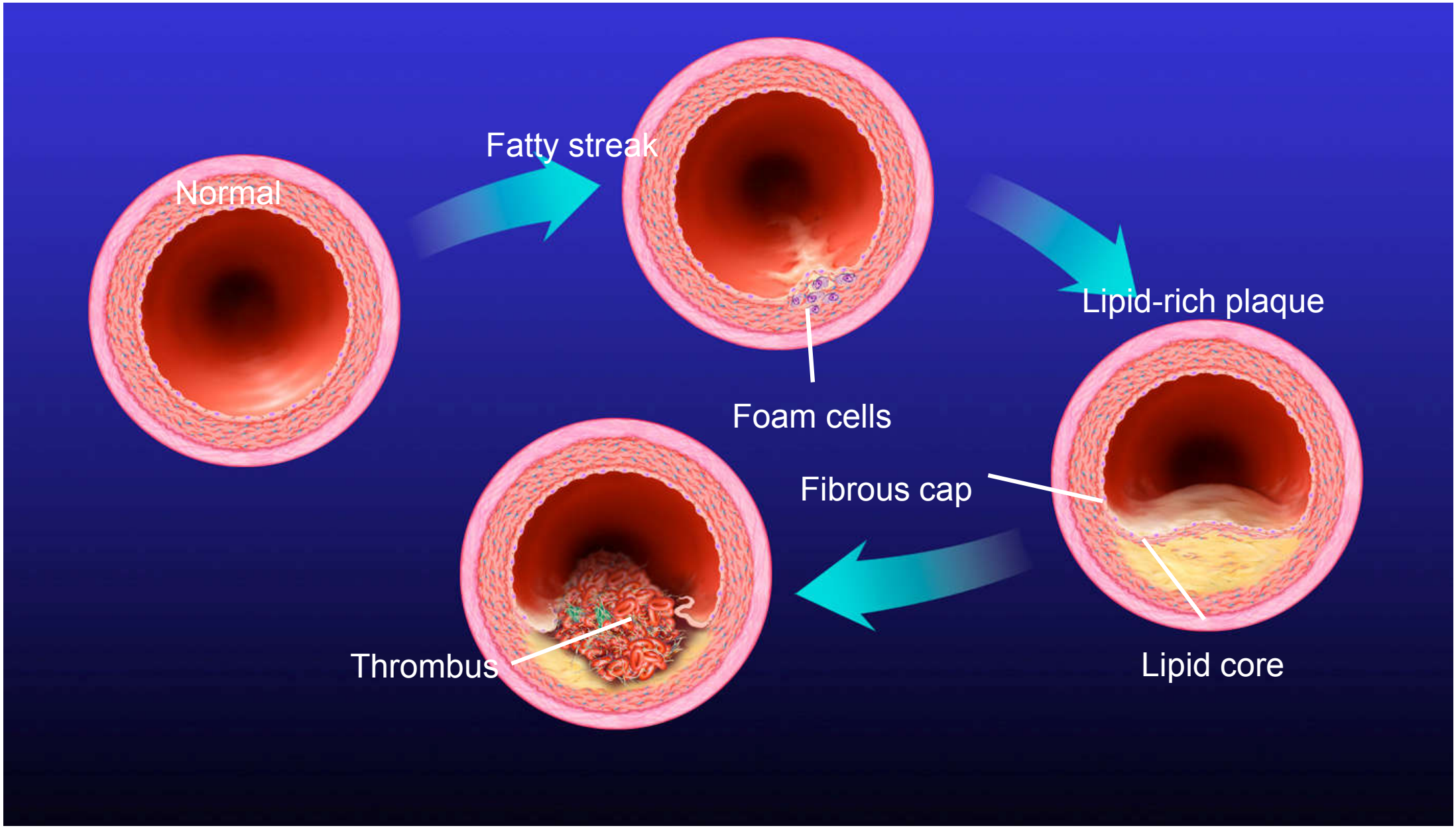
B



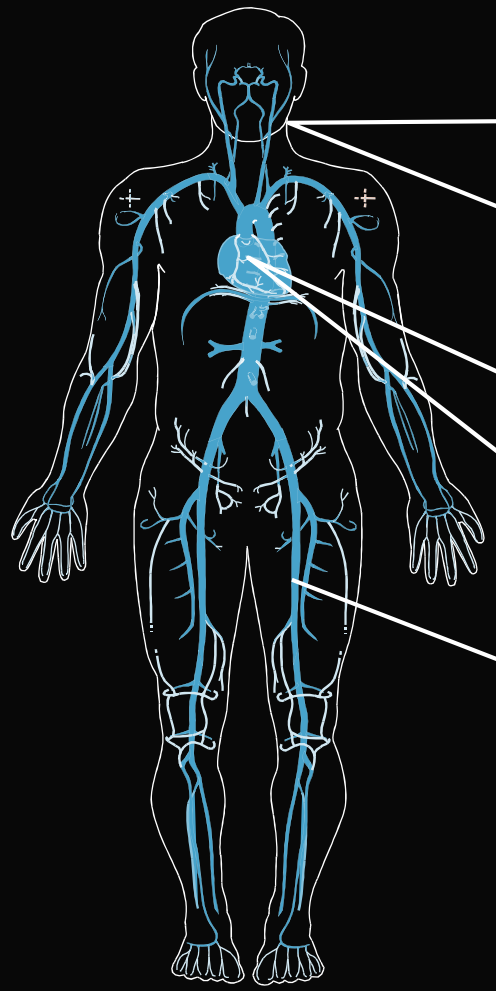
European Heart Journal (2016) **37**, 3232–3245

Figure 1 Proportion of all deaths due to major causes in Europe, latest available year, among women (*B*)

Development of Atherosclerotic Plaques



Clinical Manifestations of Atherothrombosis



Cerebral

Ischemic stroke

Transient ischemic attack

Cardiac

Myocardial infarction

Angina pectoris (stable, unstable)

Peripheral Arterial Disease

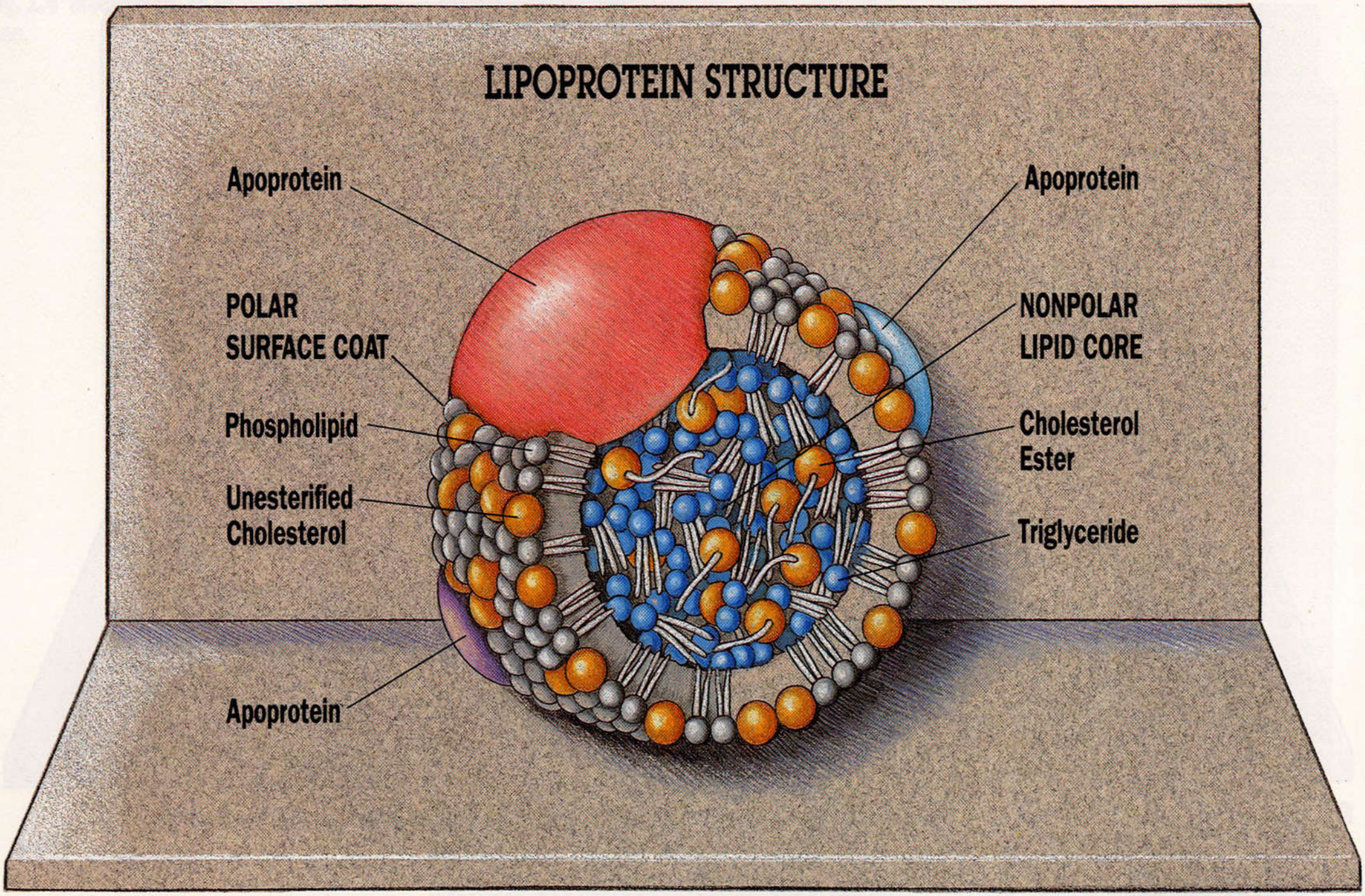
Critical limb ischemia, claudication

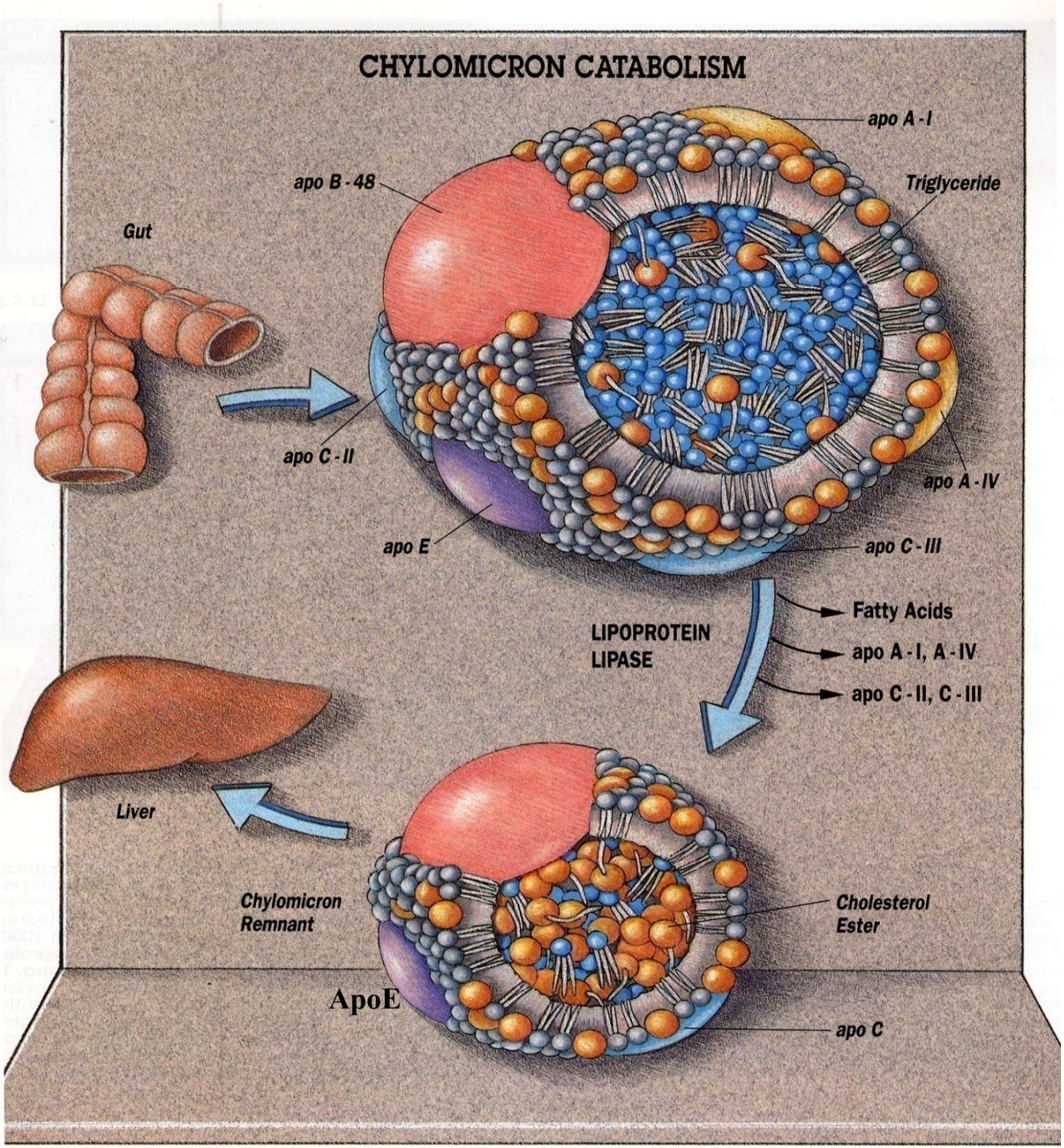
Risk Factors for CHD

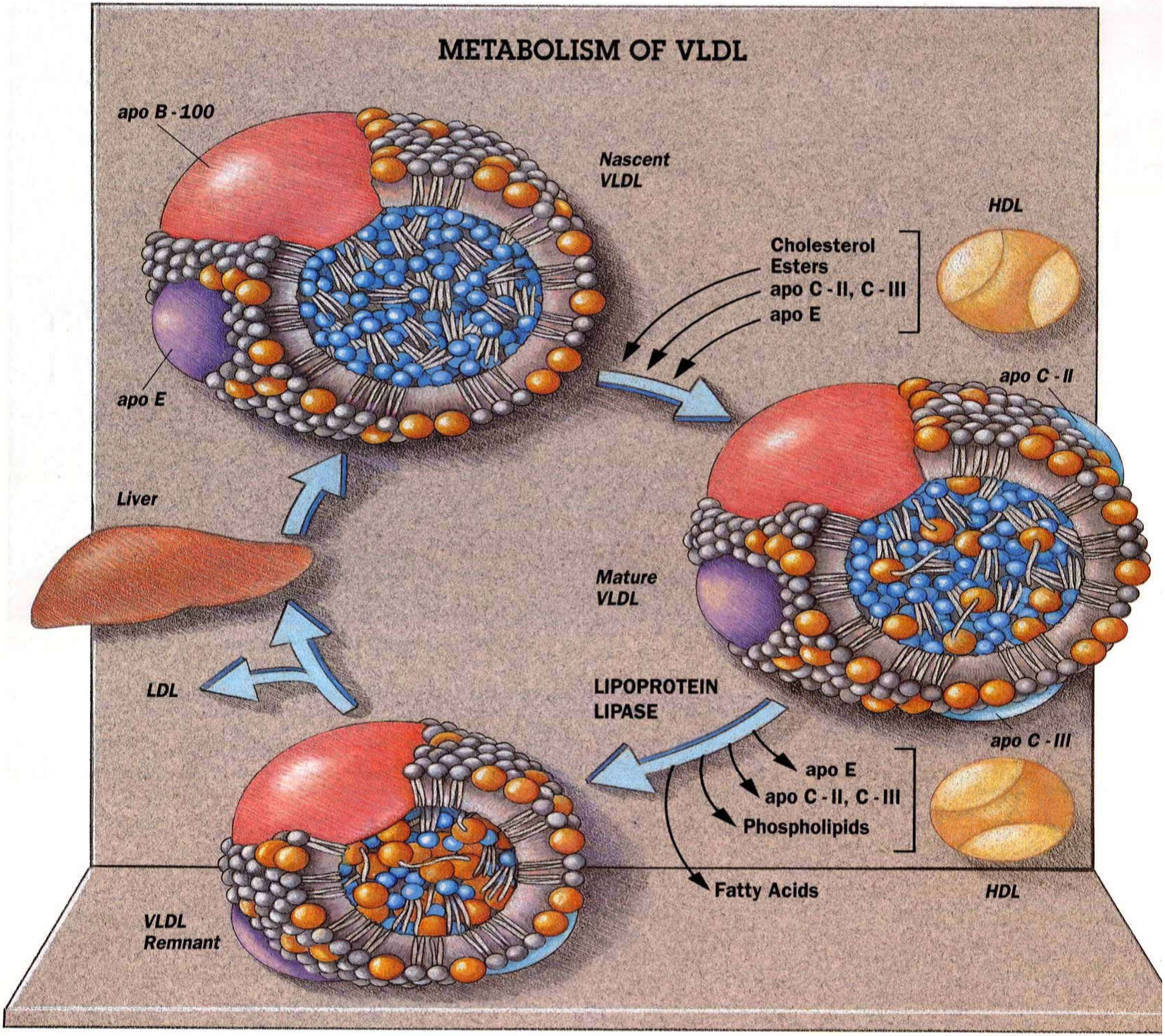
- **Modifiable**
  - Dyslipidemia
    - Raised LDL
    - Low HDL
    - Raised TGs
  - Smoking
  - Hypertension
  - Diabetes mellitus and IGT-MetSyn
  - Obesity
  - Dietary factors
  - Thrombogenic factors
  - Sedentary lifestyle
  - Psychosocial factors
- **Nonmodifiable**
  - Age
  - Sex
  - Family history of premature CHD
  - Personal history of atherosclerosis
  - Ethnic origin

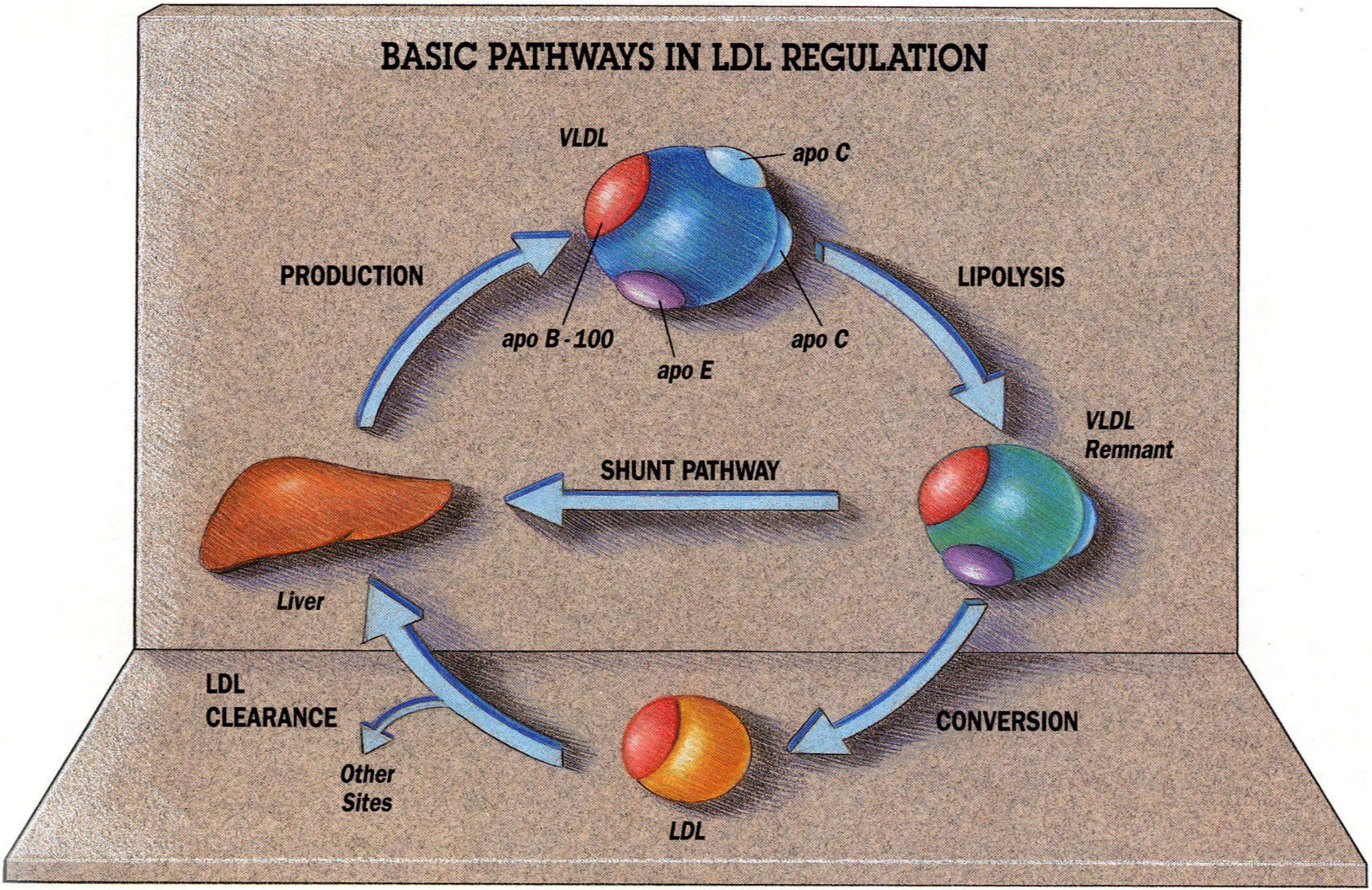
Wood D, et al. *Atherosclerosis*. 1998;140:199-270.

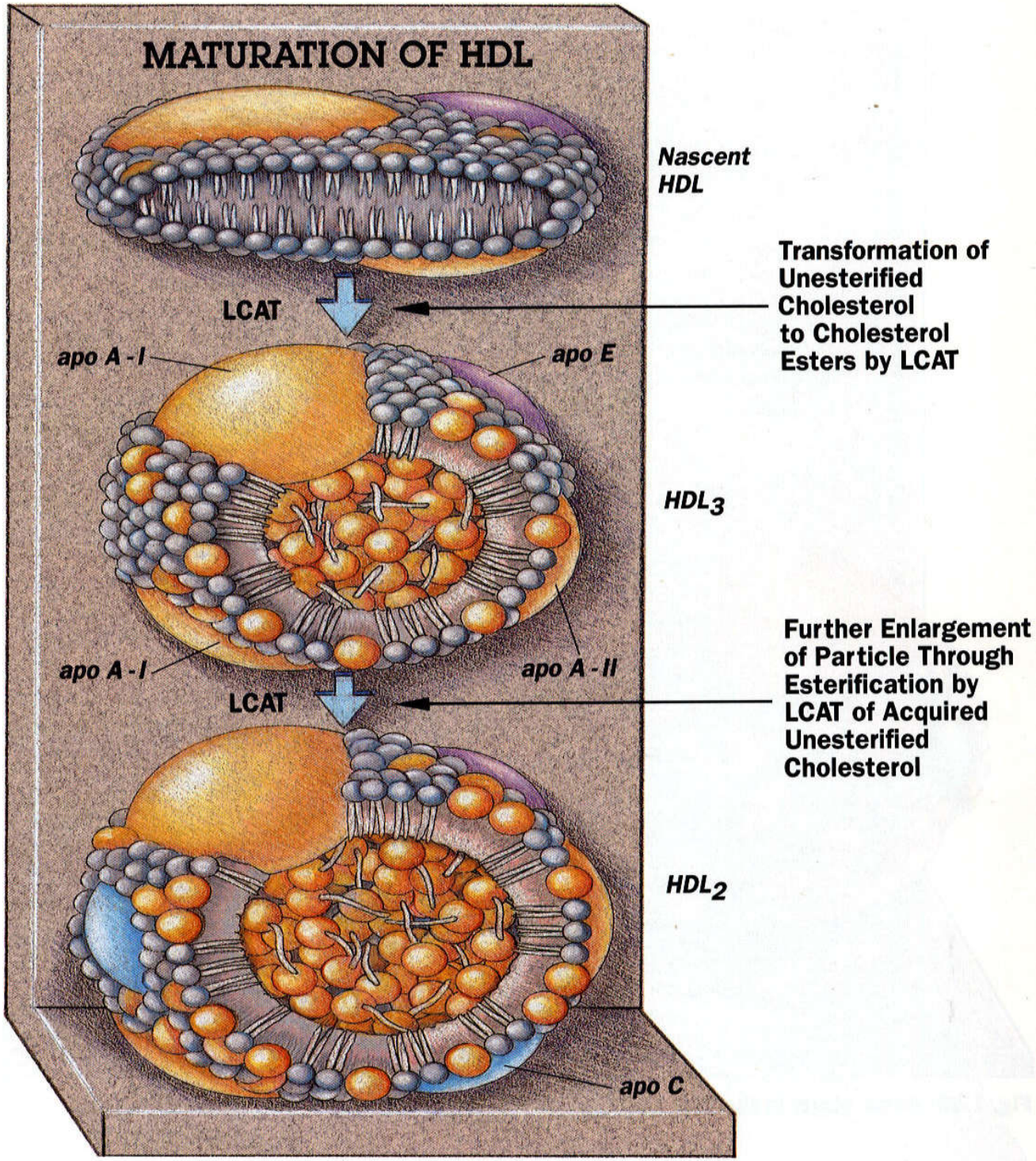
ΜΕΤΑΒΟΛΙΣΜΟΣ ΤΩΝ ΛΙΠΟΠΡΩΤΕΪΝΩΝ

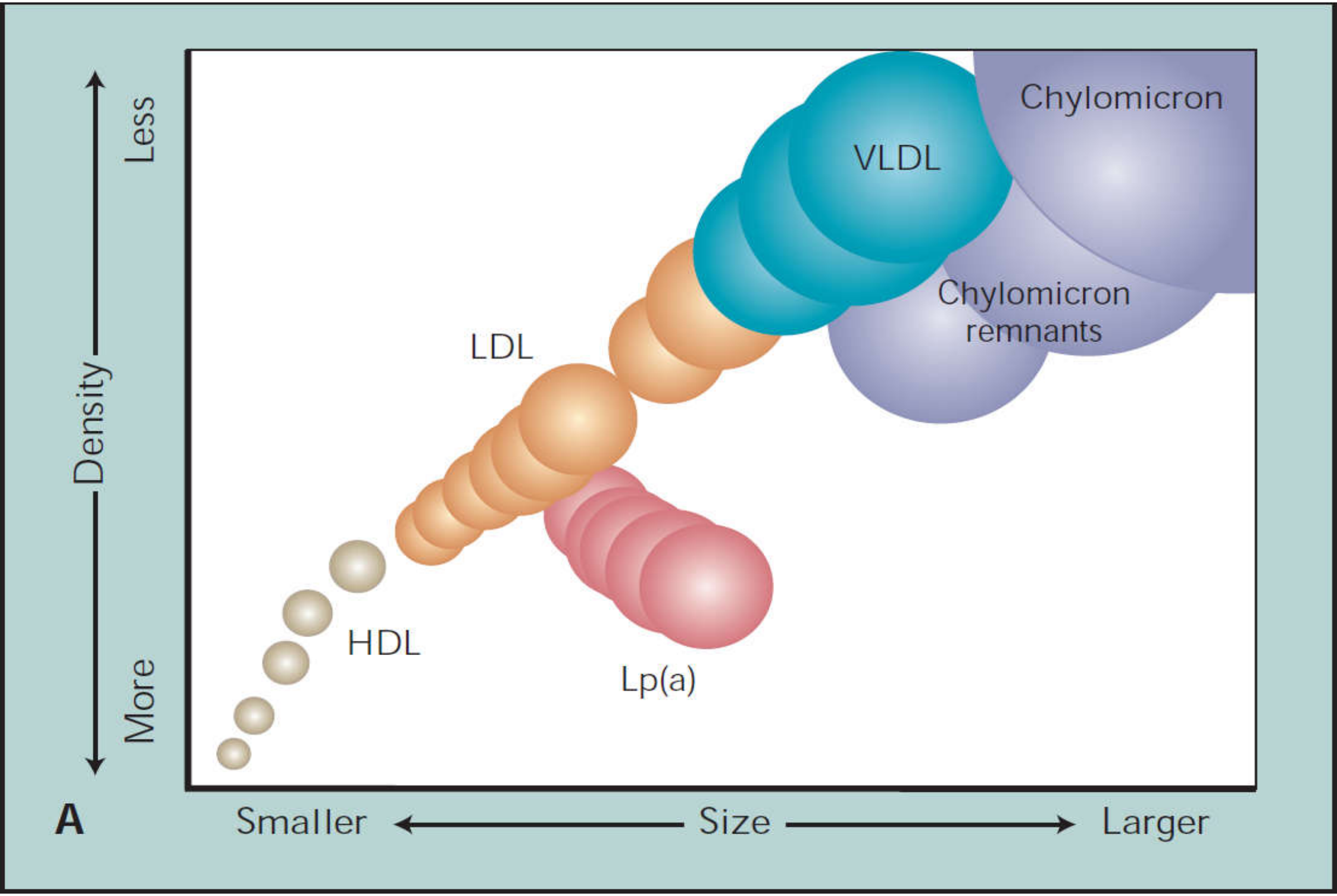

LIPOPROTEIN STRUCTURE
Apoprotein
POLAR
SURFACE COAT
Phospholipid
Unesterified
Cholesterol
Apoprotein
Apoprotein
NONPOLAR
LIPID CORE
Cholesterol
Ester
Triglyceride


CHYLOMICRON CATABOLISM
apo A-I
apo B-48
Triglyceride
Gut
apo C-II
apo A-IV
apo E
apo C-III
LIPOPROTEIN LIPASE
Fatty Acids
apo A-I, A-IV
apo C-II, C-III
Liver
Chylomicron Remnant
Cholesterol Ester
ApoE
apo C


METABOLISM OF VLDL
apo B - 100
Nascent VLDL
HDL
Cholesterol Esters
apo C - II, C - III
apo E
apo E
apo C - II
Liver
Mature VLDL
LDL
LIPOPROTEIN LIPASE
apo C - III
apo E
apo C - II, C - III
Phospholipids
Fatty Acids
HDL
VLDL Remnant


BASIC PATHWAYS IN LDL REGULATION
VLDL
apo C
PRODUCTION
LIPOLYSIS
apo B-100
apo E
apo C
VLDL
Remnant
SHUNT PATHWAY
Liver
LDL
CLEARANCE
CONVERSION
Other
Sites
LDL


MATURATION OF HDL
Nascent HDL
LCAT
Transformation of Unesterified Cholesterol to Cholesterol Esters by LCAT
apo A - I
apo E
HDL3
apo A - I
apo A - II
LCAT
Further Enlargement of Particle Through Esterification by LCAT of Acquired Unesterified Cholesterol
HDL2
apo C


Less
Density
More
Chylomicron
VLDL
Chylomicron
remnants
LDL
HDL
Lp(a)
A
Smaller
Size
Larger

ΠΡΟΣΔΙΟΡΙΣΜΟΣ ΛΙΠΙΔΑΙΜΙΚΩΝ ΠΑΡΑΜΕΤΡΩΝ

✓T CHOL, HDL CHOL, TRG μετά νηστεία 12-14h

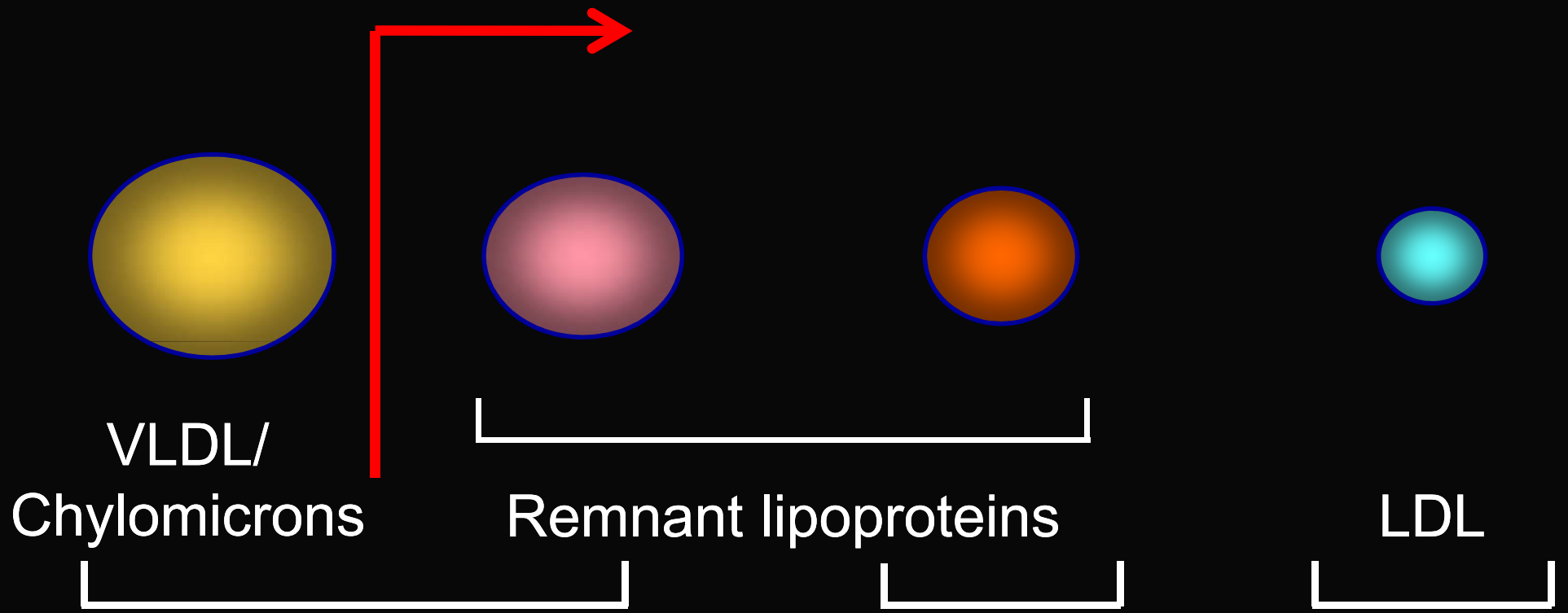
T CHOL = LDL CHOL + HDL CHOL + VLDL CHOL

VLDL CHOL = TRG/5

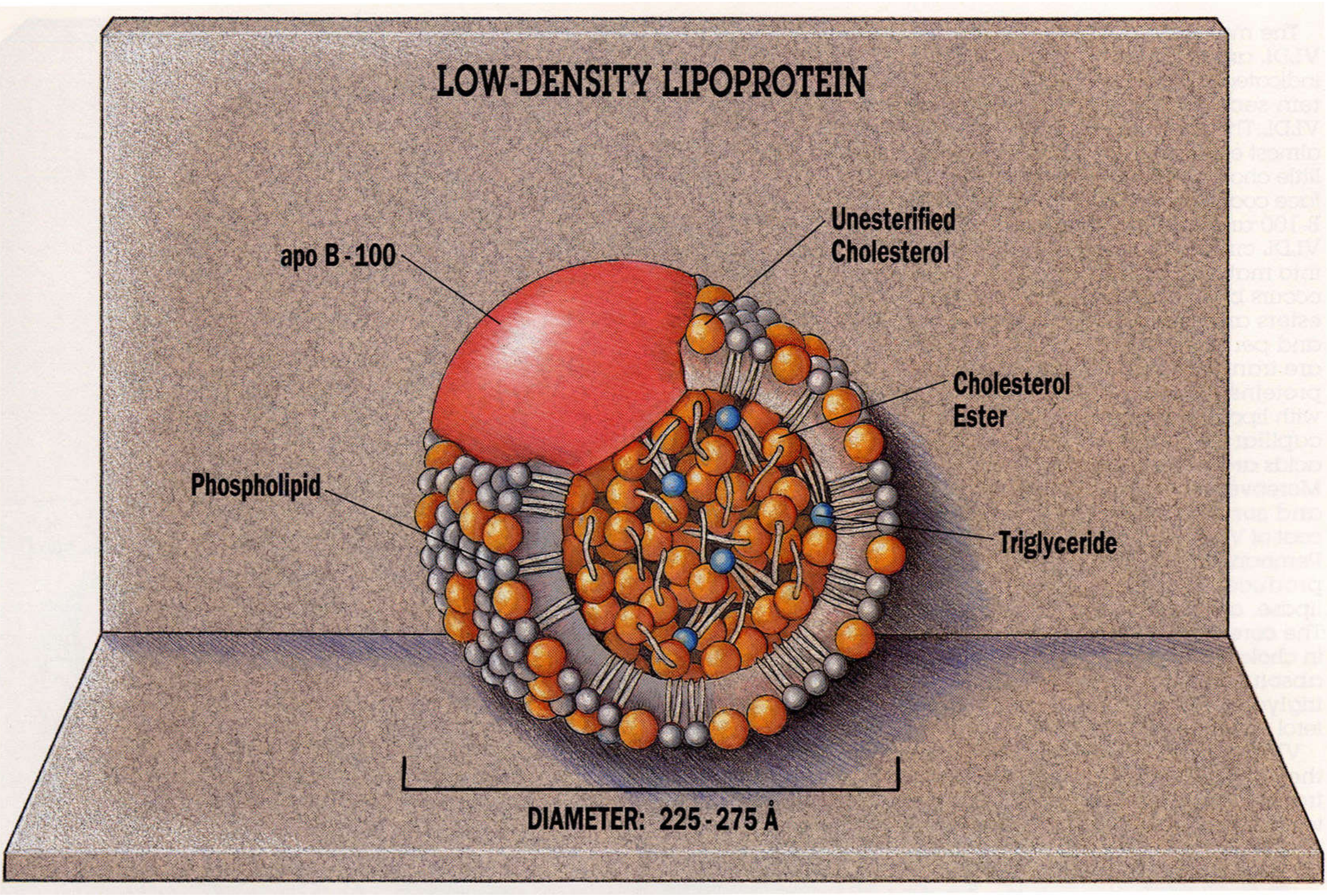
LDL CHOL = T CHOL - HDL CHOL - TRG/5

όταν TRG <400 mg/dL

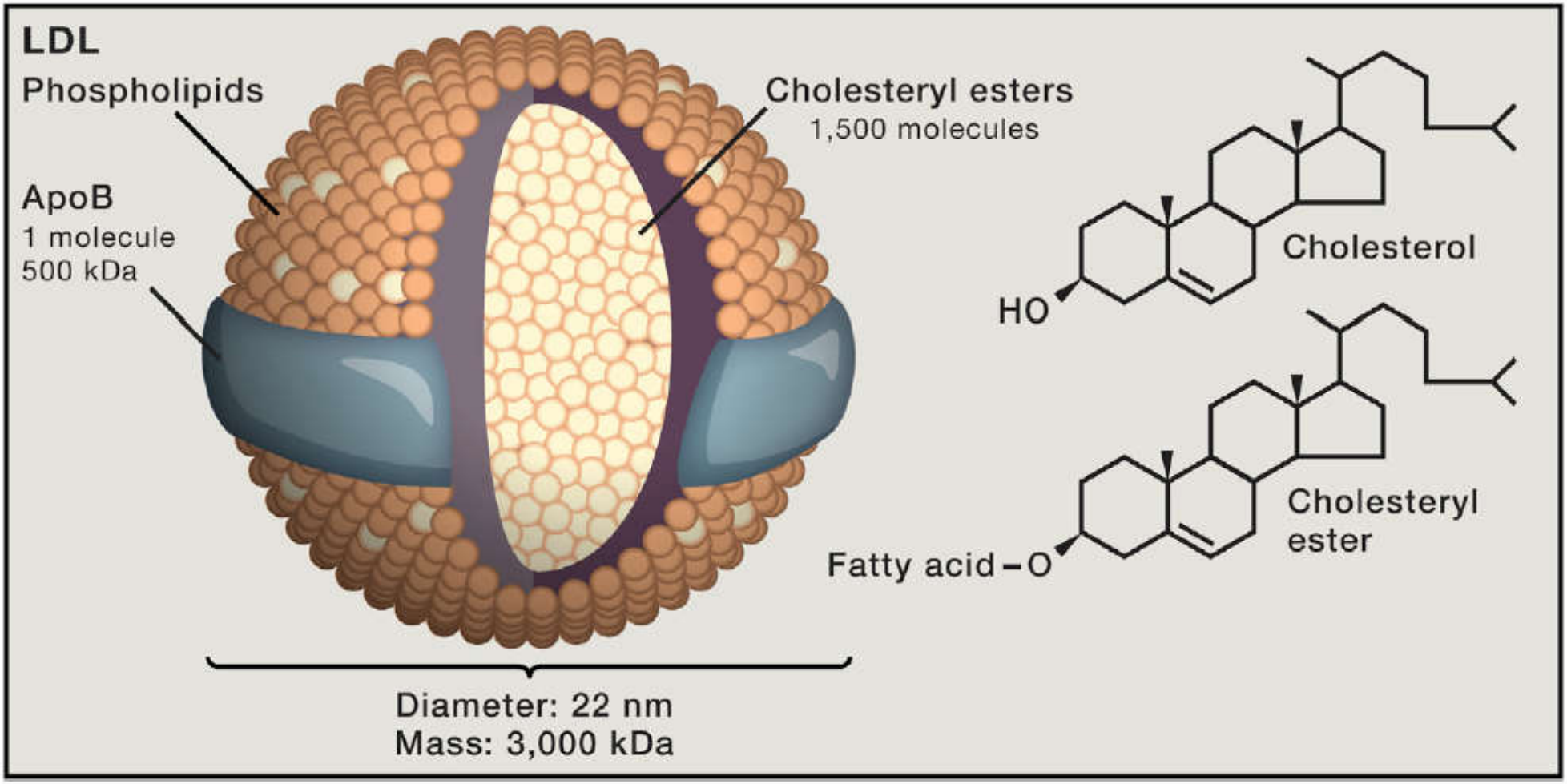
ATHEROGENIC LIPOPROTEINS



LOW-DENSITY LIPOPROTEINS (LDL) & LDL ΧΟΛΗΣΤΕΡΟΛΗ


LOW-DENSITY LIPOPROTEIN
apo B-100
Unesterified Cholesterol
Cholesterol Ester
Phospholipid
Triglyceride
DIAMETER: 225-275 Å

LDL: A Cholesterol Carrier

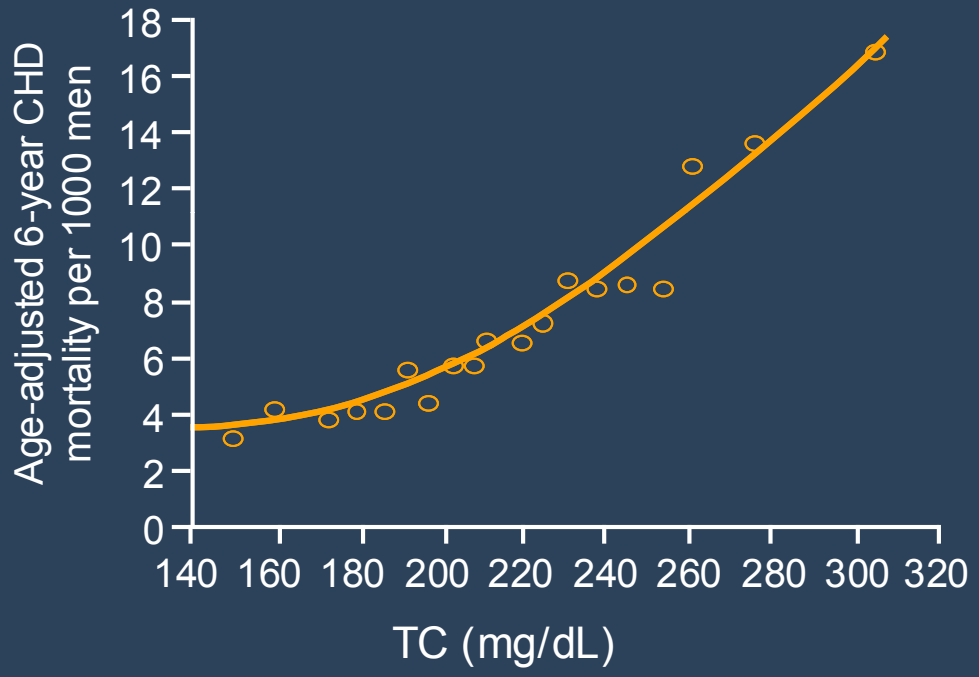


Goldstein JL, Brown MS. Cell. 2015

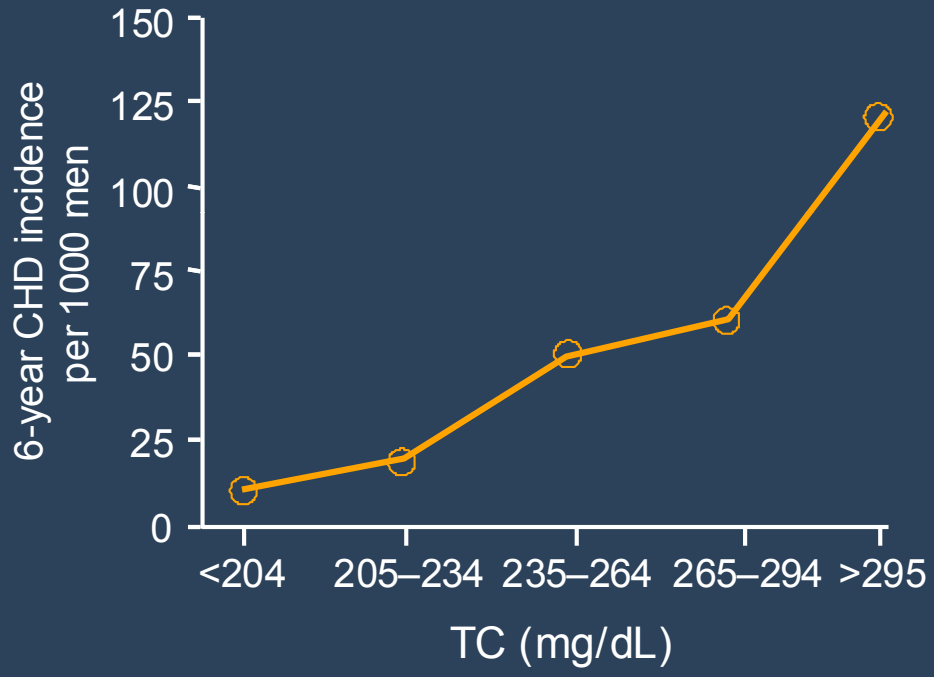
↑ LDL-CHOL → ↑ ΑΘΗΡΩΜΑΤΩΣΗΣ: ΕΠΙΔΗΜΙΟΛΟΓΙΚΑ ΔΕΔΟΜΕΝΑ

Epidemiologic Data Demonstrated a Strong Causal Link Between Elevated TC and CHD

Multiple Risk Factor Intervention Trial (MRFIT) N=361,662



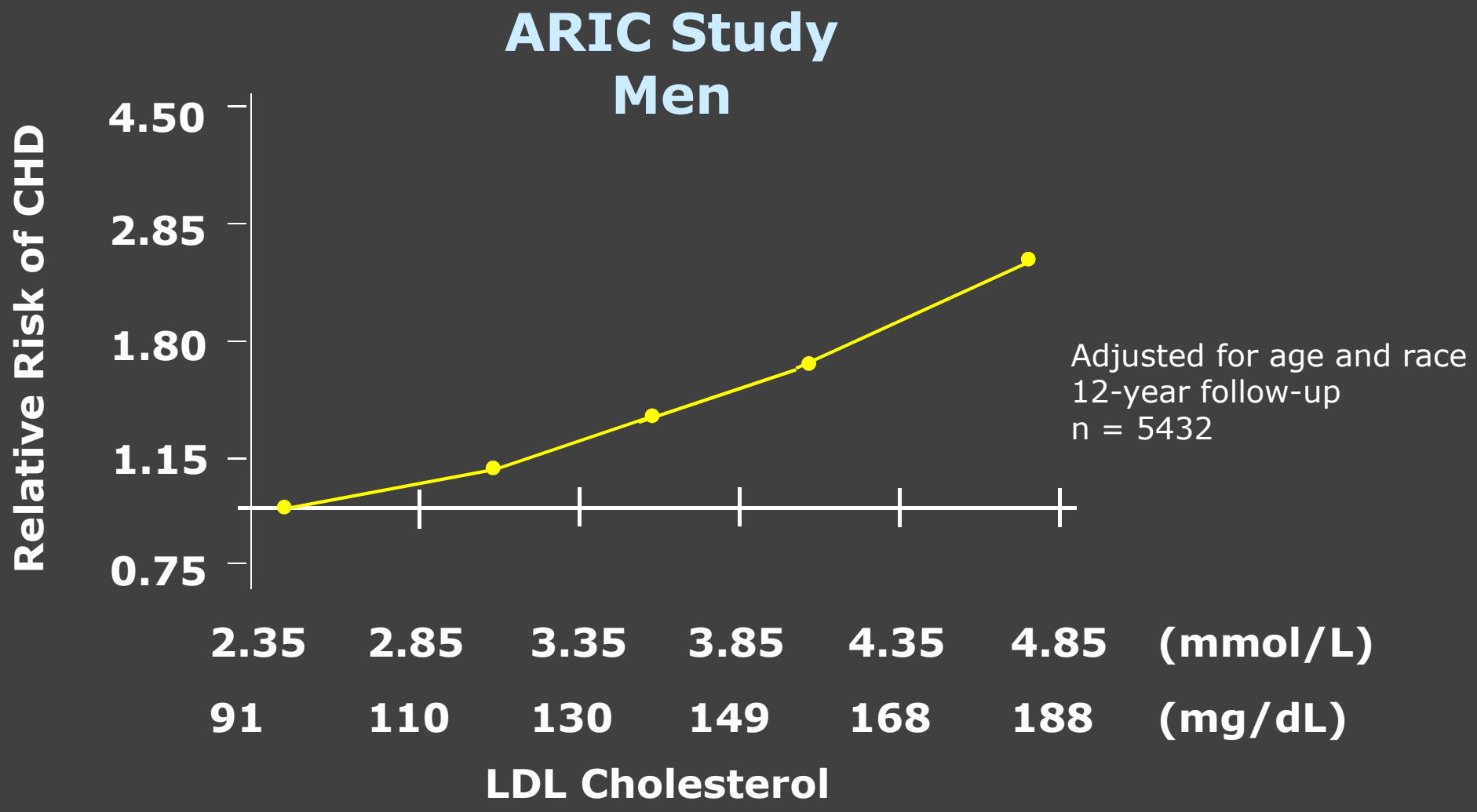
Framingham Heart Study (FHS) N=5209



TC=total cholesterol; CHD=coronary heart disease.

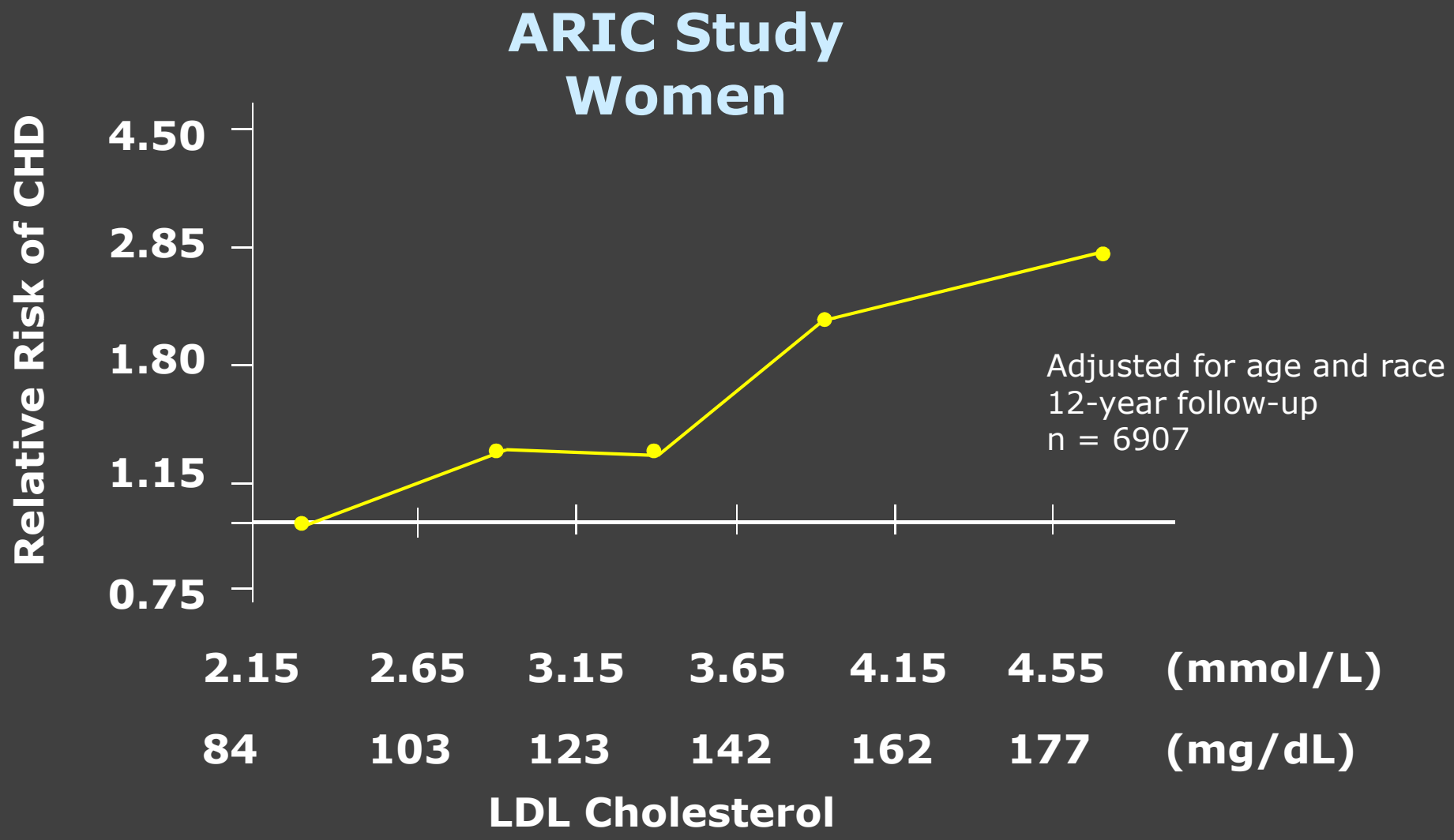
Martin MJ et al. *Lancet*. 1986;2:933-936; Castelli WP. *Am J Med*. 1984;76:4-12.

Increased Relative Risk of CHD Associated With Increasing LDL Levels



Adapted from Sharrett AR, et al. *Circulation*. 2001;104:1108-1113.

Increased Relative Risk of CHD Associated With Increasing LDL Levels



Adapted from Sharrett AR, et al. *Circulation*. 2001;104:1108-1113.

Blood cholesterol and vascular mortality by age, sex, and blood pressure: a meta-analysis of individual data from 61 prospective studies with 55 000 vascular deaths

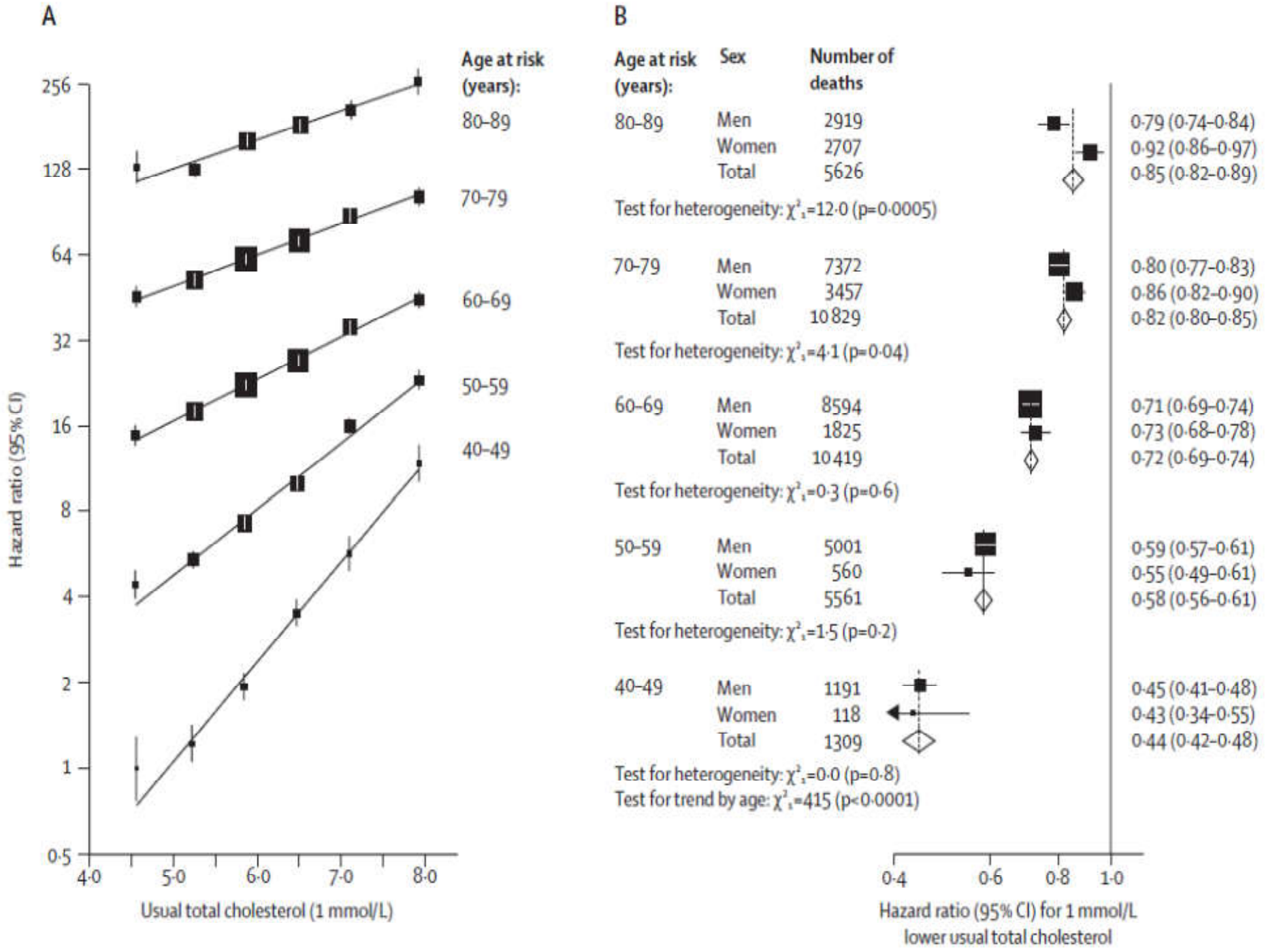
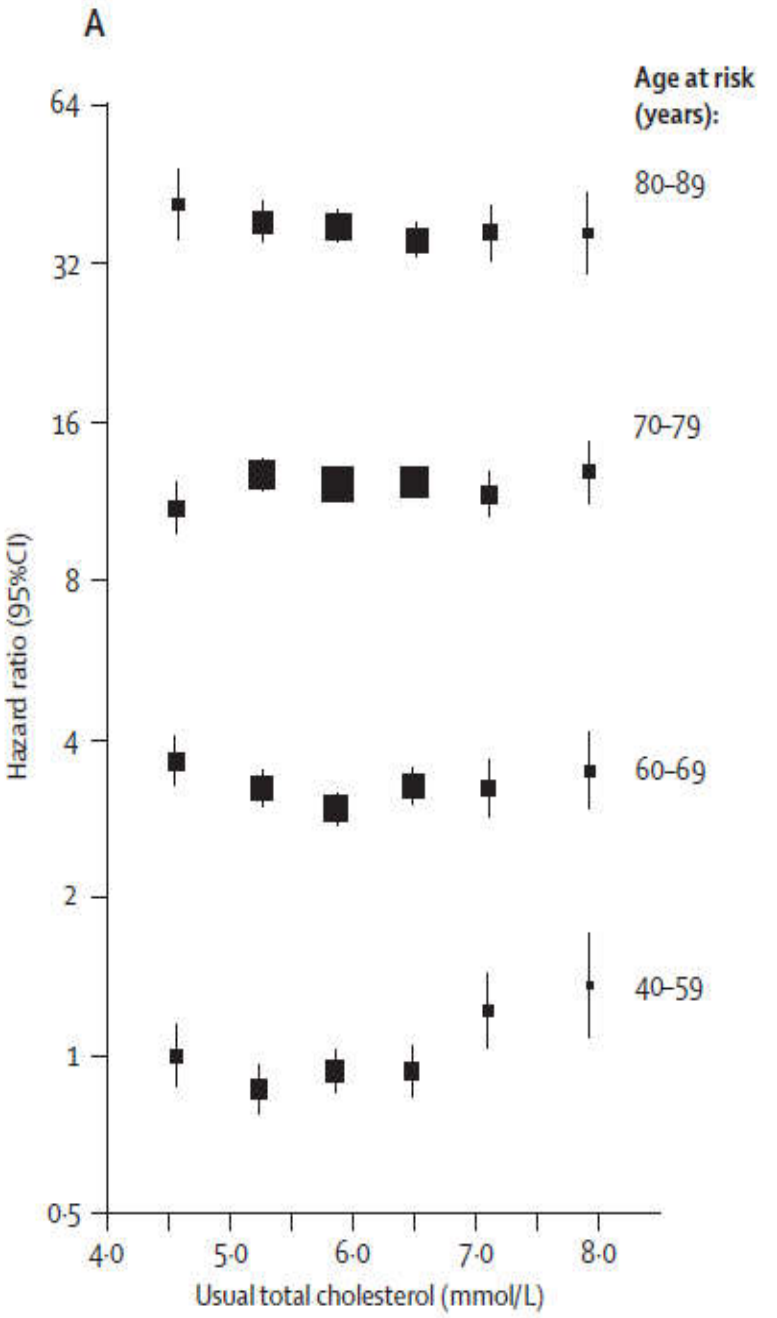


Figure 1: IHD mortality (33744 deaths) versus usual total cholesterol

Lancet 2007; 370: 1829–39

Blood cholesterol and vascular mortality by age, sex, and blood pressure: a meta-analysis of individual data from 61 prospective studies with 55 000 vascular deaths



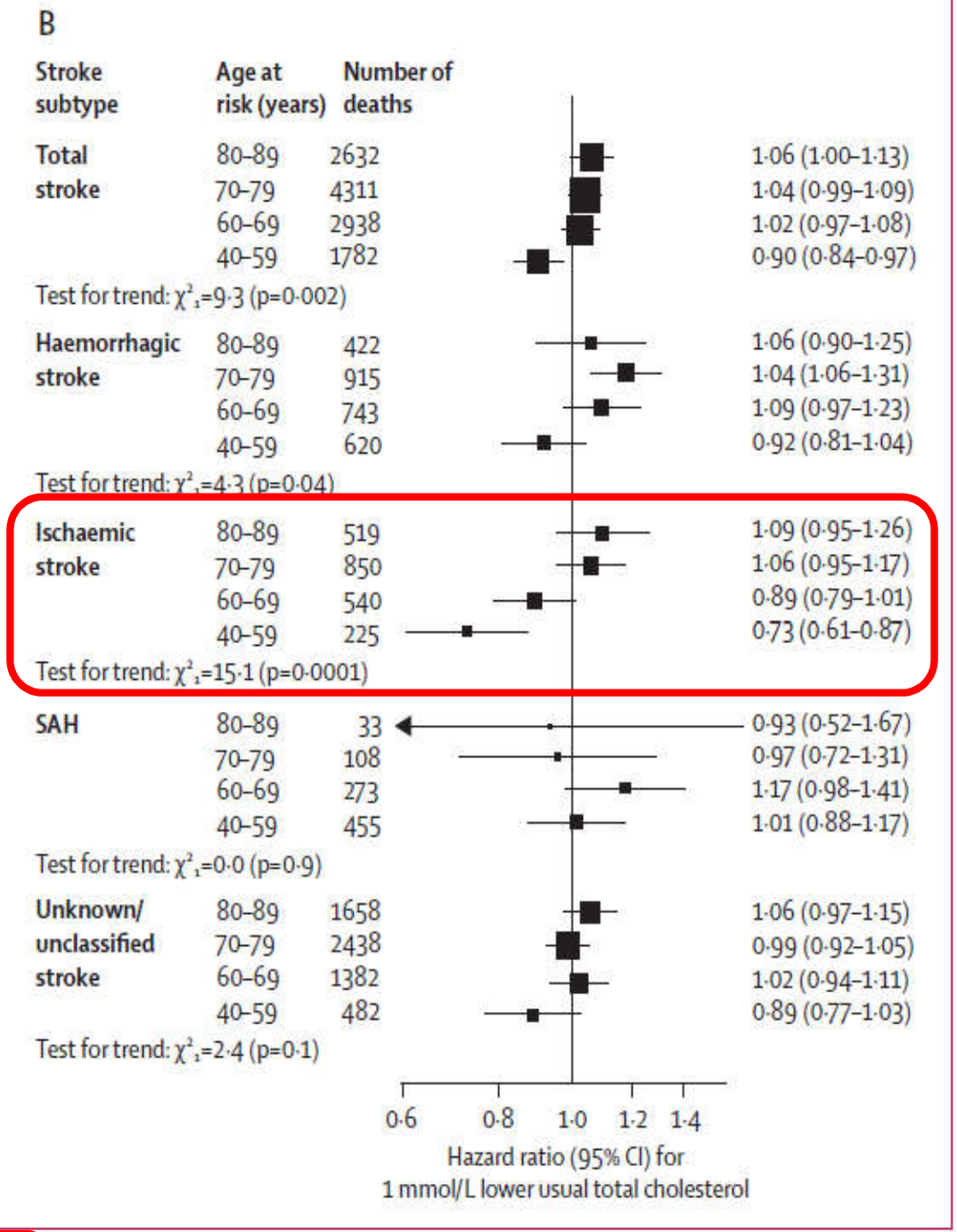
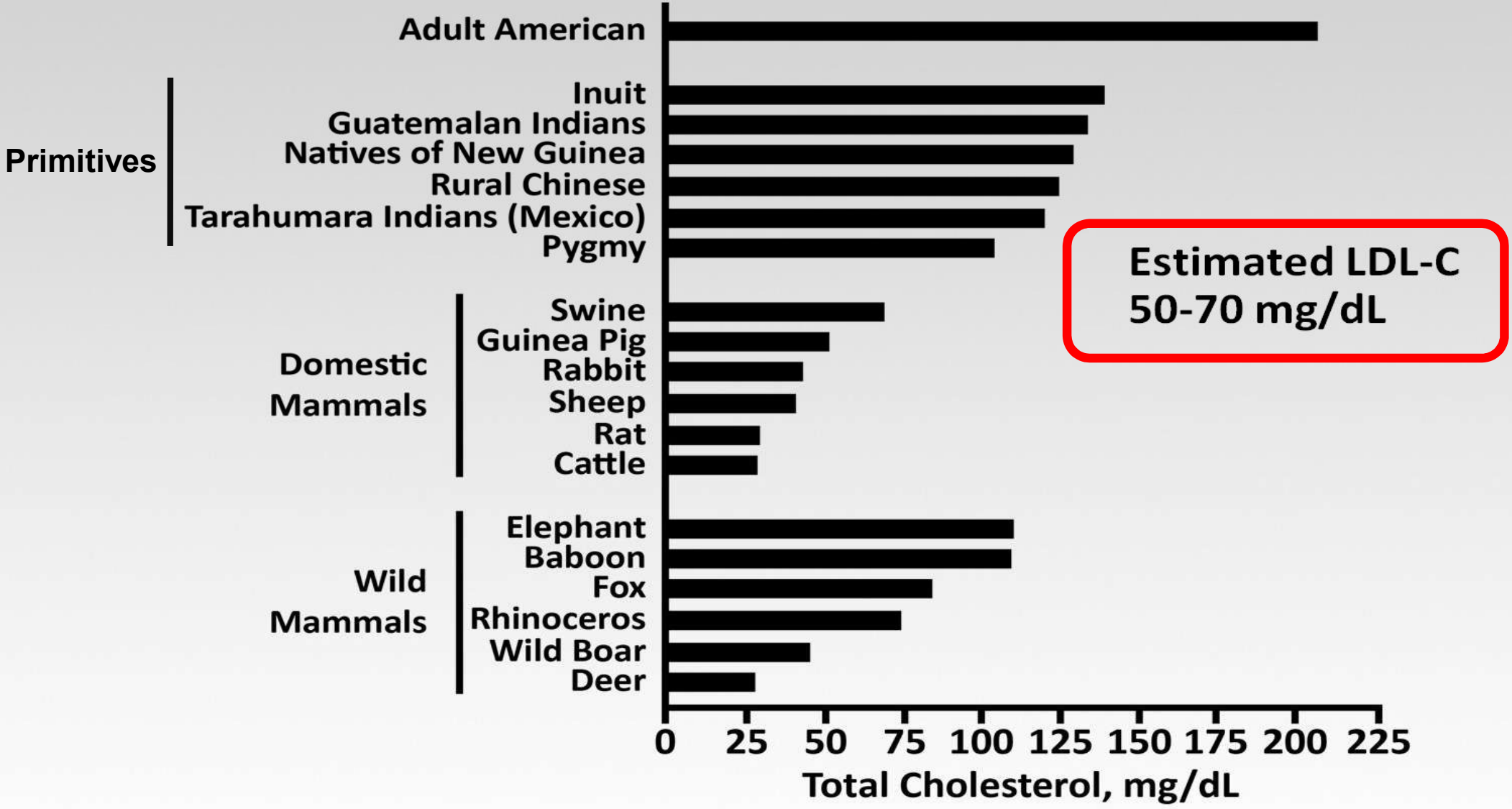


Figure 4: Stroke mortality (11 663 deaths) versus usual total cholesterol

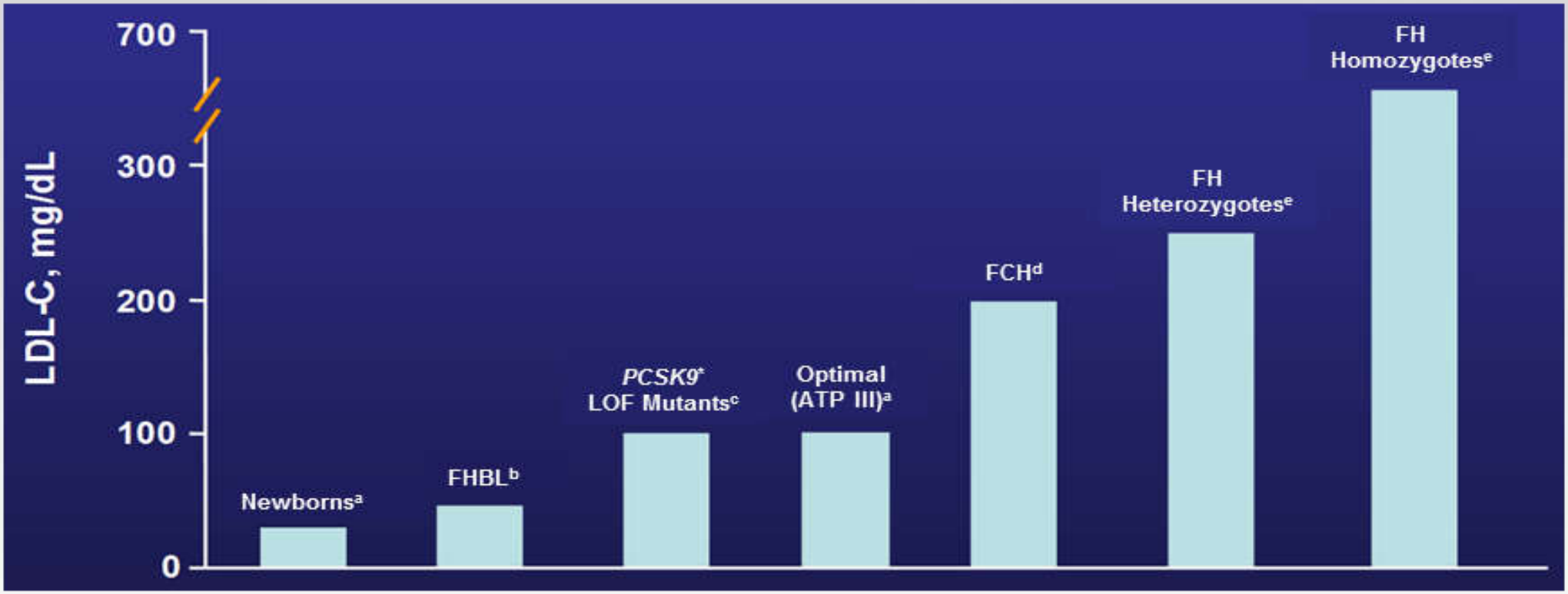
Lancet 2007; 370: 1829–39

Lipid-Lowering Goals: Back to Nature?



Hochholzer W, Giugliano RP.[8]

LDL-C Levels Vary With Genetic Variants in Cholesterol Metabolism



*Loss-of-function *PCSK9*^{142X} or *PCSK9*^{679X} mutants.

a. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *Circulation*. 2002;106:3143-3421; b. Glueck CJ, et al. *J Lab Clin Med*. 1976;88:941-957; c. Cohen JC, et al. *N Engl J Med*. 2006;354:1264-1272; d. Pauciullo P, et al. *Atherosclerosis*. 2009;203:320-324; e. Brown MS, et al. *Science*. 1986;232:34-47.

ΓΕΝΕΤΙΚΗ (MENDELIAN) ΕΠΙΔΗΜΙΟΛΟΓΙΑ-Ι

- Πρέπει να γνωρίζω ένα ή περισσότερα γονίδια που να επηρεάζουν τον παράγοντα που θέλω να μελετήσω και αυτά τα γονίδια να έχουν μεταλλάξεις ή πολυμορφισμούς που να επηρεάζουν τα επίπεδα του ΜΟΝΟ αυτού του παράγοντα

ΓΕΝΕΤΙΚΗ (MENDELIAN) ΕΠΙΔΗΜΙΟΛΟΓΙΑ-ΙΙ

- Κατά τη μείωση παρατηρείται τυχαία και ανεξάρτητη κατανομή των γονιδίων (2ος νόμος γενετικής του Mendel)
- Η επίδραση ξεκινά από την αρχή της ζωής

ΓΕΝΕΤΙΚΗ (MENDELIAN) ΕΠΙΔΗΜΙΟΛΟΓΙΑ-ΙΙΙ

- Πρέπει να έχω μεγάλες πληθυσμιακές μελέτες και να μπορώ να κάνω σε μεγάλη κλίμακα γενετικές αναλύσεις

Randomized trial vs. Mendelian randomization

Randomization methods

Placebo

Drug: (lipo)protein levels ↑ or ↓

Confounders evenly distributed

Cardiovascular disease ↓ or ↑

Random distribution of alleles

Normal allele

Allele: (lipo)protein levels ↓ or ↑

Confounders evenly distributed

Cardiovascular disease ↓ or ↑

Reverse causation

Nordestgaard & Tybjærg-Hansen Curr Opin Lipidol 2011;22:113-22

Mendelian randomisation applied to drug development in cardiovascular disease: a review

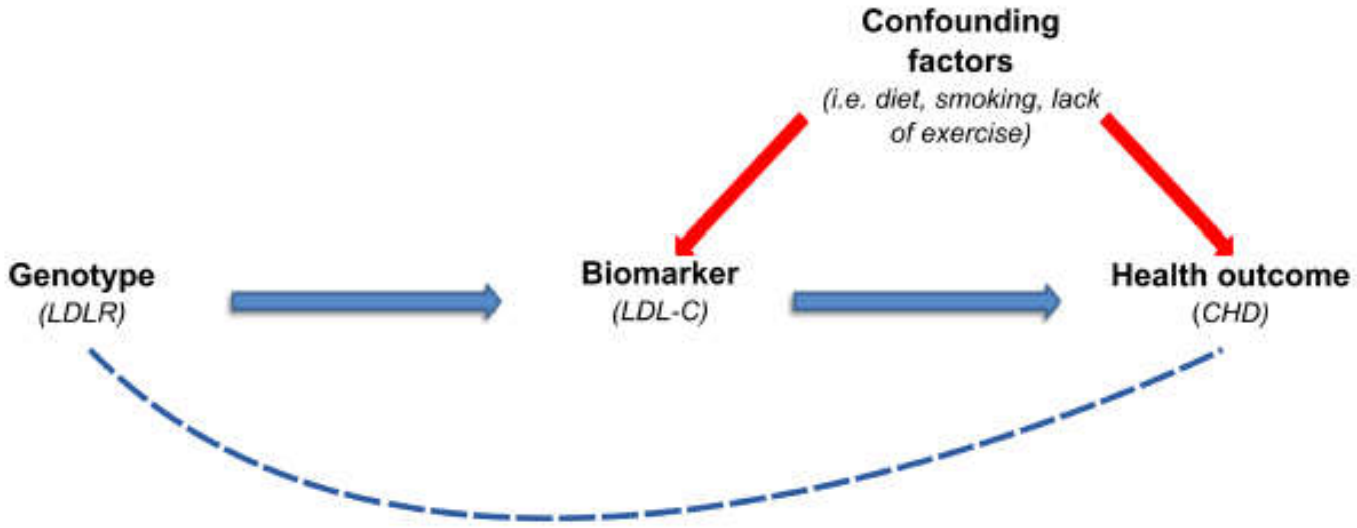
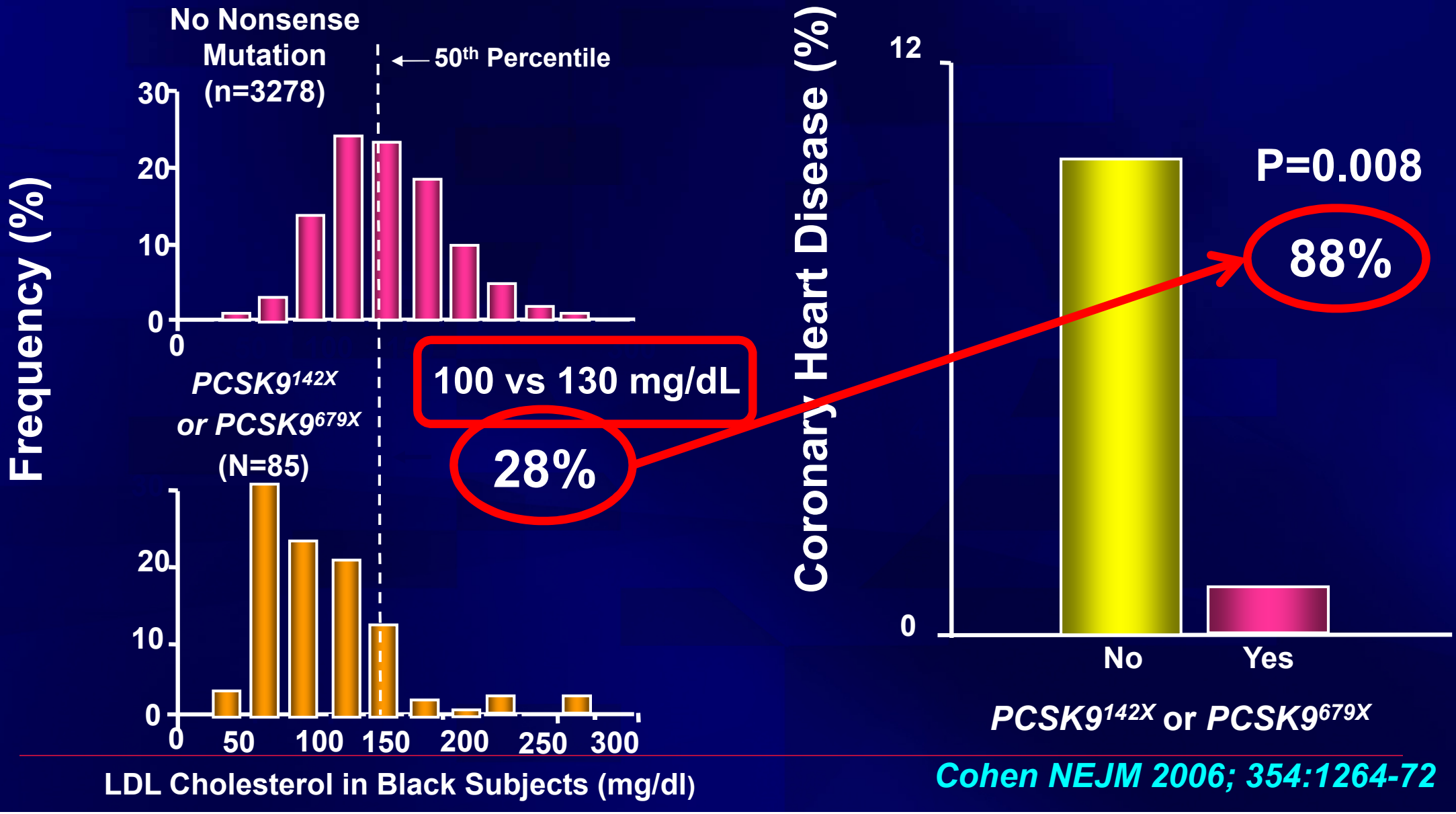


Figure 1 Mendelian randomisation study design: if a biomarker is causal for a disease, then genetic variants which influence the levels of the biomarker should result in a higher risk of the disease. Figure adapted from Timpson *et al*.[15]

Mokry LE, *et al*. *J Med Genet* 2015;**52**:71–79. doi:10.1136/jmedgenet-2014-102438

LDL Cholesterol and Coronary Heart Disease among Black Subjects by *PCSK9*^{142X} or *PCSK9*^{679X} Allele



Cohen NEJM 2006; 354:1264-72

Effect of Long-Term Exposure to Lower Low-Density Lipoprotein Cholesterol Beginning Early in Life on the Risk of Coronary Heart Disease

A Mendelian Randomization Analysis

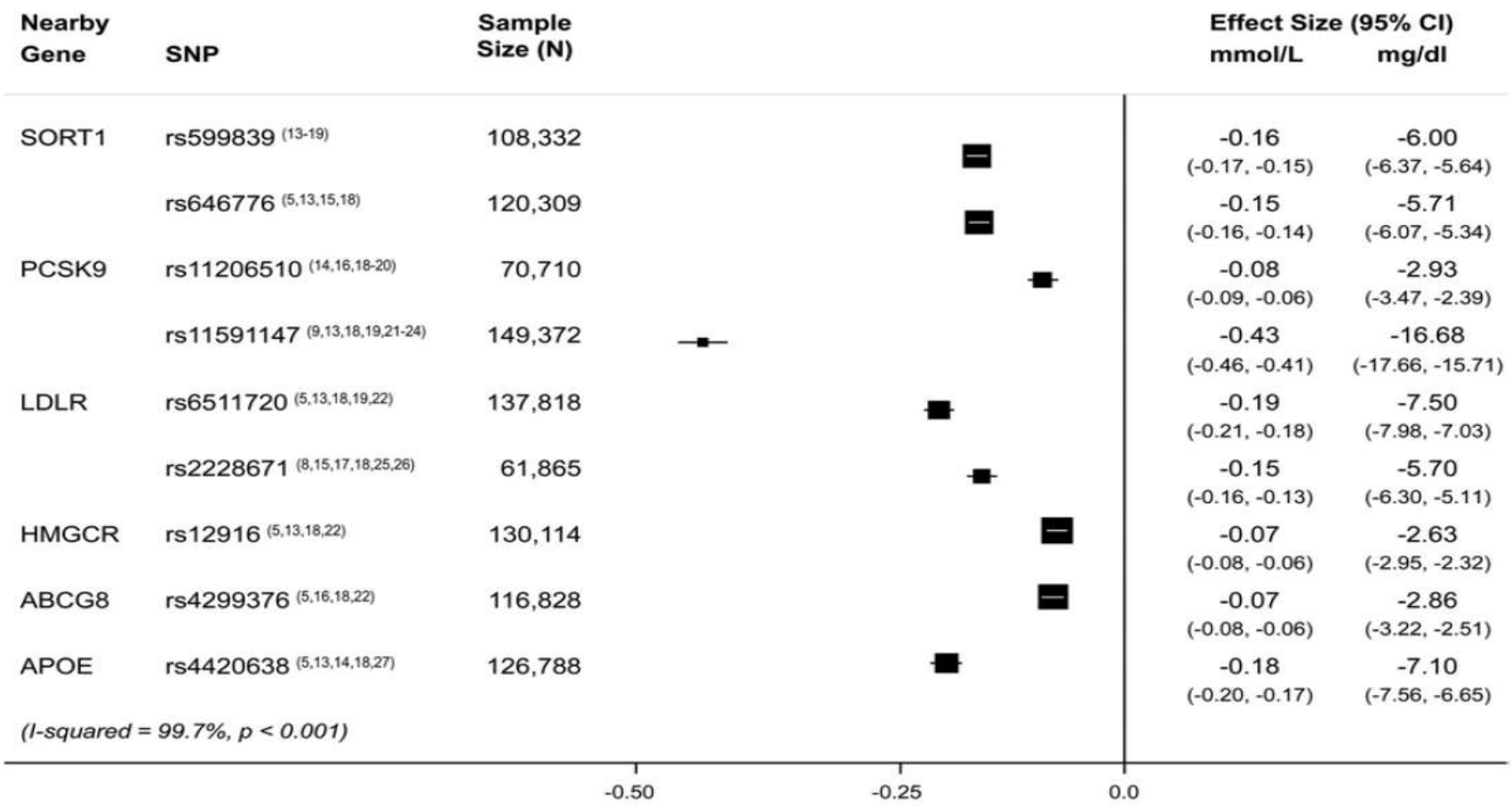


Figure 1 **Association Between Exposure Alleles and LDL-C**

JACC Vol. 60, No. 25, 2012
December 25, 2012:2631–9

Effect of Long-Term Exposure to Lower Low-Density Lipoprotein Cholesterol Beginning Early in Life on the Risk of Coronary Heart Disease

A Mendelian Randomization Analysis

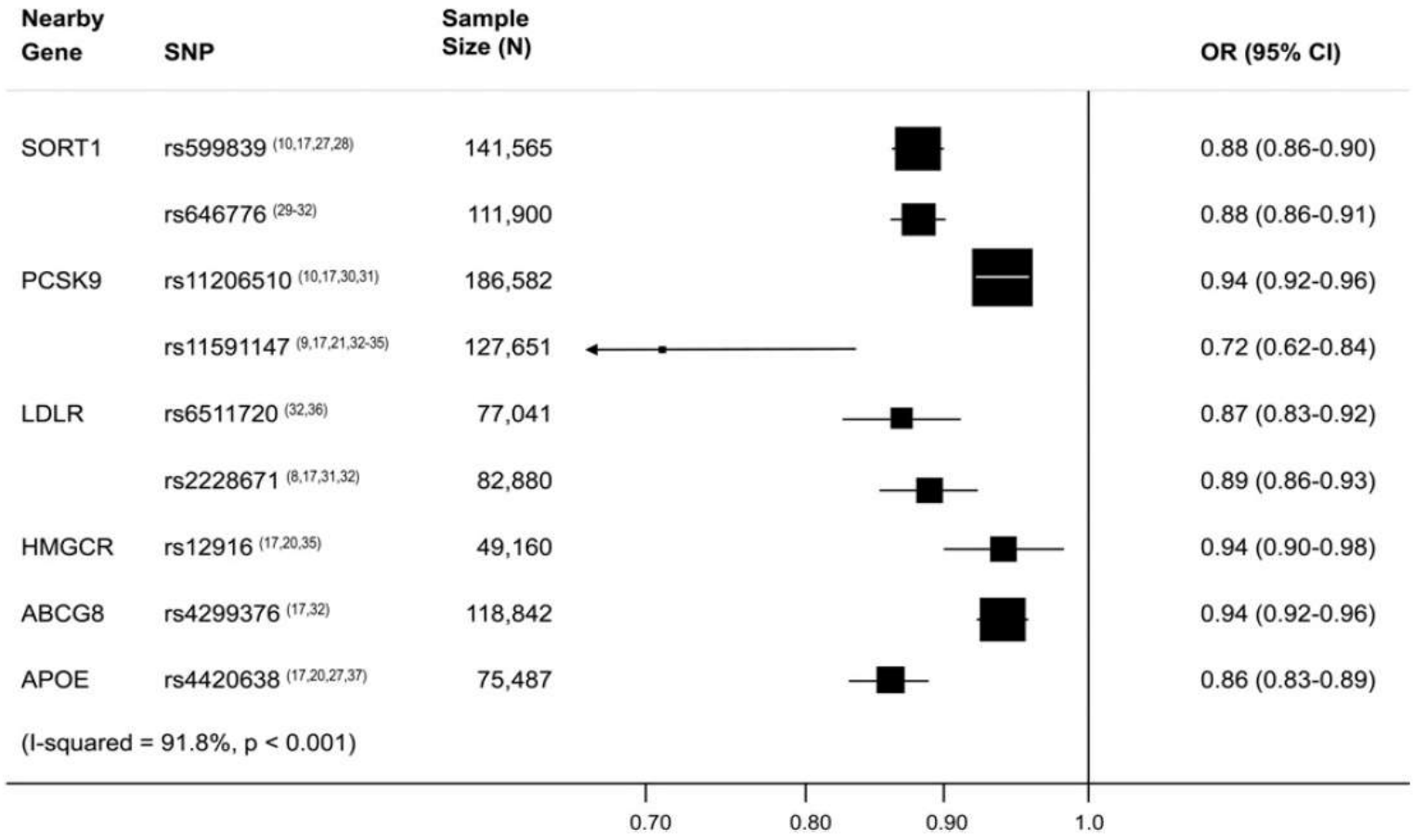


Figure 2 Association Between Exposure Alleles and Risk of CHD

Effect of Long-Term Exposure to Lower Low-Density Lipoprotein Cholesterol Beginning Early in Life on the Risk of Coronary Heart Disease

A Mendelian Randomization Analysis

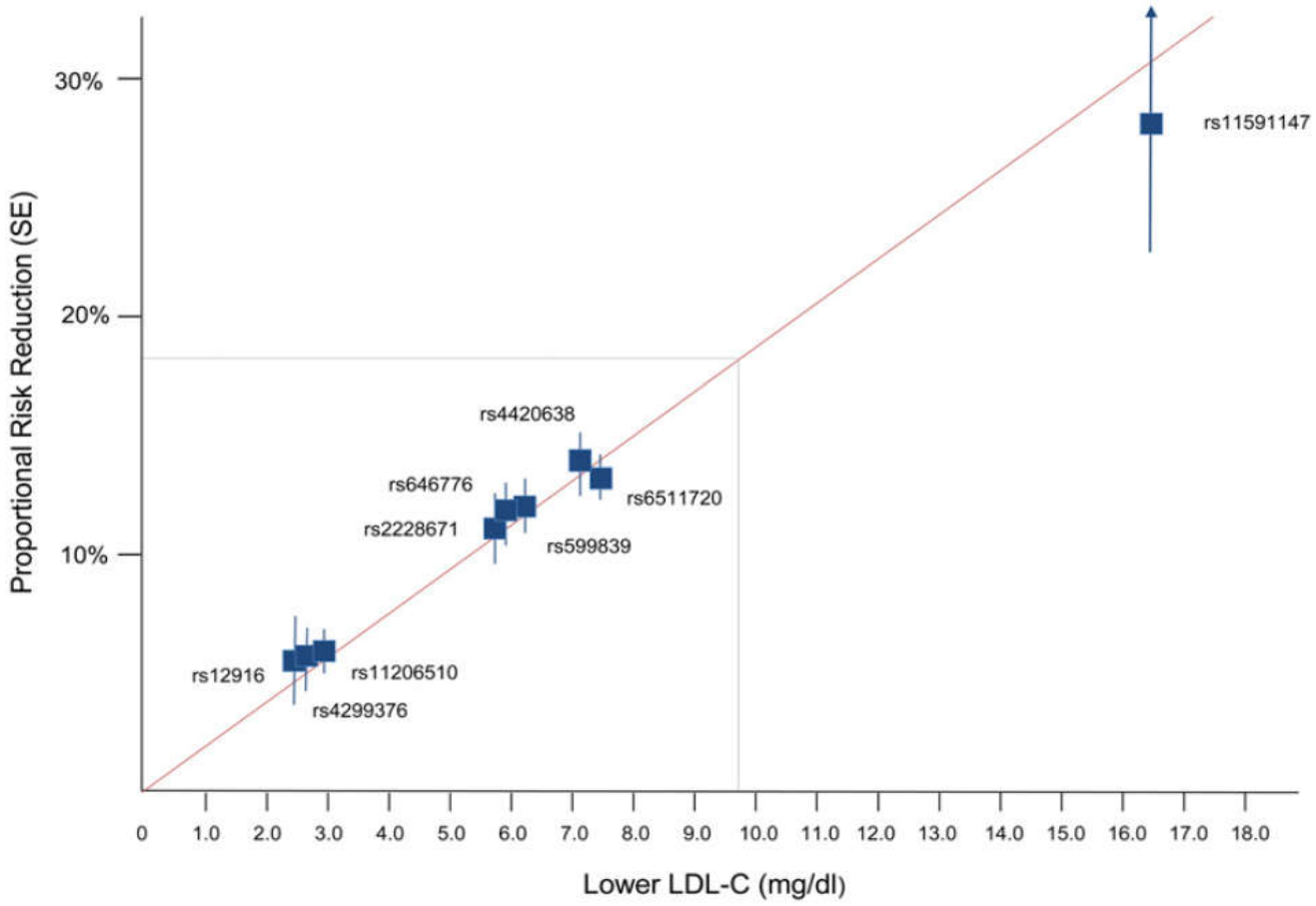
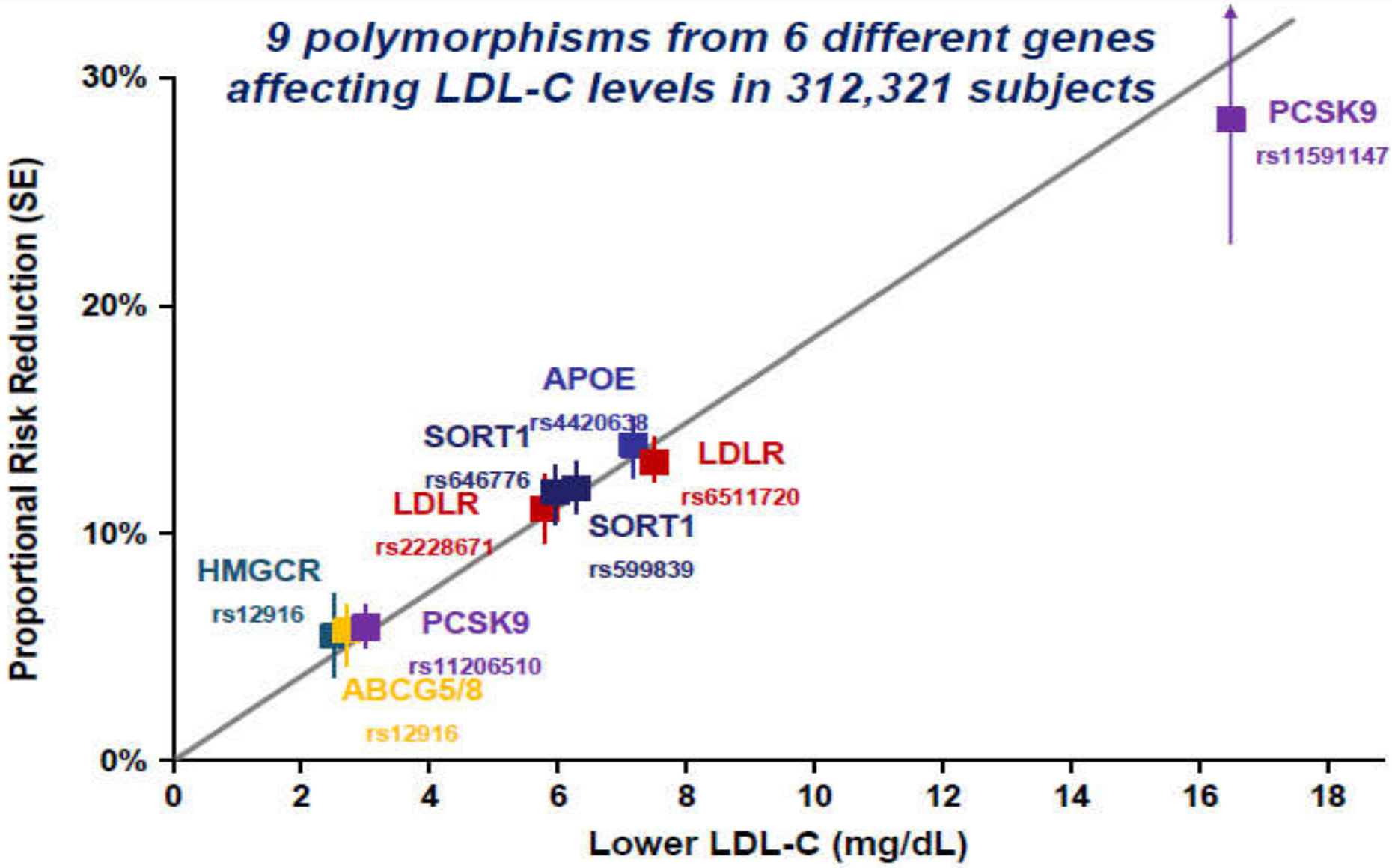


Figure 3 Log-Linear Effect of Each Unit Long-Term Exposure to Lower LDL-C on Risk of CHD

Lower Risk of Cardiovascular Events via Multiple Genetic Variants Affecting LDL-C



Ference BA et al. JACC 2012;60:2631–9

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Variation in *PCSK9* and *HMGCR* and Risk of Cardiovascular Disease and Diabetes

Brian A. Ference, M.D., Jennifer G. Robinson, M.D., M.P.H., Robert D. Brook, M.D., Alberico L. Catapano, Ph.D., M. John Chapman, Ph.D., David R. Neff, D.O., Szilard Voros, M.D., Robert P. Giugliano, M.D., George Davey Smith, M.D., D.Sc., Sergio Fazio, M.D., Ph.D., and Marc S. Sabatine, M.D., M.P.H.

C Effect of *PCSK9* and *HMGCR* Scores on Risk of Myocardial Infarction or Death from CHD per Unit Change in LDL Cholesterol

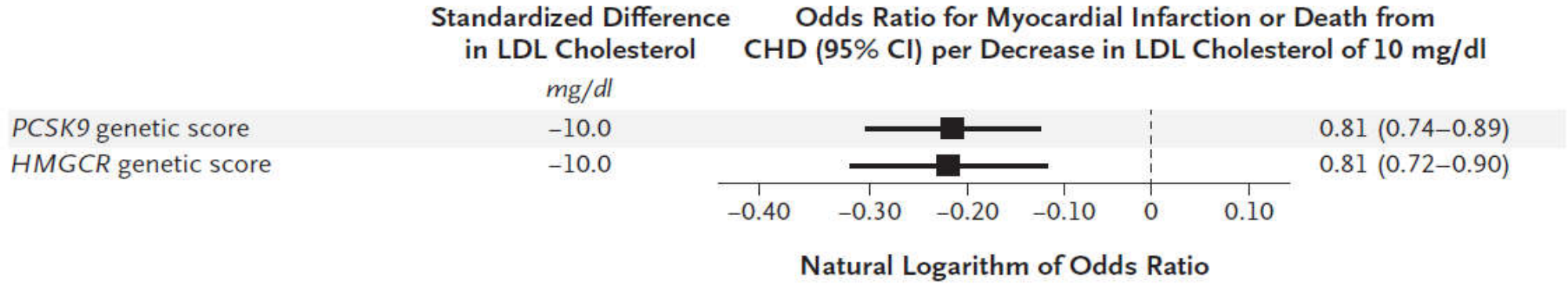
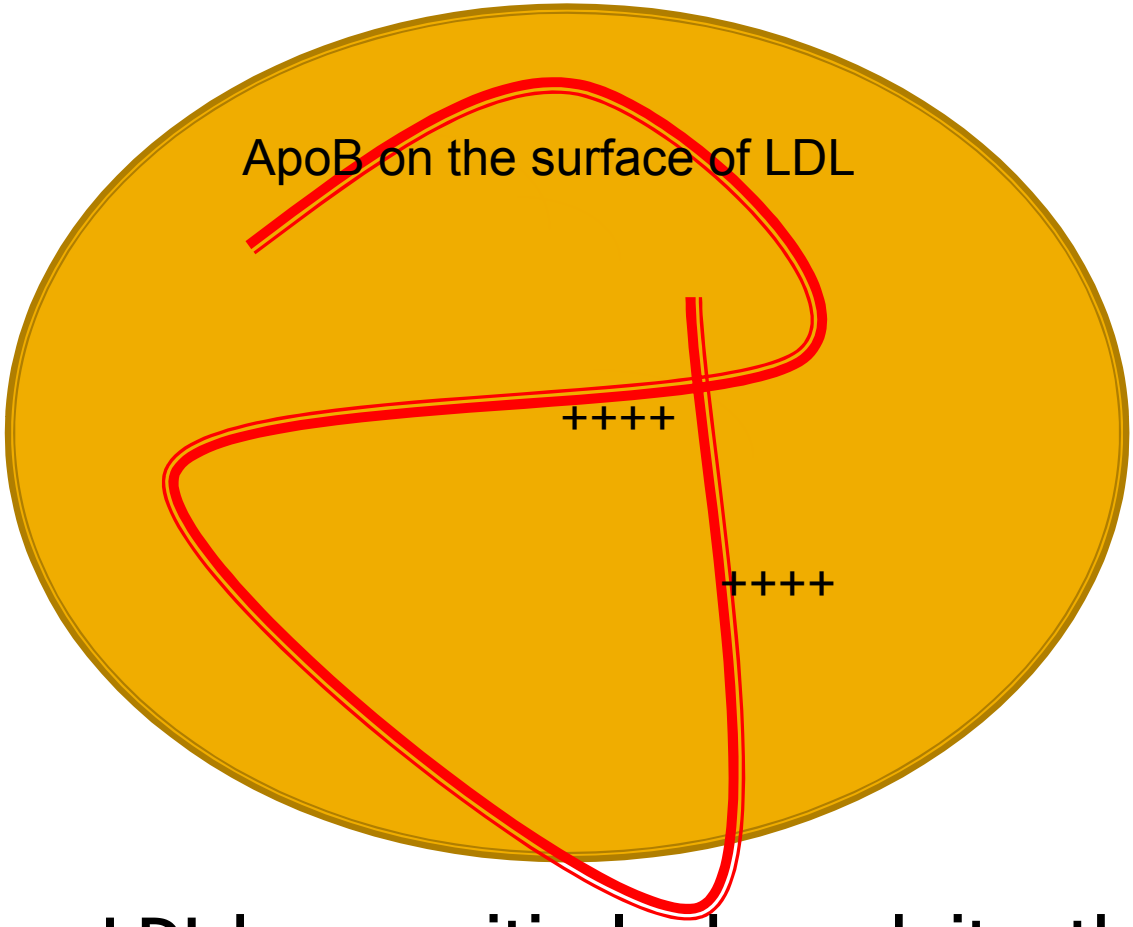


Figure 1. Effect of *PCSK9* and *HMGCR* Genetic Scores on the Risk of Myocardial Infarction or Death from Coronary Heart Disease.

Figure 3. Dose–Response Relationship between *PCSK9* and *HMGCR* Scores and Risk of Diabetes.

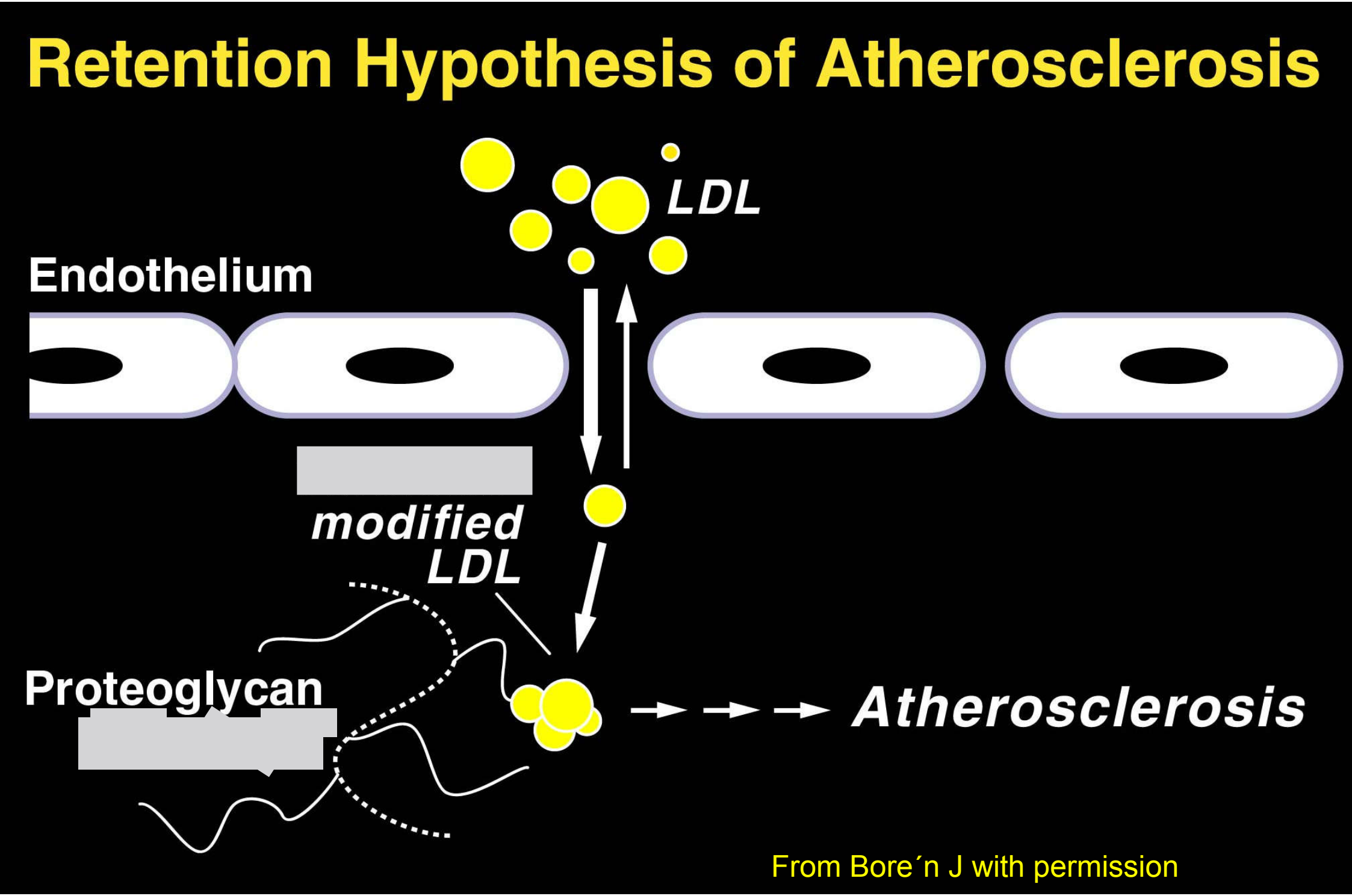
↑ LDL-CHOL → ↑ ΑΘΗΡΩΜΑΤΩΣΗΣ:
ΠΑΘΟΦΥΣΙΟΛΟΓΙΚΑ ΔΕΔΟΜΕΝΑ

Atherogenic mechanisms of LDL- the response to retention hypothesis



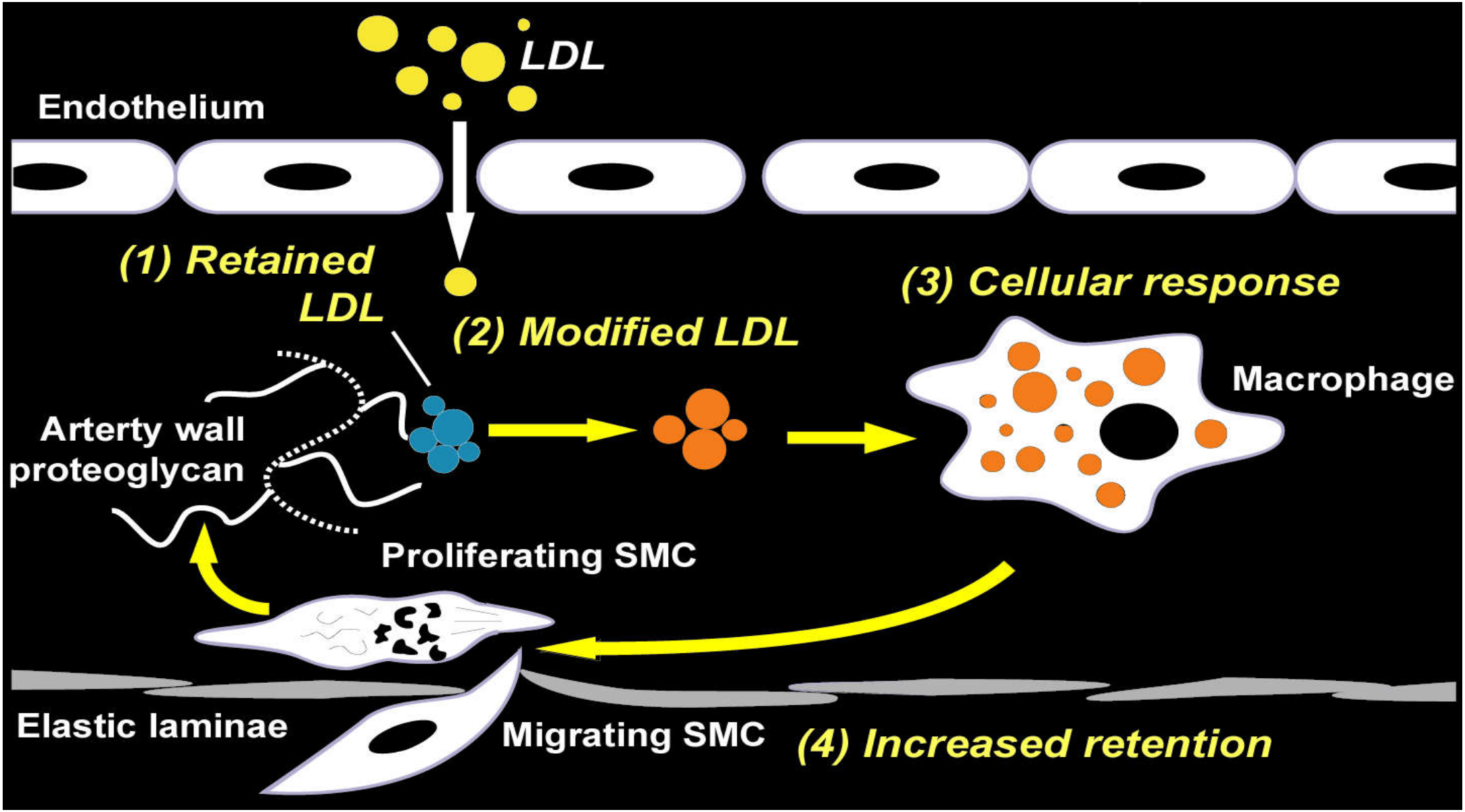
ApoB on LDL have positively charged sites that bind to negatively charged proteoglycans in tissue

Retention Hypothesis of Atherosclerosis

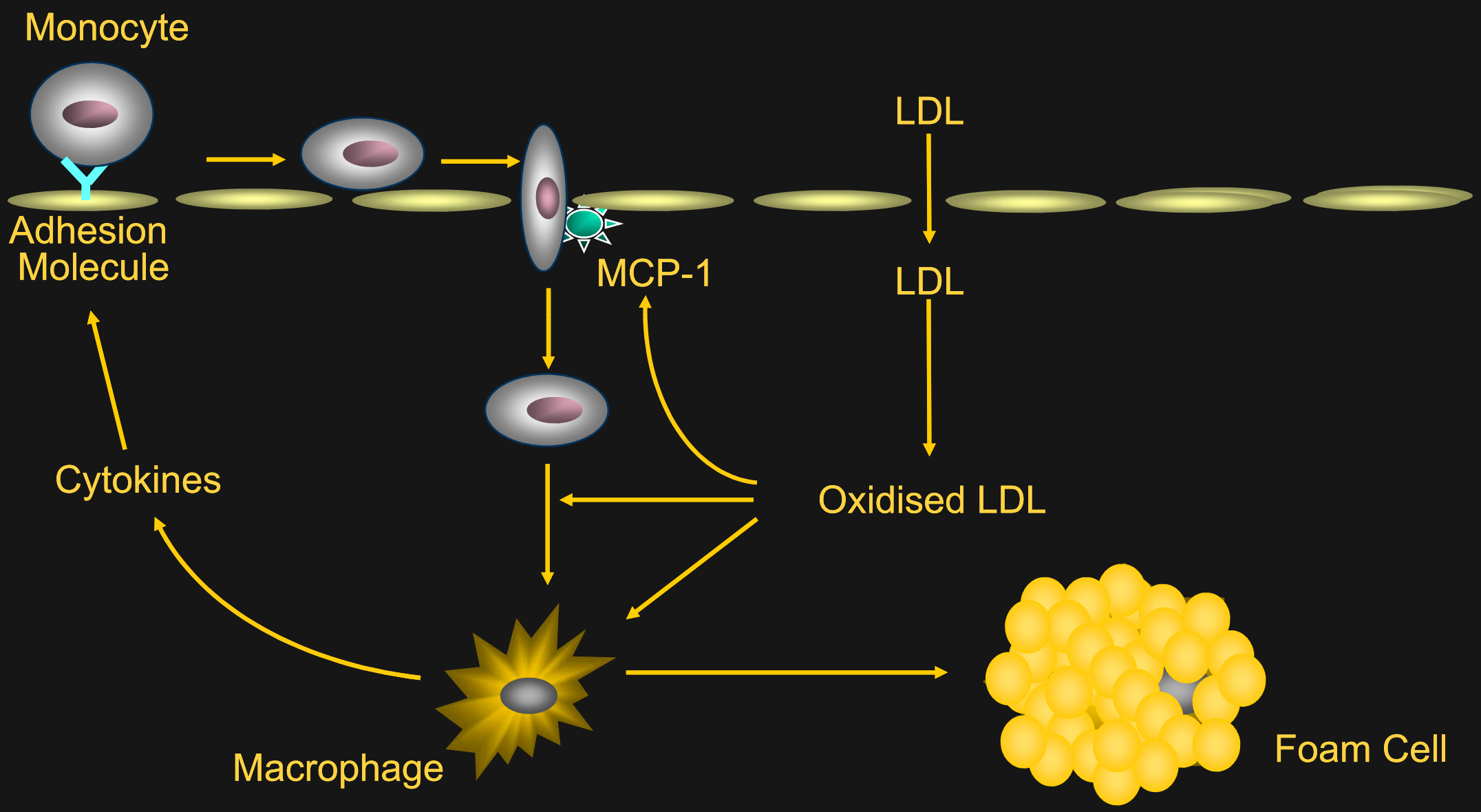


From Bore´n J with permission

Atherogenesis: ”Response to retention hypothesis”



ROLE OF LDL IN CAUSING ATHEROSCLEROSIS



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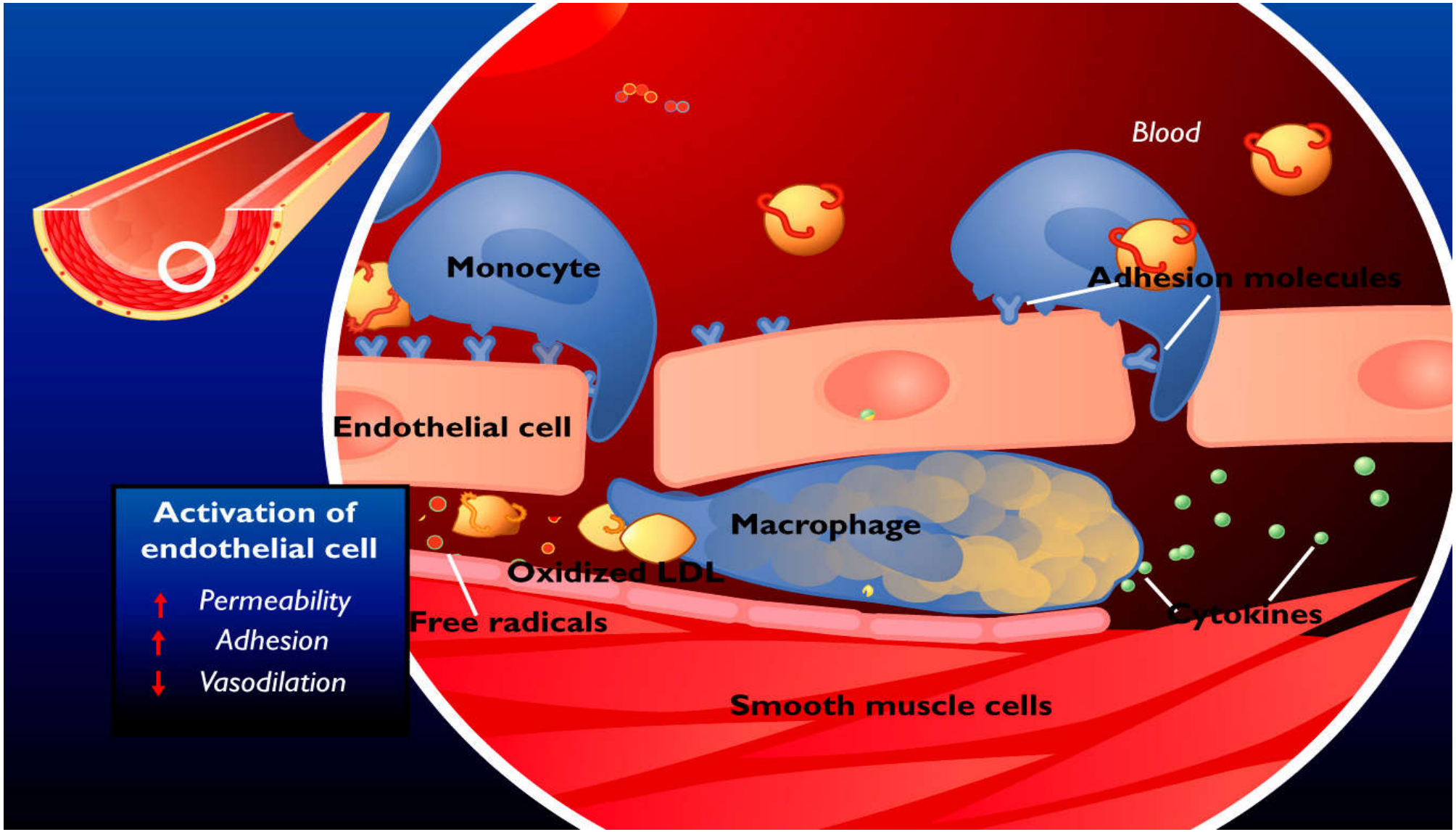
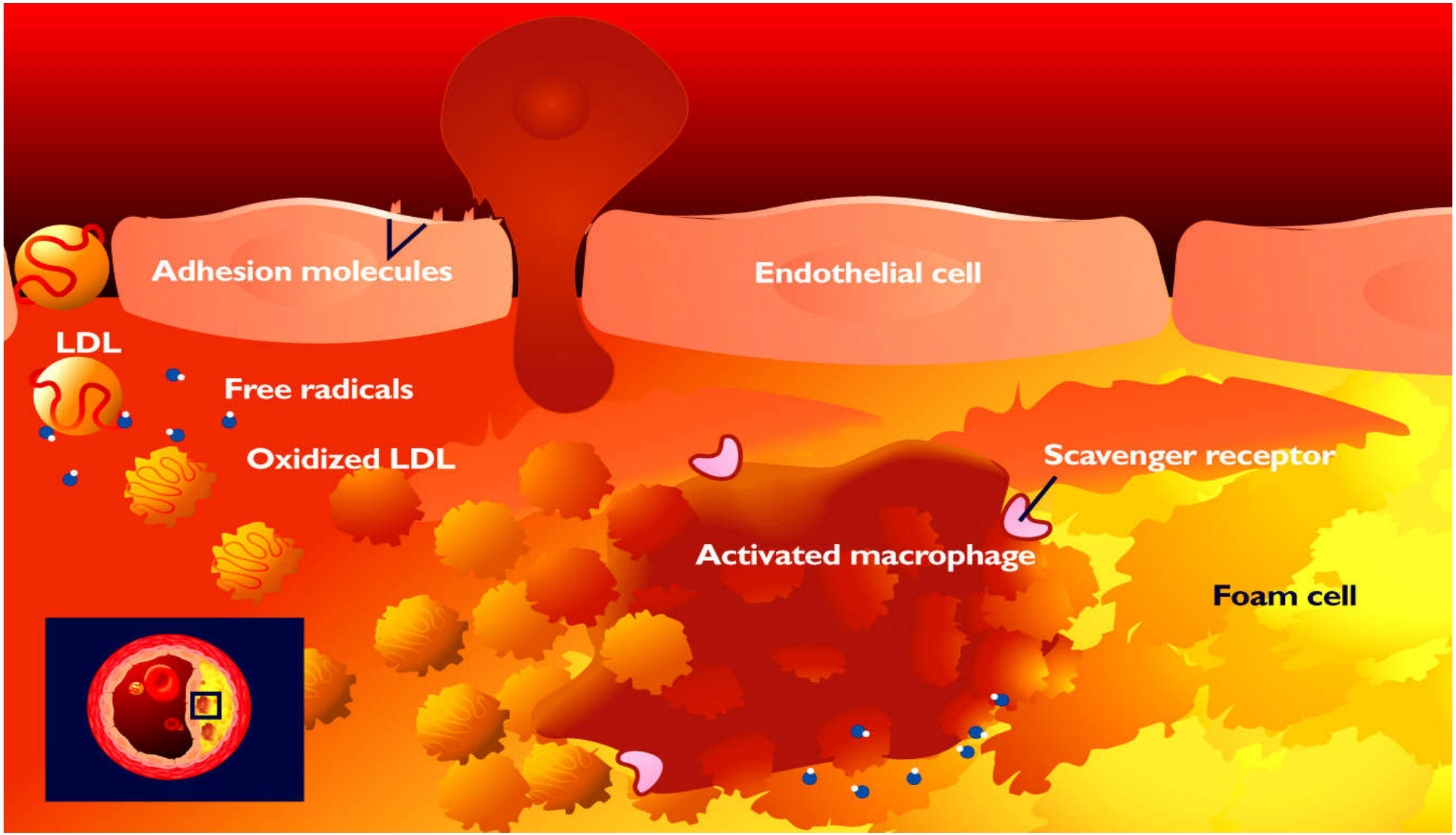
Vascular endothelium modification in atherosclerosis



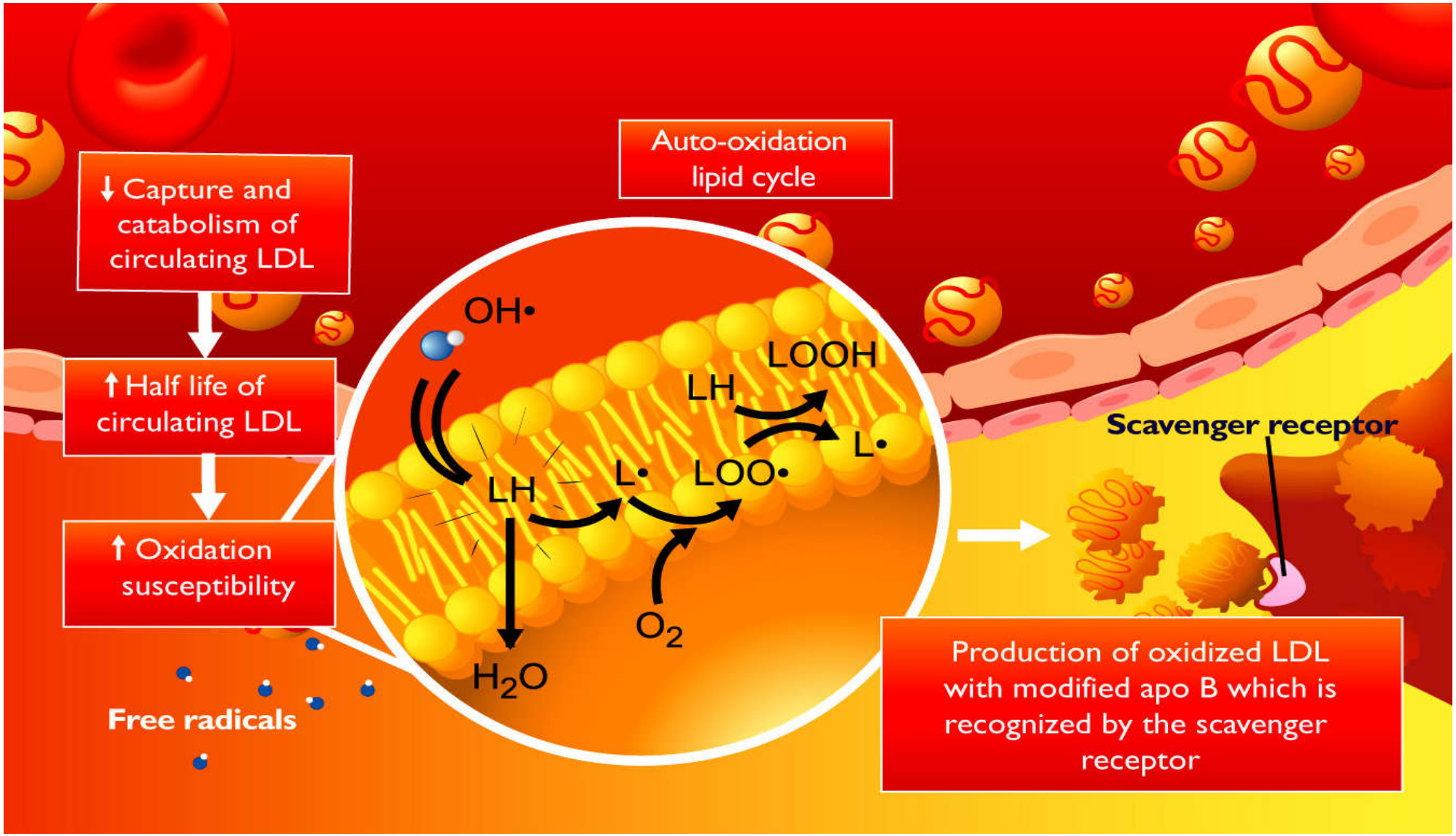
Lipid core constitution

Activated macrophages accumulate lipids



Lipid core constitution

LDL oxidation



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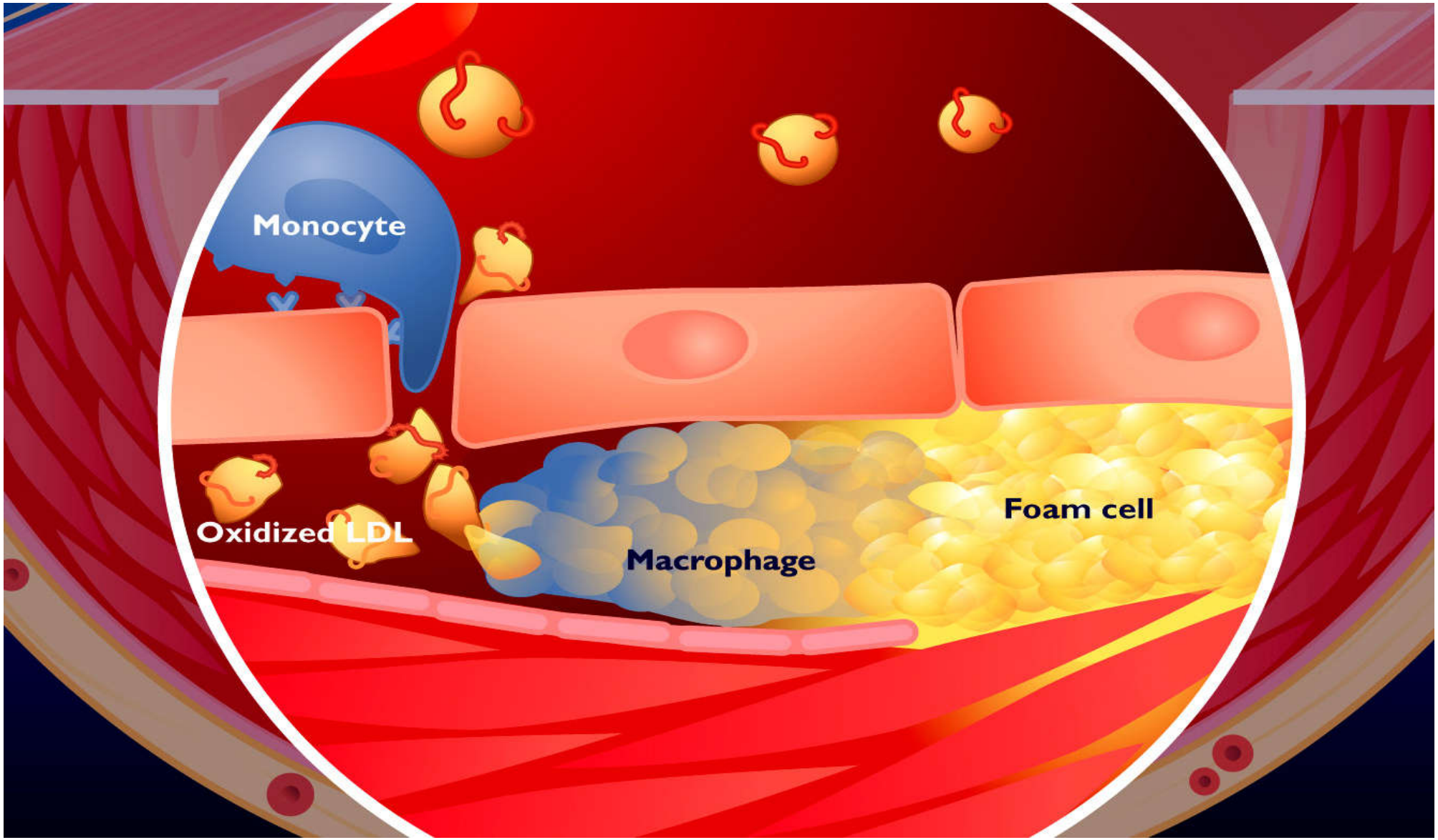
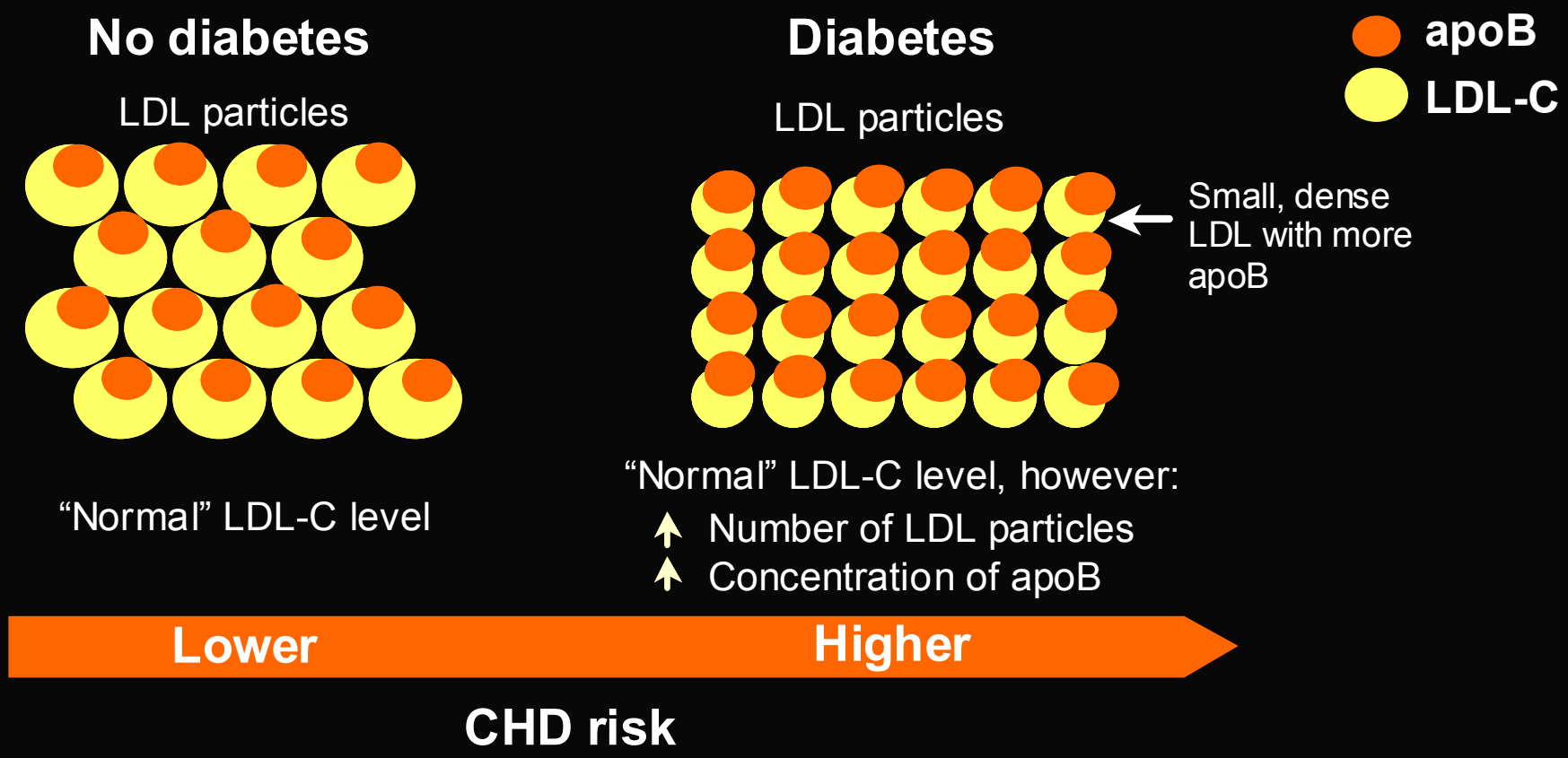
Plaque formation

1 — Fatty streak



"Normal" LDL-C Levels in People with Diabetes Can Be Misleading...

Small, Dense LDL-C Particles Are More Atherogenic



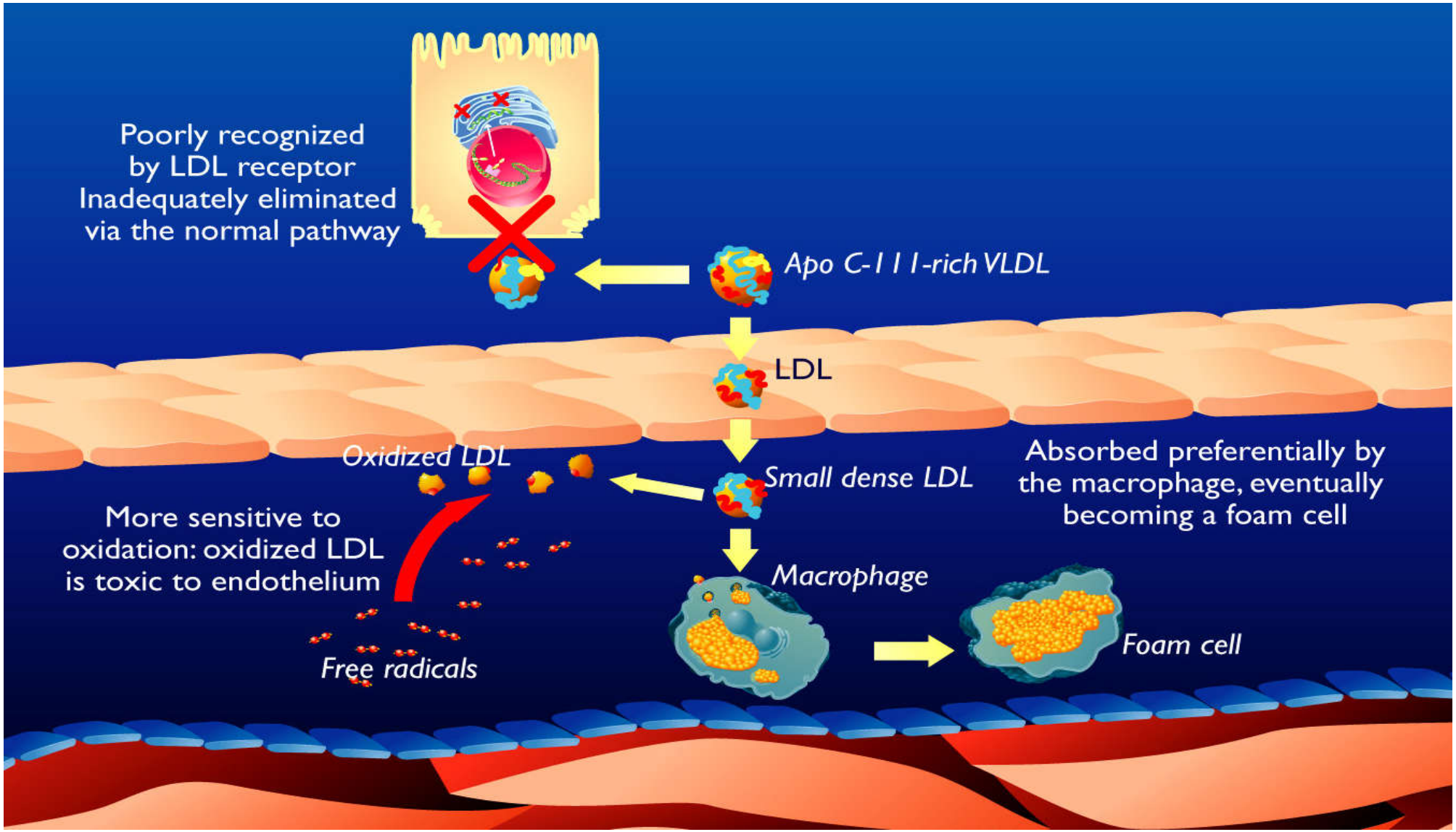
Adapted from Austin MA, Edwards KL *Curr Opin Lipidol* 1996;7:167-171; Austin MA et al *JAMA* 1988;260:1917-1921; Sniderman AD et al *Diabetes Care* 2002;25:579-582.

Small dense LDL

- Increased levels of small dense LDL associated with CVD

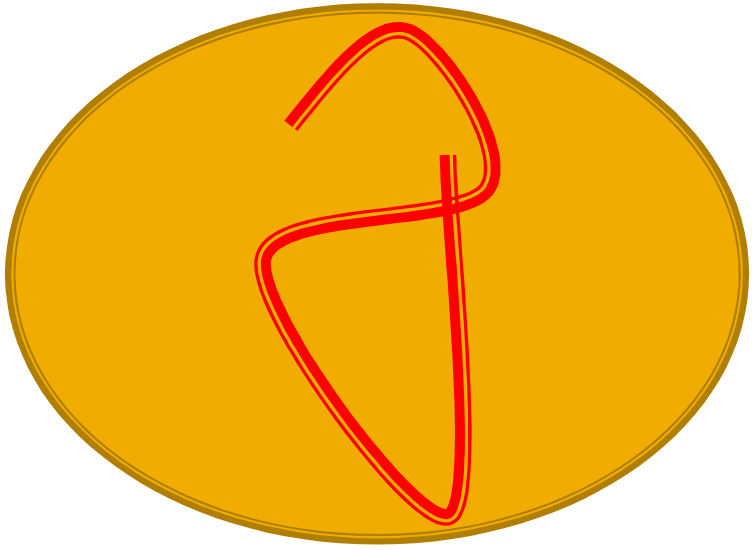
- Small dense LDL a component of the **atherogenic triad** in diabetes and the metabolic syndrome
  - Small dense LDL
  - Low HDL
  - High triglycerides

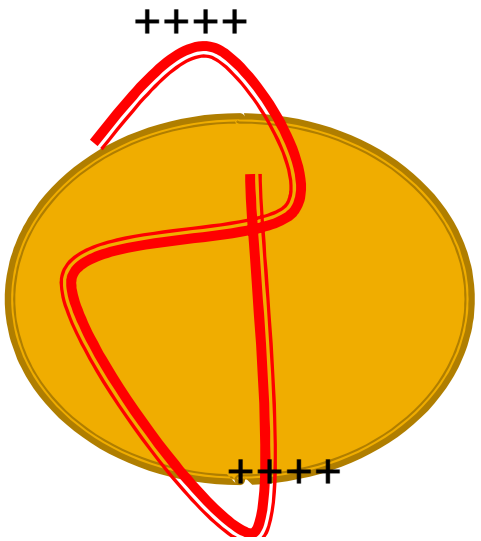
Atherogenicity of small dense LDL



Atherogenic mechanisms of small dense LDL

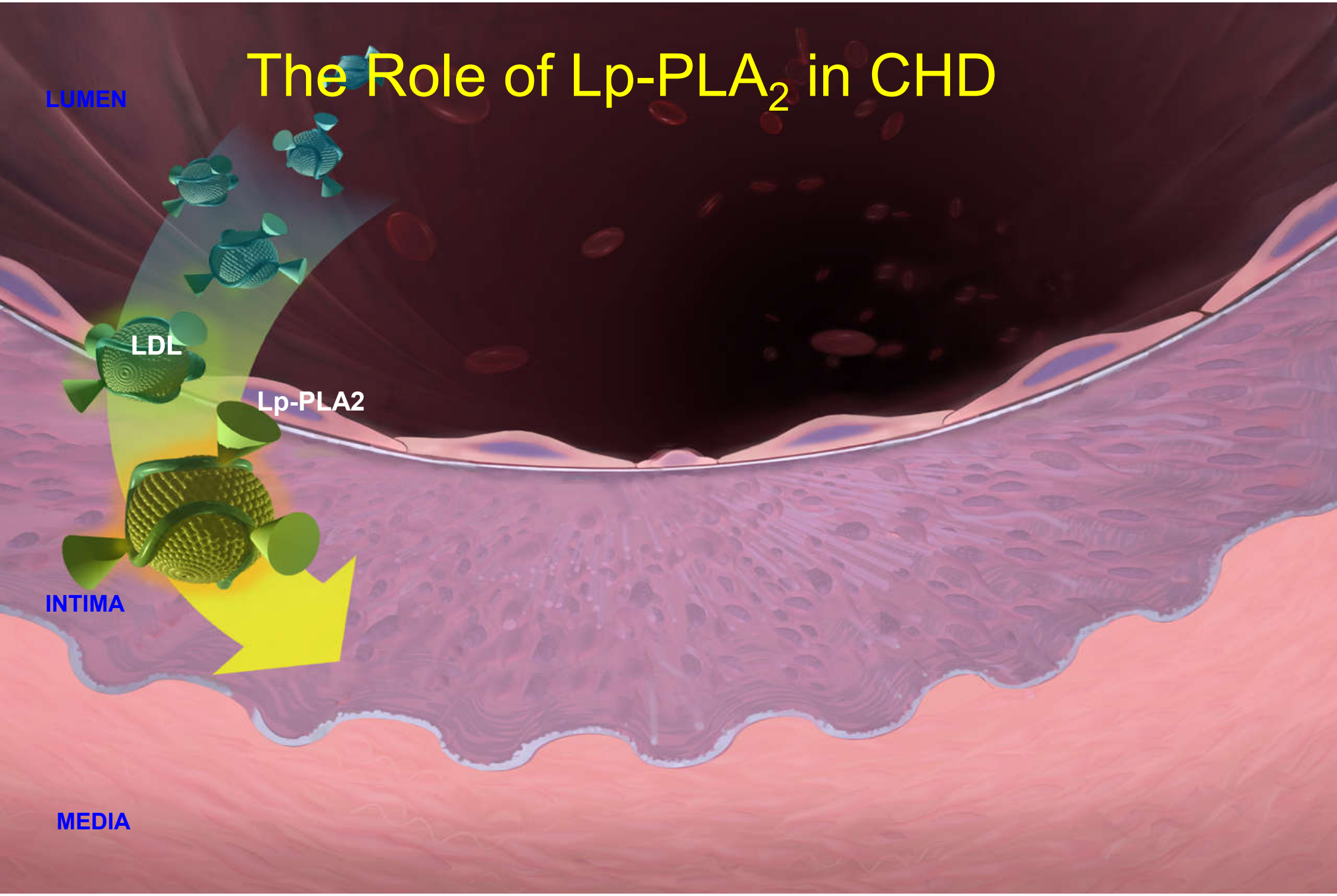
- Prolonged half-life in plasma
- Better penetration into the intima
- Binding to proteoglycans due to exposure of binding sites on the particle surface
- More easily modified by oxidation

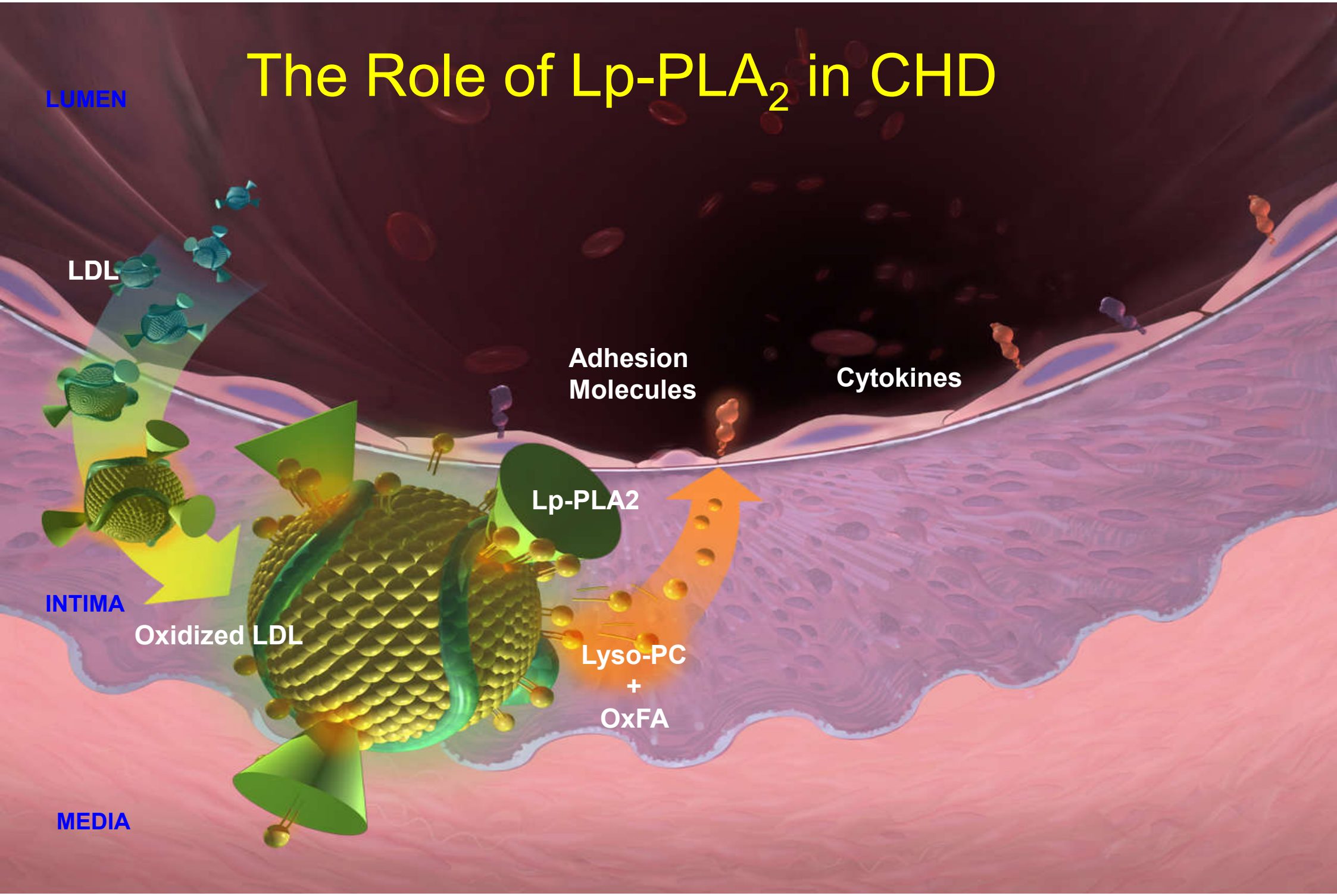


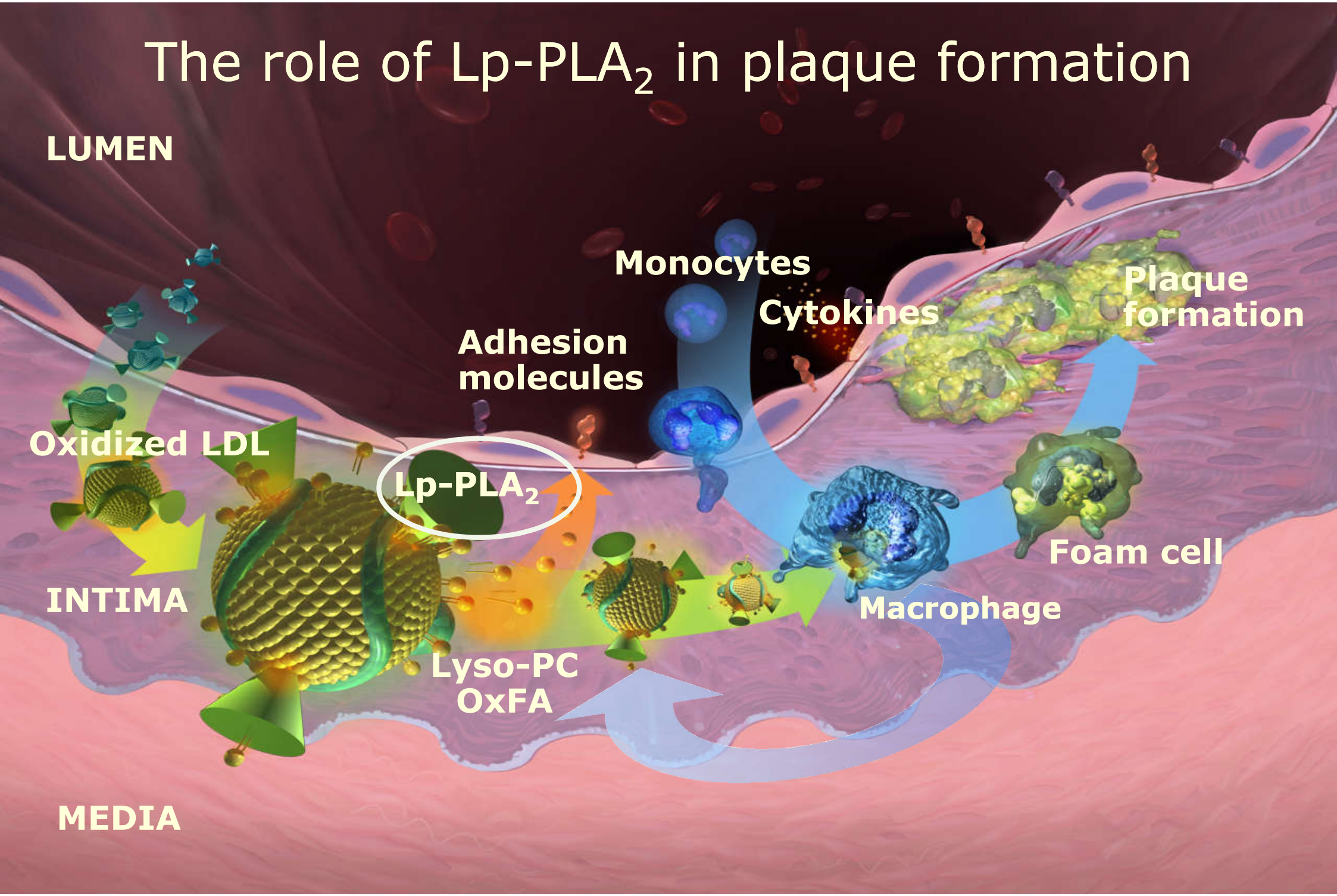


"European Panel on Low Density Lipoprotein (LDL) Subclasses": A Statement on the Pathophysiology, Atherogenicity and Clinical Significance of LDL Subclasses

Dimitri P. Mikhailidis[1,*], Moses Elisaf[2], Manfredi Rizzo[3], Kaspar Berneis[4], Bruce Griffin[5], Alberto Zambon[6], Vasilios Athyros[7], Jacqueline de Graaf[8], Winfried März[9], Klaus G. Parhofer[10], Giovam Battista Rini[3], Giatgen A. Spinas[4], Gerald H. Tomkin[11], Alexandros D. Tselepis[12], Anthony S. Wierzbicki[13], Karl Winkler[14], Matilda Florentin[2] and Evangelos Liberopoulos[2]

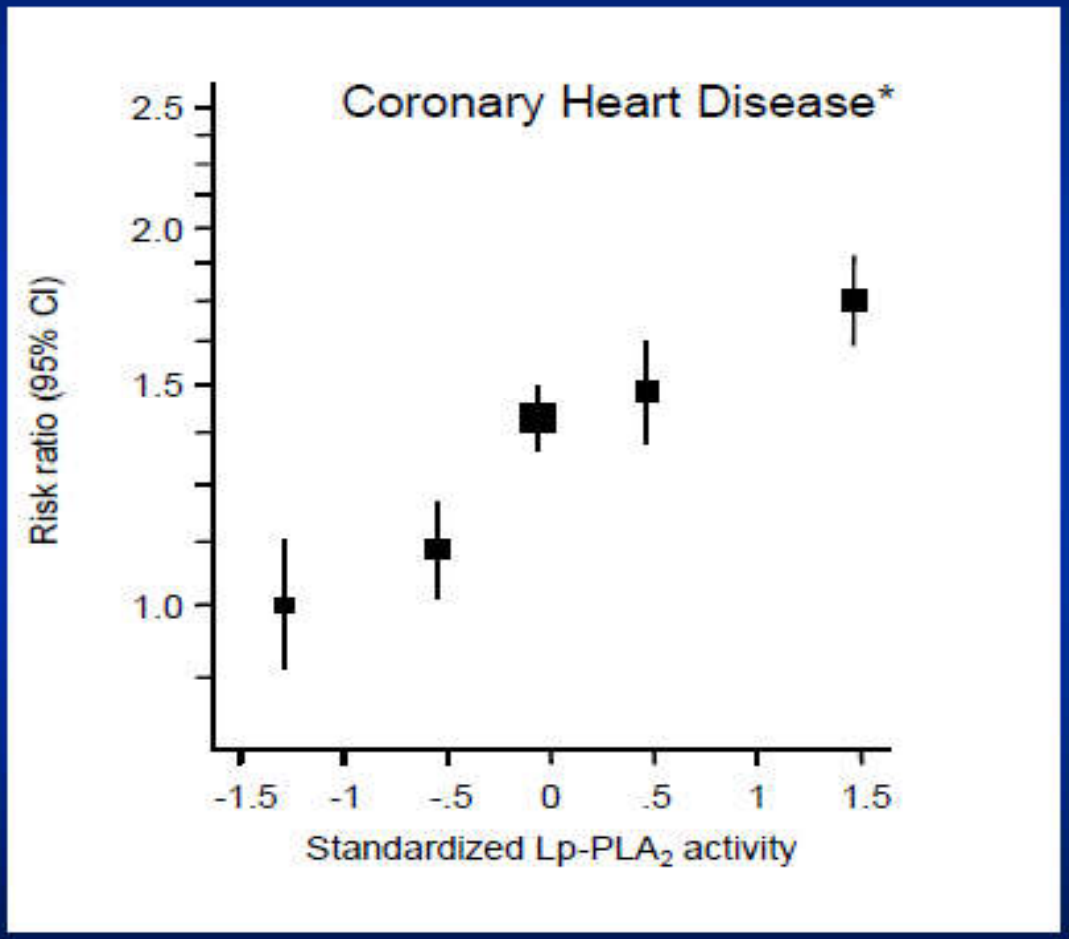

The Role of Lp-PLA2 in CHD
LUMEN
LDL
Lp-PLA2
INTIMA
MEDIA

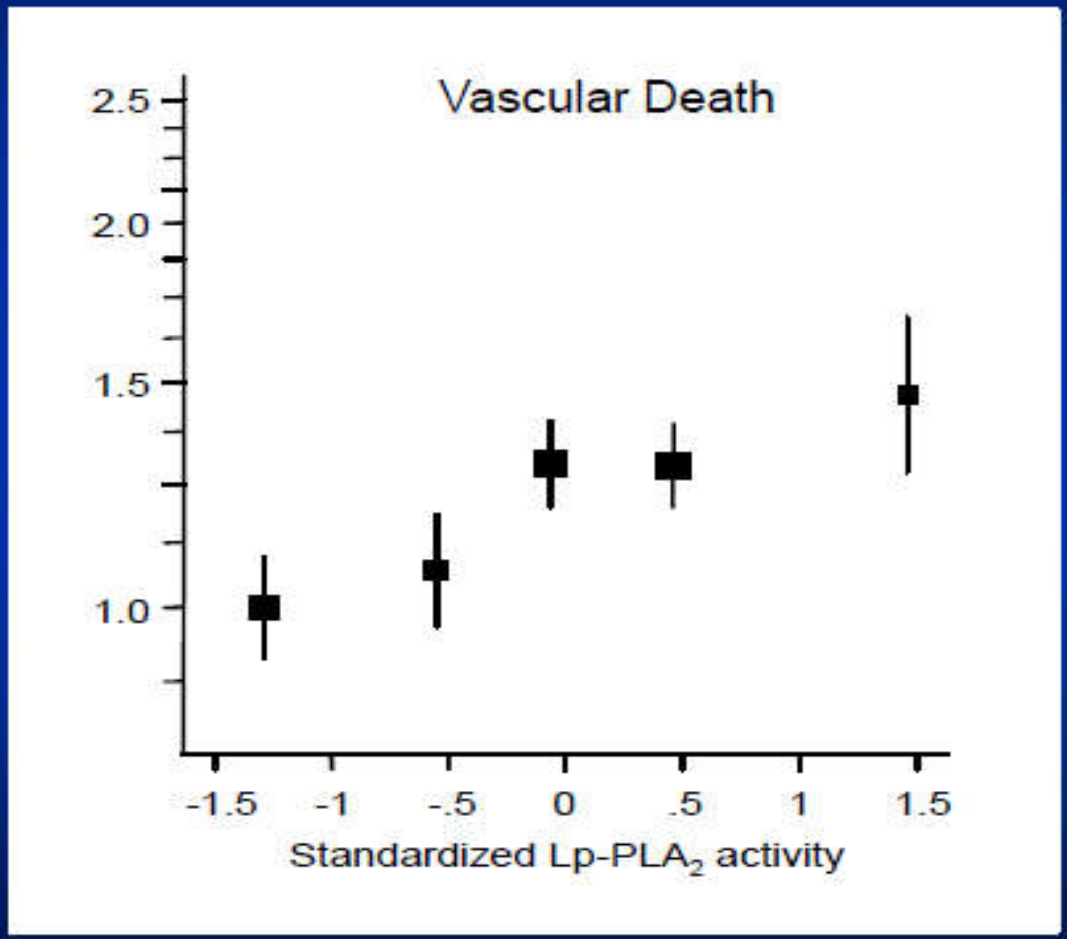

The Role of Lp-PLA2 in CHD
LUMEN
LDL
Adhesion Molecules
Cytokines
Lp-PLA2
INTIMA
Oxidized LDL
Lyso-PC
+
OxFA
MEDIA


The role of Lp-PLA2 in plaque formation
LUMEN
Monocytes
Cytokines
Plaque formation
Adhesion molecules
Oxidized LDL
Lp-PLA2
Foam cell
INTIMA
Macrophage
Lyso-PC
OxFA
MEDIA

Lp-PLA$_2$ activity and risk of CV outcomes

79,036 participants, 32 prospective studies





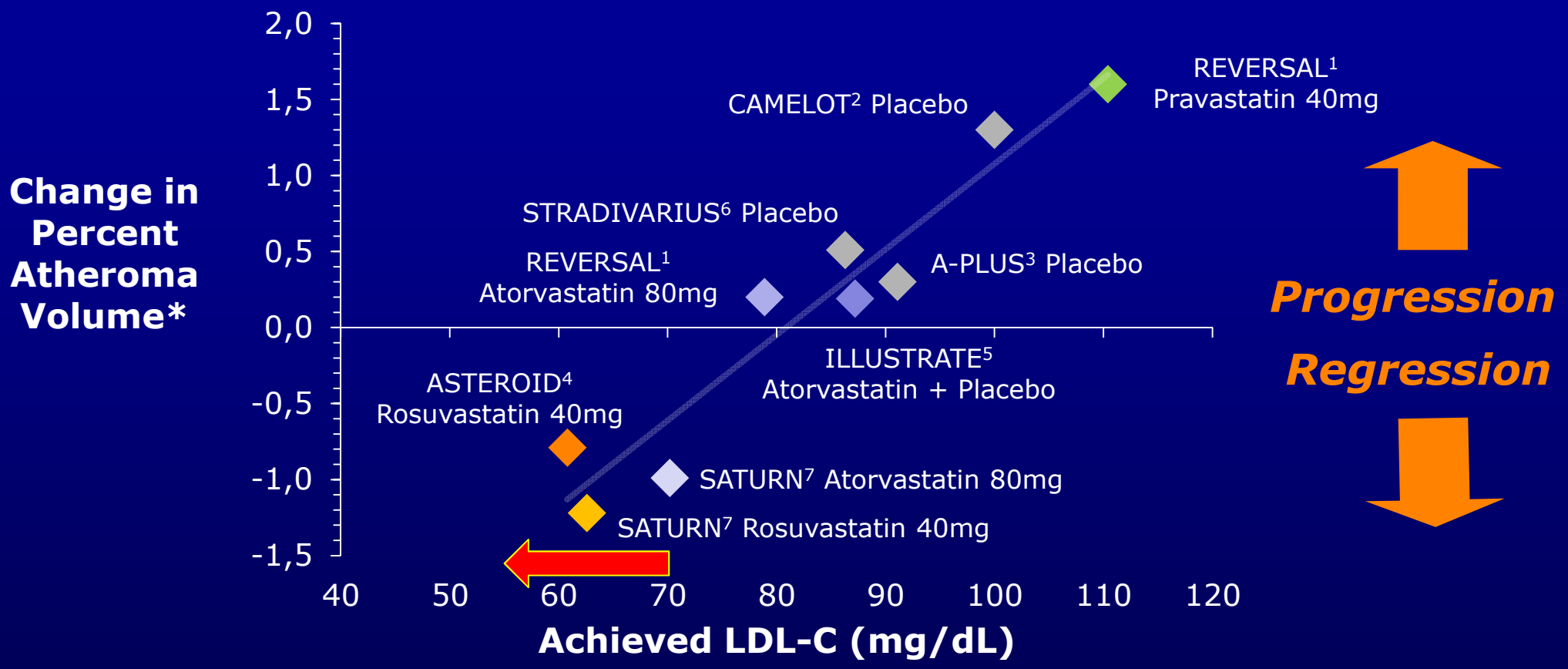
Adjusted for age, sex, diabetes and baseline history of vascular disease

Lp-PLA$_2$ Studies Collaboration. *Lancet* 2010;375:1536-44

↓ LDL-CHOL → ↓ ΑΘΗΡΩΜΑΤΩΣΗΣ: ΔΕΔΟΜΕΝΑ ΚΛΙΝΙΚΩΝ ΜΕΛΕΤΩΝ

Results

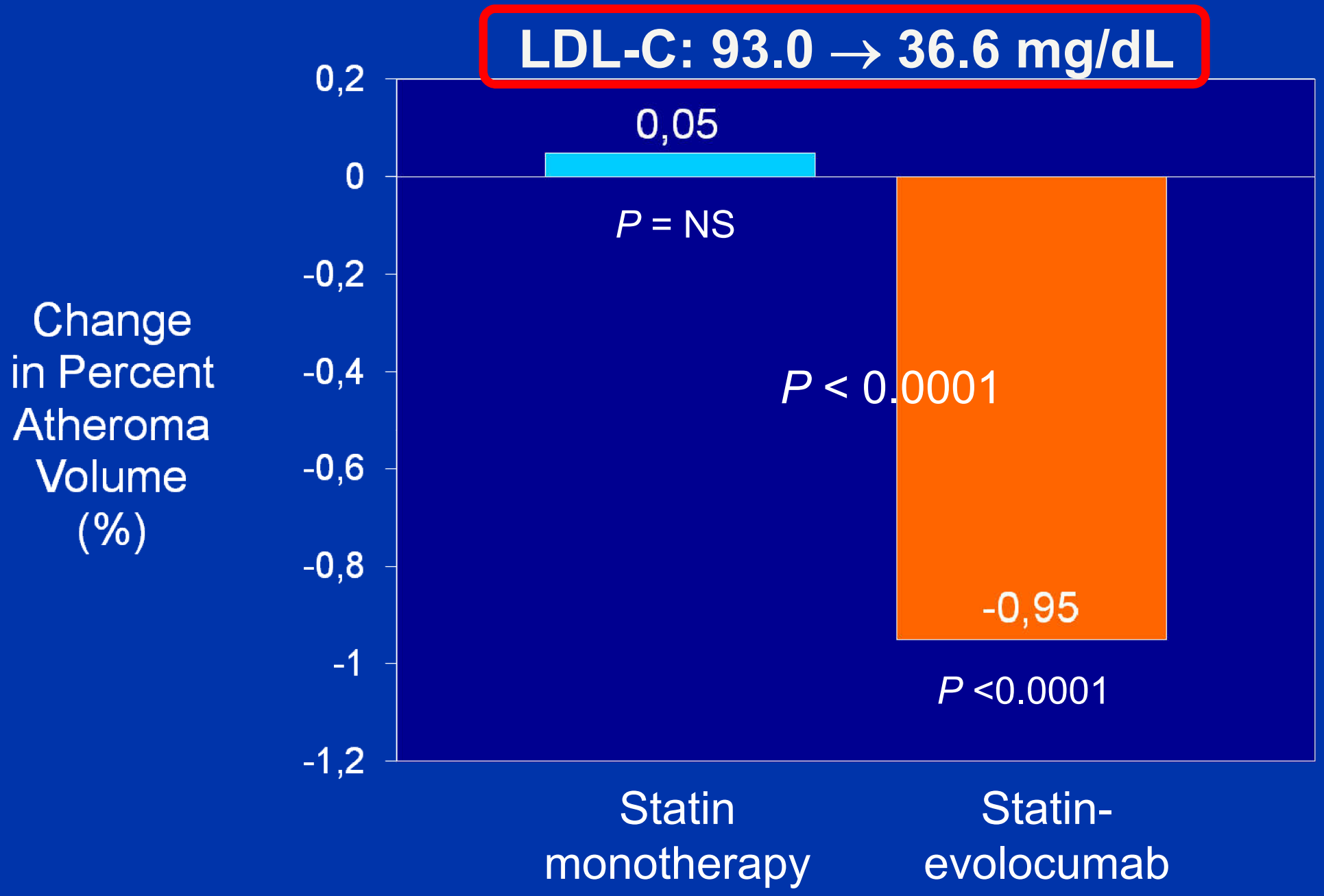
Relationship between achieved LDL-C and change in PAV



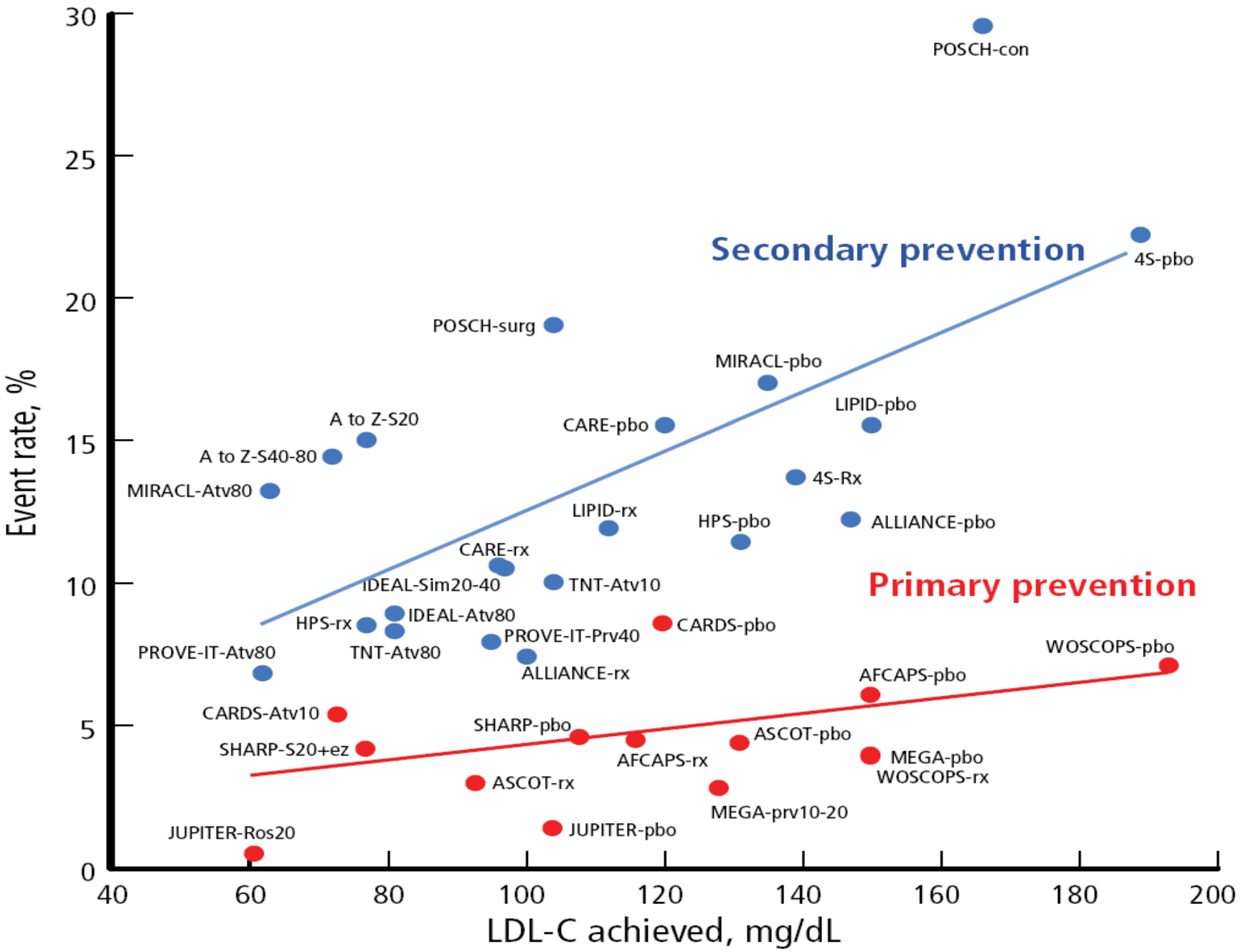
Summary of trials employing IVUS to measure changes in atheroma burden. A-PLUS, CAMELOT, ILLUSTRATE and STRADIVARIUS investigated non-statin therapies but included placebo arms who received background statin therapy (62%, 80%, 84%, 100% and 82% respectively). † In ILLUSTRATE atorvastatin was initiated at 10mg during the run-in period and dose titrated up to 80mg to a target LDL-C within 15mg/dL of 100mg/dL. The average dose was 23mg. Patients then remained on this dose during the study. LDL-C levels in CAMELOT are baseline and in A-PLUS are calculated from change from baseline. *Median change in PAV from ASTEROID, REVERSAL & SATURN; LS mean change in PAV from A-PLUS, CAMELOT, ILLUSTRATE & STRADIVARIUS.

1) Nissen S et al. *JAMA* 2004; 291: 1071–80; 2) Nissen S et al. *JAMA* 2004; 292: 2217–2225; 3) Tardif J et al. *Circulation* 2004; 110: 3372–77; 4) Nissen S et al. *JAMA* 2006; 295: 1556–1565; 5) Nissen S *et al. N Engl J Med* 2007; 356: 1304–16; 6) Nissen S et al. *JAMA* 2008; 299: 1547-1560; 7) Nicholls SJ et al. New Eng J. Med. 2011: DOI: 10.1056/NEJMoa1110874

GLACOV STUDY Primary Endpoint: Percent Atheroma Volume

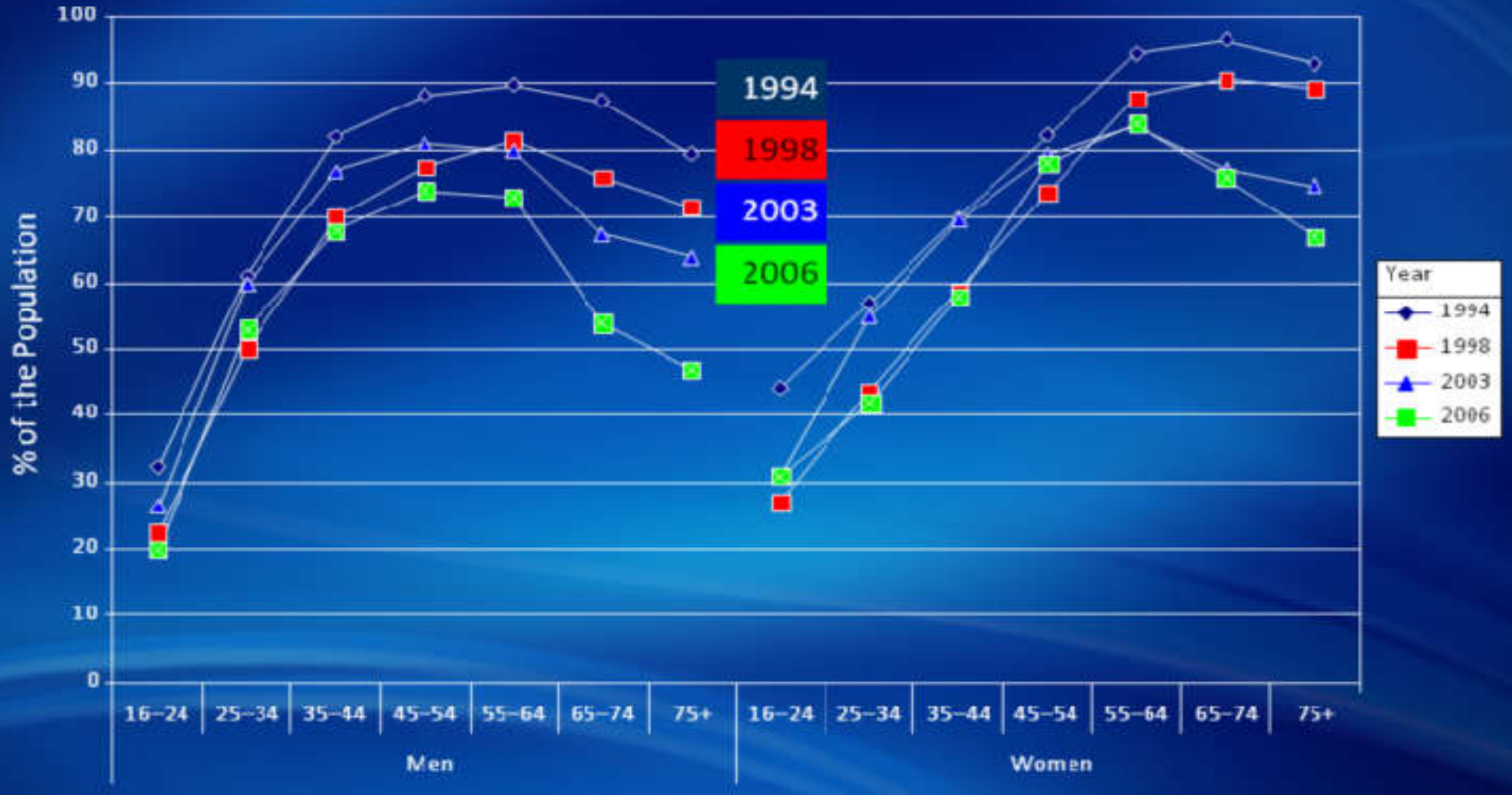


Major lipid trials:
LDL-C levels vs rates of coronary events

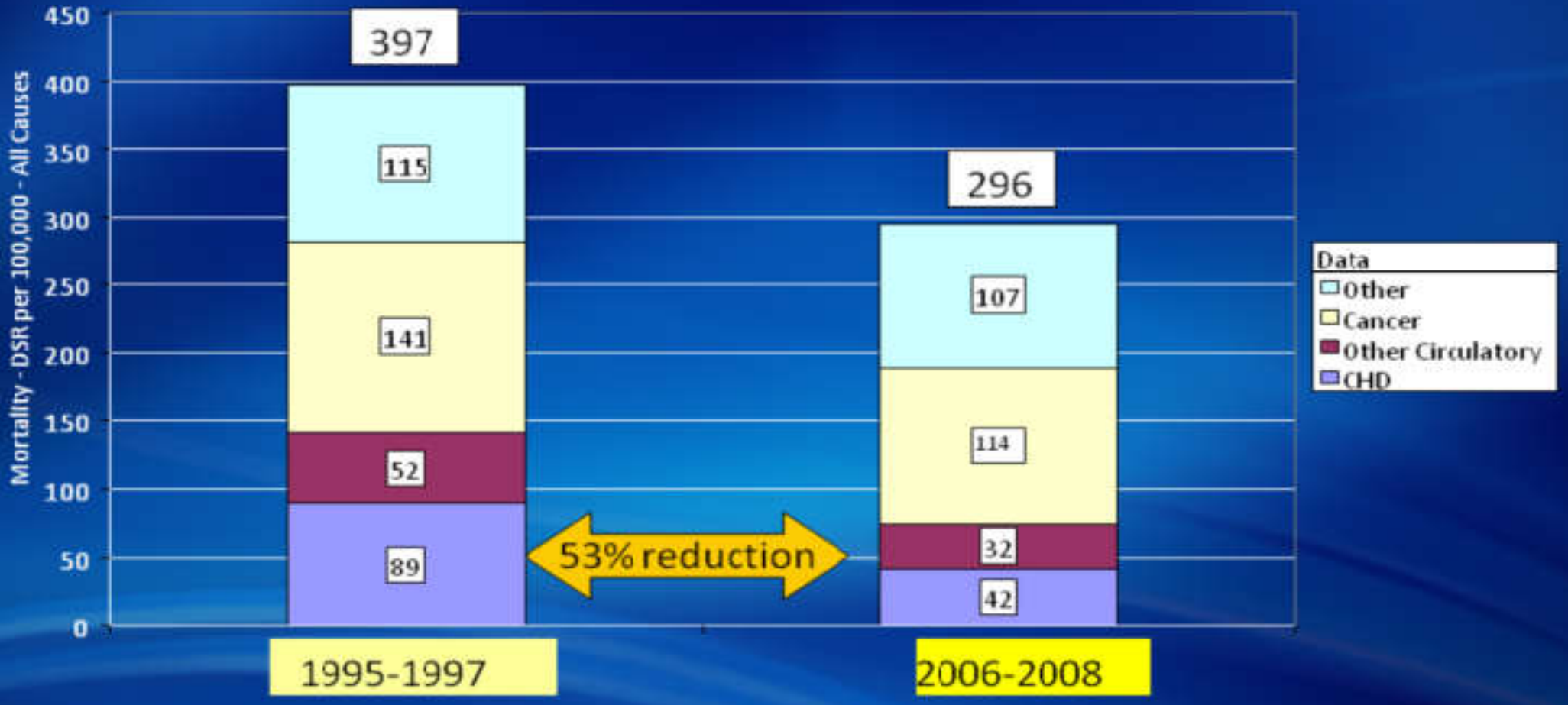


Percentage of the UK-population with TC > 5 mmol/l

(>193 mg/dL)



All-Cause Mortality in the UK in those < 75 Years



Effect of Long-Term Exposure to Lower Low-Density Lipoprotein Cholesterol Beginning Early in Life on the Risk of Coronary Heart Disease

A Mendelian Randomization Analysis

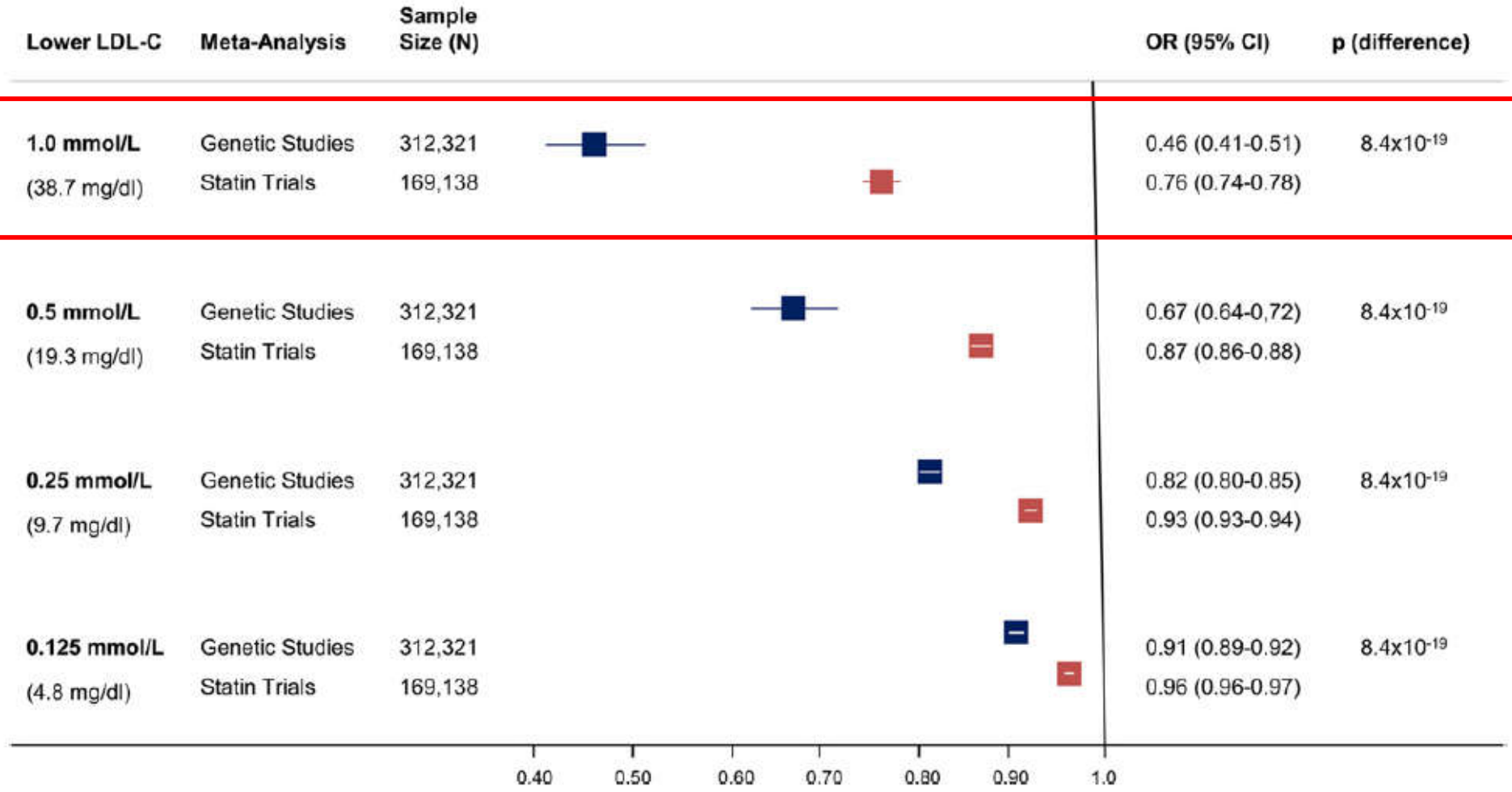
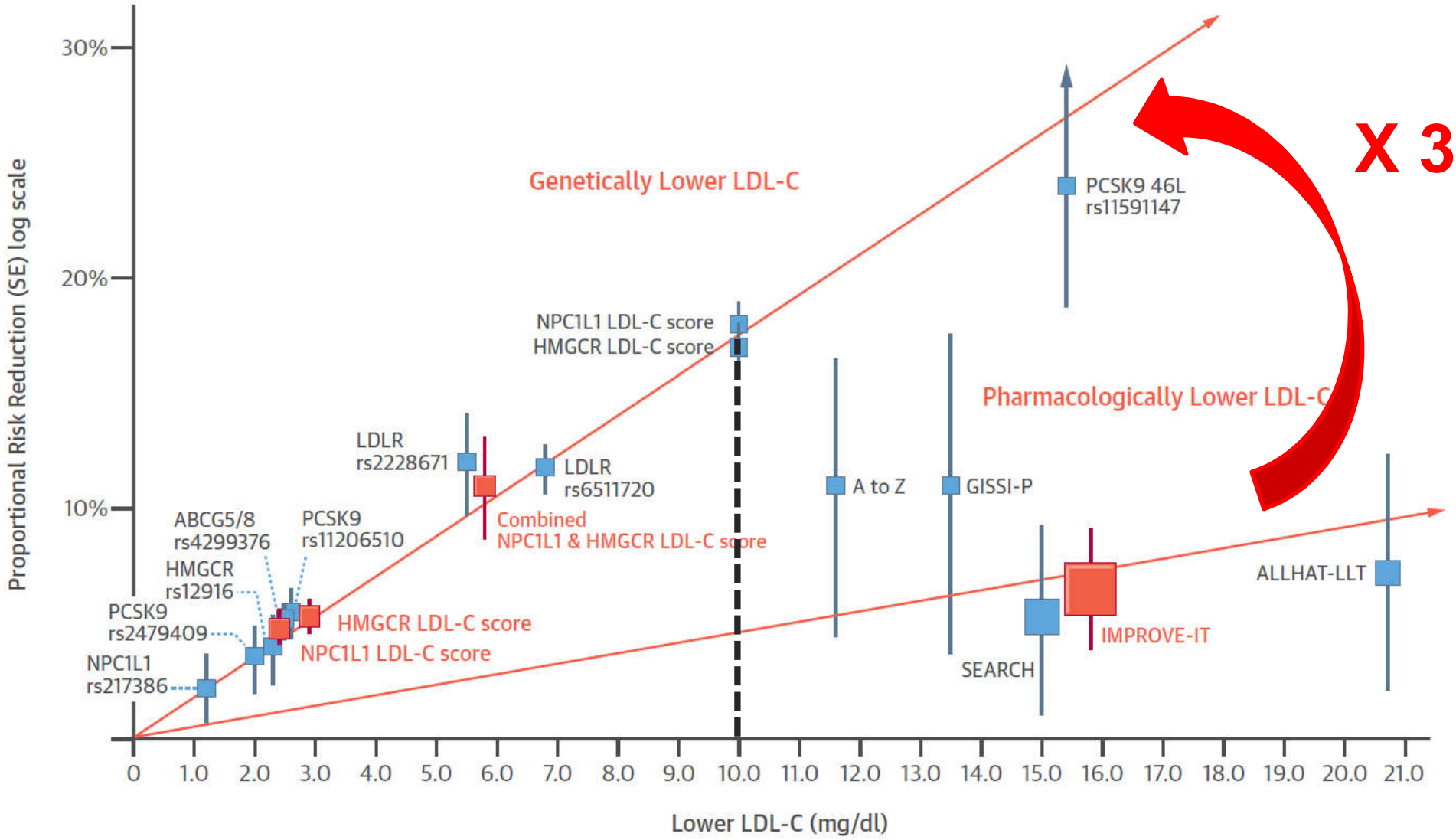


Figure 5 Comparative CHD Risk Reduction of Earlier and Later LDL-C Lowering

JACC Vol. 60, No. 25, 2012
December 25, 2012:2631–9

CENTRAL ILLUSTRATION **2 × 2 Factorial Mendelian Randomization Study: Log-Linear Association Between Genetically and Pharmacologically Mediated Lower Low-Density Lipoprotein Cholesterol and Risk of Coronary Heart Disease**



JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY

LDL-CHOL: LOWER IS BETTER

+

EARLIER IS BETTER

Darapladib Phase III Clinical Program

Chronic CHD patients with high-risk features*

Randomization to Darapladib or Placebo

n= 15,898
(3.7 year median follow-up)

ACS patients (NSTE- or STE-ACS) with high-risk features*

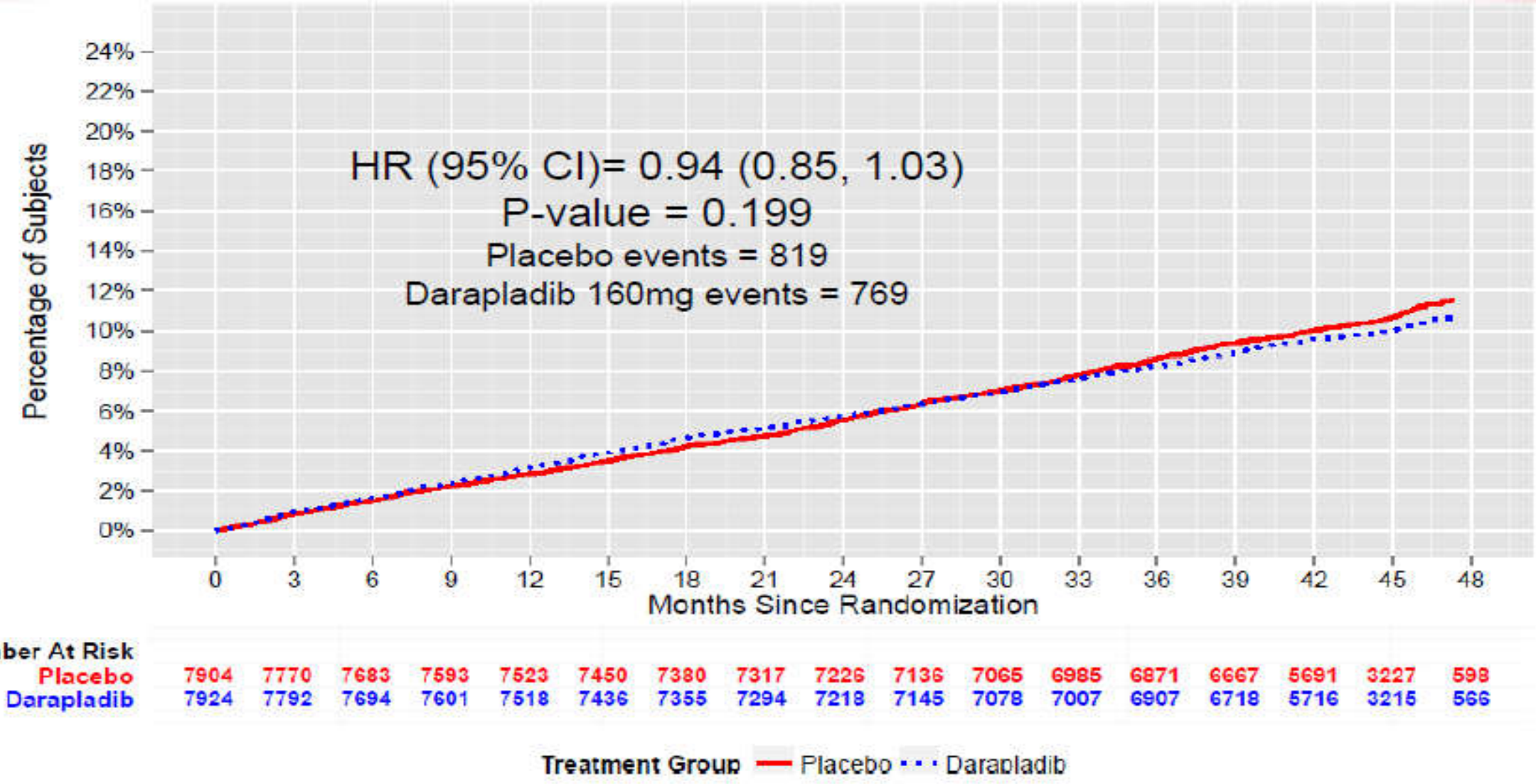
Randomization ≤30 days from hospitalization with ACS

Randomization to Darapladib or Placebo

n= 13,026
(2.5 year median follow-up)

* High-risk criteria (≥1 of the following): age ≥60 years, diabetes mellitus requiring Rx, eGFR 30-59 ml/min/1.73 m^2, polyvascular disease, HDL <40 mg/dl (STABILITY only), tobacco use (STABILITY only), or prior MI (SOLID-TIMI 52 only)

Primary Endpoint:
Time to First Occurrence CV Death, MI, Stroke



STABILITY

STABILITY Trial

15,828 patients with stable CHD randomized to darapladib 160mg QD vs placebo

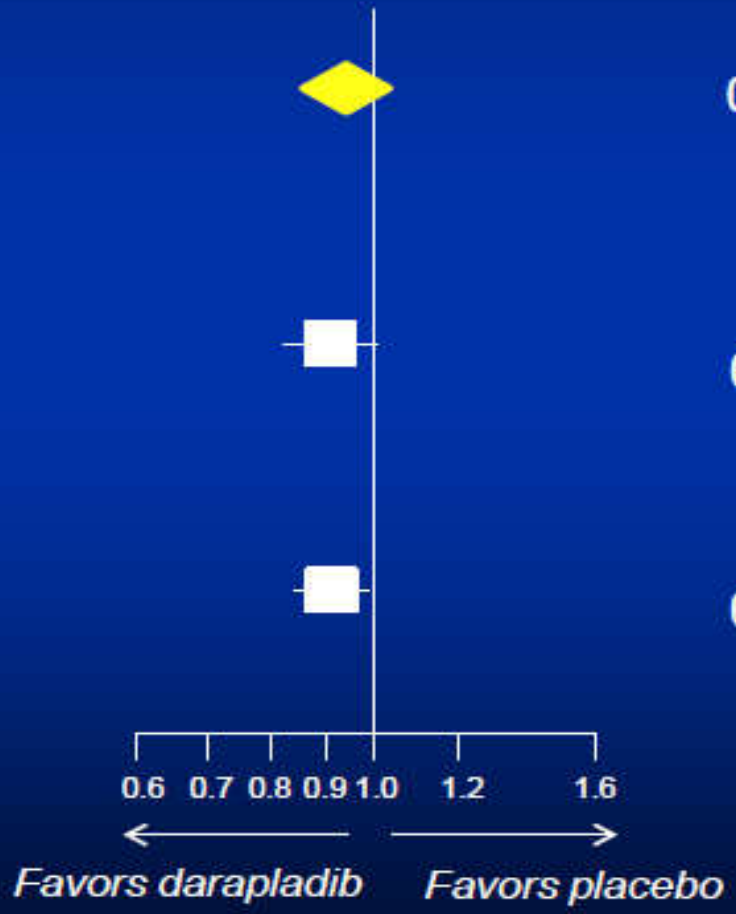
Primary Endpoint

CV death, MI or stroke

Selected Secondary Endpoints

Major Coronary Events:
(CHD death, MI or urgent coronary revascularization for myocardial ischemia)

Total Coronary Events:
(CHD death, MI, hospitalization for UA or any coronary revascularization)



White et al., *N Engl J Med* 2014; 370:1702-11.

SOLID TIMI 52

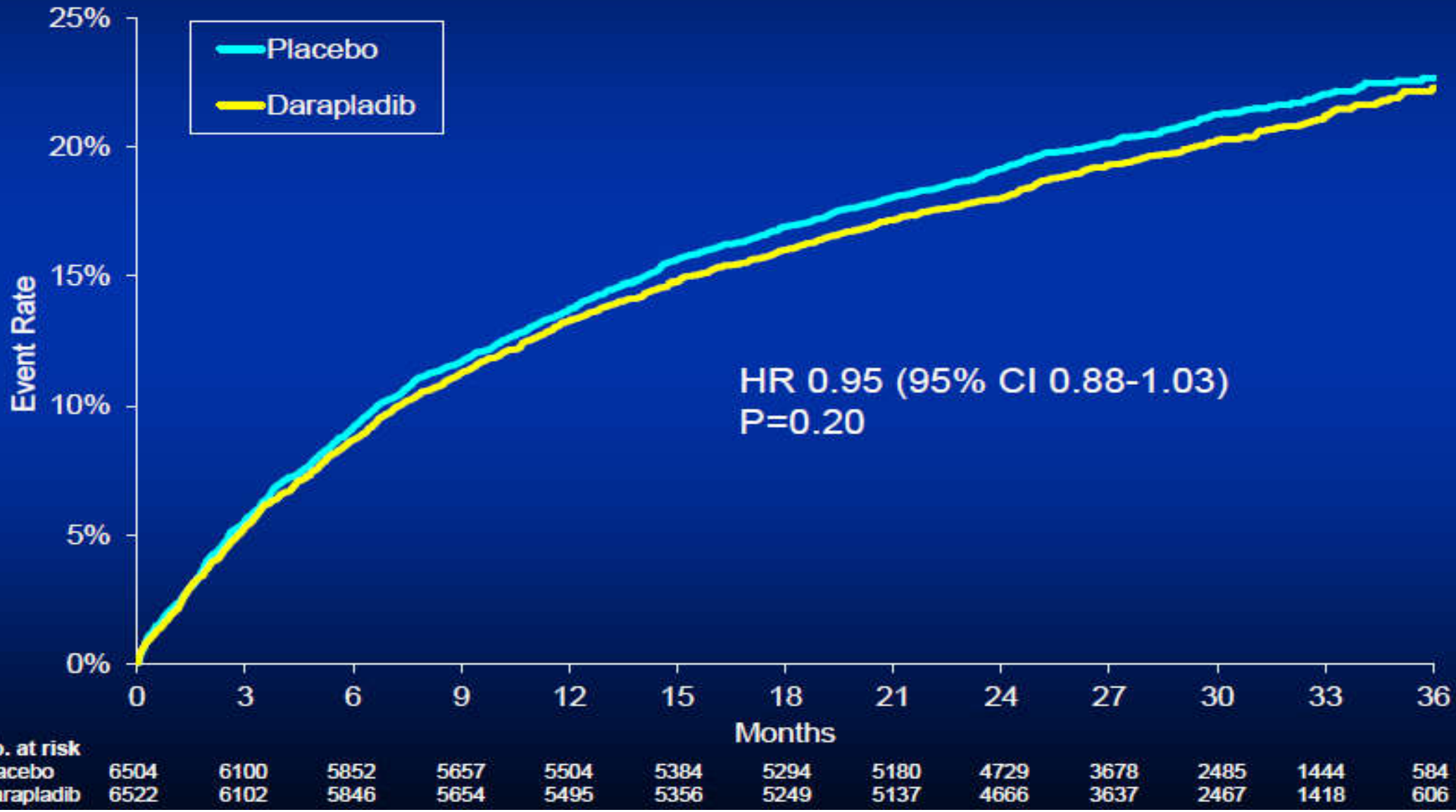
Primary Endpoint: CHD death, MI or urgent coronary revascularization

No. at risk													
Placebo	6522	6219	6060	5945	5825	5726	5638	5544	5046	3942	2684	1550	669
Darapladib	6504	6201	6038	5902	5787	5708	5636	5534	5061	3955	2673	1558	634

SOLID TIMI 52

Total coronary events

(CHD death, MI, UA or any coronary revascularization)



No. at risk													
Placebo	6504	6100	5852	5657	5504	5384	5294	5180	4729	3678	2485	1444	584
Darapladib	6522	6102	5846	5654	5495	5356	5249	5137	4666	3637	2467	1418	606

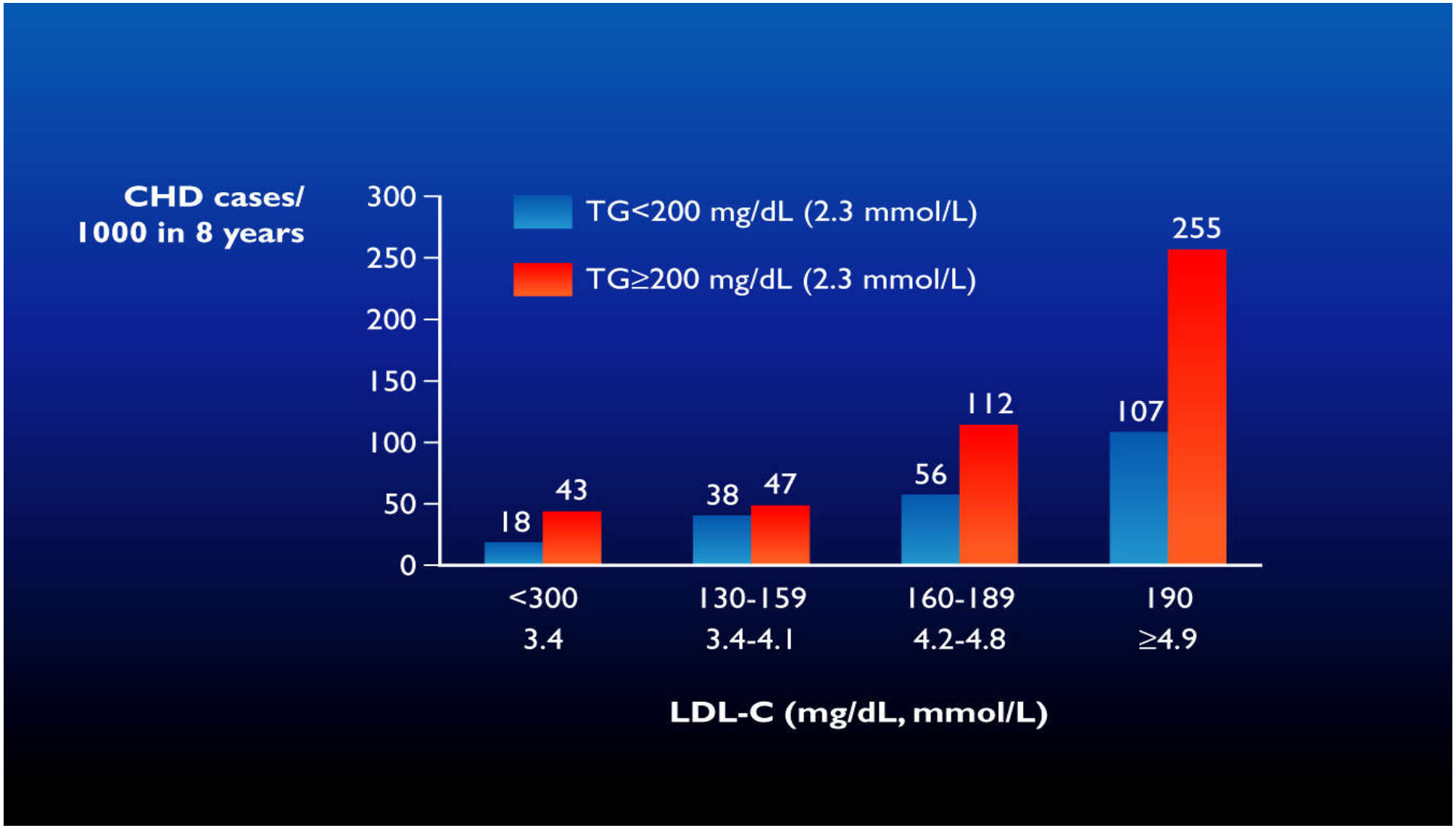
ΠΛΟΥΣΙΕΣ ΣΕ ΤΡΙΓΛΥΚΕΡΙΔΙΑ ΛΙΠΟΠΡΩΤΕΪΝΕΣ-VERY LOW-DENSITY LIPOPROTEINS (VLDL) & REMNANTS

↑ TGs → ↑ ΑΘΗΡΩΜΑΤΩΣΗΣ: ΕΠΙΔΗΜΙΟΛΟΓΙΚΑ ΔΕΔΟΜΕΝΑ

PROCAM Study

CHD risk according to LDL-C and TG

increased TG confers raised CHD risk at all levels of LDL-C



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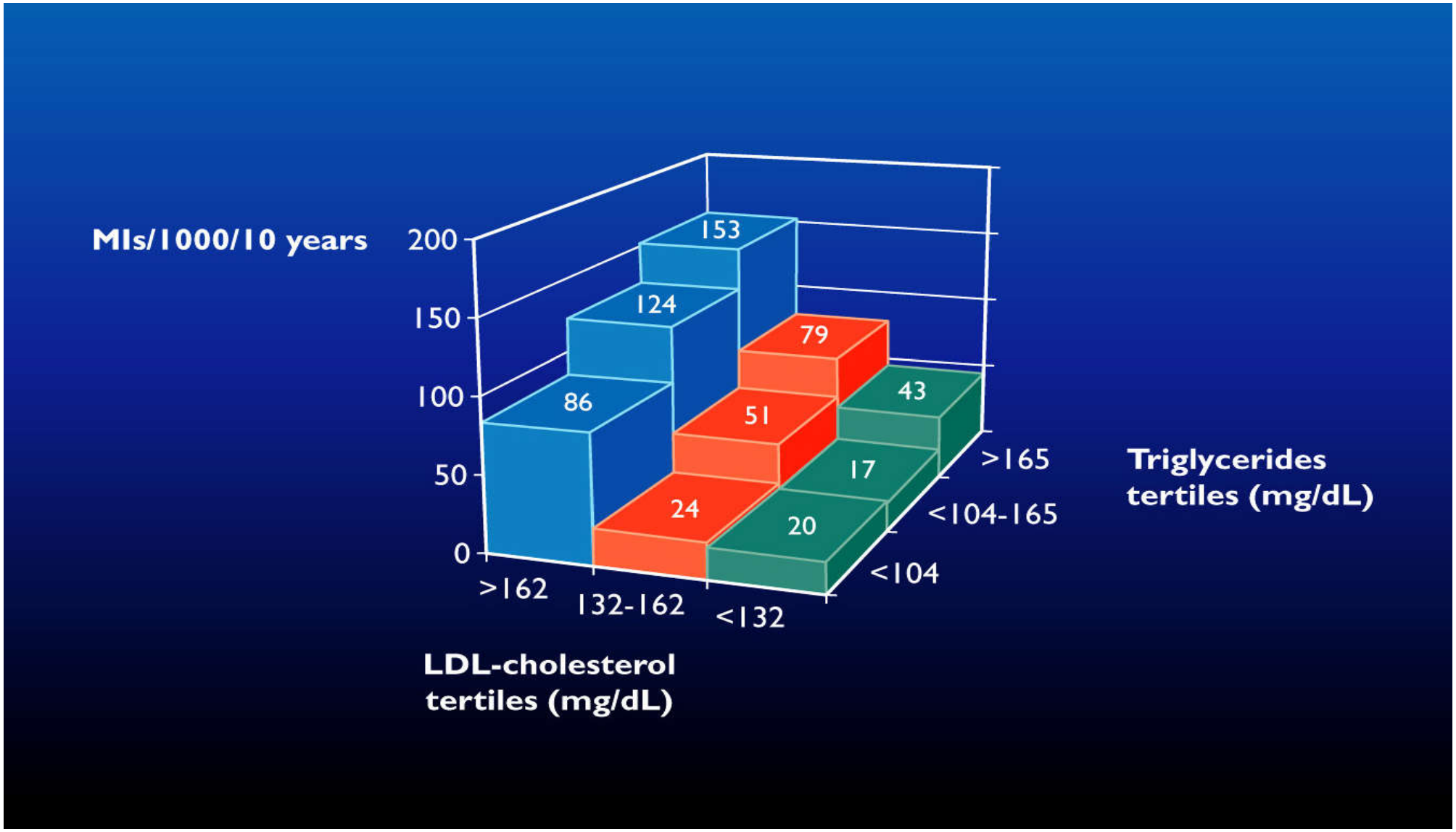
PROCAM Study

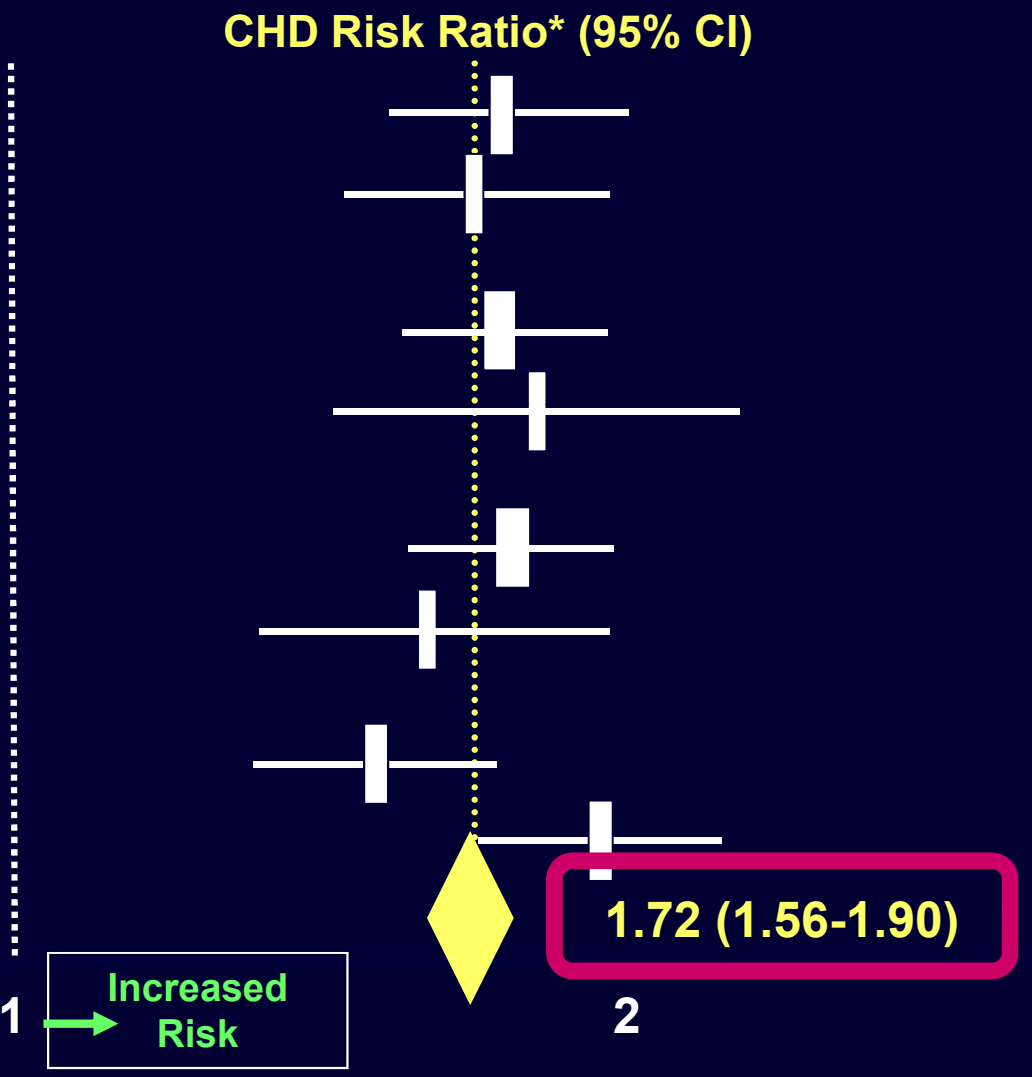
MI-Incidence according to LDL-cholesterol and triglycerides



Triglycerides and CVD Factor Recent Meta-Analysis of 29 Studies

N = 262 525

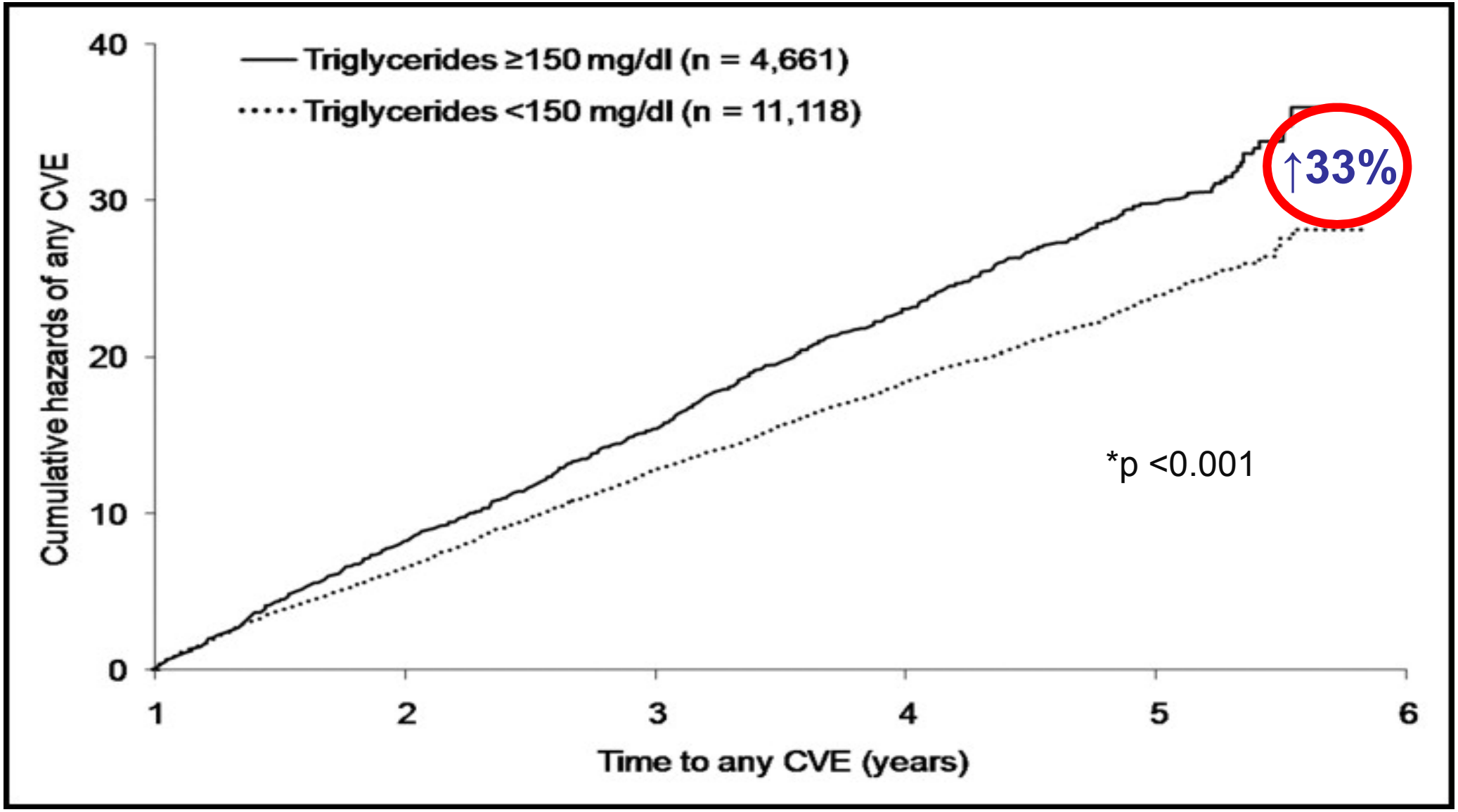
Groups	CHD Cases
Duration of follow-up	
≥10 years	5902
<10 years	4256
Sex	
Male	7728
Female	1994
Fasting status	
Fasting	7484
Nonfasting	2674
Adjusted for HDL	
Yes	4469
No	5689
Overall CHD Risk Ratio*	



↑ TGs κατά 100 mg/dL → ↑ κινδύνου κατά 70%

Sarwar N, et al. *Circulation.* 2007;115:450-458.

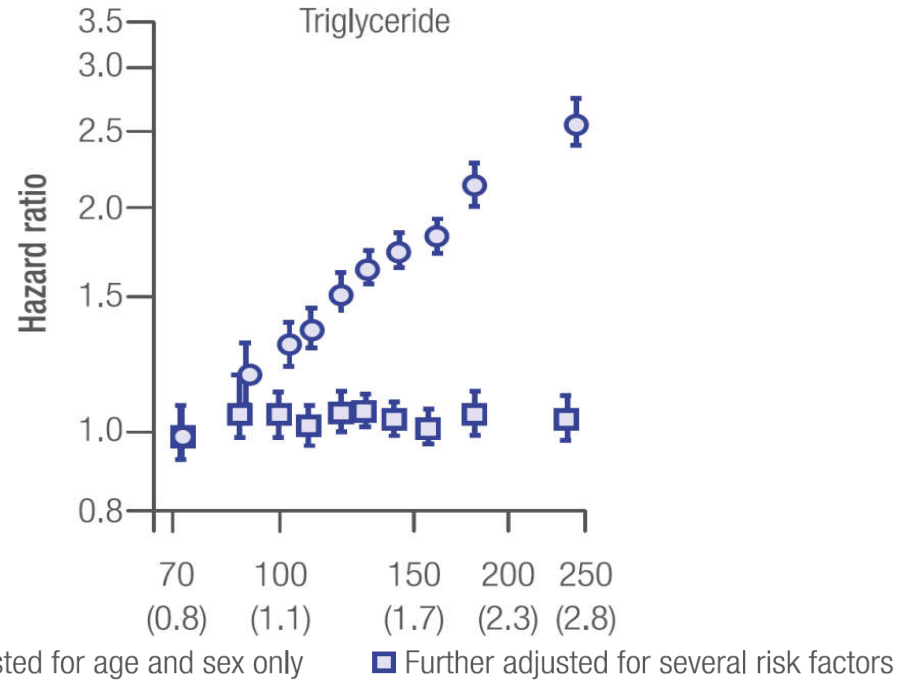
CUMULATIVE HAZARDS OF ANY CVE BY ON-TREATMENT TGs IN THE IDEAL AND TNT STUDIES



Am J Cardiol 2009;104:459-63

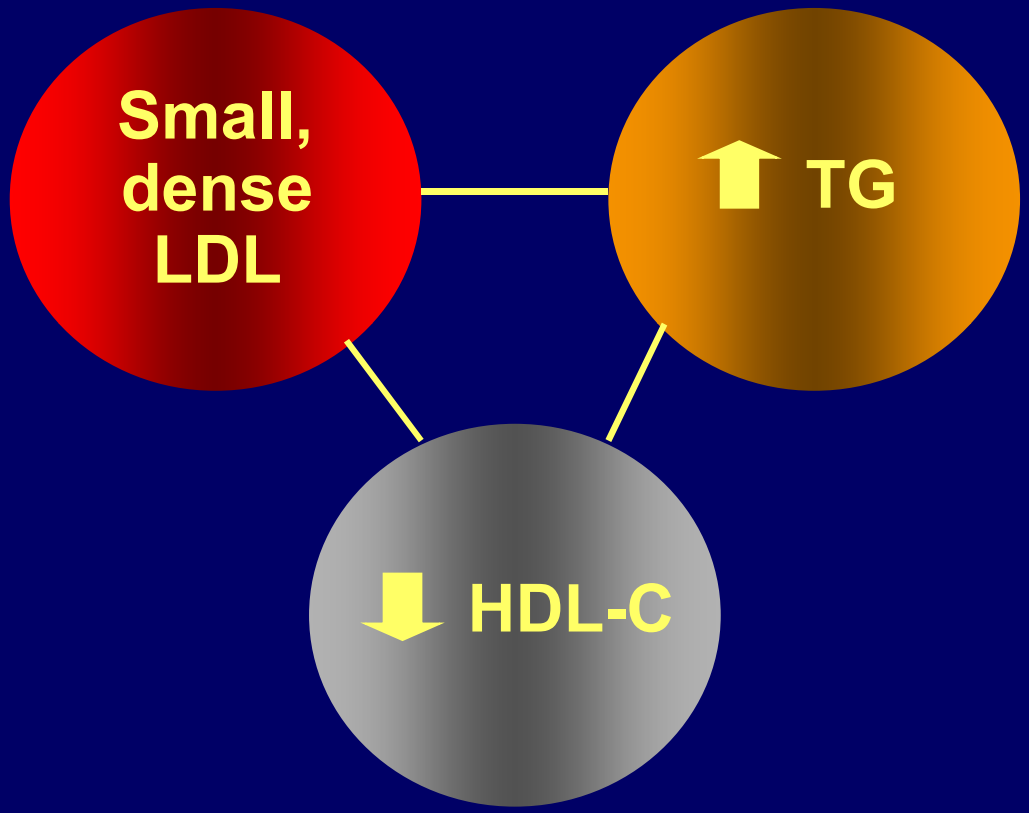
What about hypertriglyceridemia in cardiovascular prevention?

- Triglycerides is a strong risk factor.
- However never shown to be independent of other risk factors.
- Is triglycerides causing disease?



The Emerging Risk Factors Collaboration. Major lipids, apolipoproteins, and risk of vascular disease. *JAMA* 2009;**302**:1993–2000.

Low HDL cholesterol – dyslipidaemia in type 2 diabetes and metabolic syndrome



- Low levels of HDL-C
- High levels of triglycerides (especially triglyceride-rich VLDL)
- LDL-C normal or below average; increase in small, dense LDL particles

American Diabetes Association, Diabetes Care 2006; **29** (Suppl 1): S4-S42.

Genetic studies support that high TG causes CVD

- Mendelian randomisation, strongly suggest causal relation between TG-rich lipoprotein sand risk of CVD
  - Gene variants associated with TG-level associated with risk.

Common variants associated with plasma triglycerides and risk for coronary artery disease

In summary, we utilize common polymorphisms and employ a statistical framework to dissect causal influences among a set of correlated biomarkers. By applying this framework to a correlated set of plasma lipid measures and CAD risk, we suggest a causal role of triglyceride-rich lipoproteins in the development of CAD.

Nat Genet. 2013 November ; 45(11): 1345–1352. doi:10.1038/ng.2795.

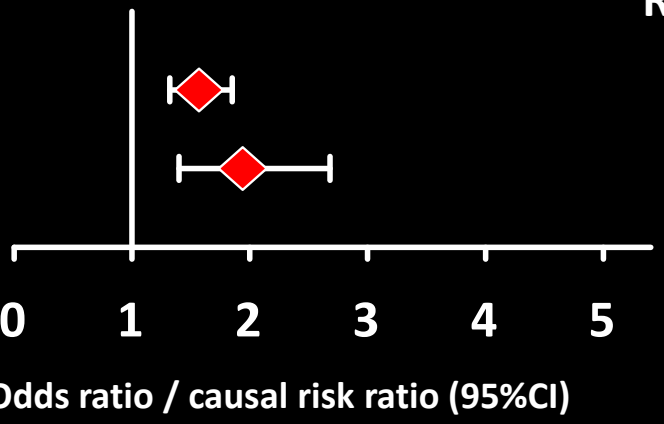
Apolipoprotein A5

Triglyceride doubling in levels

	N total	N events	Risk estimate
Observational	10,391	1,098	1.6
Causal using genetics	60,113	5,705	1.9

From Jørgensen Eur Heart J 2013; 34: 1826-33

Myocardial infarction



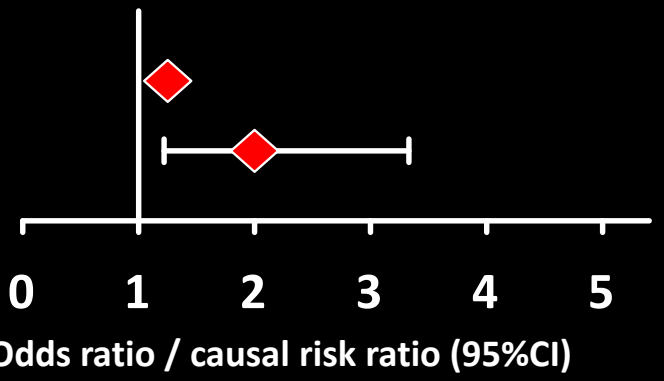
Lipoprotein lipase (LPL)

Triglyceride increase of 1 mmol/L

Observational	13,957	9,991	1.2
Causal using genetics	10,208	4,005	2.0

From Thomsen Clin Chem 2014; 60: 737-46

All-cause mortality



Nordestgaard & Varbo, Lancet 2014; 384: 626-635

Clinical Chemistry 60:5
737–746 (2014)

fast track

Low Nonfasting Triglycerides and Reduced All-Cause Mortality: A Mendelian Randomization Study

Mette Thomsen,[1,2] Anette Varbo,[1,2] Anne Tybjærg-Hansen,[2,3,4] and Børge G. Nordestgaard[1,3,4*]

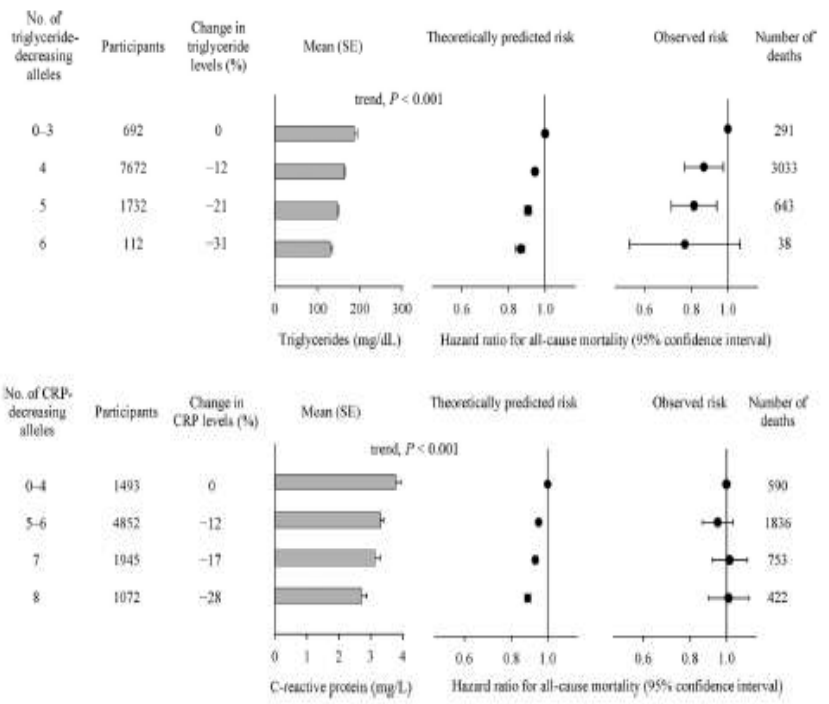


Fig. 4. Theoretically predicted and observed all-cause mortality by number of triglyceride-decreasing alleles and CRP-decreasing alleles.

Hazard ratios were adjusted for age (as timescale), sex, hypertension, smoking status, alcohol intake, and use of lipid-lowering medication.

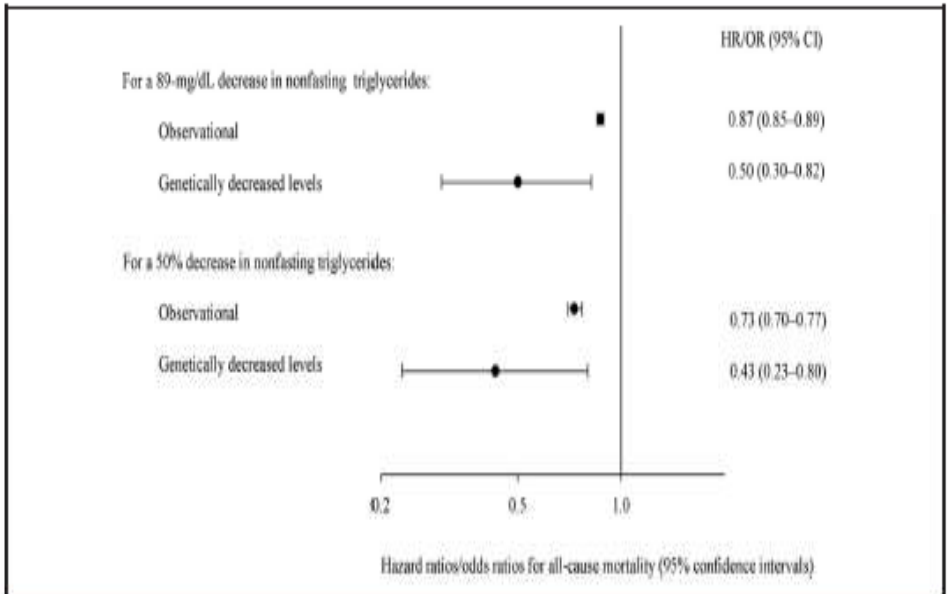


Fig. 5. Genetic and observational risk estimates for an 89-mg/dL (1-mmol/L) decrease and a 50% decrease of nonfasting plasma triglycerides.

Instrumental variable analyses were used to estimate genetically derived odds ratios. Hazard ratios were adjusted for age (as timescale), sex, hypertension, smoking status, alcohol intake, and use of lipid-lowering medication. HR, hazard ratio; OR, odds ratio.

Apo C3, TRG και καρδιαγγειακή νόσος: Complexities of Mendelian Randomization

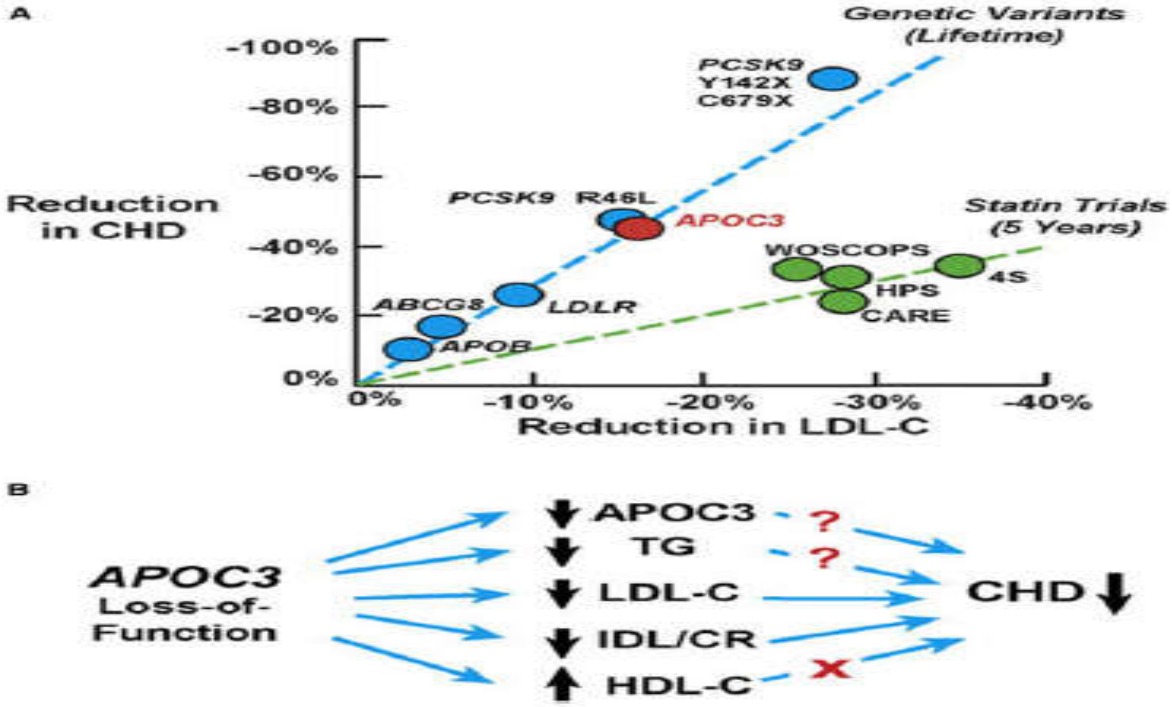


Figure 1. Genetic and Pharmacological Reduction in LDL-C and Coronary Heart Disease
(A) Reduction in CHD risk associated with genetic variants (blue circles) and pharmacological agents (green circles) that lower plasma levels of LDL-C. Genetic variations that reduce plasma LDL-C levels are associated with a greater reduction in CHD compared to that seen in statin trials. The sources of the data shown in this figure are as follows: *APOB* rs754523 (PMID: 18193043), *LDLR* rs2228671 (PMID: 18714375), *ABCG8* rs4245791 (PMID: 24657701), and *PCSK9* (PMID: 16554528). The red circle represents the CHD reduction (~46%) that is predicted for a loss-of-function mutation in *APOC3* (R19X) (Crosby et al., 2014; Pollin et al., 2008). WOSCOPS, The West of Scotland Coronary Prevention Study (PMID: 7566020); CARE, Cholesterol and Recurrent Events Trial (PMID: 8801446); HPS, Heart Protection Study (PMID: 12114036); 4S, The Scandinavian Simvastatin Survival Study (PMID: 7968073).
(B) Effects of *APOC3* loss-of-function variants on circulating lipid and lipoprotein levels and on CHD. Proven causal links are indicated by blue arrows. Question marks indicate where causality has not been established. The red X indicates no causal relationship. IDL, intermediate density lipoprotein; CR, chylomicron remnant.

ΑΥΞΗΣΗ ΤΩΝ TRG ΚΑΙ ΚΑΡΔΙΑΓΓΕΙΑΚΗ ΝΟΣΟΣ (1)

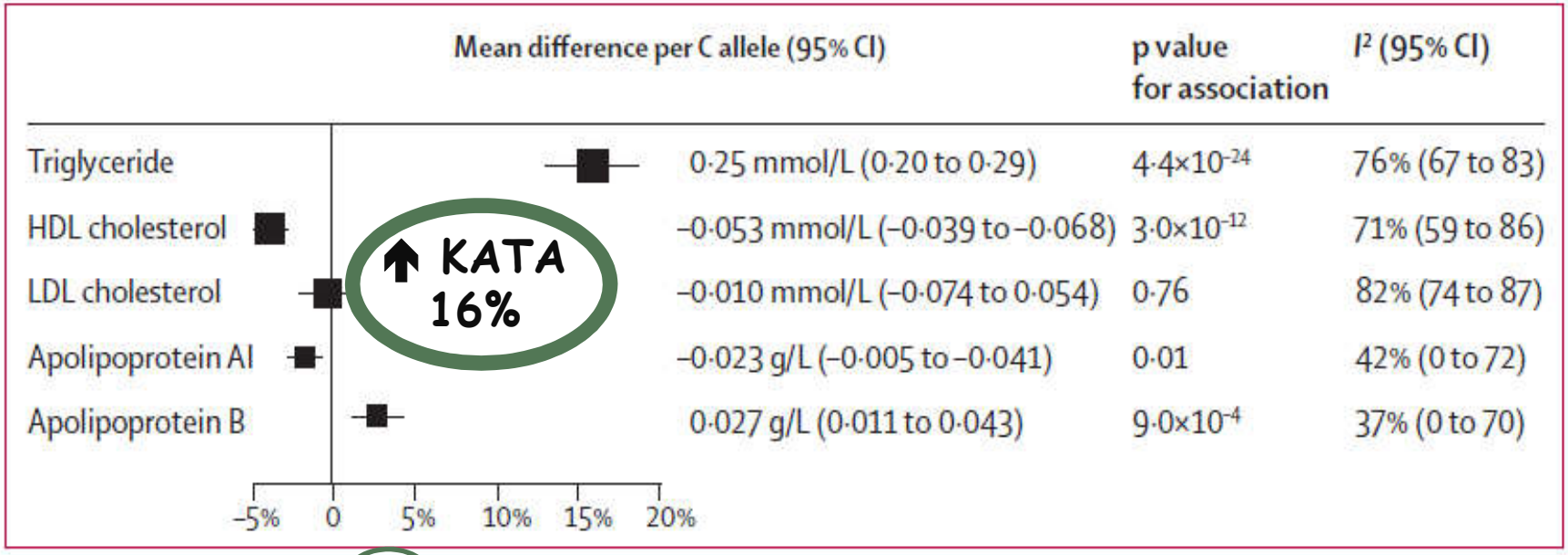


Figure 2: **Association of *APOA5* −1131T>C with circulating lipid concentration per C allele**
Size of data markers is proportional to the inverse of the variance of the weighted mean difference, and the horizontal lines represent 95% CIs. To enable comparison of associations across lipids and apolipoproteins, associations are presented as percentage differences (calculated in reference to the weighted mean of each marker in common homozygotes).

Lancet 2010;375:1634-39

ΑΥΞΗΣΗ ΤΩΝ TRG ΚΑΙ ΚΑΡΔΙΑΓΓΕΙΑΚΗ ΝΟΣΟΣ (2)

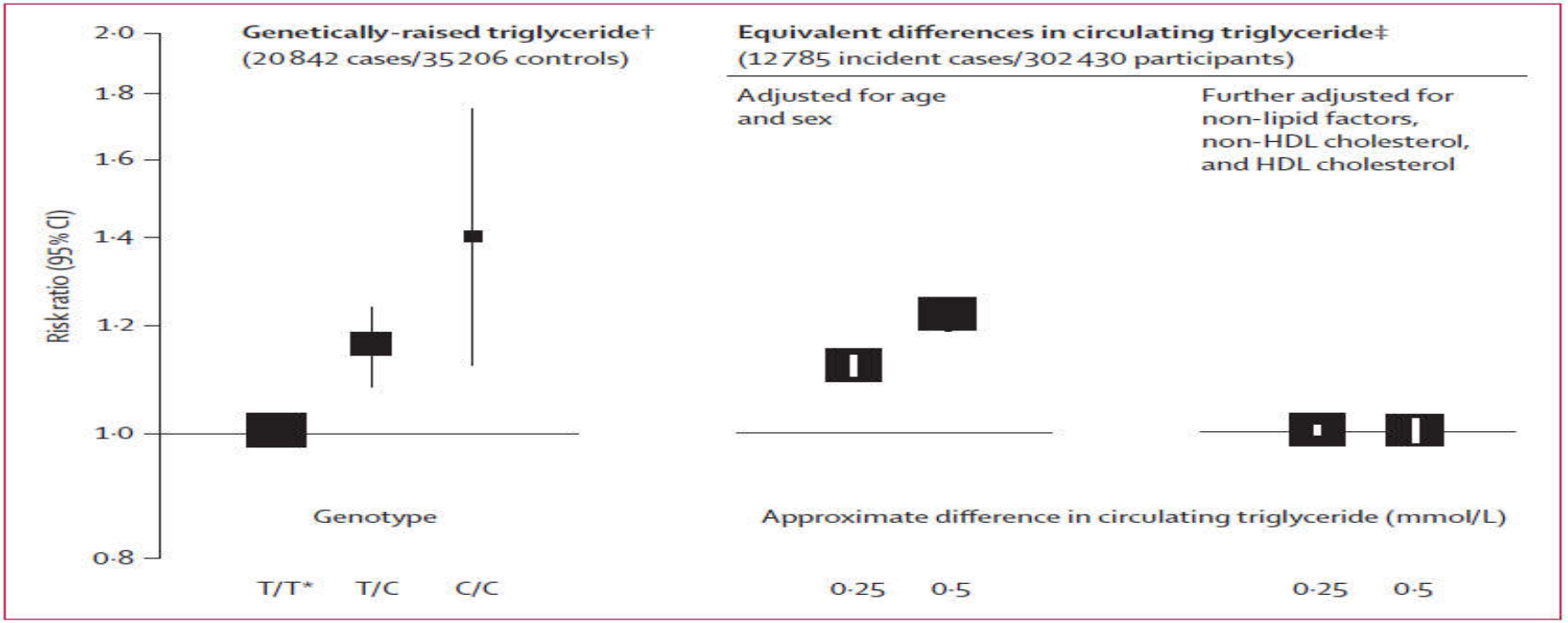


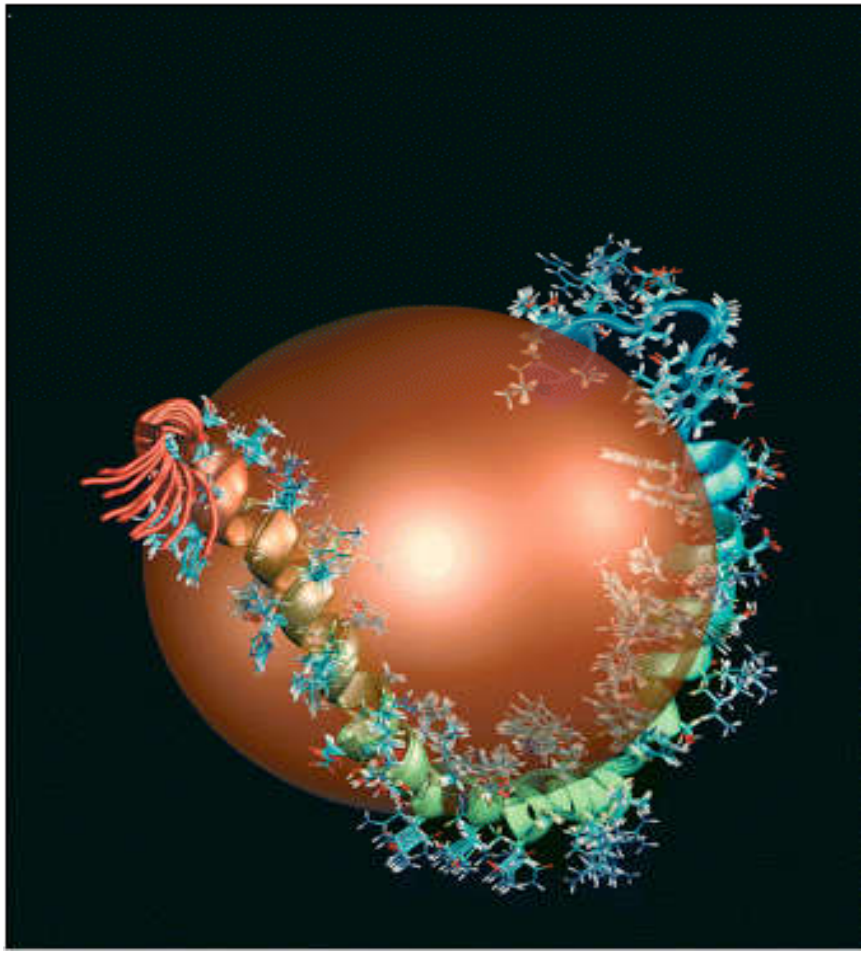
Figure 3: **Association of *APOA5* –1131T>C genotypes and equivalent differences in circulating triglyceride concentration with risk of coronary heart disease**

Non-lipid factors adjusted for included smoking status, systolic blood pressure, body-mass index, and history of diabetes (webappendix p 5). Size of data markers is proportional to the inverse of the variance of the weighted mean difference (the reference group is represented by a square with an arbitrary fixed size) and the vertical lines represent 95% CIs. *Reference group. †Odds ratio for coronary heart disease associated with *APOA5* –1131T>C. ‡Hazard ratio for coronary heart disease in prospective studies for differences in usual triglyceride concentration equal to those recorded with *APOA5* –1131T>C (as reported in figure 1).

Lancet 2010;375:1634-39

Apolipoprotein C-III

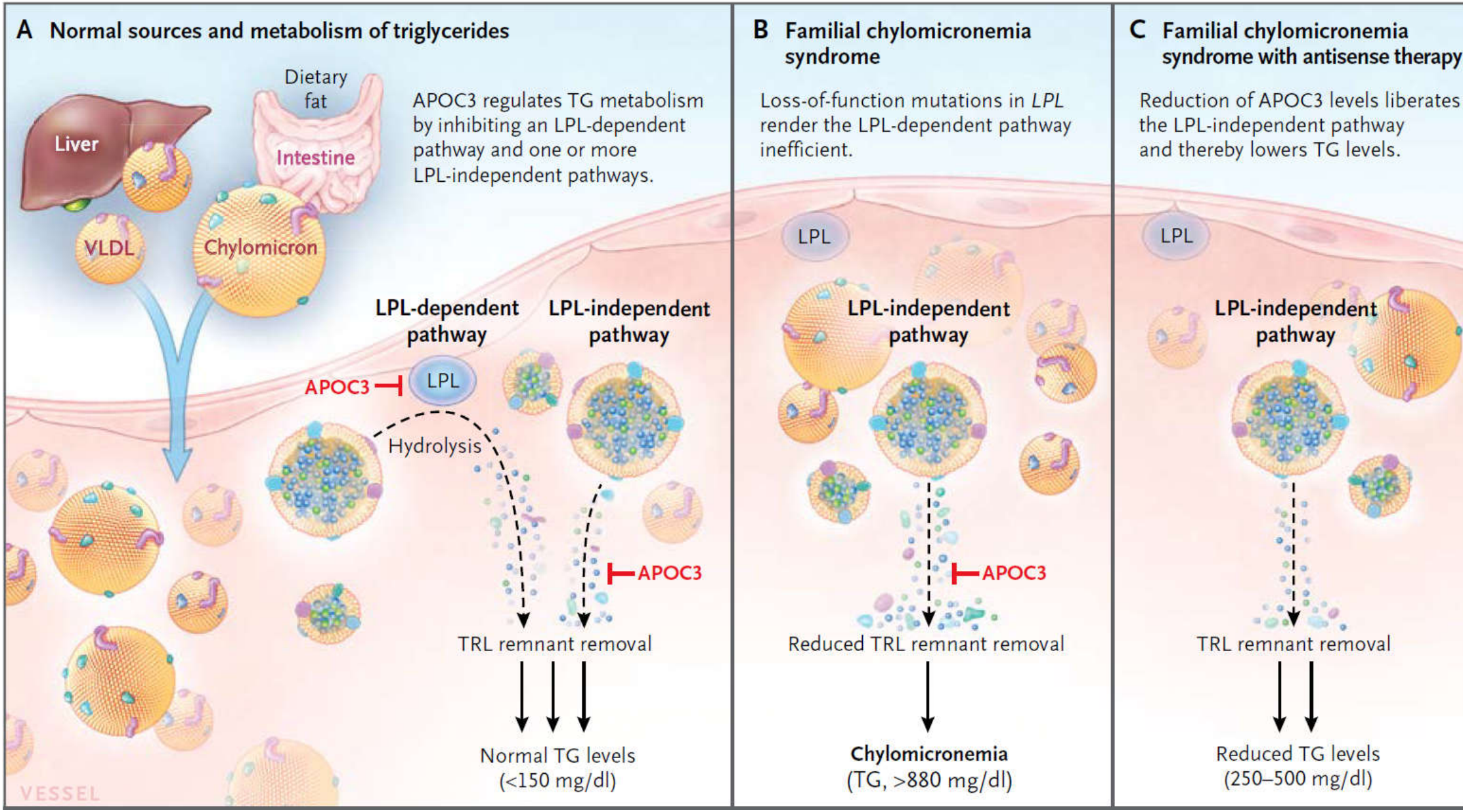
Key Regulator of Serum Triglyceride Levels



ApoC-III in a complex with an SDS micelle as derived by NMR

- ApoC-III is a 79 amino acid glycoprotein
- Links to apoB-containing lipoproteins and HDL
- Potent inhibitor of LPL-catalyzed lipolysis of TG-rich lipoproteins
- Inhibits hepatic lipase which also plays an important role in the conversion of VLDL to IDL
- Inhibits receptor-mediated uptake of lipoprotein remnants by the liver
- Independent risk factor for cardiovascular disease

Figure 2. Plasma Triglyceride Metabolism and the Role of APOC3.

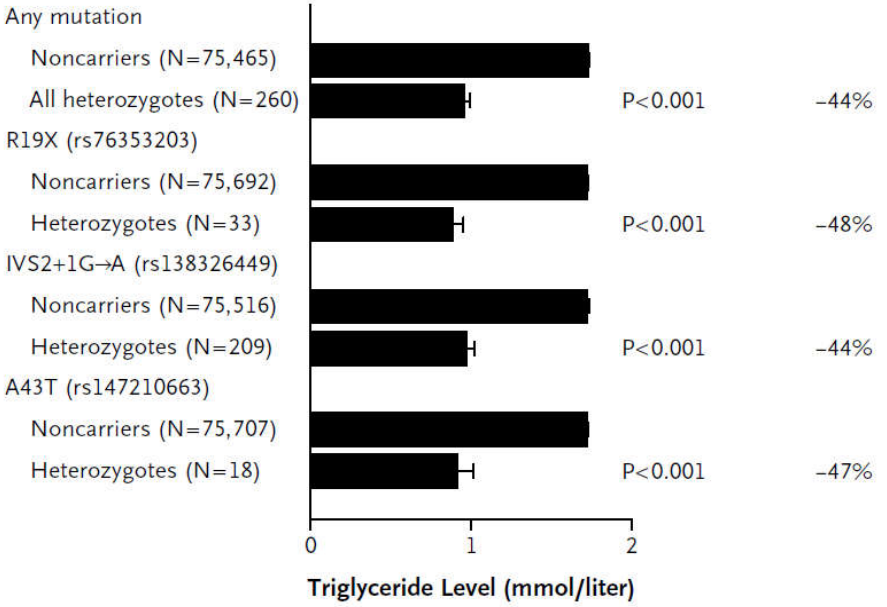


ORIGINAL ARTICLE

Loss-of-Function Mutations in *APOC3* and Risk of Ischemic Vascular Disease

A Risk of Ischemic Vascular Disease

	No. of Participants	No. of Events	Hazard Ratio (95% CI)	P Value
Triglyceride level — mmol/liter				
≥4.00	3,245	331	1.00	<0.001
3.00–3.99	4,026	397	0.80 (0.62–1.02)	
2.00–2.99	11,606	1082	0.67 (0.54–0.83)	
1.00–1.99	32,578	2562	0.51 (0.42–0.63)	
<1.00	18,871	1038	0.43 (0.35–0.54)	



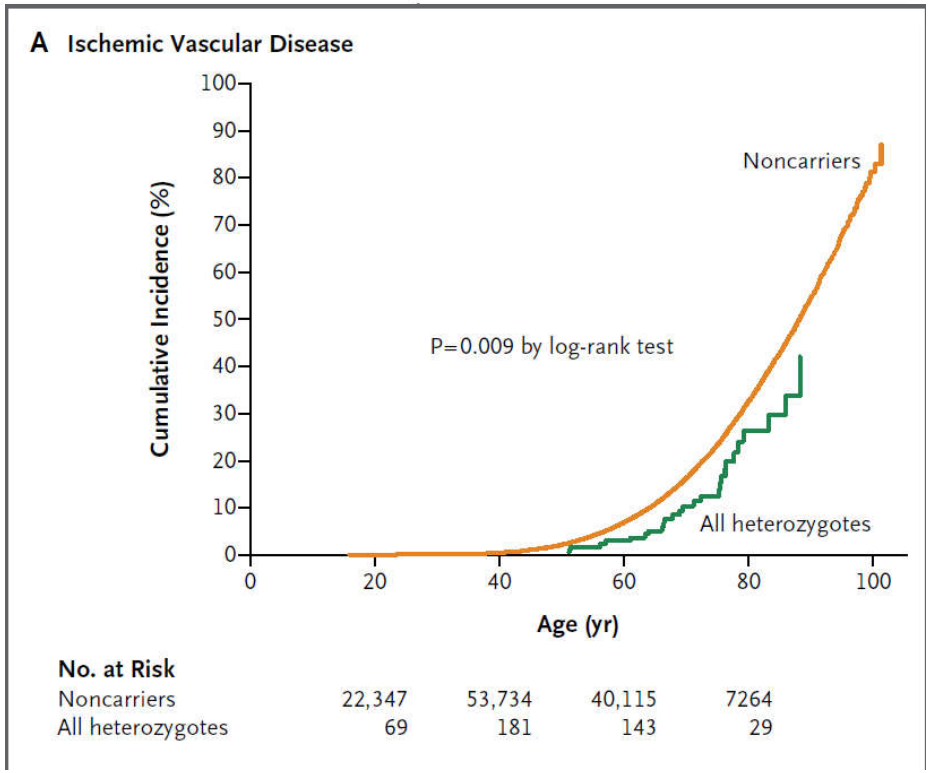
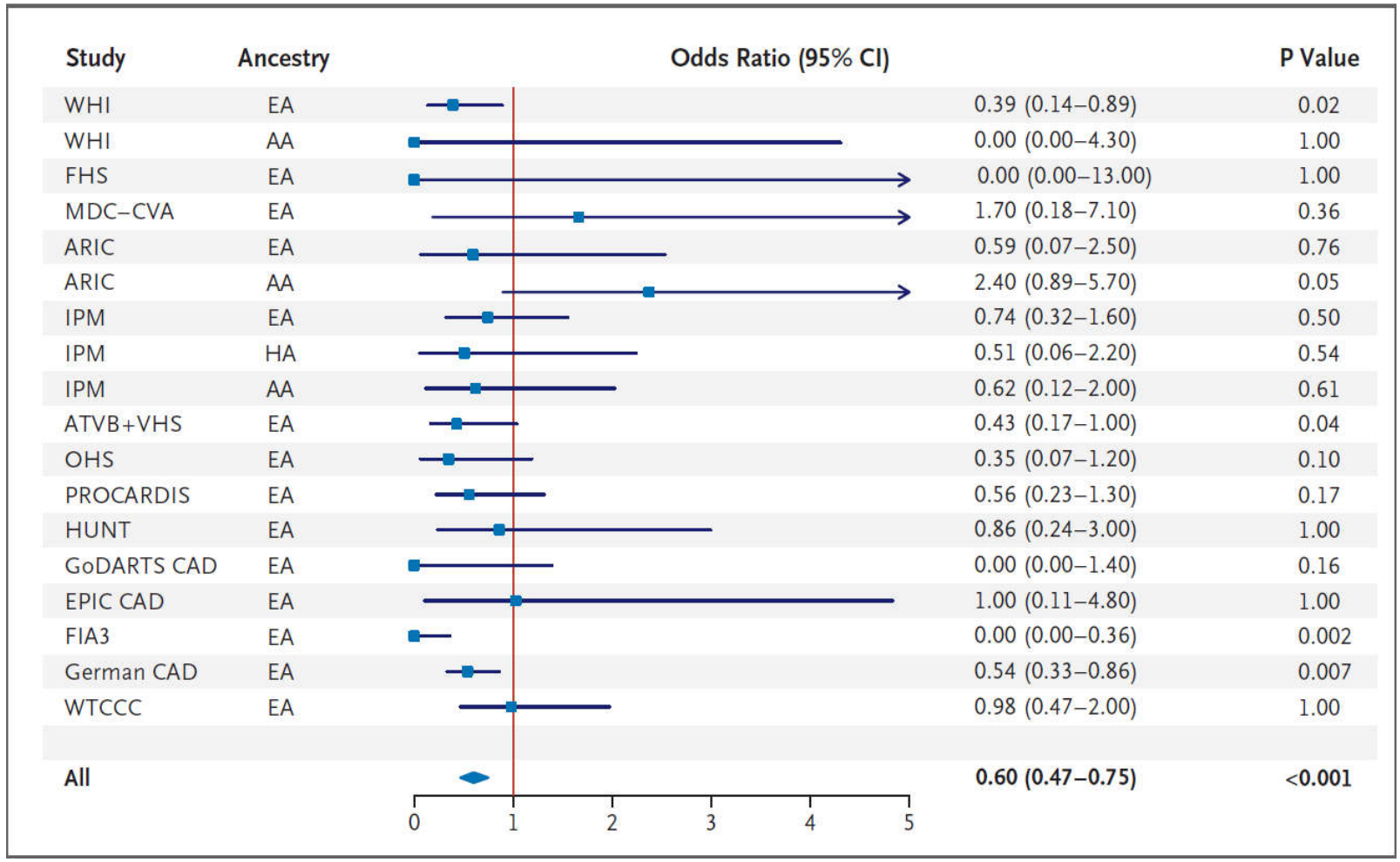


Figure 2. Mean Plasma Levels of Nonfasting Triglycerides as a Function of *APOC3* Genotype.

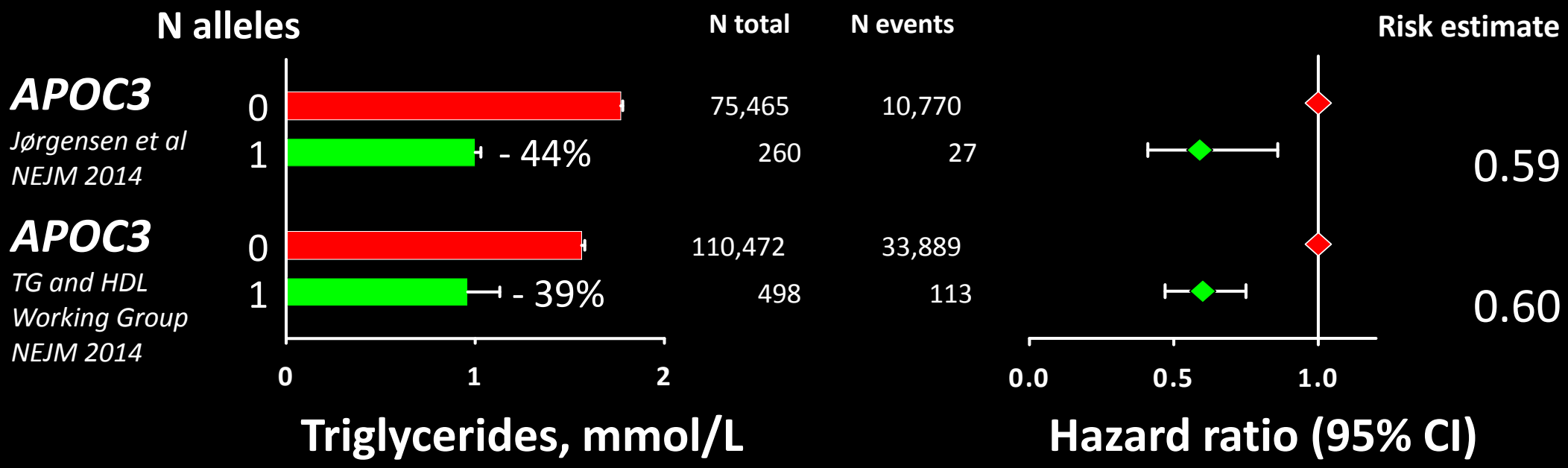
Loss-of-Function Mutations in *APOC3*, Triglycerides, and Coronary Disease

The TG and HDL Working Group of the Exome Sequencing Project, National Heart, Lung, and Blood Institute*

Figure 2. Association of *APOC3* Loss-of-Function Mutations with Risk of Coronary Heart Disease among 110,970 Participants in 15 Studies.



Ischemic vascular disease



Nordestgaard & Varbo, Lancet 2014; 384: 626-635

National Lipid Association Recommendations for Patient-Centered Management of Dyslipidemia: Part 1—Full Report

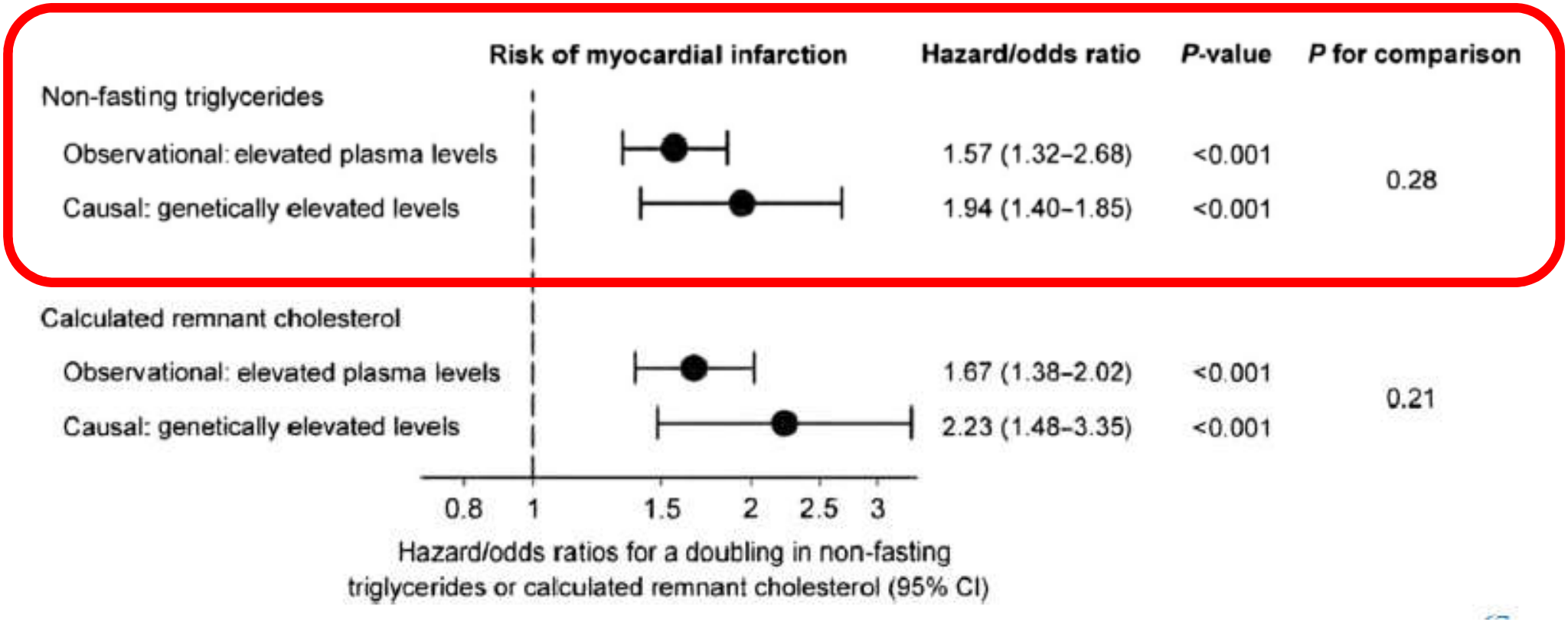
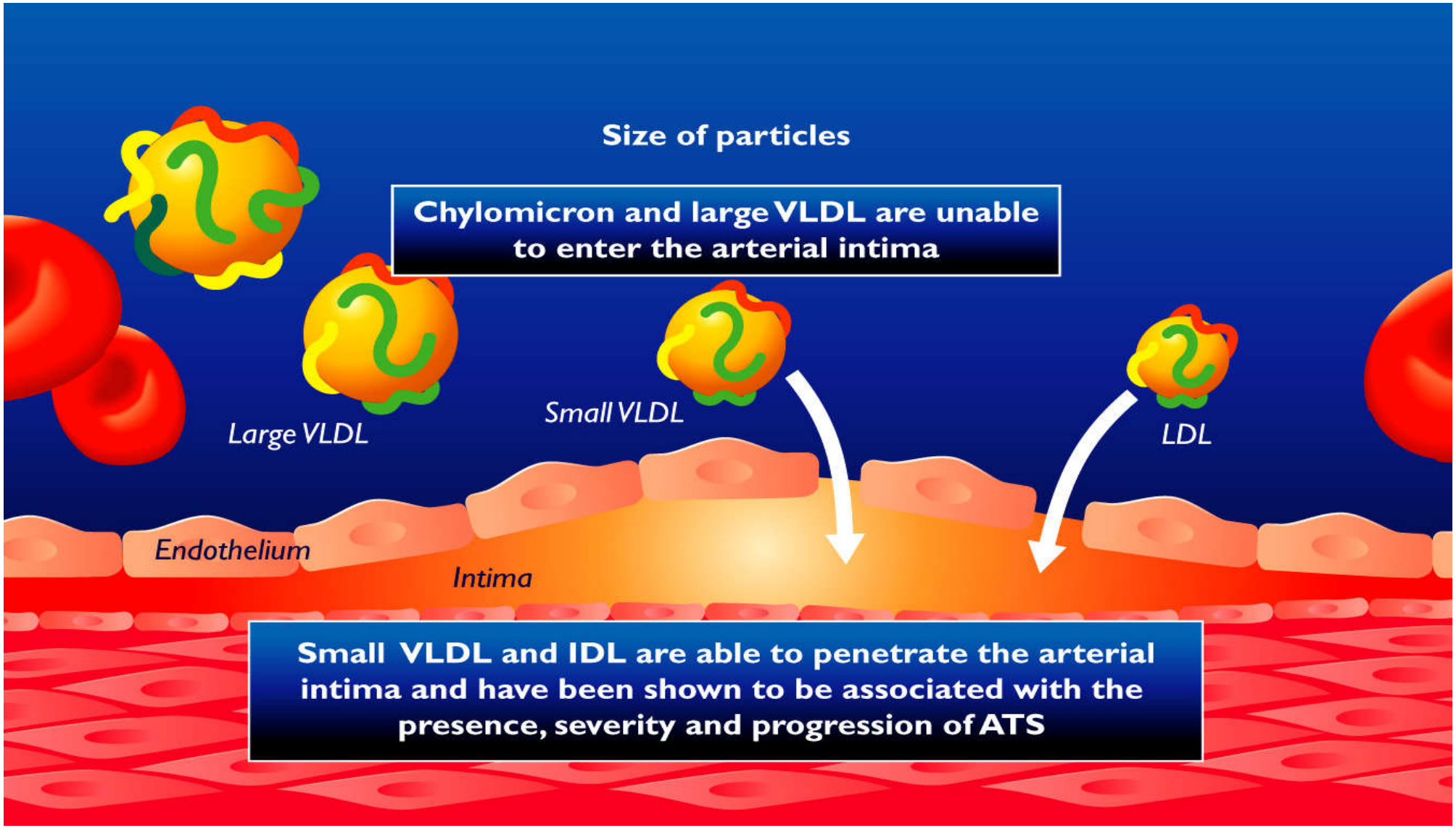


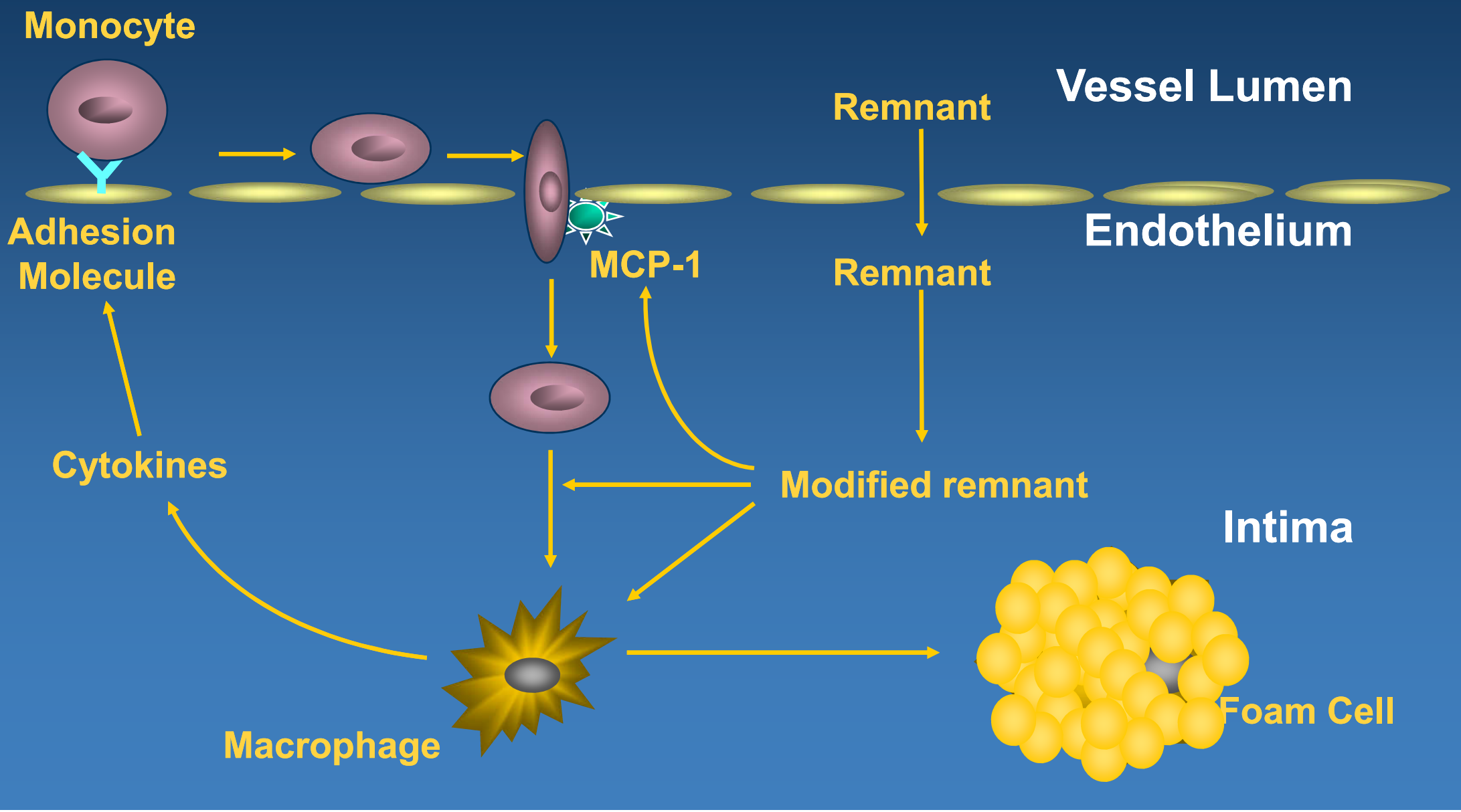
Figure 3 Association between elevated triglycerides and remnant cholesterol and risk of myocardial infarction.

↑ TGs → ↑ ΑΘΗΡΩΜΑΤΩΣΗΣ:
ΠΑΘΟΦΥΣΙΟΛΟΓΙΚΑ ΔΕΔΟΜΕΝΑ

Size and apolipoprotein composition are the main factors determining atherogenicity of triglyceride-rich particles



INITIATION OF ATHEROSCLEROSIS BY REMNANTS



↓ TGs → ↓ ΑΘΗΡΩΜΑΤΩΣΗΣ:
ΔΕΔΟΜΕΝΑ ΚΛΙΝΙΚΩΝ ΜΕΛΕΤΩΝ

HPS2-THRIVE: Randomized placebo-controlled trial of ER niacin and laropiprant in 25,673 patients with pre-existing cardiovascular disease.

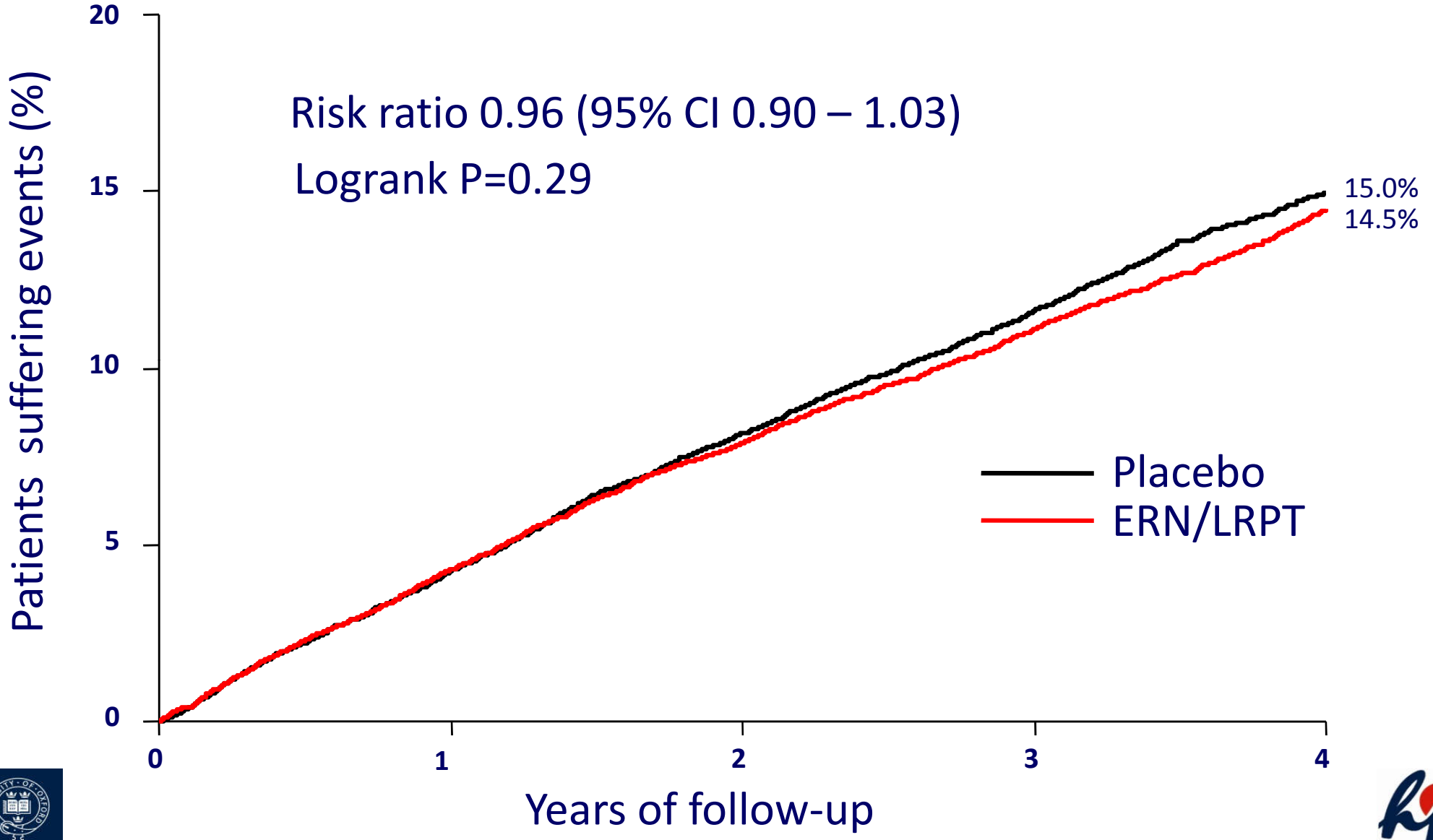
Jane Armitage on behalf of the
HPS2-THRIVE Collaborative Group

Financial Disclosure: Grant to Oxford University. Designed, conducted and analysed independently of the grant source (Merck & Co). No honoraria or consultancy fees accepted.

UNIVERSITY OF OXFORD

hps2 THRIVE

Effect of ERN/LRPT on MAJOR VASCULAR EVENTS



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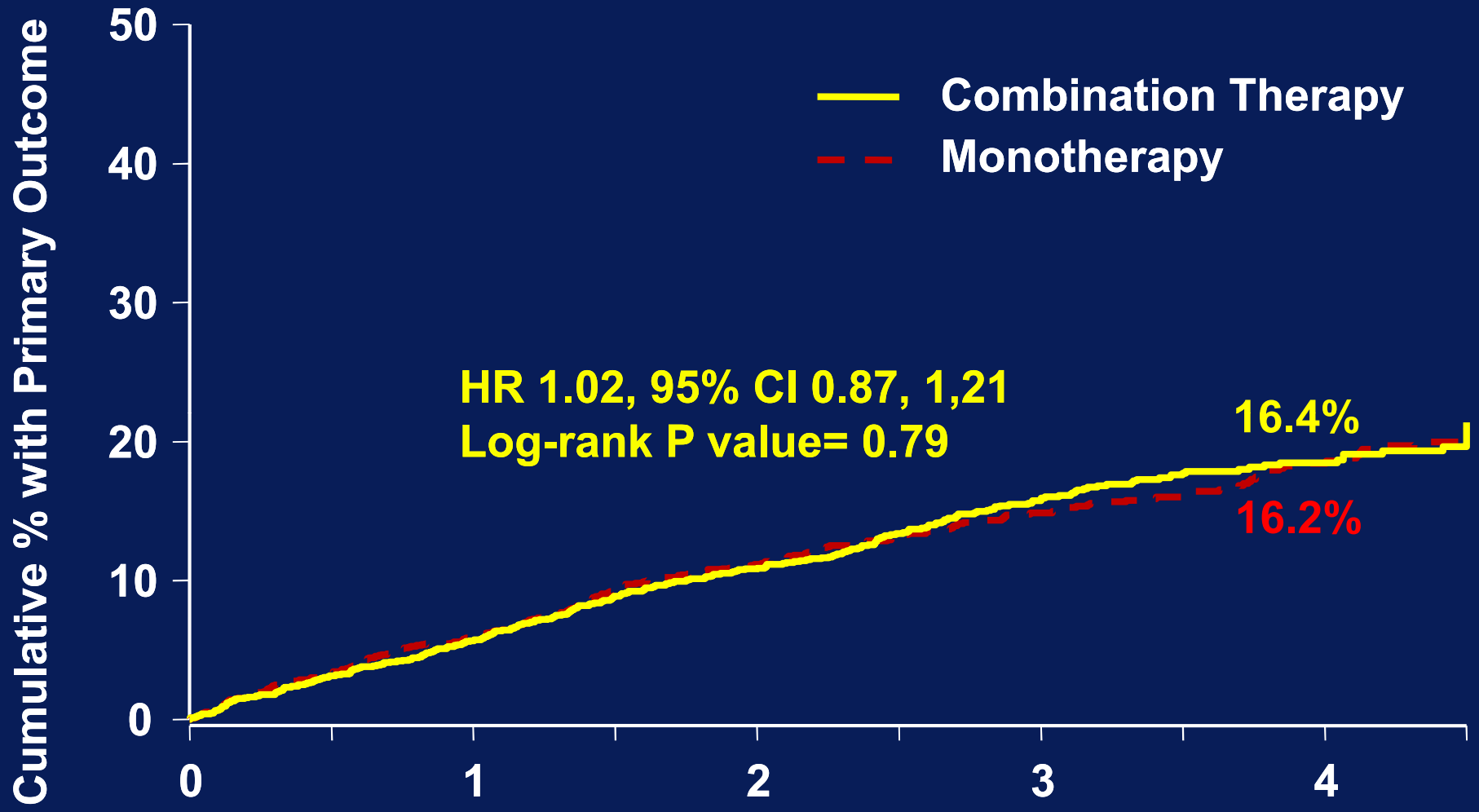
hps2 THRIVE

AIM-HIGH Trial

Atherothrombosis
Intervention in
Metabolic Syndrome with Low

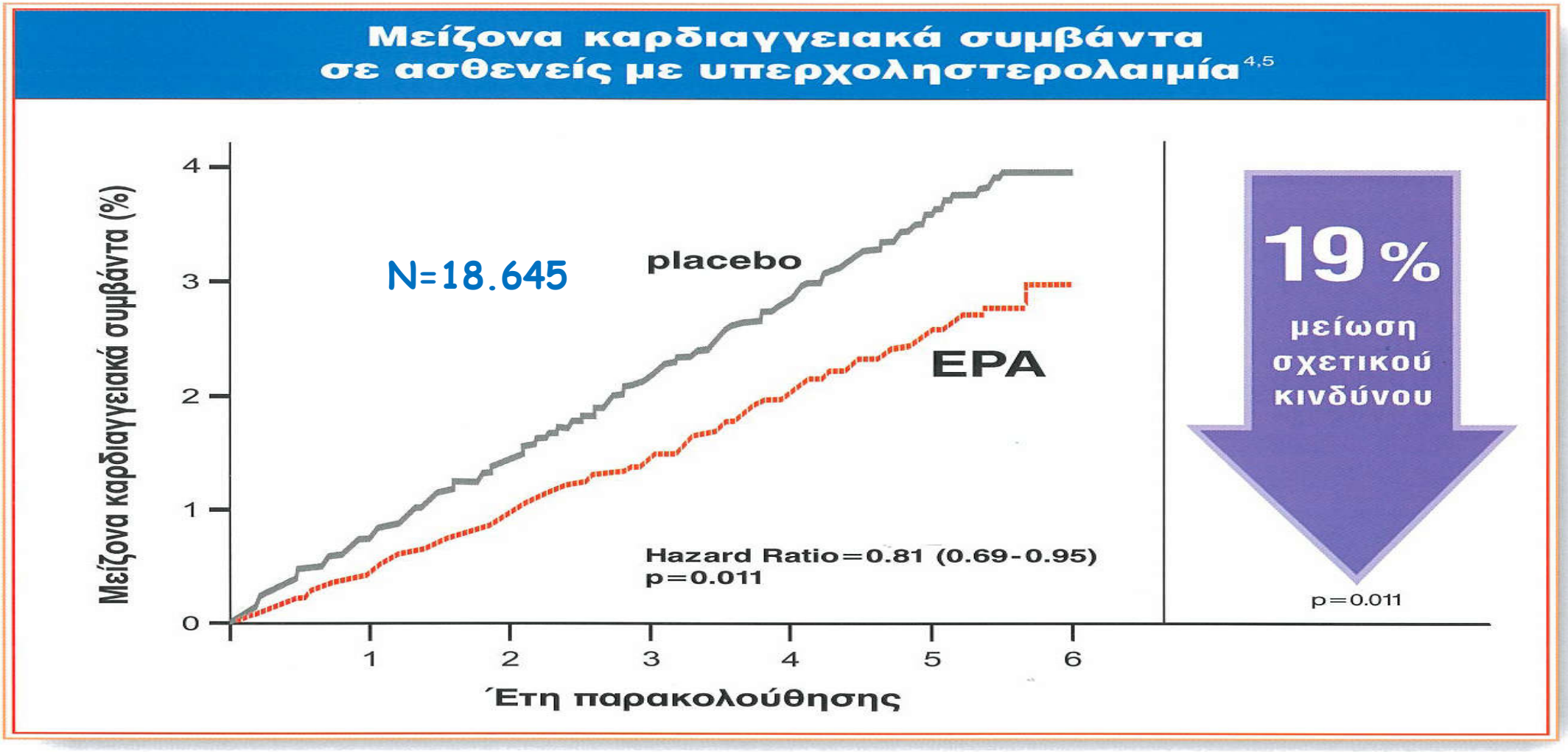
HDL/High Triglycerides and
Impact on
Global
Health Outcomes

AIM-HIGH Trial: Primary Outcome



N at risk					
Monotherapy	1696	1581	1381	910	436
Combination Therapy	1718	1606	1366	903	428

Μελέτη JELIS

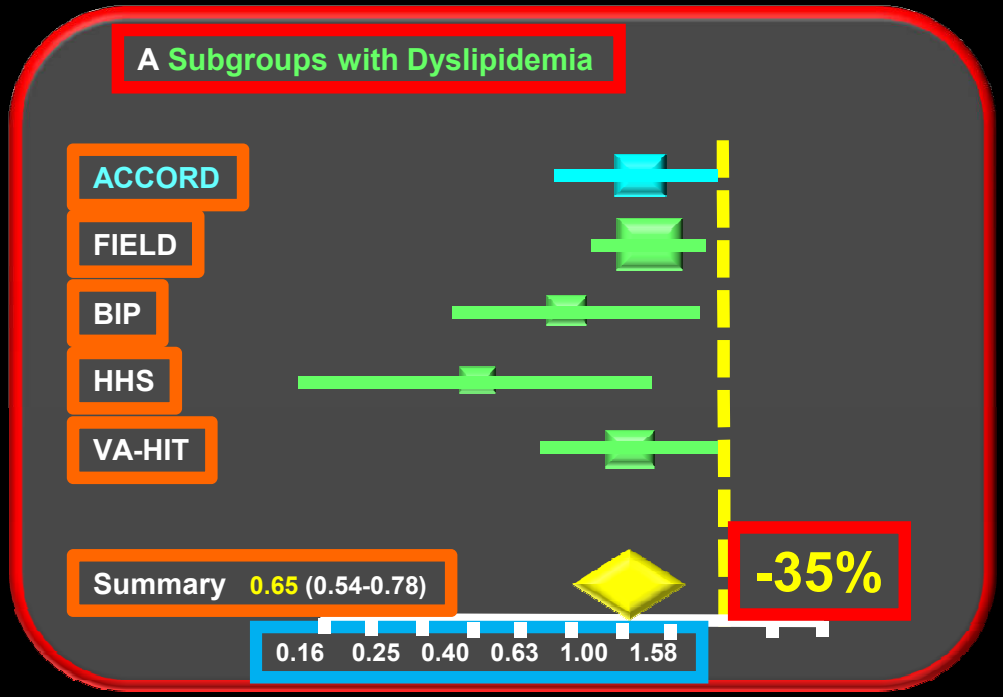


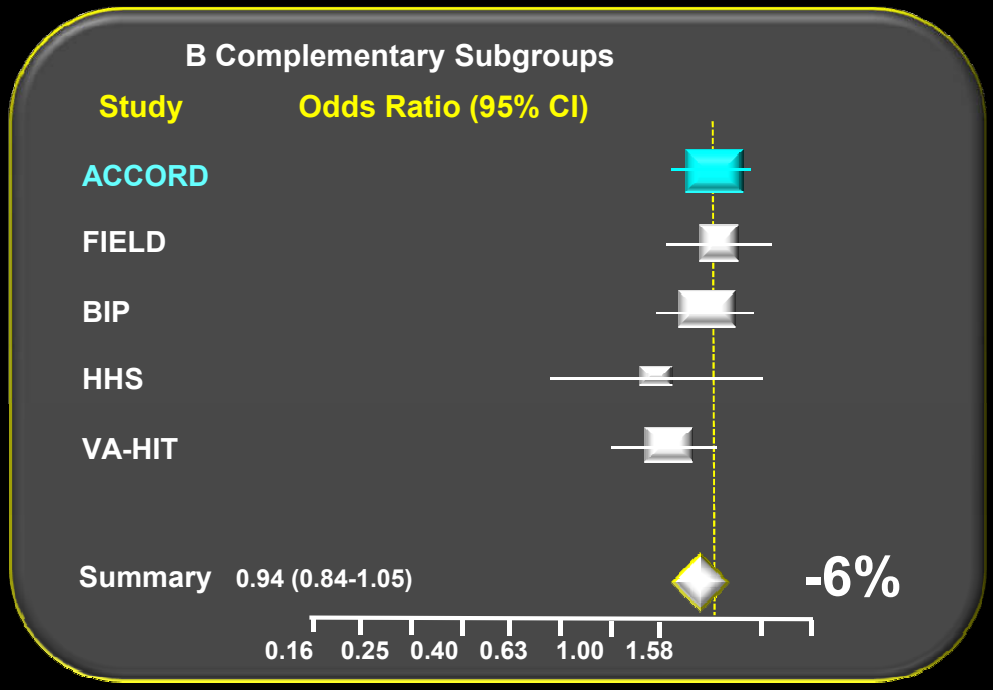
- Η μείωση του συνδυασμένου κινδύνου στα μείζονα καρδιαγγειακά συμβάντα ήταν 19% για την ομάδα που έλαβε (Ω-3 + στατίνη) σε σύγκριση με την ομάδα ελέγχου που έλαβε μόνο στατίνη (p=0.011)[4,5]

JELIS study: Lancet 2007;367

Effect of fibrates in subgroups with (A) and without (B) dyslipidemia

A total of 2428 fibrate-treated subjects (302 events) and 2298 placebo-treated subjects (408 events) with dyslipidemia were included in the analysis





LIPID CRITERIA FOR DYSLIPIDEMIA

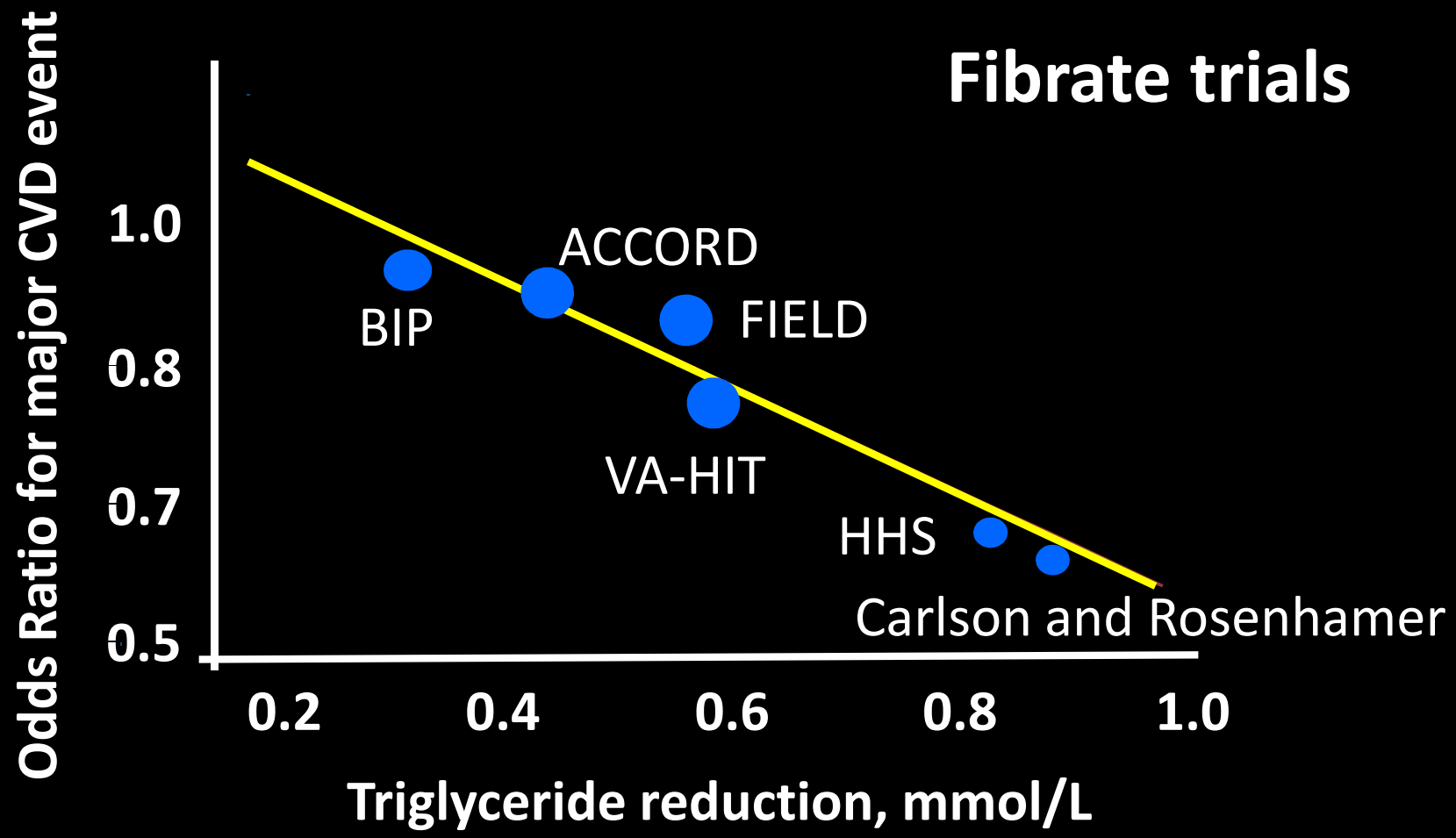
Trial	Triglycerides cut-off (mg/dL)	HDL cholesterol cut-off (mg/dL)
FIELD	≥204	<40 in men; <50 in women
BIP	≥200	<35
Helsinki Heart Study	>204	<42
VA-HIT	>180	<40

TG 200 mg/dl: 2.26 mmol/L; HDL 40 mg/dl: 1.0 mmol/L

Sacks FM et al. N Engl J Med 2010

All study participants

54% reduction in major CVD event per 1 mmol/L triglyceride reduction

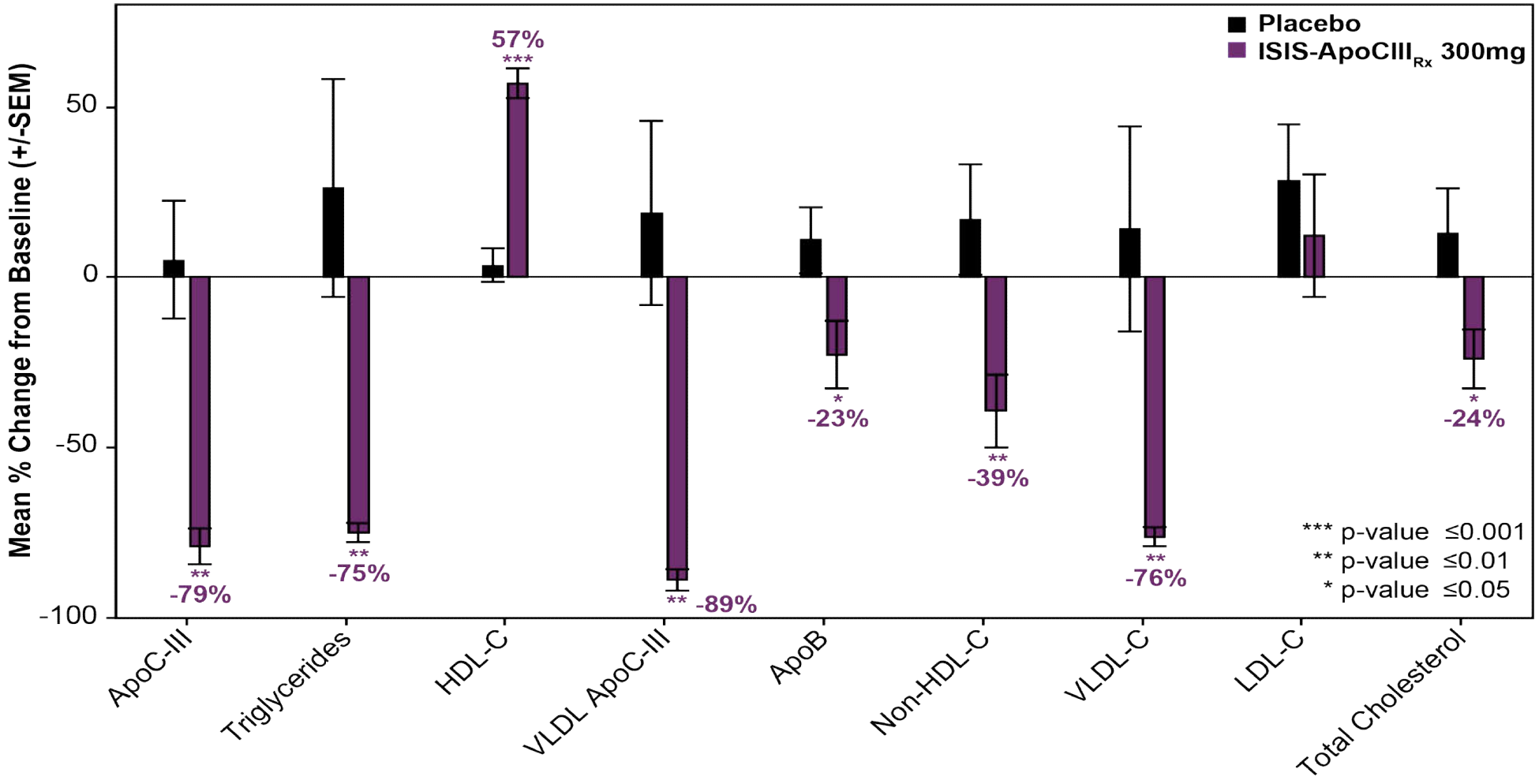


Nordestgaard & Varbo, Lancet 2014; 384: 626-635

TGs: new approaches

1. Antisense to Apo CIII – phase I by Isis had reduction in CIII up to 78% and TG up to 44%
2. DGAT1 inhibition – efficacy for familial chylomicronemia syndrome and severe Tg elevations
3. Lopitamide for chylomicronemia
4. Gene therapy with LPL for familial chlyomicronemia syndrome – alipogene tiparvovec, uniQure, approved by EMA

ISIS-APOCIII$_{Rx}$ Treatment Improved Overall Lipid Profile in Monotherapy Patients: 300 mg group



ApoC-III Anti-Sense Therapy

	DM/High TG	Very High TG	Very High TG + Fibrate	FCS
ApoC-III	-88%	-80%	-70%	-81%
TG	-72%	-71%	-64%	-69%
HDL-C	+40%	+46%	+52%	+78%

FCS: familial hyperchylomicronaemia syndrome

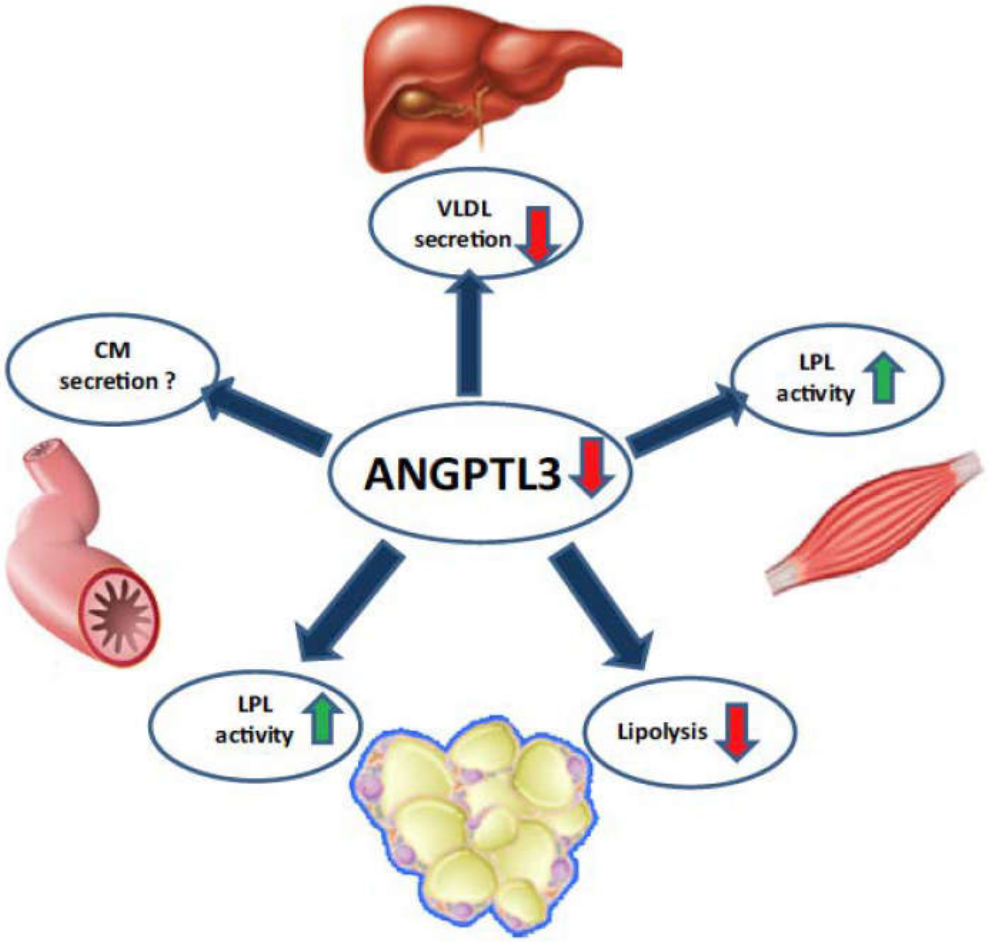
Angiopoietin-Like 3 (ANGPTL3) is a Genetically Validated Lipid and Metabolic Target in Humans

American Heart Association. life is why™ | SCIENTIFIC SESSIONS

- Genome-wide association and exome sequencing studies have identified *ANGPTL3* genetic variations that are associated with very low plasma LDL-C, HDL-C and TG[1-3]
- ANGPTL3 complete loss-of-function mutations result in familial combined hypolipidemia (FHBL2), which is manifested by a reduction of all lipoproteins, except Lp(a)[4]
- Loss of function of *ANGPTL3* results in increased lipoprotein lipase and endothelial lipase activities, enhanced insulin sensitivity and decreased serum FFAs[5]

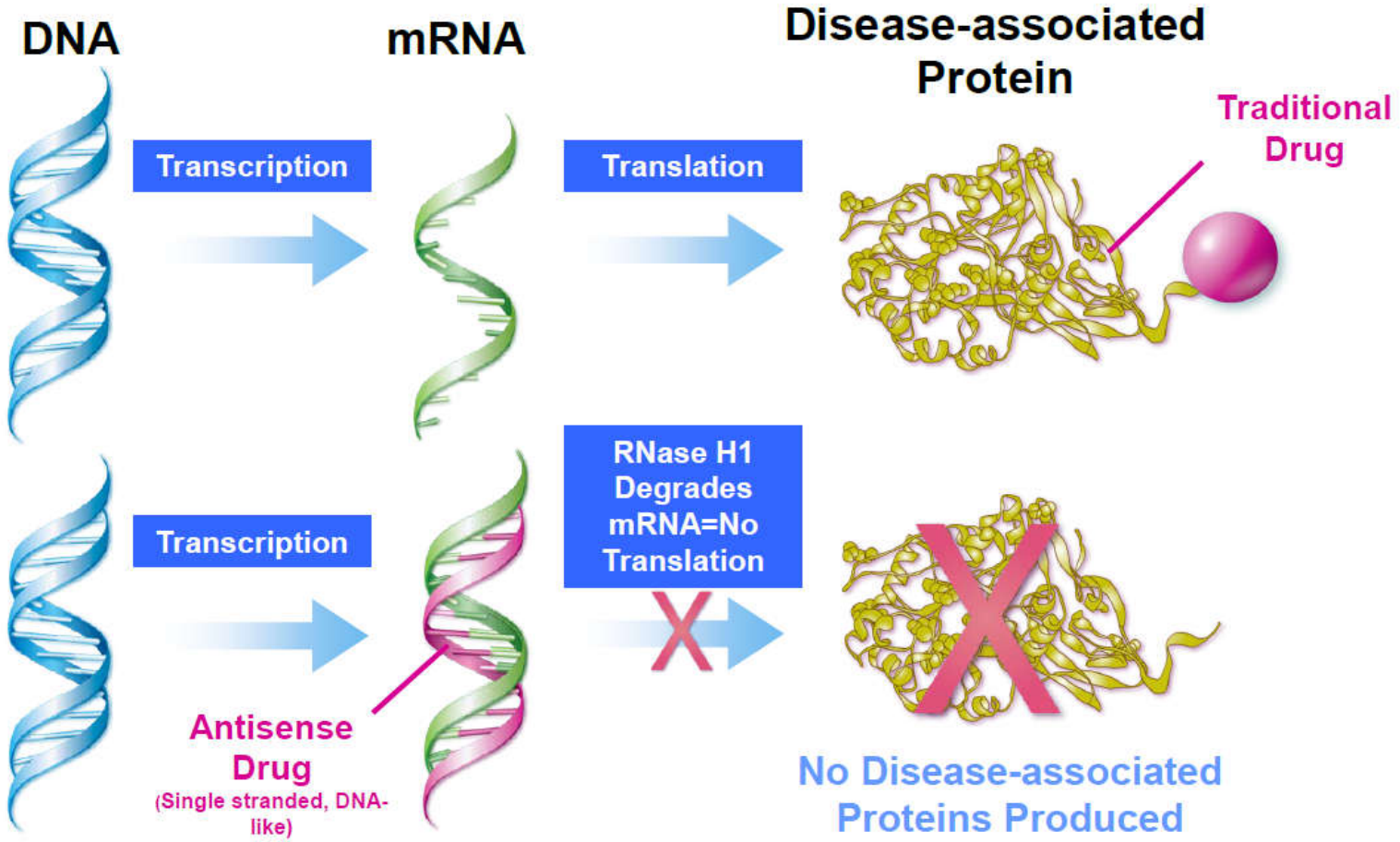
1) Willer et al. *Nat Gen*, 2008; 2) Teslovich TM, et al. *Nature*, 2010; 3) Musunuru K, et al. *NEJM*, 2010; 4) Minicocci I, et al. *JLR*, 2013; 5) Robciuc et al. *ATVB*, 2013.

Inhibition of ANGPTL3 May Have Multiple Beneficial Effects in Lipoprotein Metabolism



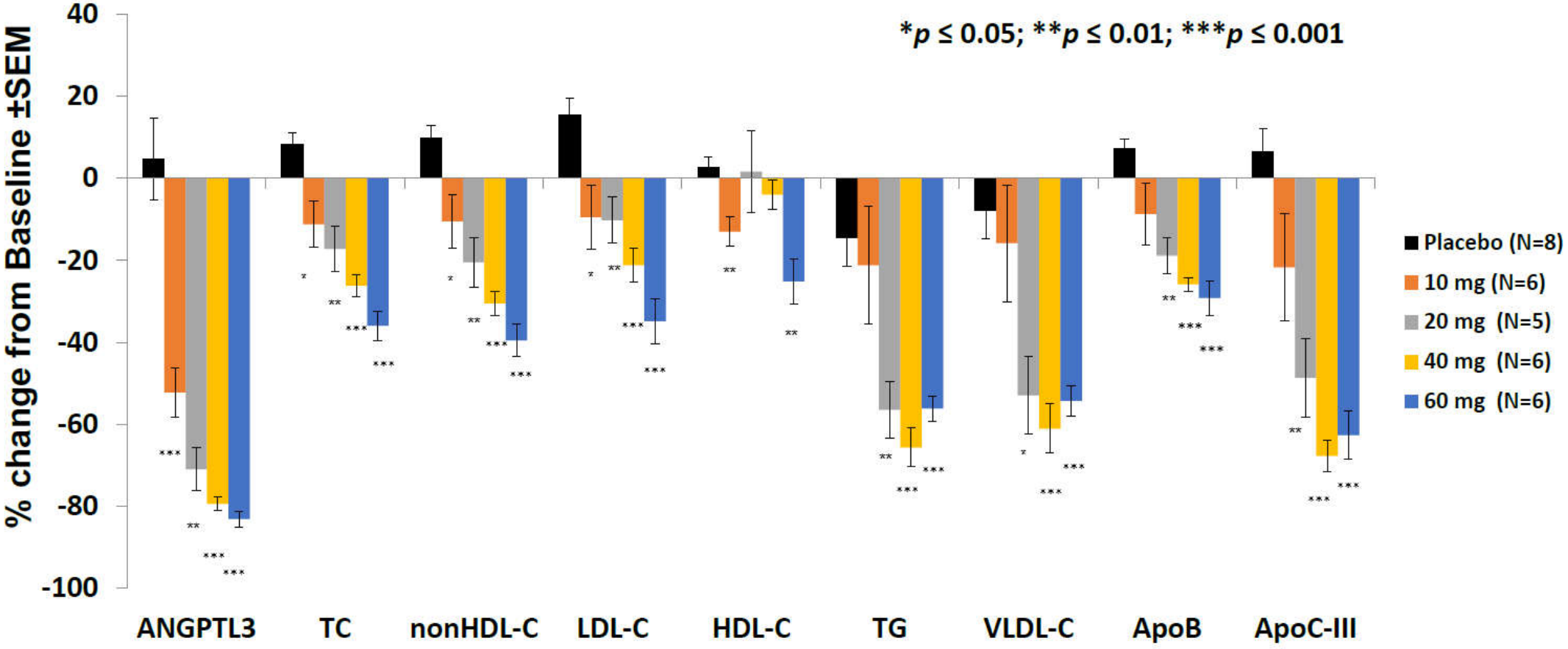
Tikka et al *Endocrine* (2016) 52:187–193

RNA-Targeted Antisense Drugs Block the Translation of ANGPTL3 Protein

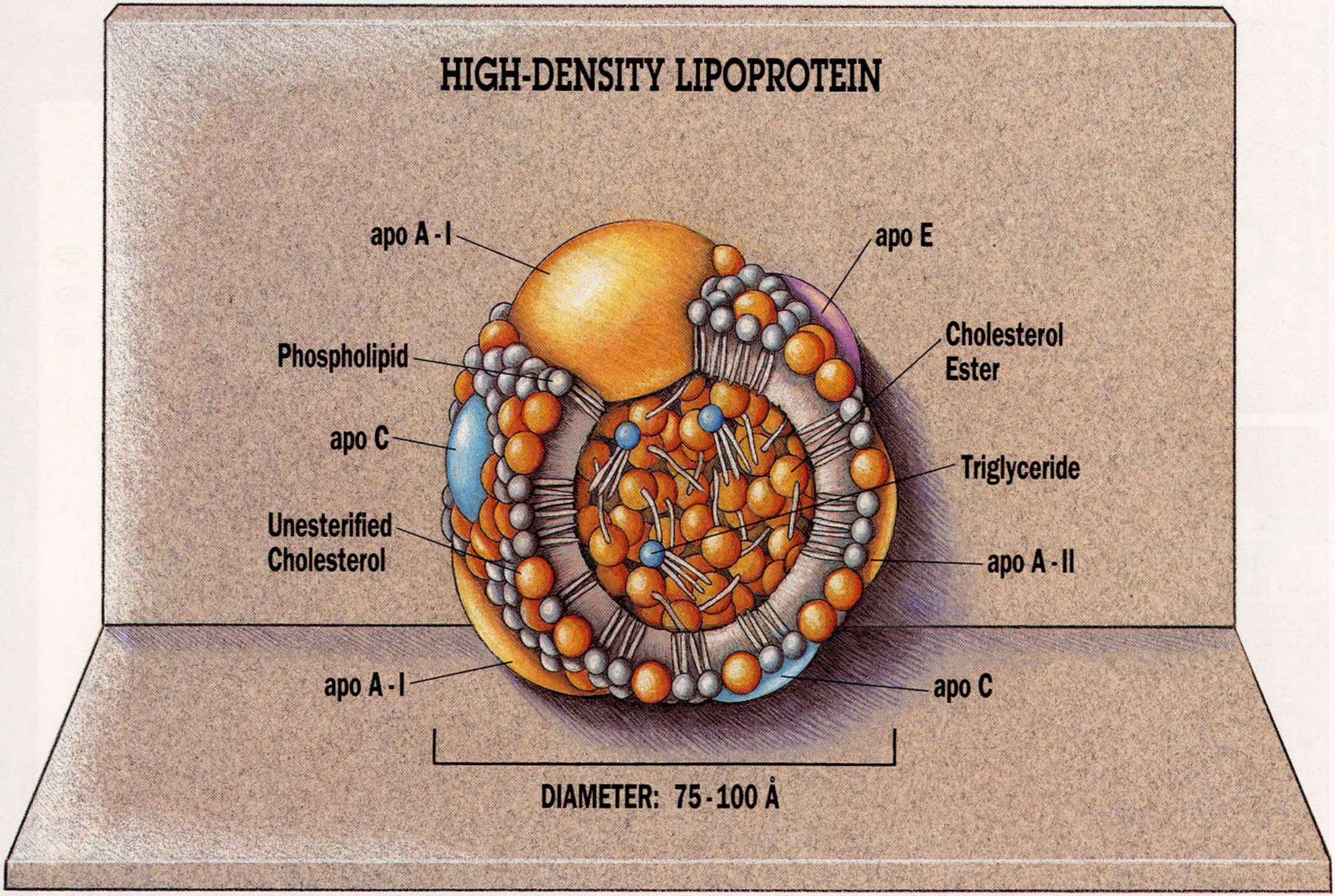


Adapted from: Crooke ST, ed. *Antisense Drug Technology: Principles, Strategies and Applications.* 2nd ed. Boca Raton, FL: CRC Press; 2007:601-639.

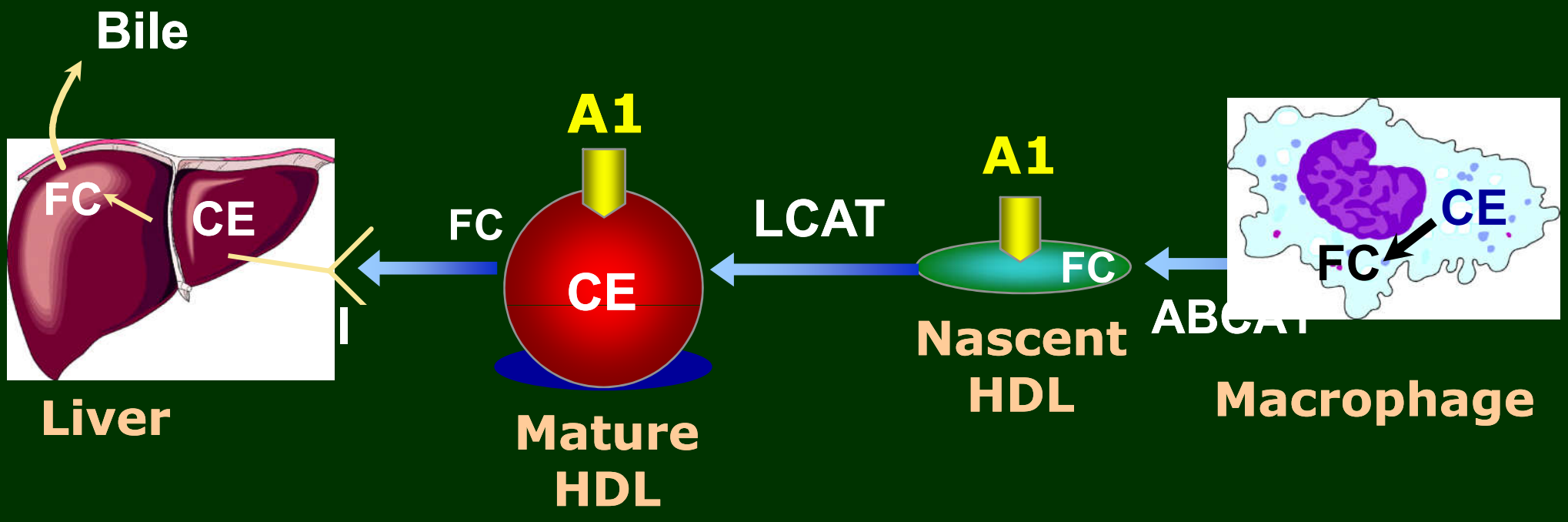
RESULTS: IONIS-ANGPTL3-L_{Rx} MAD Cohort
Mean % Change in Lipid Levels (Day 37)



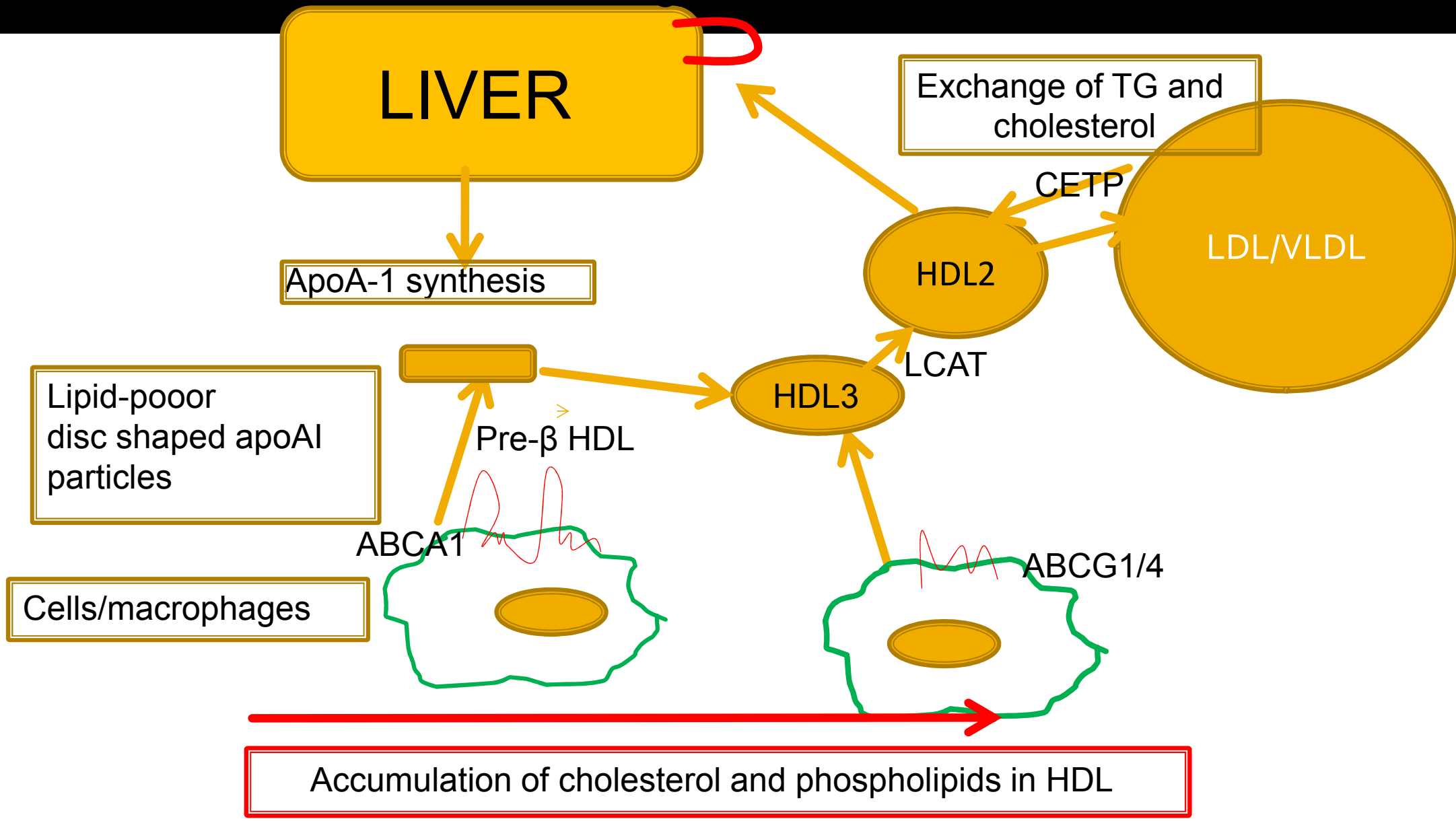
HIGH-DENSITY LIPOPROTEINS (HDL) & HDL ΧΟΛΗΣΤΕΡΟΛΗ


HIGH-DENSITY LIPOPROTEIN
apo A - I
apo E
Phospholipid
Cholesterol
Ester
apo C
Triglyceride
Unesterified
Cholesterol
apo A - II
apo A - I
apo C
DIAMETER: 75 - 100 Å

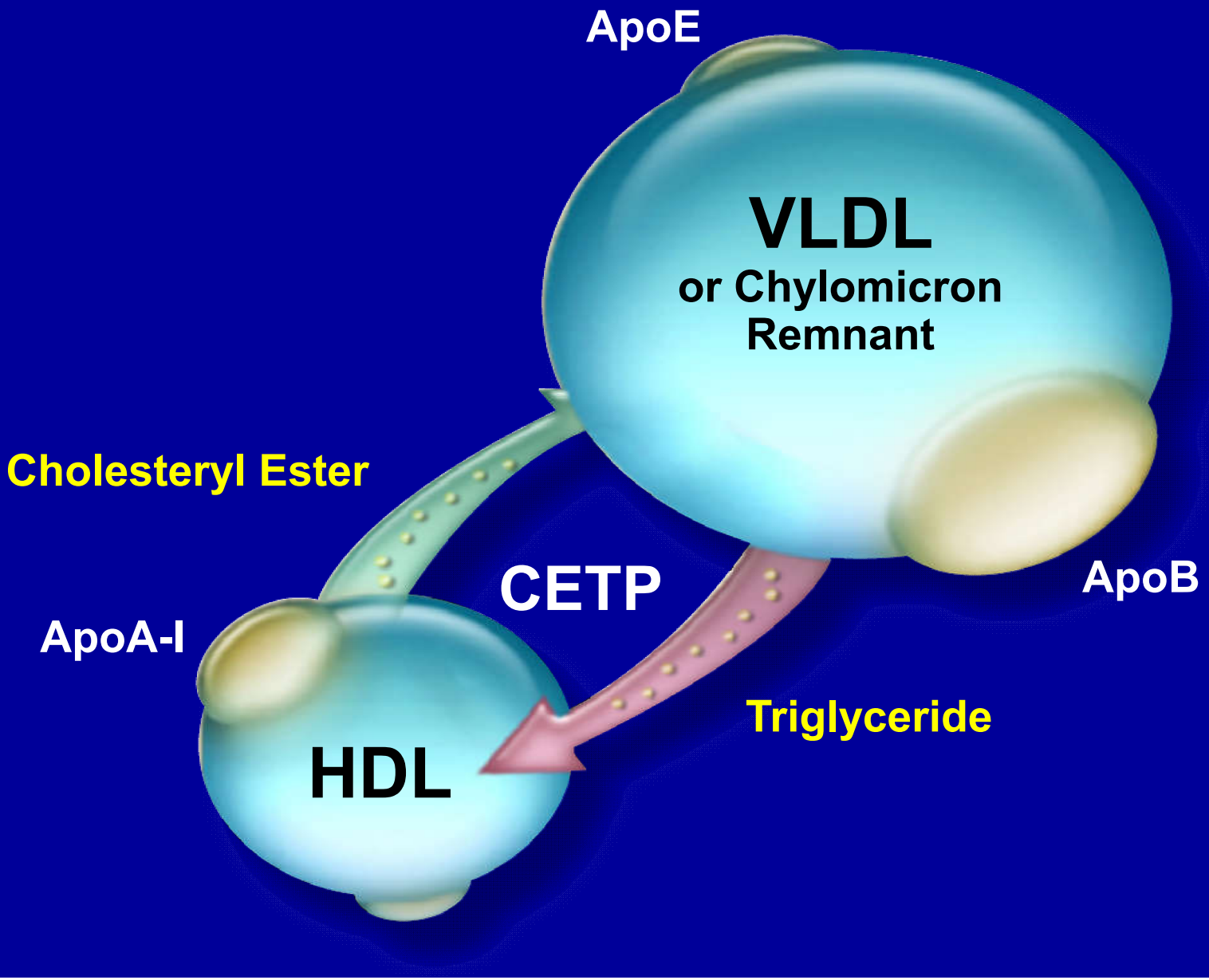
HDL and Reverse Cholesterol Transport Overview

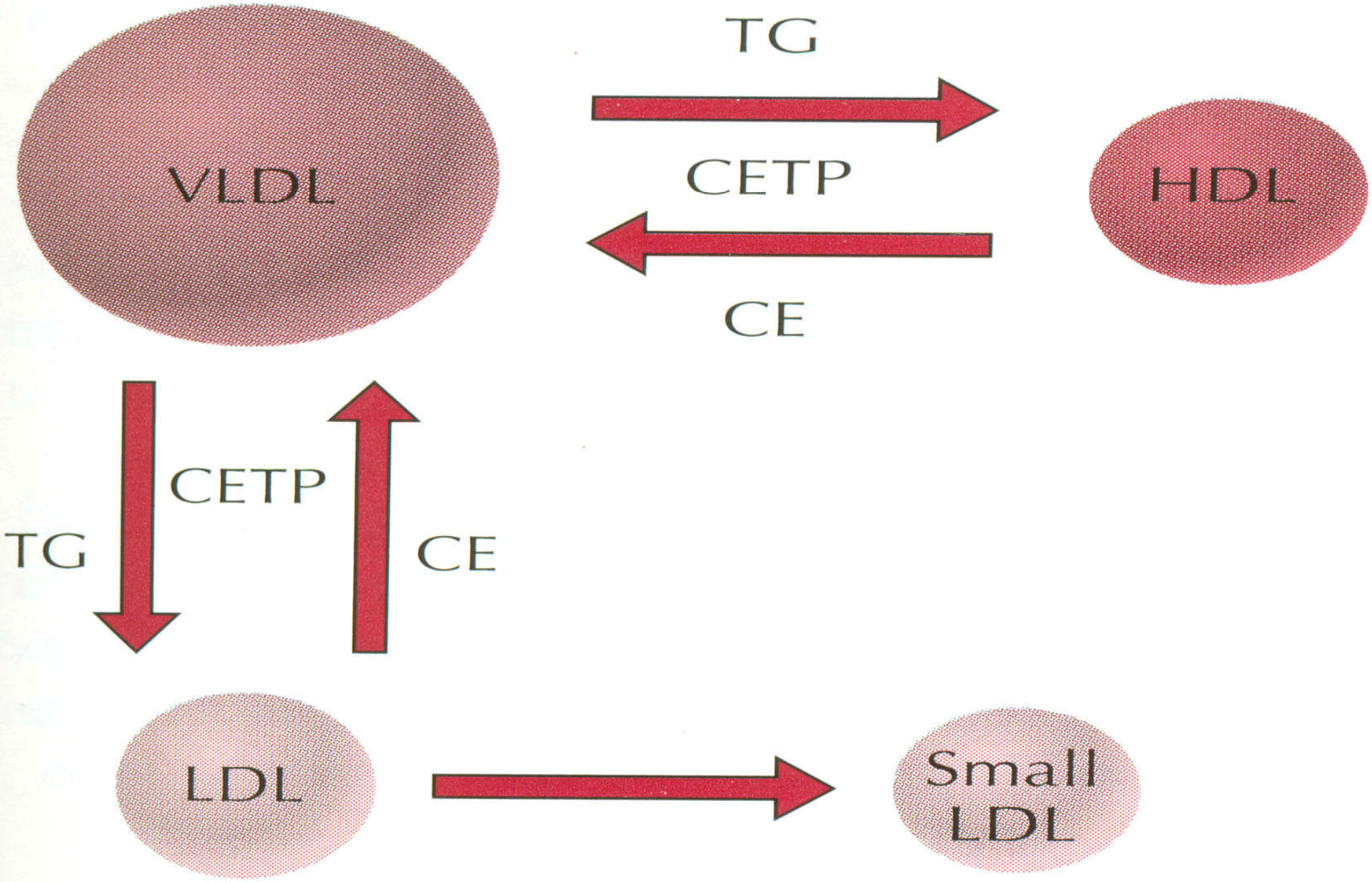


Simplified scheme on HDL metabolism



Cholesteryl Ester Transfer Protein (CETP)



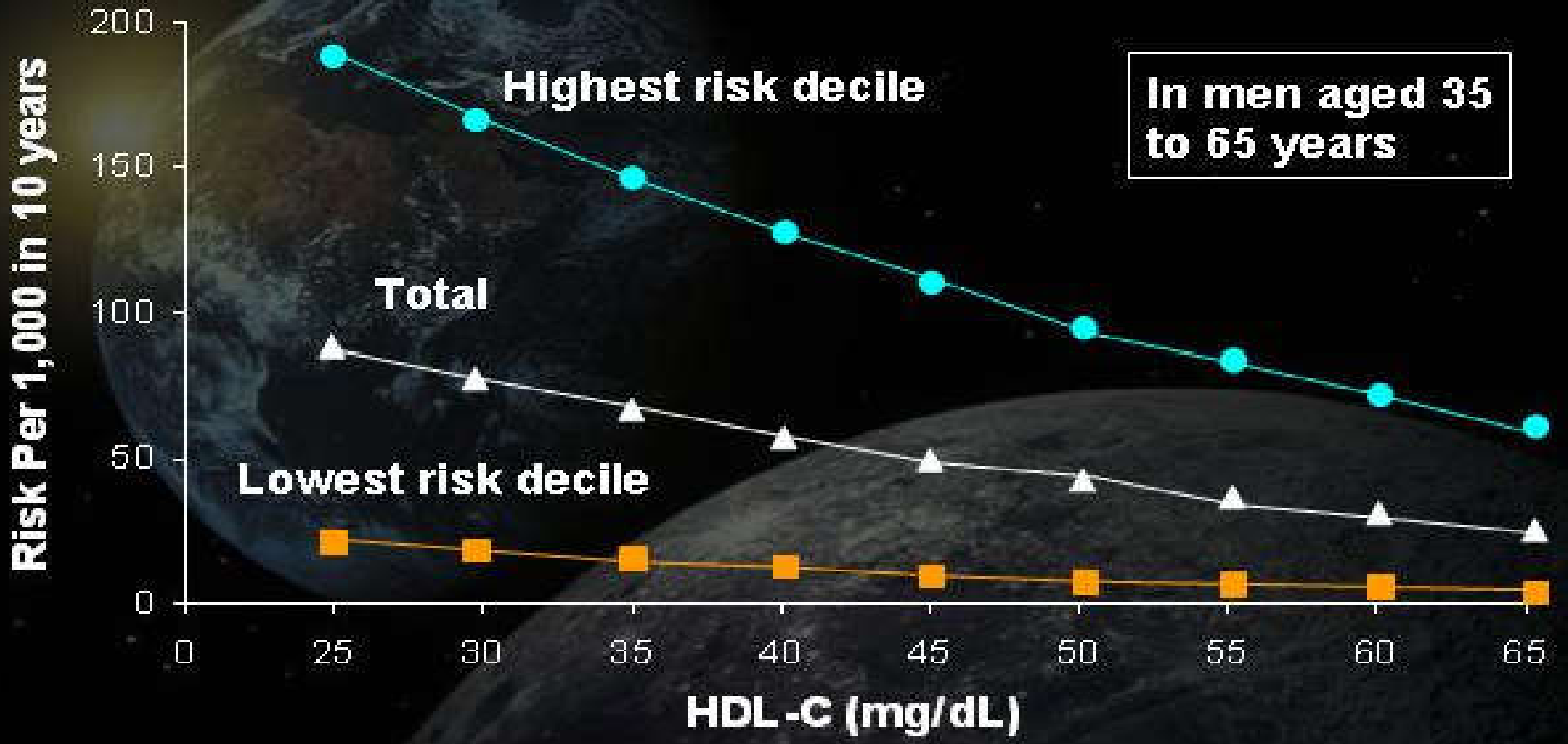

VLDL
TG
CETP
CE
HDL
TG
CETP
CE
LDL
Small
LDL

The diversity of the HDL proteom

- The apolipoproteins AI, AII, CII, CIII, E, D etc
- Lipolytic enzymes and transport proteins
  - CETP
  - PLTP
  - LCAT
  - PON1
- Acute phase response proteins
  - SAA
  - apoJ

↓ HDL-C → ↑ ΑΘΗΡΩΜΑΤΩΣΗΣ: ΕΠΙΔΗΜΙΟΛΟΓΙΚΑ ΔΕΔΟΜΕΝΑ

HDL-C Levels in the Context of Global Risk Factors for CAD: PROCAM

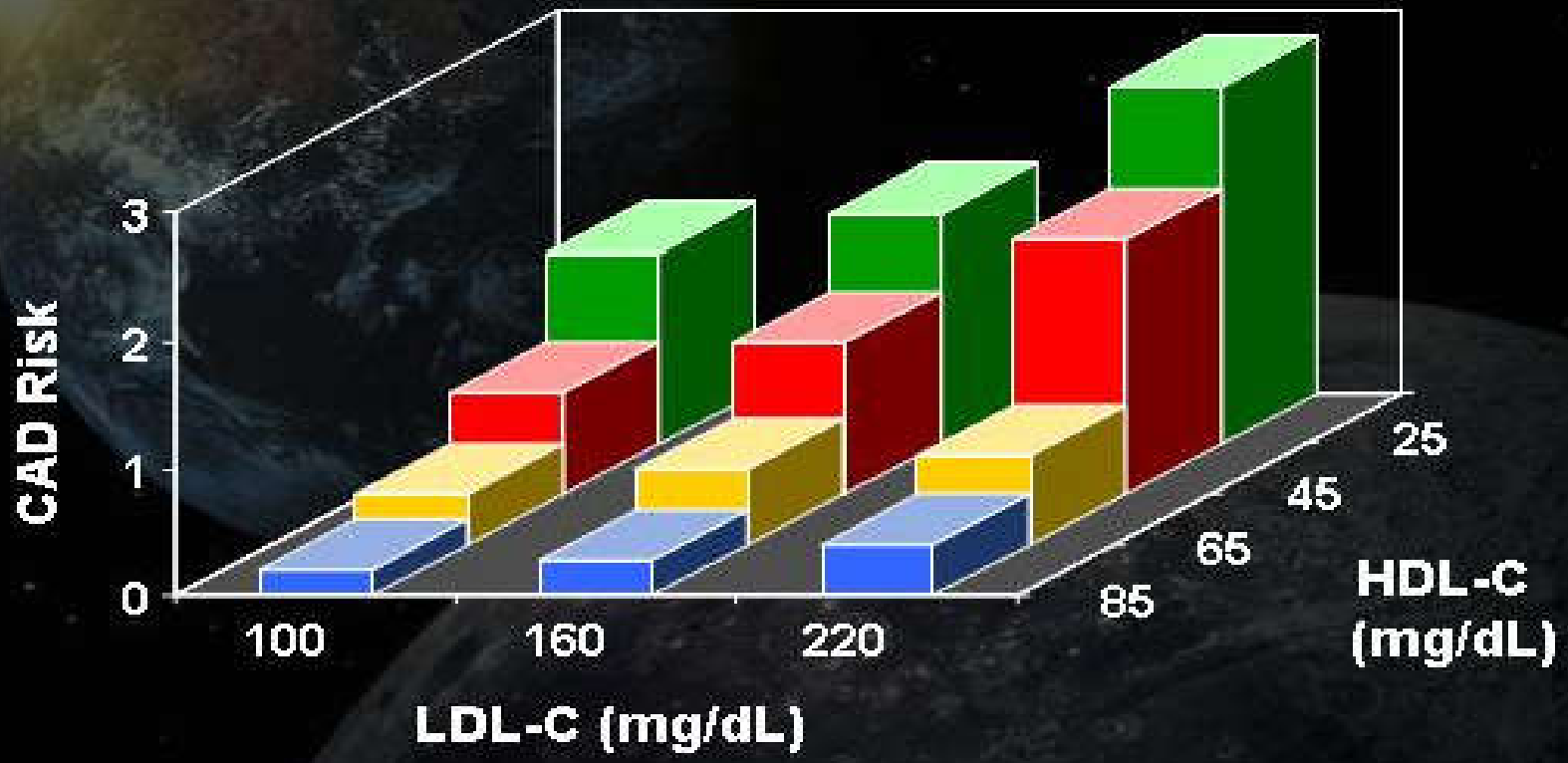


HDL-C = high-density lipoprotein cholesterol; CAD = coronary artery disease; PROCAM = Münster Heart Study.

International Task Force for Prevention of Coronary Heart Disease. PROCAM (Prospective Cardiovascular Münster Heart Study): HDL cholesterol and myocardial infarction [slide kit]. Available at: www.chd-taskforce.com. Accessed November 15, 2004.

HDL-C, LDL-C, and Risk for CAD: Framingham Heart Study

Incidence of CAD over 4 years in men aged 50-70, by HDL-C and LDL-C levels

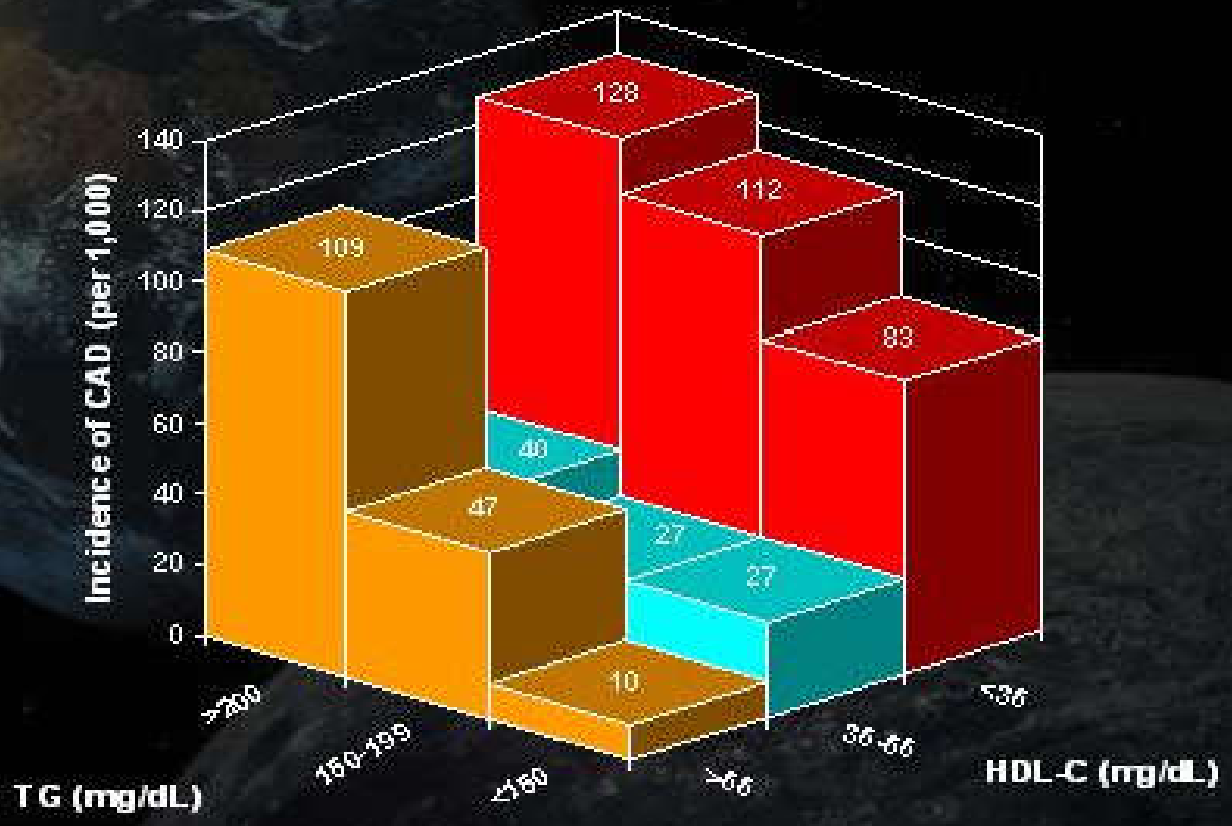


HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; CAD = coronary artery disease.

Castelli WP, et al. *Can J Cardiol.* 1988;4(suppl A):5A-10A.

HDL-C, TG, and Risk for CAD: PROCAM

6-year incidence of CAD by HDL-C and TG levels (PROCAM – The Münster Heart Study)

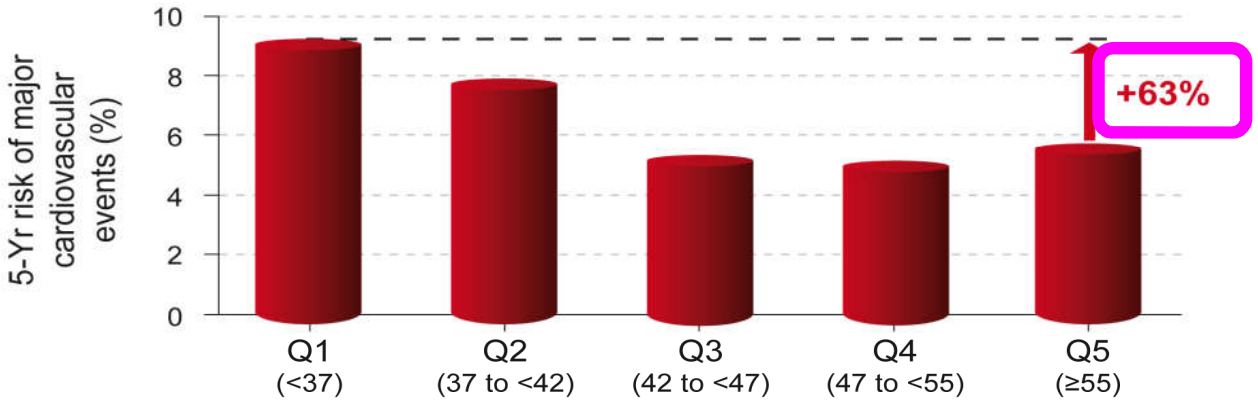


HDL-C = high-density lipoprotein cholesterol; TG = triglyceride; CAD = coronary artery disease.

Assmann G, et al. *Atherosclerosis*. 1996;124(suppl):S11-S20.

Low HDL-C contributes to MACROvascular residual risk even when LDL-C is well controlled

- TNT study:
  CV event rate was increased by 63% in the lowest HDL-C quintile compared with the highest (HR: 0.61, 95% CI: 0.38-0.97) even in patients with low LDL-C (<70 mg/dL or 1.8 mmol/L)[1]



	Q1 (<37)	Q2 (37 to <42)	Q3 (42 to <47)	Q4 (47 to <55)	Q5 (≥55)
No. of events	57	50	34	34	35
No. of patients	473	525	550	569	544

Hazard ratio (95% CI) versus Q1

Q2	0.85 (0.57-1.25)	Q3	0.57 (0.36-0.88)
Q4	0.55 (0.35-0.86)	Q5	0.61 (0.38-0.97)

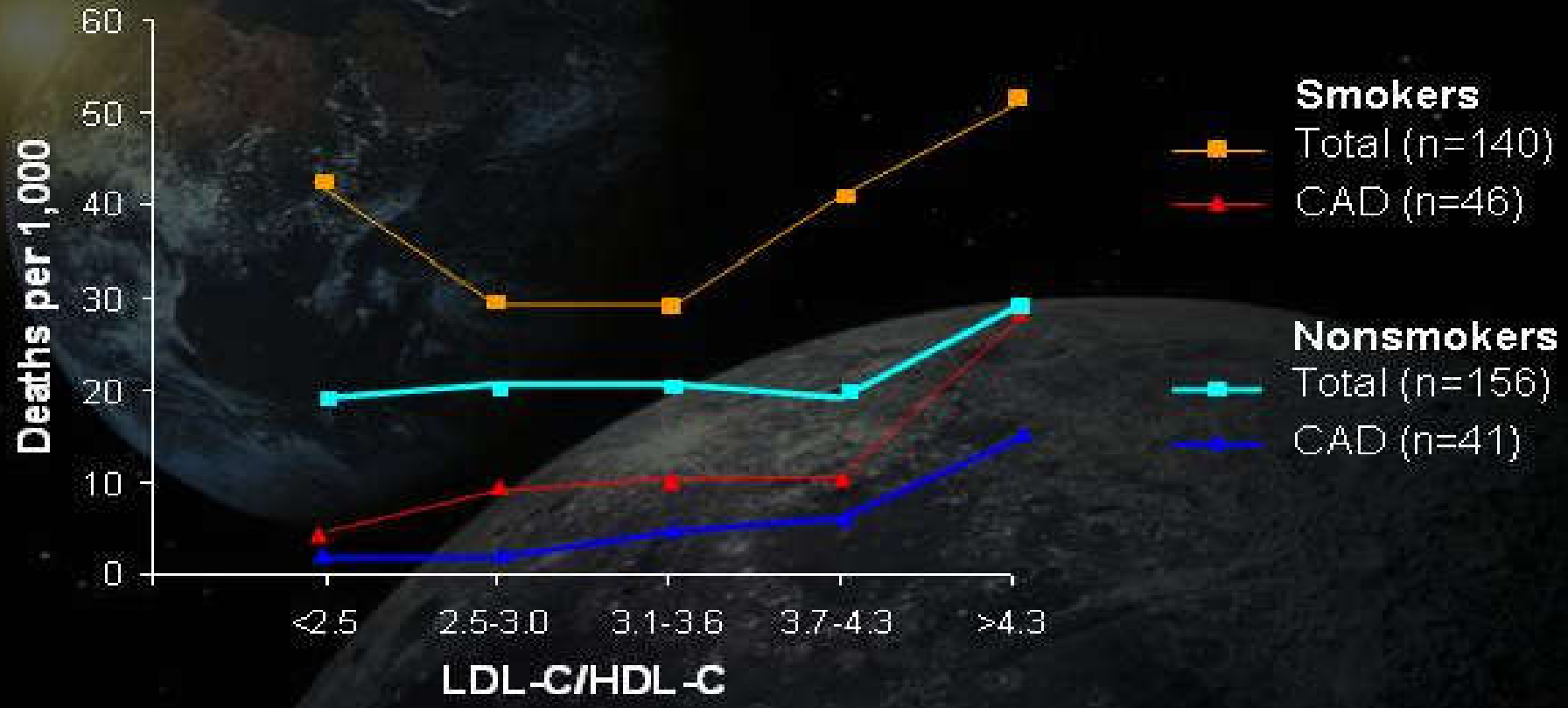
1 – Barter P *et al.* TNT sub-analysis. N Engl J Med 2007;357:1301-10.

Relationship Between LDL-C and HDL-C Levels and CHD Risk

Third Report of the NCEP Expert Panel. NIH Publication No. 01-3670. 2001.

LDL-C/HDL-C Ratio as Risk Indicator for Total and CAD Mortality: PROCAM

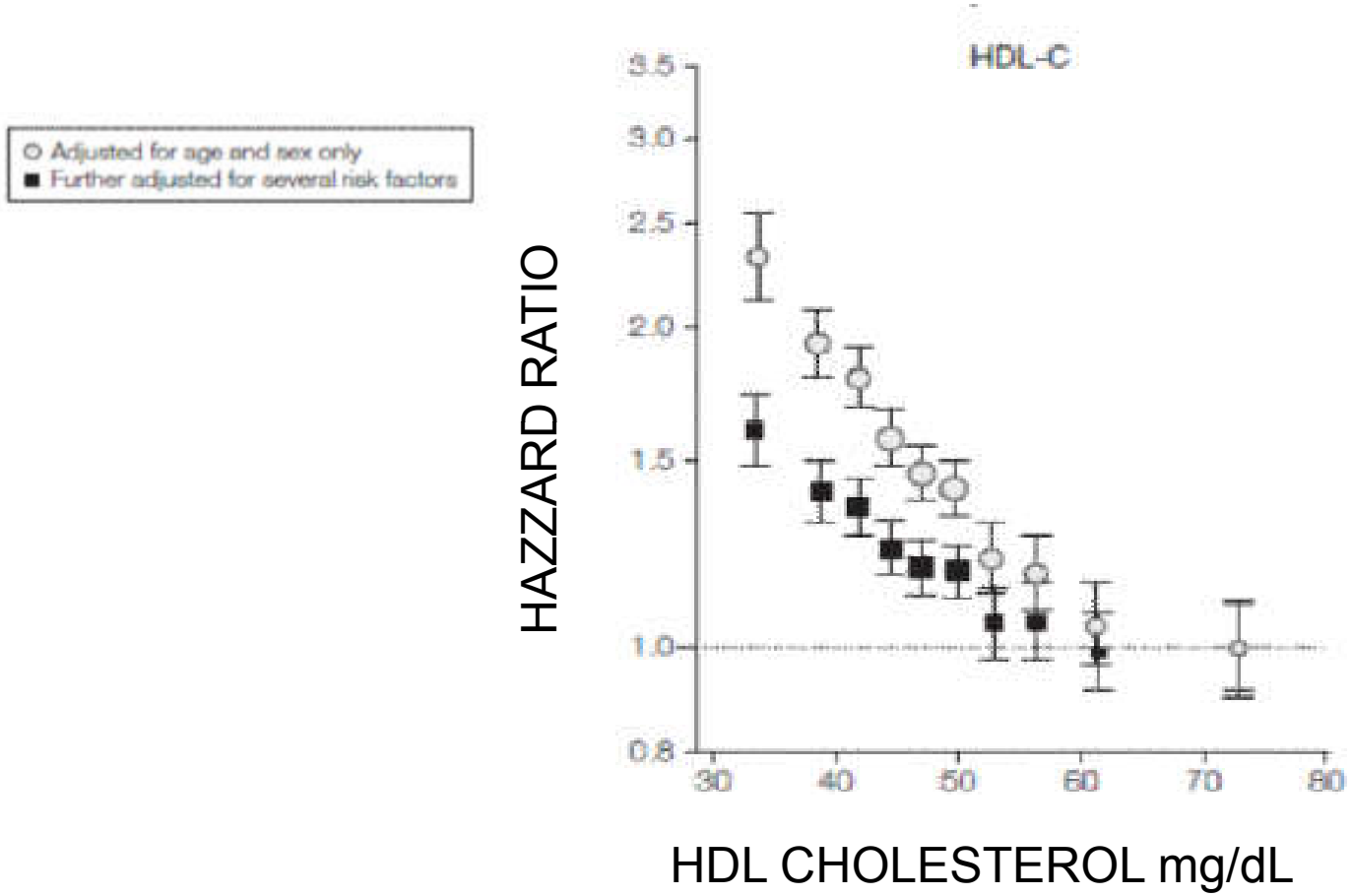
Total and CAD death rates in smoking and nonsmoking men aged 35 to 65 years in the Münster Heart Study—PROCAM



LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol; CAD = coronary artery disease.

Adapted from Cullen P, et al. *Circulation*. 1997;96:2128-2136.

HDL the good cholesterol, a complicated story



Adapted from: **The Emerging Risk Factors Collaboration***

JAMA. 2009 November 11; 302(18): 1993–2000.

THE LANCET

Plasma HDL cholesterol and risk of myocardial infarction: a mendelian randomisation study

Benjamin F Voight, Gina M Peloso*, Marju Orho-Melander, Ruth Frikke-Schmidt, Maja Barbalic, Majken K Jensen, George Hindy, Hilma Hólm, Eric L Ding, Toby Johnson, Heribert Schunkert, Nilesh J Samani, Robert Clarke, Jemma C Hopewell, John F Thompson, Mingyao Li, Gudmar Thorleifsson, Christopher Newton-Cheh, Kiran Musunuru, James P Pirruccello, Danish Saleheen, Li Chen, Alexandre F R Stewart, Arne Schillert, Unnur Thorsteinsdottir, Gudmundur Thorgeirsson, Sonia Anand, James C Engert, Thomas Morgan, John Spertus, Monika Stoll, Klaus Berger, Nicola Martinelli, Domenico Girelli, Pascal P McKeown, Christopher C Patterson, Stephen E Epstein, Joseph Devaney, Mary-Susan Burnett, Vincent Mooser, Samuli Ripatti, Ida Surakka, Markku S Nieminen, Juha Sinisalo, Marja-Liisa Lokki, Markus Perola, Aki Havulinna, Ulf de Faire, Bruna Gigante, Erik Ingelsson, Tanja Zeller, Philipp Wild, Paul I W de Bakker, Olaf H Klungel, Anke-Hilse Maitland-van der Zee, Bas J M Peters, Anthonius de Boer, Diederick E Grobbee, Pieter W Kamphuisen, Vera H M Deneer, Clara C Elbers, N Charlotte Onland-Moret, Marten H Hofker, Cisca Wijmenga, W M Monique Verschuren, Jolanda M A Boer, Yvonne T van der Schouw, Asif Rasheed, Philippe Frossard, Serkalem Demissie, Cristen Willer, Ron Do, Jose M Ordovas, Gonçalo R Abecasis, Michael Boehnke, Karen L Mohlke, Mark J Daly, Candace Guiducci, Noël P Burtt, Aarti Surti, Elena Gonzalez, Shaun Purcell, Stacey Gabriel, Jaume Marrugat, John Peden, Jeanette Erdmann, Patrick Diemert, Christina Willenborg, Inke R König, Marcus Fischer, Christian Hengstenberg, Andreas Ziegler, Ian Buysschaert, Diether Lambrechts, Frans Van de Werf, Keith A Fox, Nour Eddine El Mokhtari, Diana Rubin, Jürgen Schrezenmeir, Stefan Schreiber, Arne Schäfer, John Danesh, Stefan Blankenberg, Robert Roberts, Ruth McPherson, Hugh Watkins, Alistair S Hall, Kim Overvad, Eric Rimm, Eric Boerwinkle, Anne Tybjaerg-Hansen, L Adrienne Cupples, Muredach P Reilly, Olle Melander, Pier M Mannucci, Diego Ardissino, David Siscovick, Roberto Elosua, Kari Stefansson, Christopher J O'Donnell, Veikko Salomaa, Daniel J Rader, Leena Peltonen, Stephen M Schwartz, David Altshuler, Sekar Kathiresan*

Voight BF et al. *Lancet* 2012;380(9841):572–80

Mendelian randomisation

Subjects classified according to SNP associated with HDL level

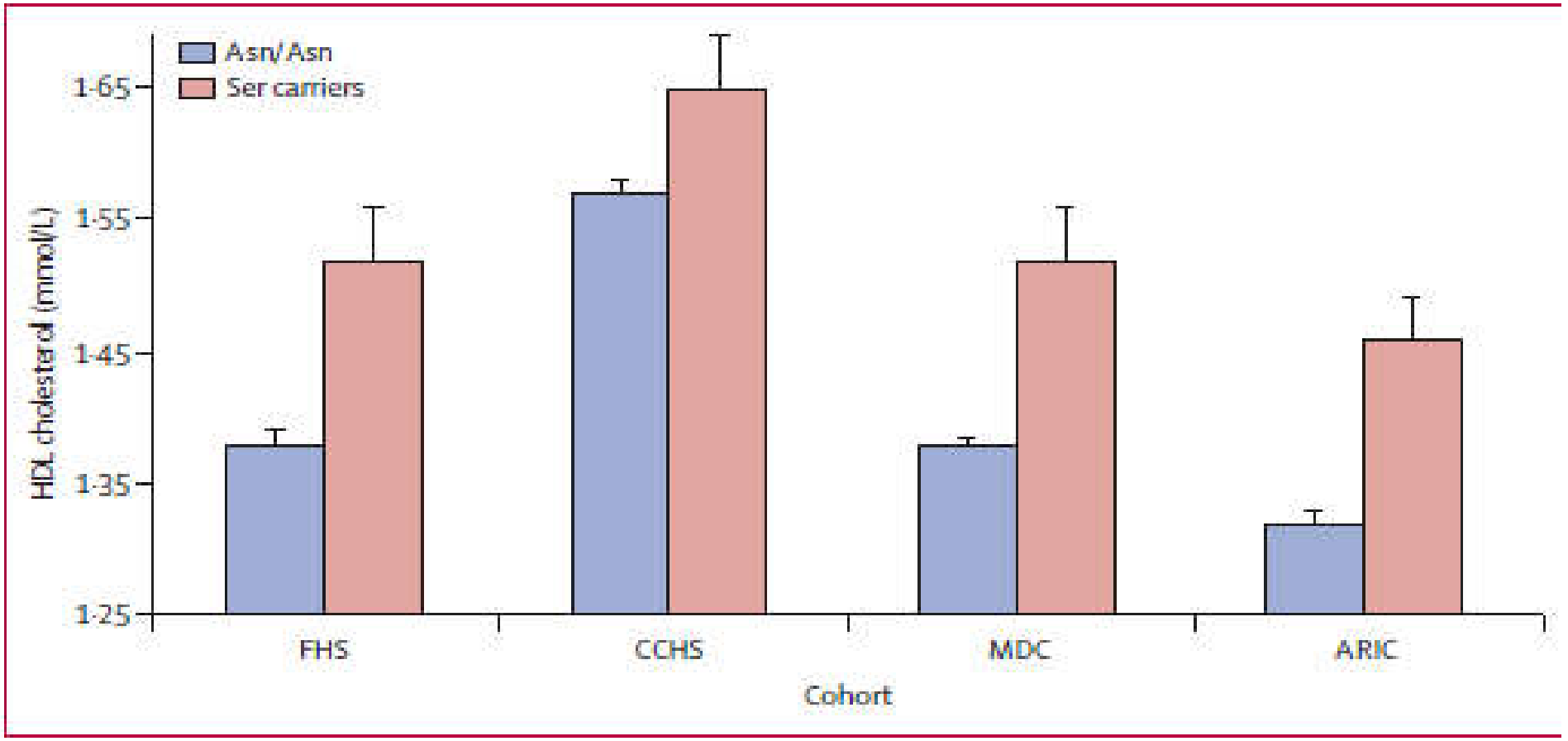


Figure 1: Plasma HDL cholesterol concentrations in carriers versus non-carriers of the Ser allele at the *LIPG* Asn396Ser polymorphism

Lancet 2012; 380: 572–80

No association to CVD risk, suggest no causal link to HDL

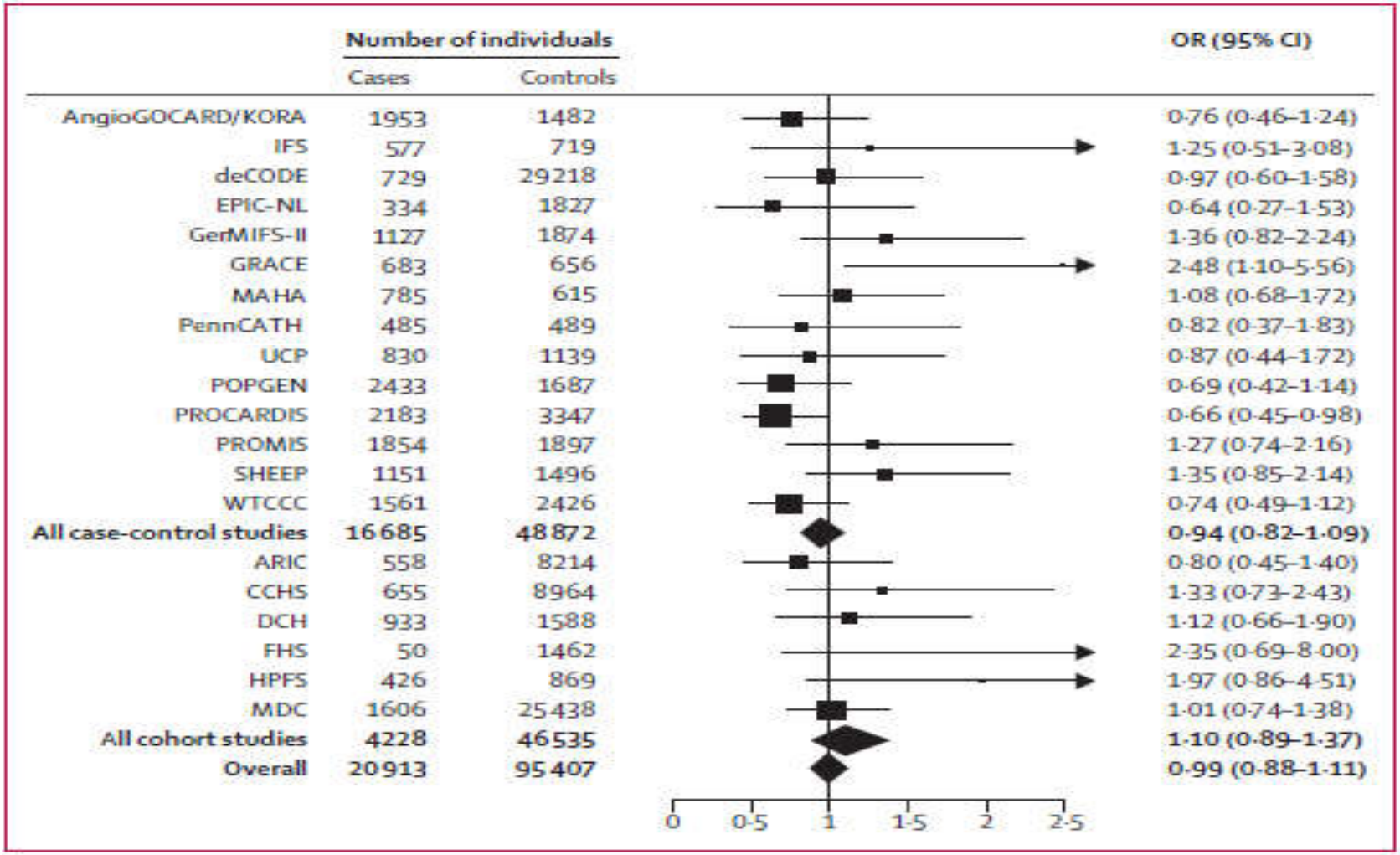
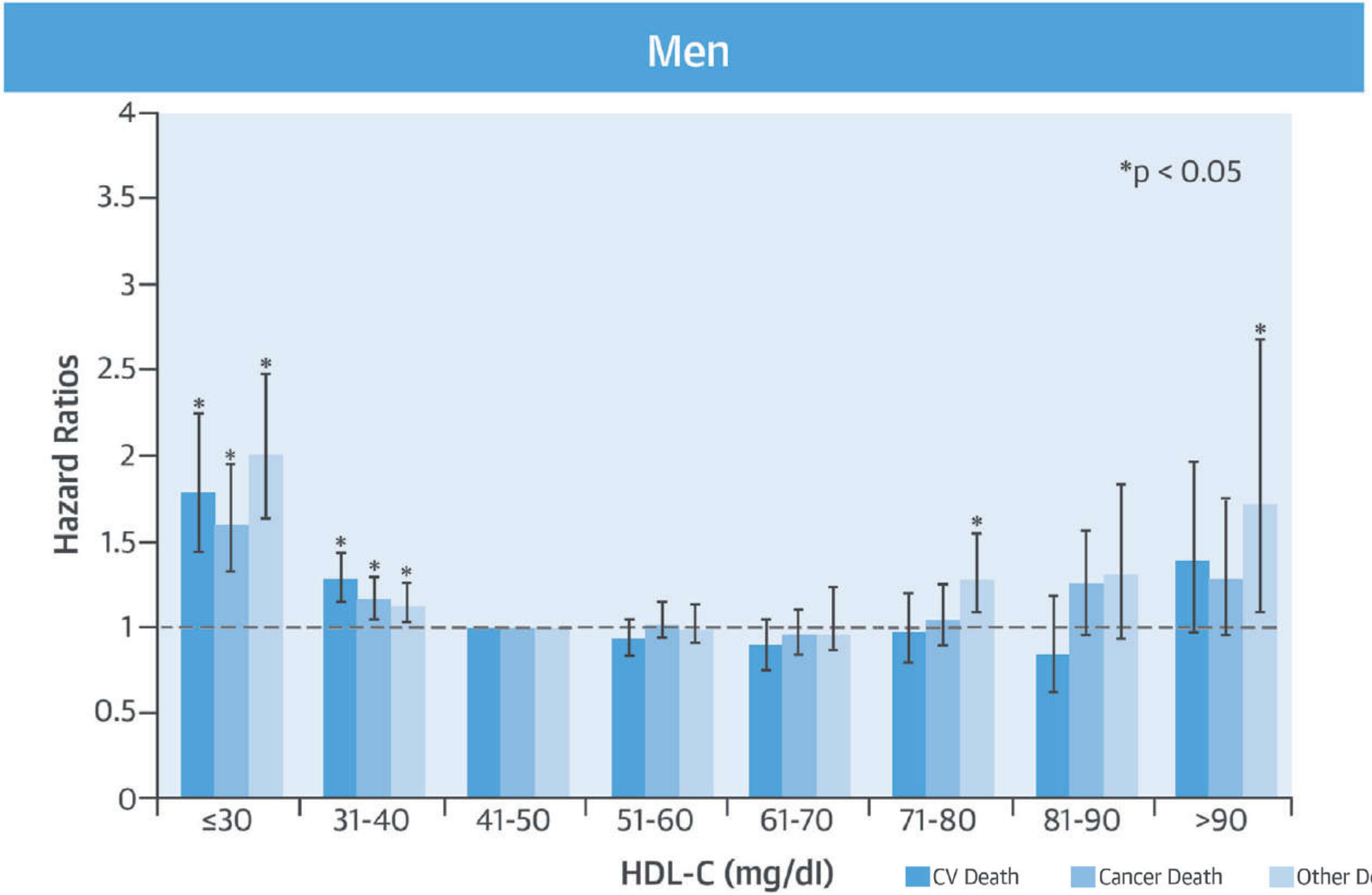


Figure 2: **Association of *LIPG* Asn396Ser with myocardial infarction in 116 320 participants from 20 studies**
In each study, the HDL-cholesterol-raising serine allele was modelled.

Lancet 2012; 380: 572–80

The CANHEART Study

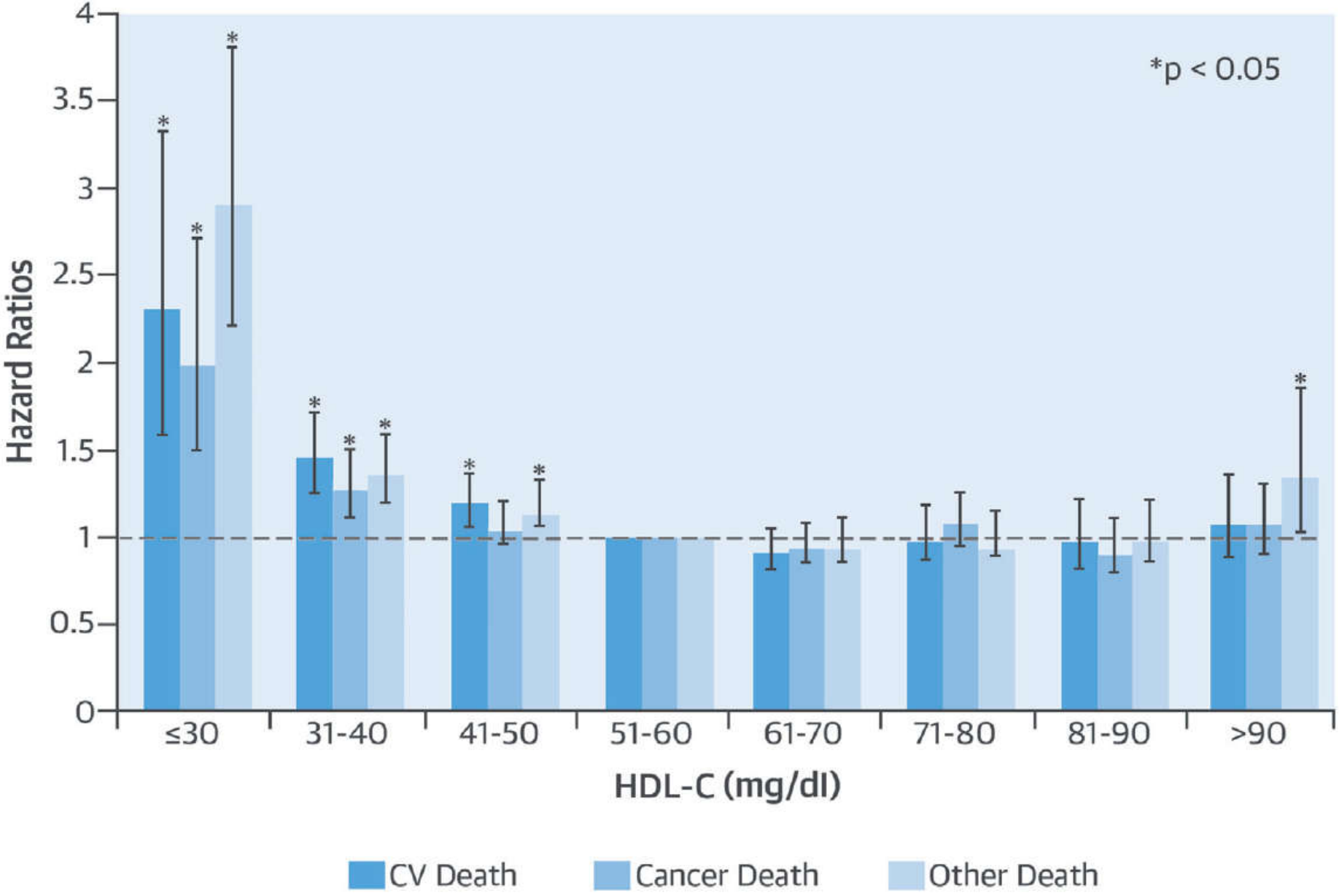
CENTRAL ILLUSTRATION **HDL-C and Cause-Specific Mortality in Individuals Without Prior CV Conditions**



Ko, D.T. et al. J Am Coll Cardiol. 2016;68(19):2073-83

The CANHEART Study

Women



Ko, D.T. et al. J Am Coll Cardiol. 2016;68(19):2073-83.

Science
AAAS

Rare variant in scavenger receptor BI raises HDL cholesterol and increases risk of coronary heart disease
Paolo Zanoni *et al.*
Science **351**, 1166 (2016);
DOI: 10.1126/science.aad3517

RESEARCH ARTICLES

HEART DISEASE

Rare variant in scavenger receptor BI raises HDL cholesterol and increases risk of coronary heart disease

11 MARCH 2016 • VOL 351 ISSUE 6278

↓ HDL-C → ↑ ΑΘΗΡΩΜΑΤΩΣΗΣ: ΠΑΘΟΦΥΣΙΟΛΟΓΙΚΑ ΔΕΔΟΜΕΝΑ

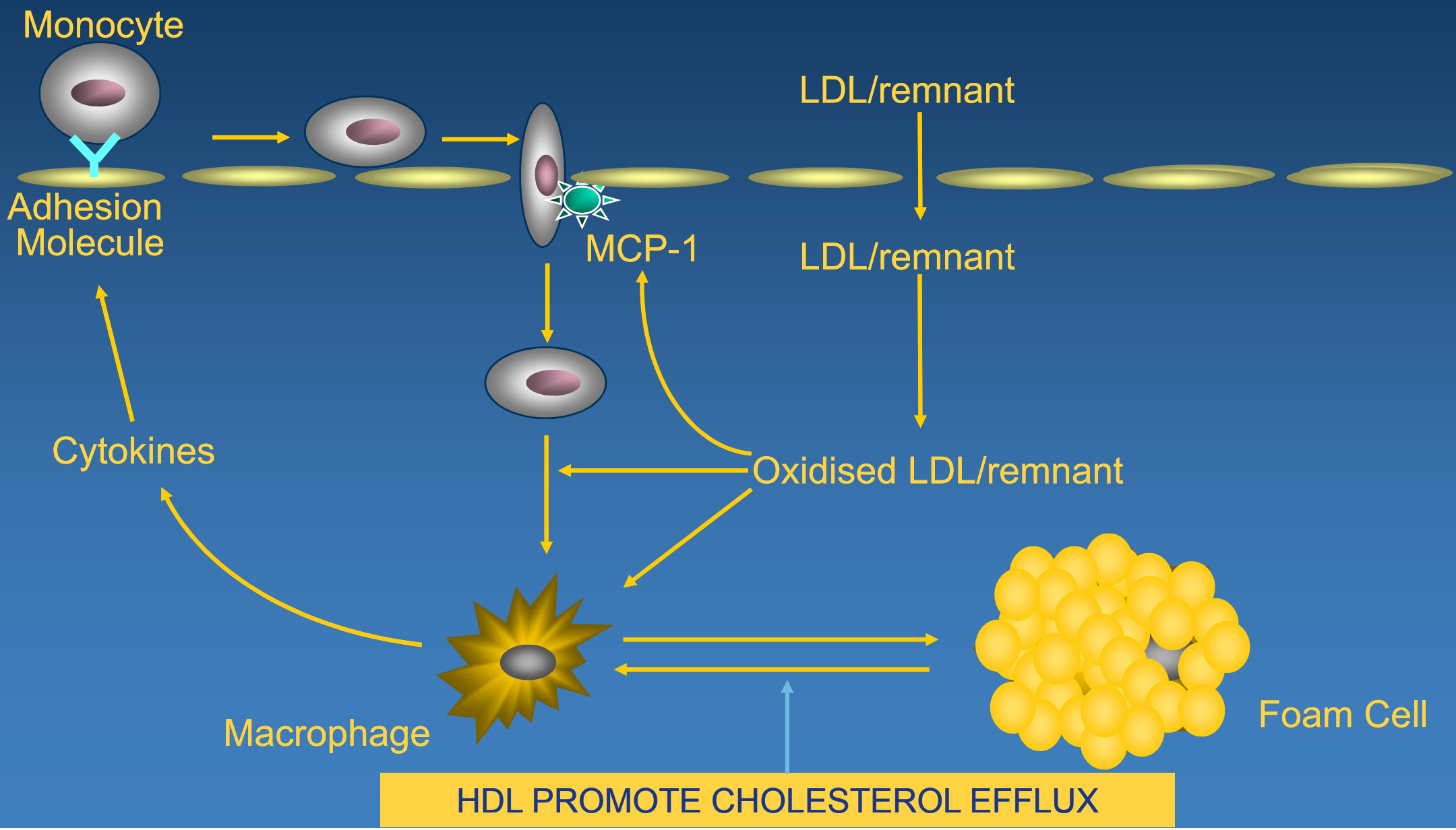
Multiple actions of high-density lipoprotein

Matilda Florentin[a], Evangelos N. Liberopoulos[a], Anthony S. Wierzbicki[b] and Dimitri P. Mikhailidis[c]

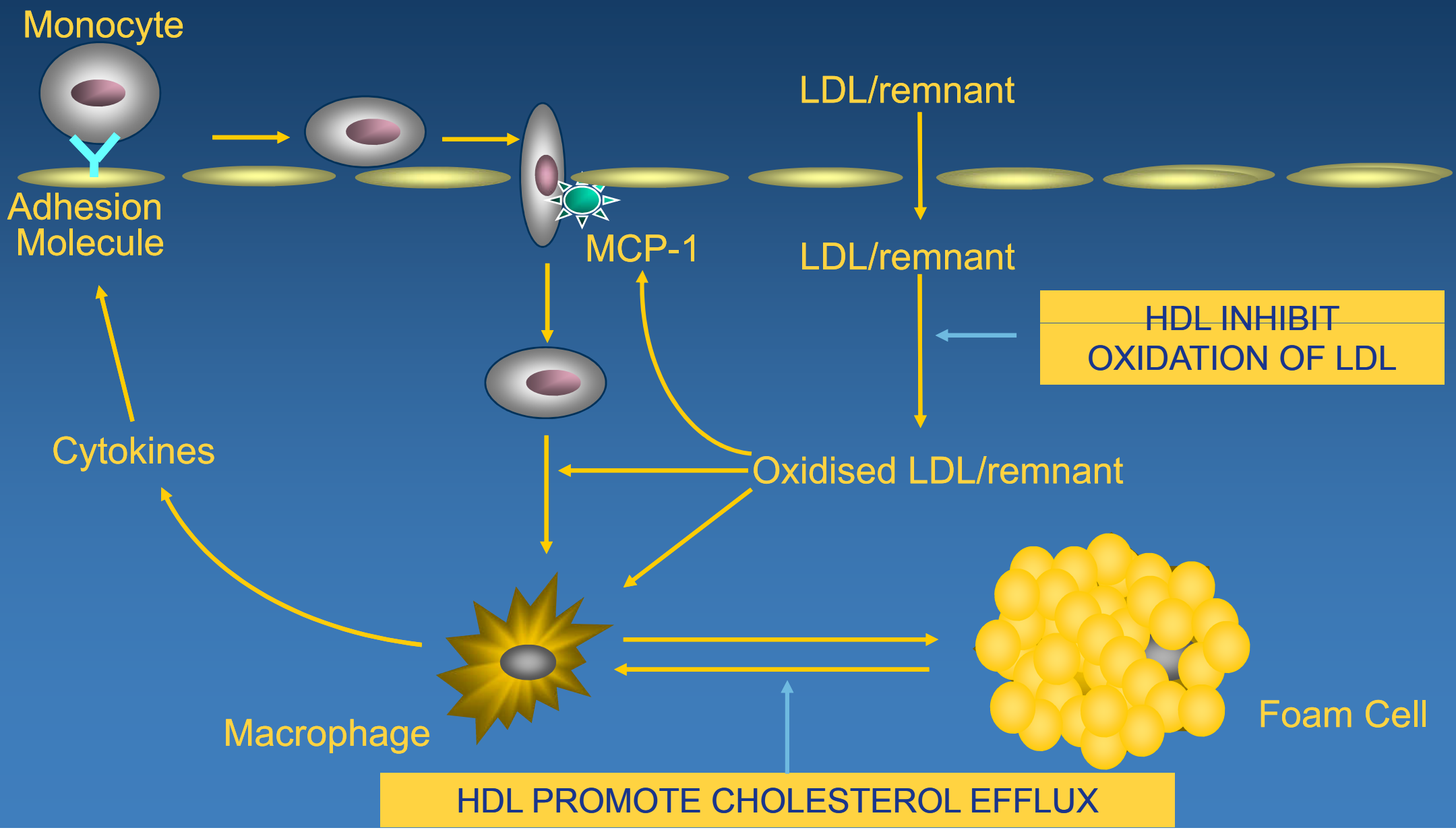
Table 1 Multiple actions of high-density lipoprotein

Action	Mechanisms
I. Antioxidant	1. Prevention of 12-lipoxygenase-mediated synthesis of lipid hydroperoxides, which oxidize LDL PLs and cholesterol [29,34] 2. Acquisition and removal of LDL lipid hydroperoxides and other lipid peroxidation products [29,30,34–36] 3. Destruction of lipid hydroperoxides [31,36–38] 4. Degradation of oxidized LDL PLs and reduced accumulation of oxidized lipids in LDL [5,30,40] 5. Removal of oxidized PLs from LDL [29,41] 6. Attenuation of monocyte–endothelial cell interaction induced by oxidized LDL [31,36] 7. Enhancement of cholesterol efflux from macrophages [42] 8. Inhibition of LDL penetration into the vessel wall [43]
II. Anti-inflammatory	1. Inhibition of vascular cell adhesion molecule-1, intercellular adhesion molecule-1, E-selectin, interleukin-1 and endotoxin expression *in vitro* [6,62] 2. Inhibition of NF-κB synthesis [56,63] 3. Inhibition of monocyte chemotactic protein-1 expression [31,64] 4. Inhibition of PAF-induced leukocyte adhesion to the endothelium [65] 5. Inhibition of C-reactive protein-induced expression of endothelial cell adhesion molecules [58]
III. Improved endothelial function	1. Restoration of endothelial NO synthase production [7,77,78] 2. Enhancement of endothelium-dependent vasodilatation [81] 3. Stimulation of prostacyclin synthesis [7,82] 4. Inhibition of endothelin-1 synthesis [83] 5. Maintenance of endothelial integrity through prevention of endothelial cell apoptosis and enhancement of endothelial cell migration and proliferation [76]
IV. Antithrombotic	1. Increased blood flow through enhanced NO and prostacyclin production [7] 2. Inhibition of E-selectin and tissue factor expression [7], resulting in decreased thrombin generation 3. Fibrinolysis promotion [73] 4. Attenuation of platelet activation and aggregation [91] 5. Attenuation of fibrinogen binding to platelets [93] 6. Inhibition of thromboxane A_2 synthesis [94] and elevation of prostacyclin/thromboxane A_2 ratio 7. Activation of proteins C and S [96] 8. Prevention of endothelial cell apoptosis [76]

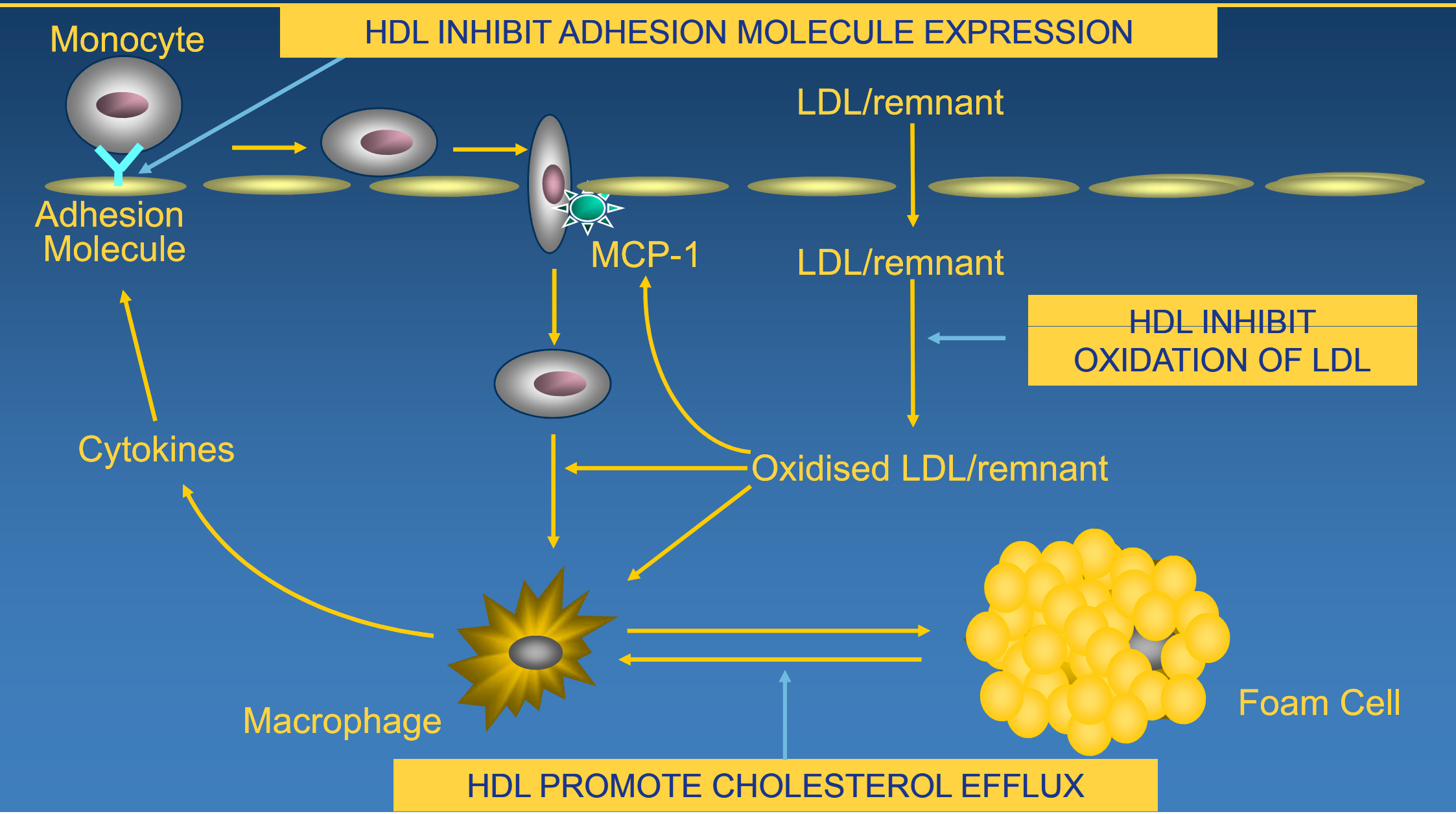
INHIBITION OF ATHEROSCLEROSIS BY HDL



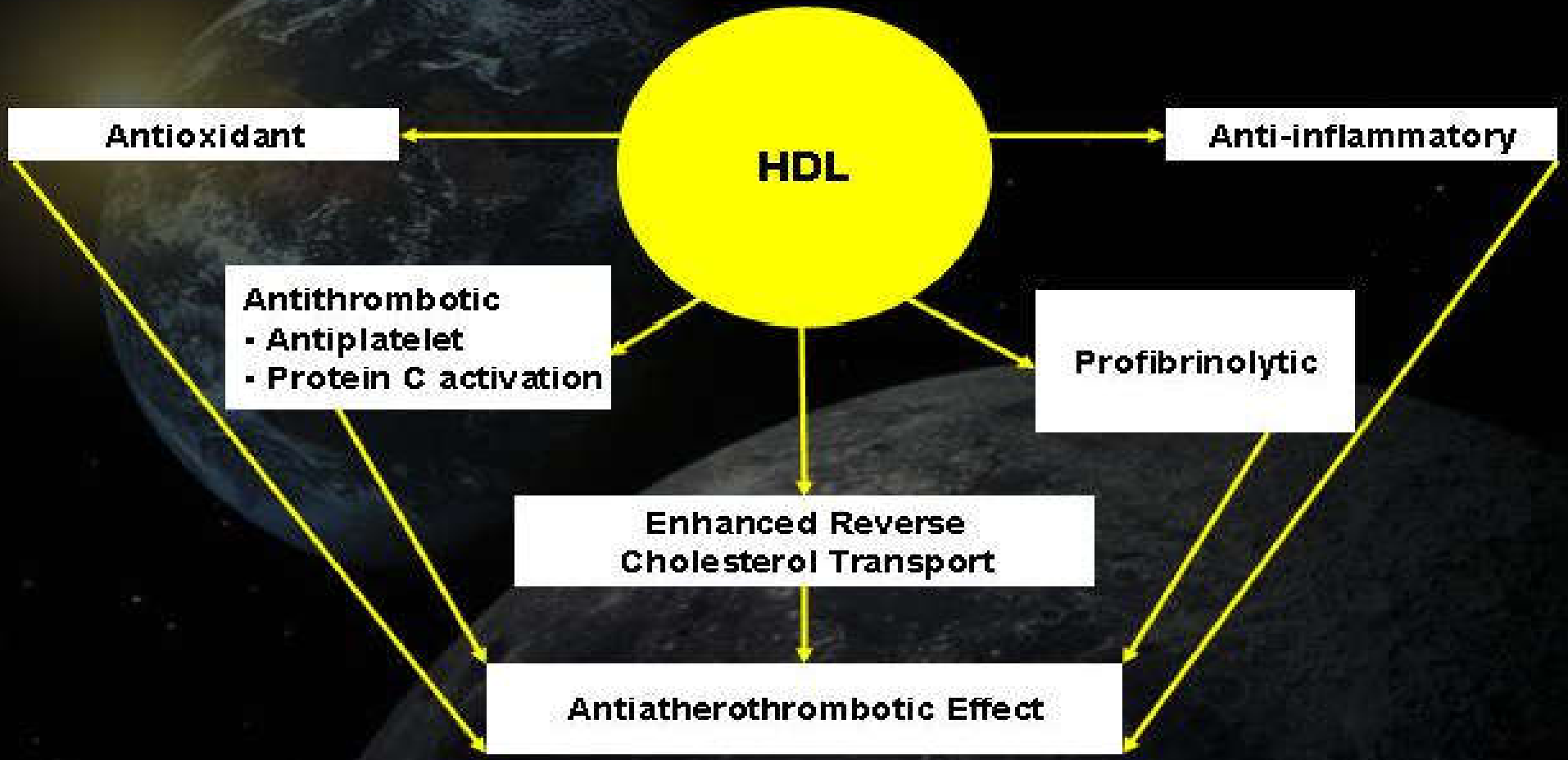
INHIBITION OF ATHEROSCLEROSIS BY HDL



INHIBITION OF ATHEROSCLEROSIS BY HDL



Potential Protective Effects of HDL-C Against Atherosclerosis



HDL-C = high-density lipoprotein cholesterol.

Shah PK, et al. *Circulation*. 2001;104:2376-2383.

Cholesterol Efflux Capacity, High-Density Lipoprotein Function, and Atherosclerosis

Amit V. Khera, M.D., Marina Cuchel, M.D., Ph.D., Margarita de la Llera-Moya, Ph.D., Amrith Rodrigues, M.S., Megan F. Burke, B.A., Kashif Jafri, B.A., Benjamin C. French, Ph.D., Julie A. Phillips, Ph.D., Megan L. Mucksavage, M.Sc., Robert L. Wilensky, M.D., Emile R. Mohler, M.D., George H. Rothblat, Ph.D., and Daniel J. Rader, M.D.

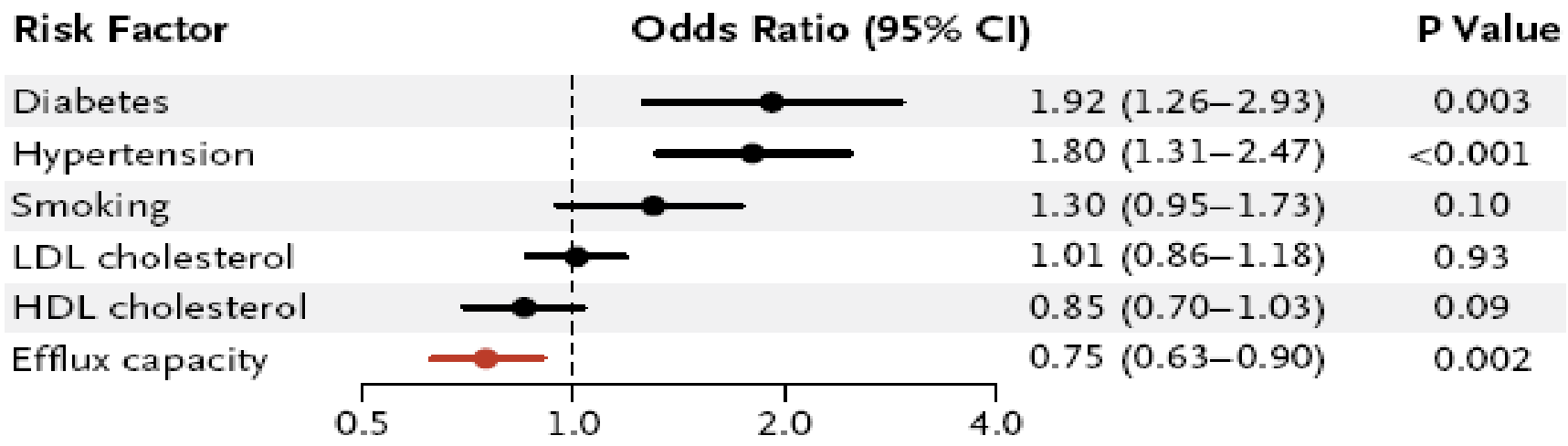
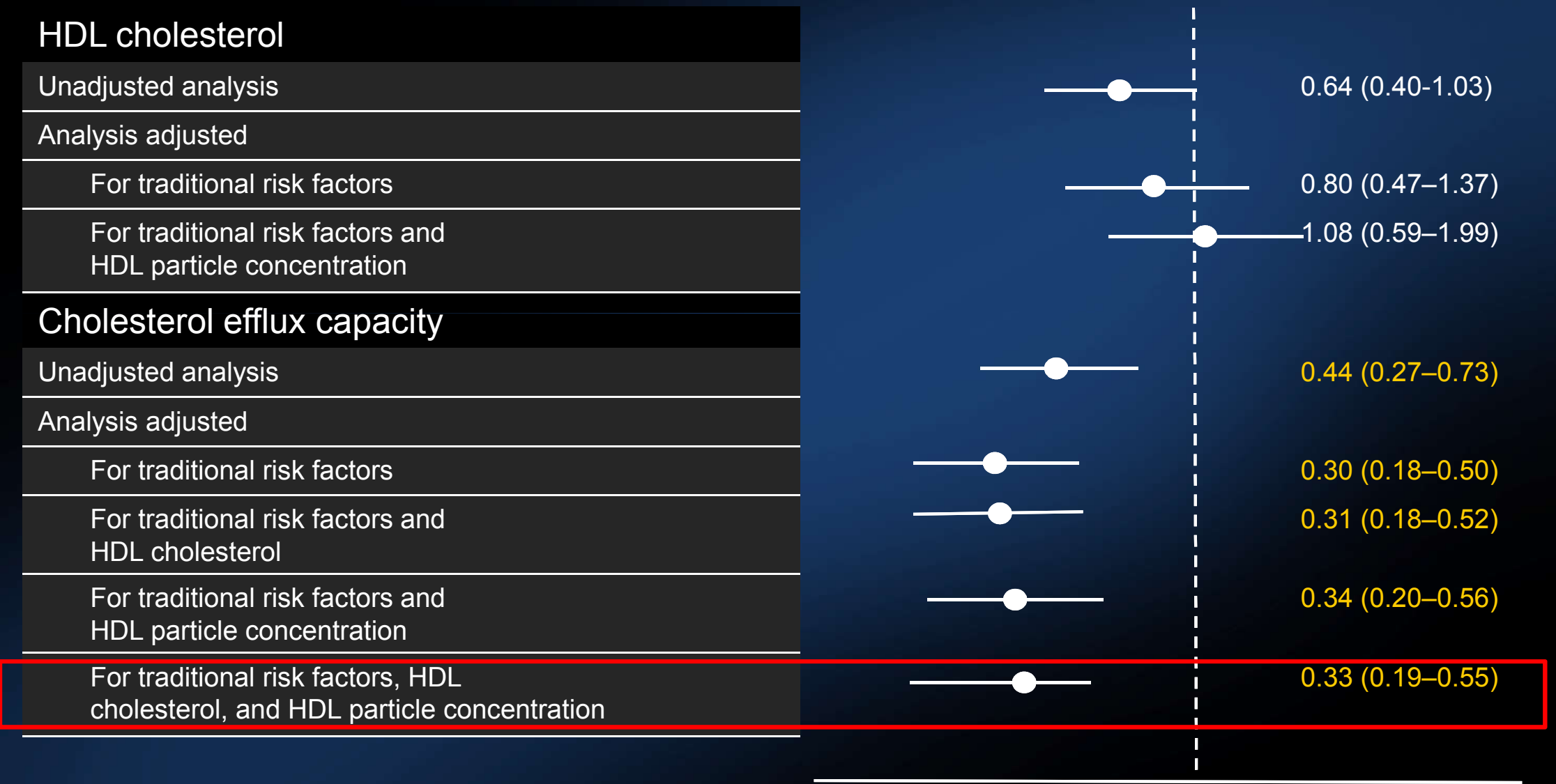


Figure 1. Odds Ratios for Coronary Artery Disease According to Efflux Capacity and Selected Risk Factors.

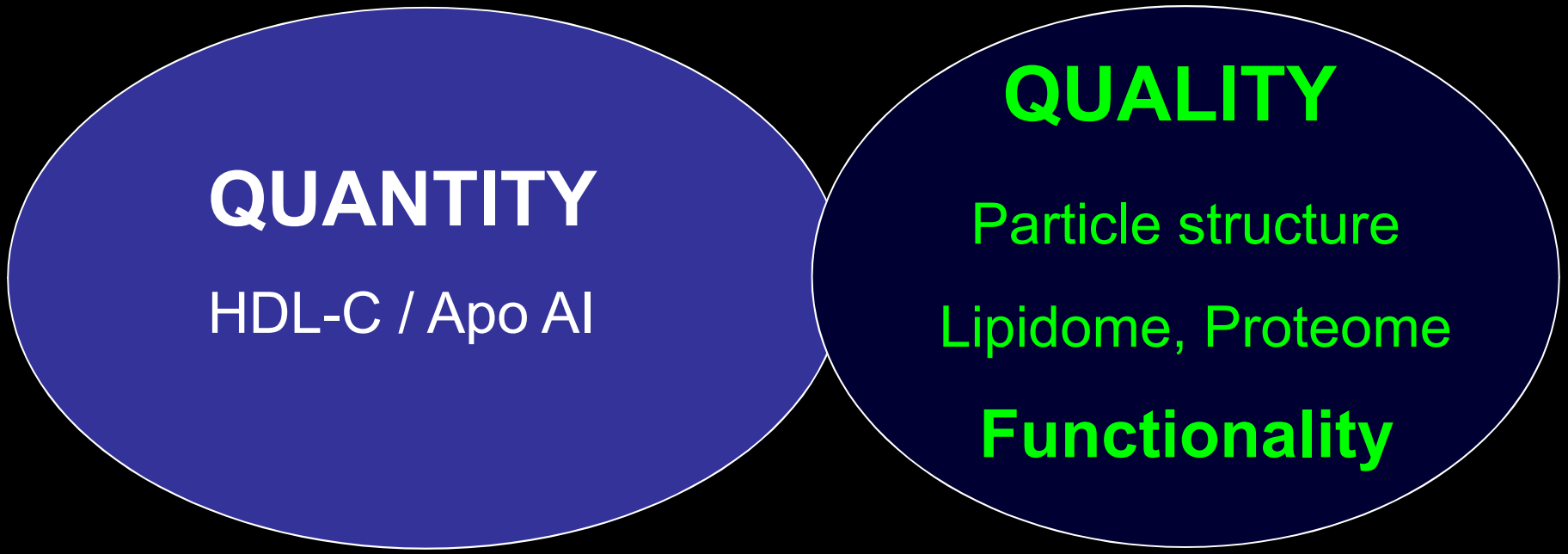
The logistic-regression model was also adjusted for age and sex. Odds ratios for continuous variables are per 1-SD increase.

Cholesterol Efflux is an Independent Predictor of Cardiovascular Risk



Rohatgi *et al. N Engl J Med*. 2014;371(25):2383-93

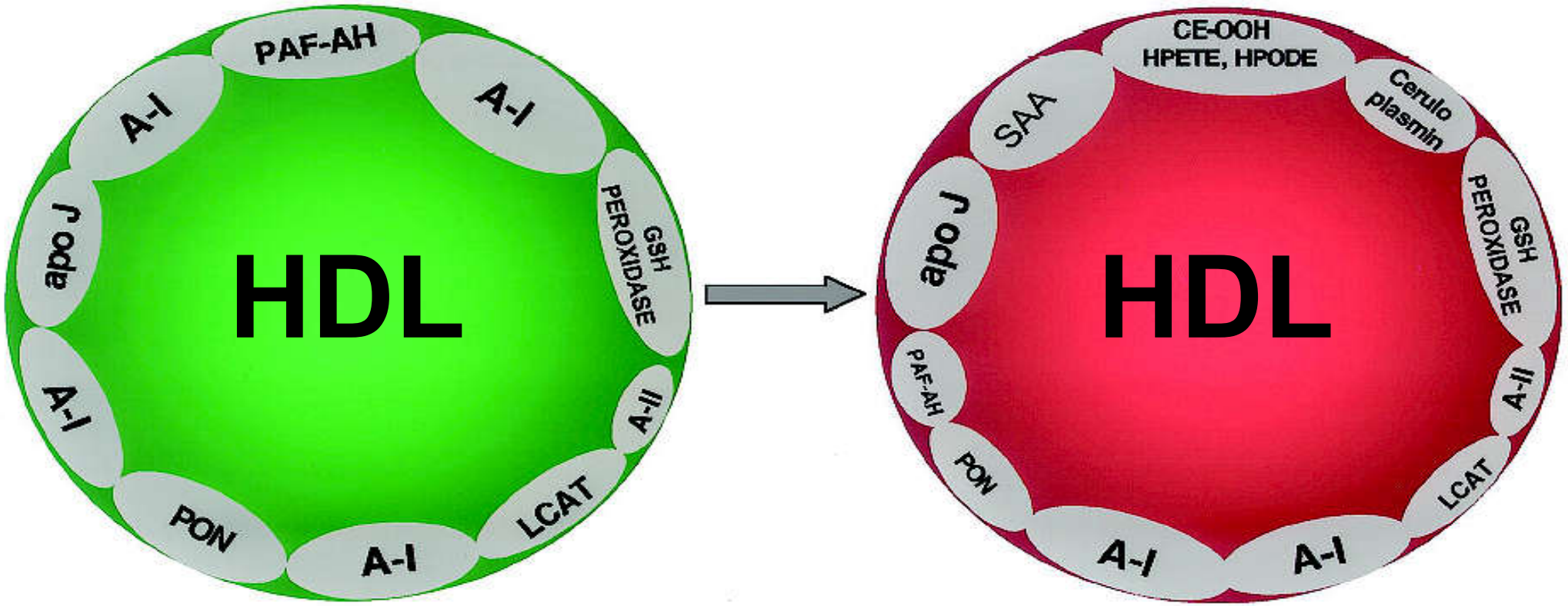
HDL: New Perspectives



Kontush A, Chapman MJ. *Pharmacol Rev*. 2006.

Potential anti atherosclerotic effects of HDL

- Reversed cholesterol transport
- Antioxidant
  - PON-1
  - Haemoglobin
- Antiinflammatory
  - Reduce ICAM-1,VCAM-1
  - Reduce LPS response
- Supress mobilisation of monocytes and neutrophils
- Enhance endothelial function, promote endothelial repair



Functional

antioxidant

anti-inflammatory

Dysfunctional

prooxidant ?

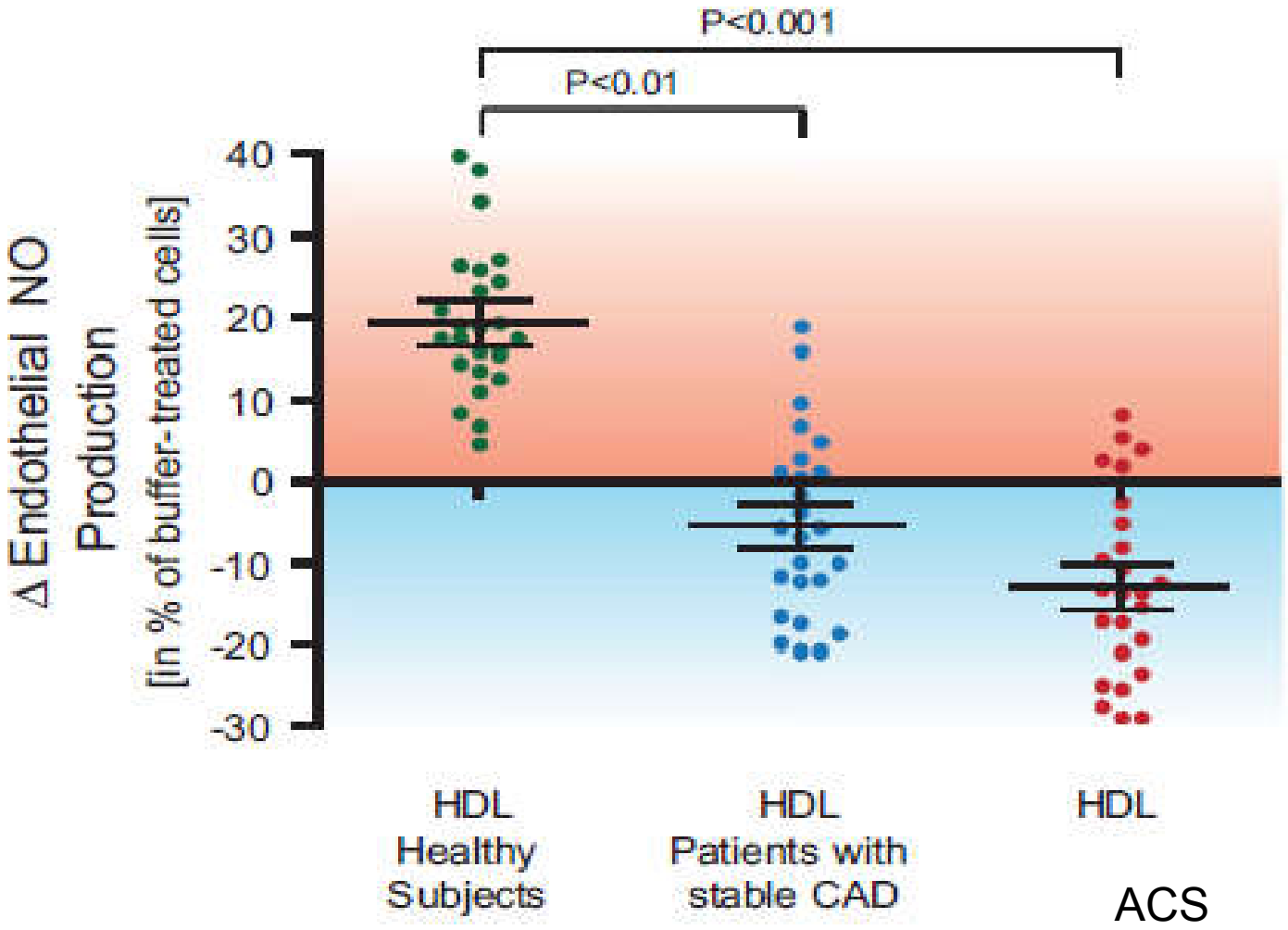
pro-inflammatory ?

Navab M et al *Arterioscler Thromb Vasc Biol*. 2001;21:481-488

Suggested functional loss of HDL during inflammation or acute CVD

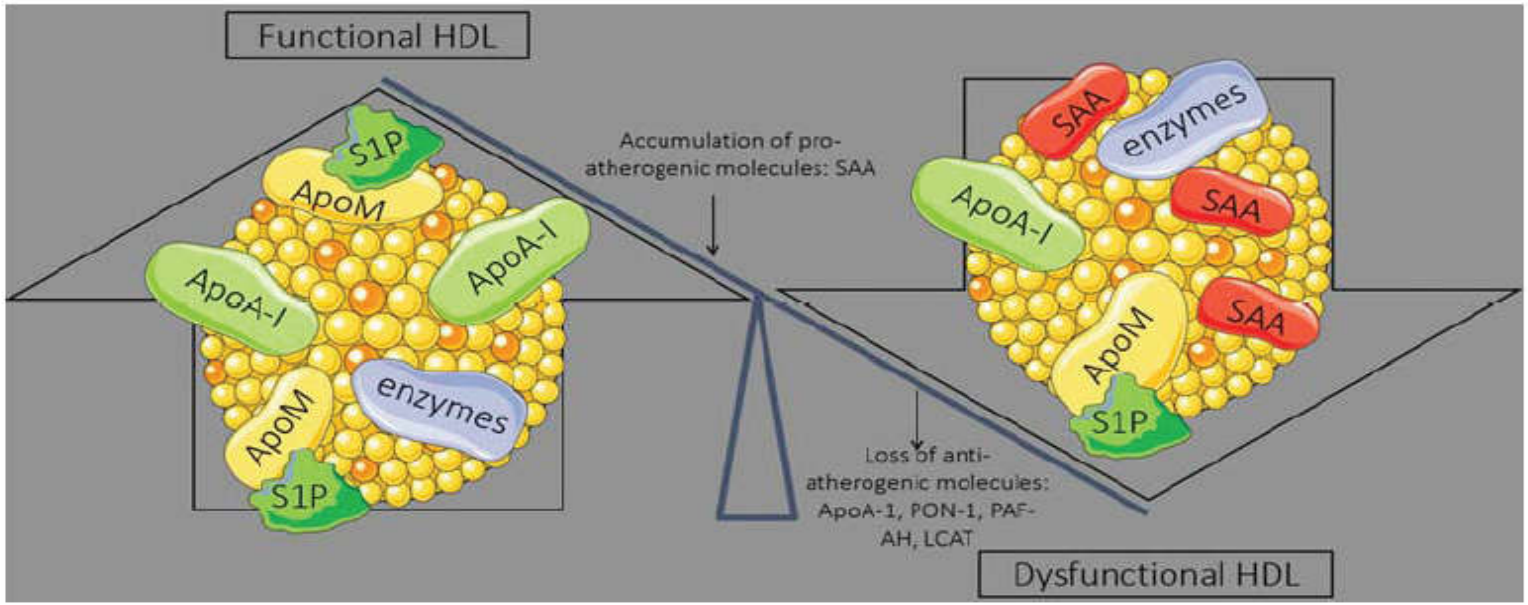
- Dysfunctional HDL
  - Loss of vasoprotective function
  - Loss of ability to stimulate cholesterol efflux
  - Loss of ability to inhibit endothelial apoptosis
  - Loss of ability to induce endothelial dependent vasodillatation
  - HDL may be proinflammatory

NO production is reduced with HDL from CHD patients



From: Besler et al JCI 2011;121:2693

Functional and dysfunctional HDL



Structural changes in HDL during acute phase response

The role of serum amyloid A and sphingosine-1-phosphate on HDL functional-ity

Nicole Prüfer[1,2], Burkhard Kleuser[2] and Markus van der Giet[1,*]

Biol.chem 2014, in press

↑ HDL-C → ↓ ΑΘΗΡΩΜΑΤΩΣΗΣ: ΔΕΔΟΜΕΝΑ ΚΛΙΝΙΚΩΝ ΜΕΛΕΤΩΝ

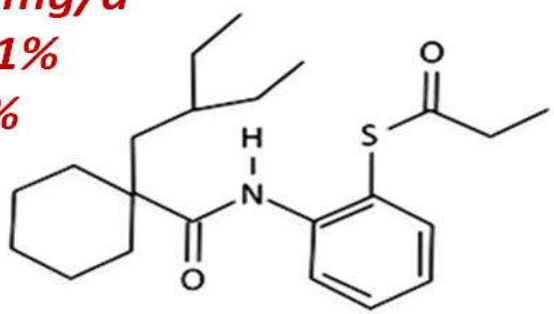
CETP Inhibitors

Dalcetrapib*

Dos[illegible]600 mg/d

HDL[illegible]~31%

LDL-C: ↓ ~2%

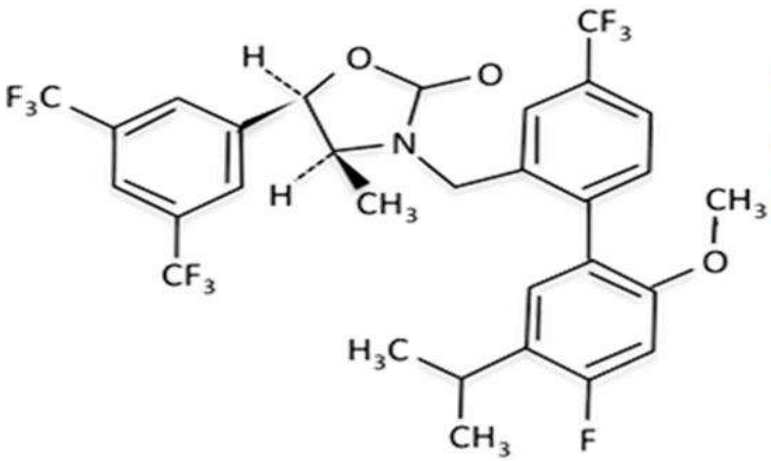


Anacetrapib

Dosage: 100 mg/d

HDL-C: ↑ ~138%

LDL-C: ↓ ~40%

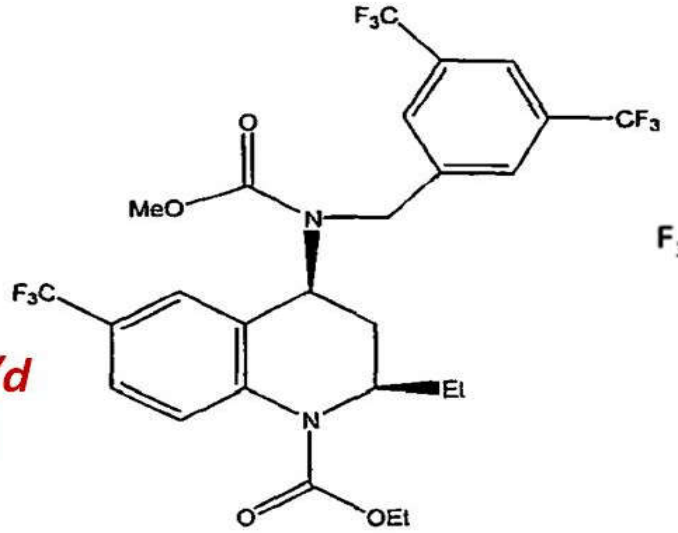


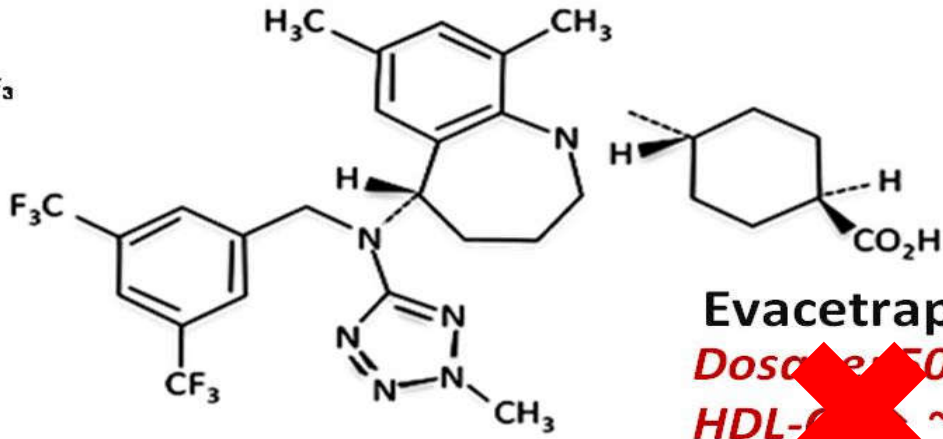
Torcetrapib*

Dosage: 60 mg/d

HDL-C: [illegible]~61%

LDL-C: ↓ [illegible]24%





Evacetrapib

Dosa[illegible]500 mg/d

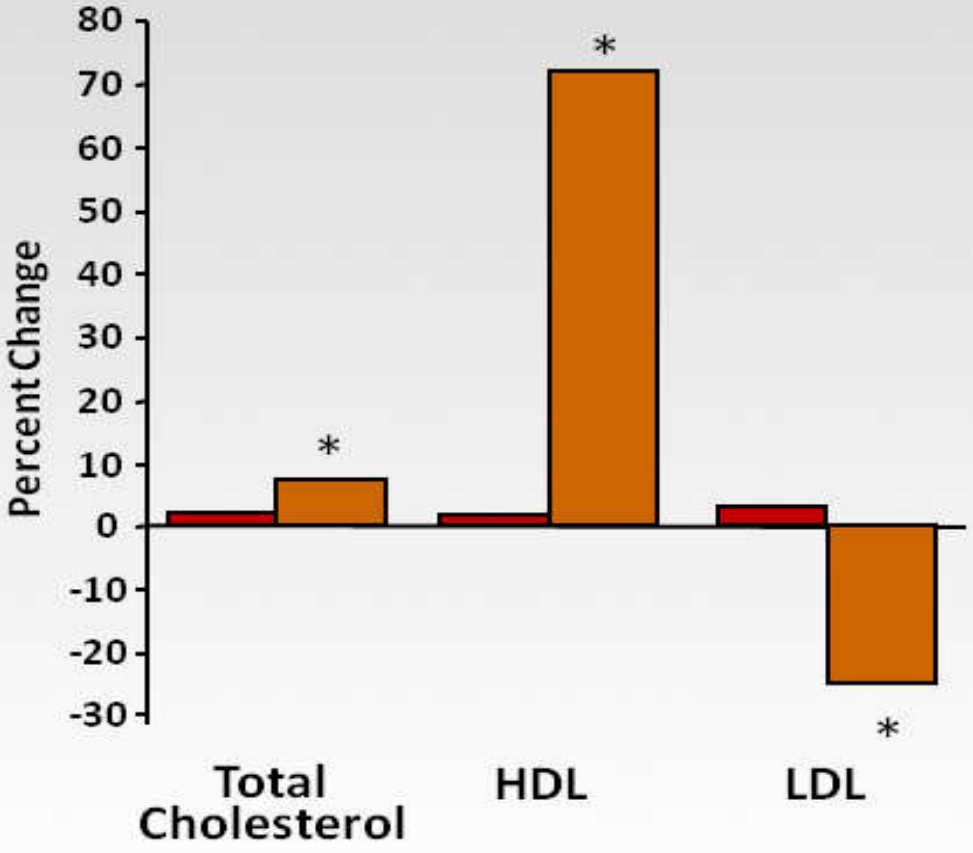
HDL-[illegible]~129%

LDL-C: ↓ ~36%

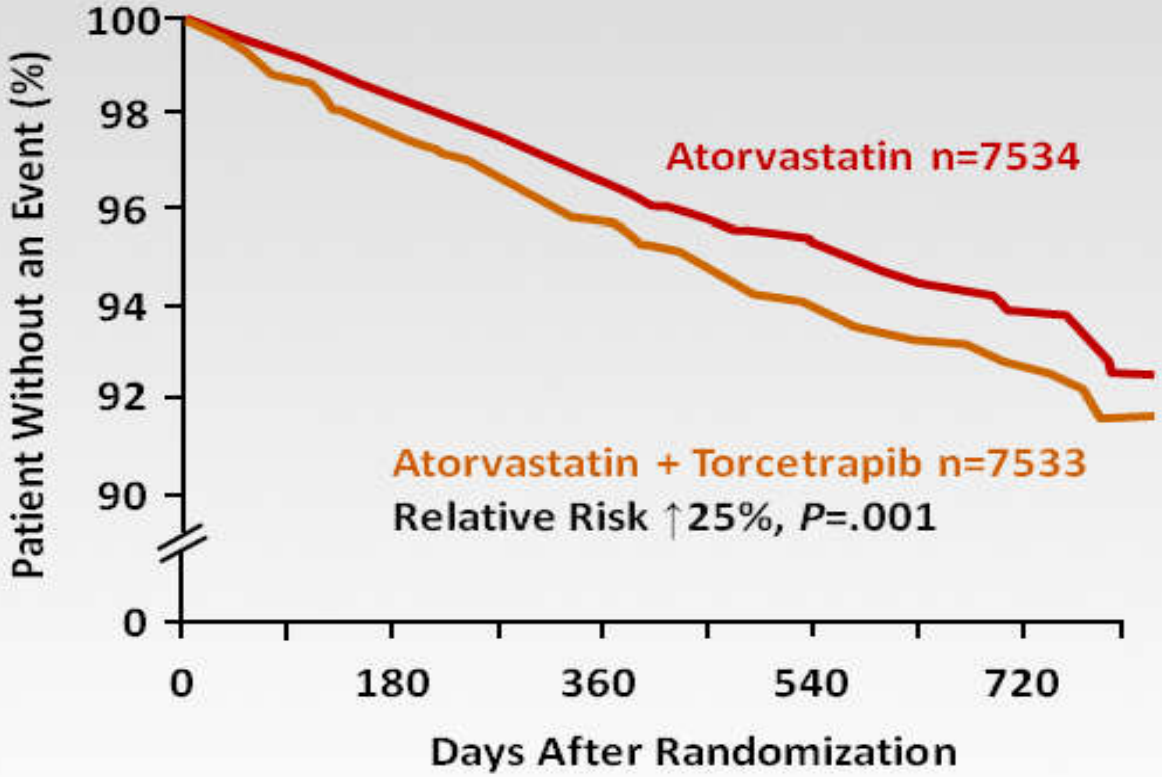
*Clinical development discontinued

ILLUMINATE: Torcetrapib in Patients With High Cardiovascular Risk (cont)

Change in Lipid Levels

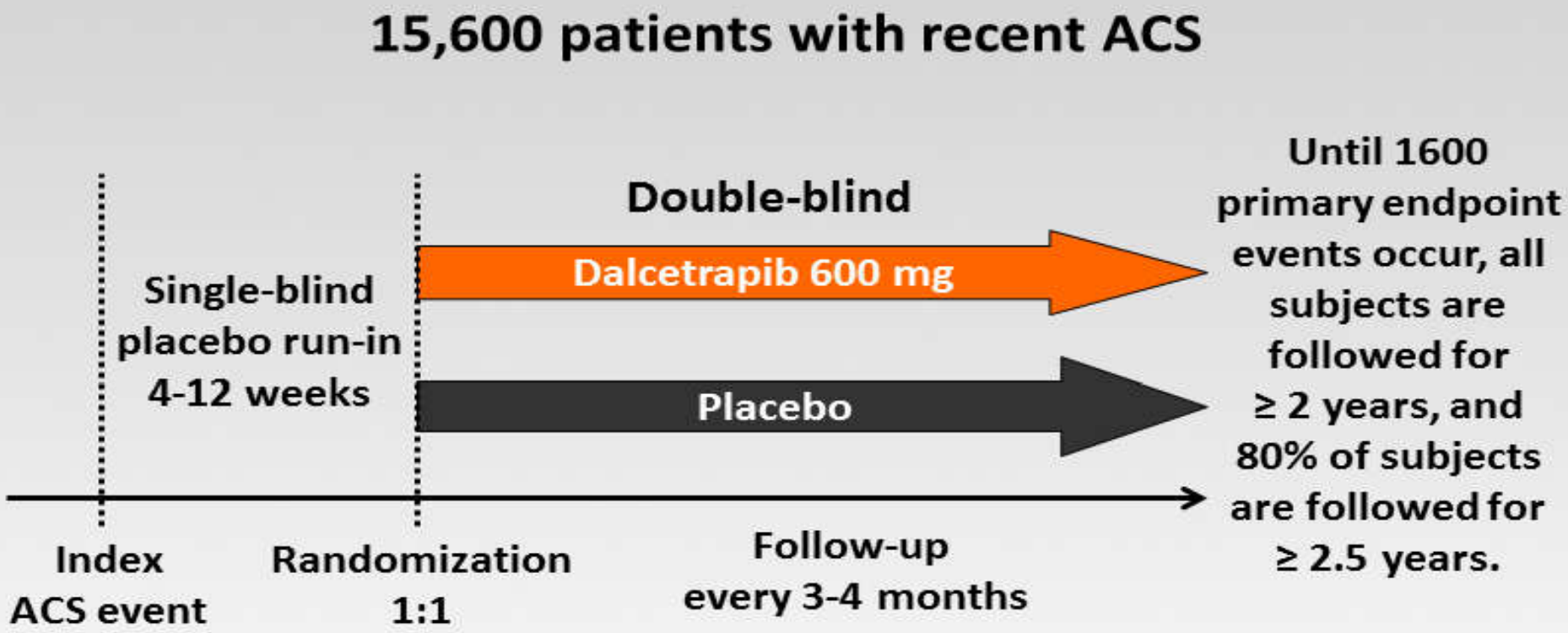


Cardiovascular Events



Barter PJ, et al. *N Engl J Med*. 2007;357:2109-2122.

dal-OUTCOMES

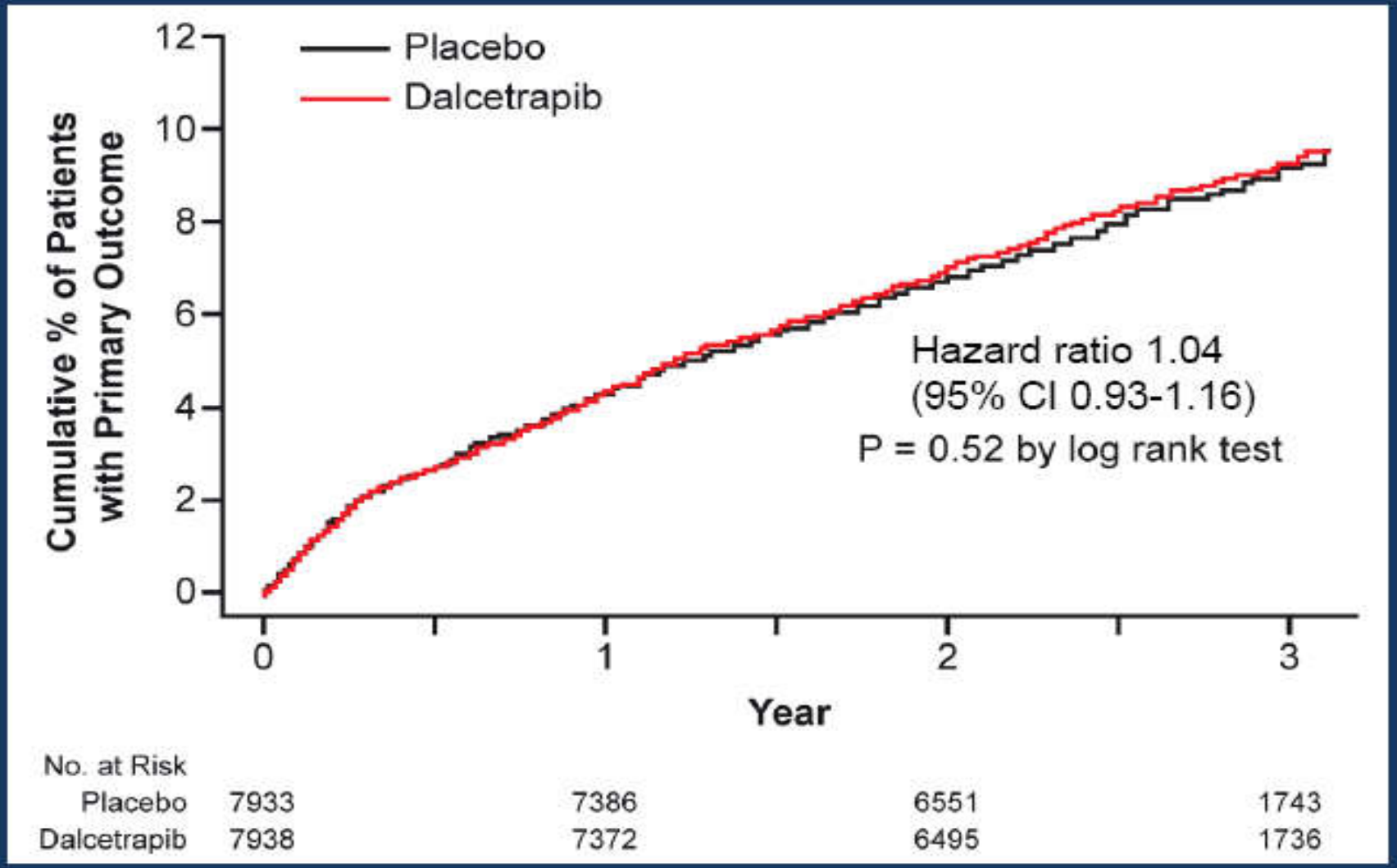


Study Start Date: April 2008

Estimated Study Completion Date: May 2013

Available at: http://clinicaltrials.gov/ct2/show/NCT00658515

Primary outcome* by treatment group



* Coronary heart disease death, non-fatal MI, ischemic stroke, hospitalization for unstable angina, resuscitated cardiac arrest

May the heterogeneity of HDL explain the results?

- Do drug treatment elevate the correct fraction of HDL?
- How is the HDL proteom changed during treatment
- How is the HDL lipidome changed during treatment?
- Is all HDL beneficial and functional ?
- Dysfunctional HDL

Infusion studies

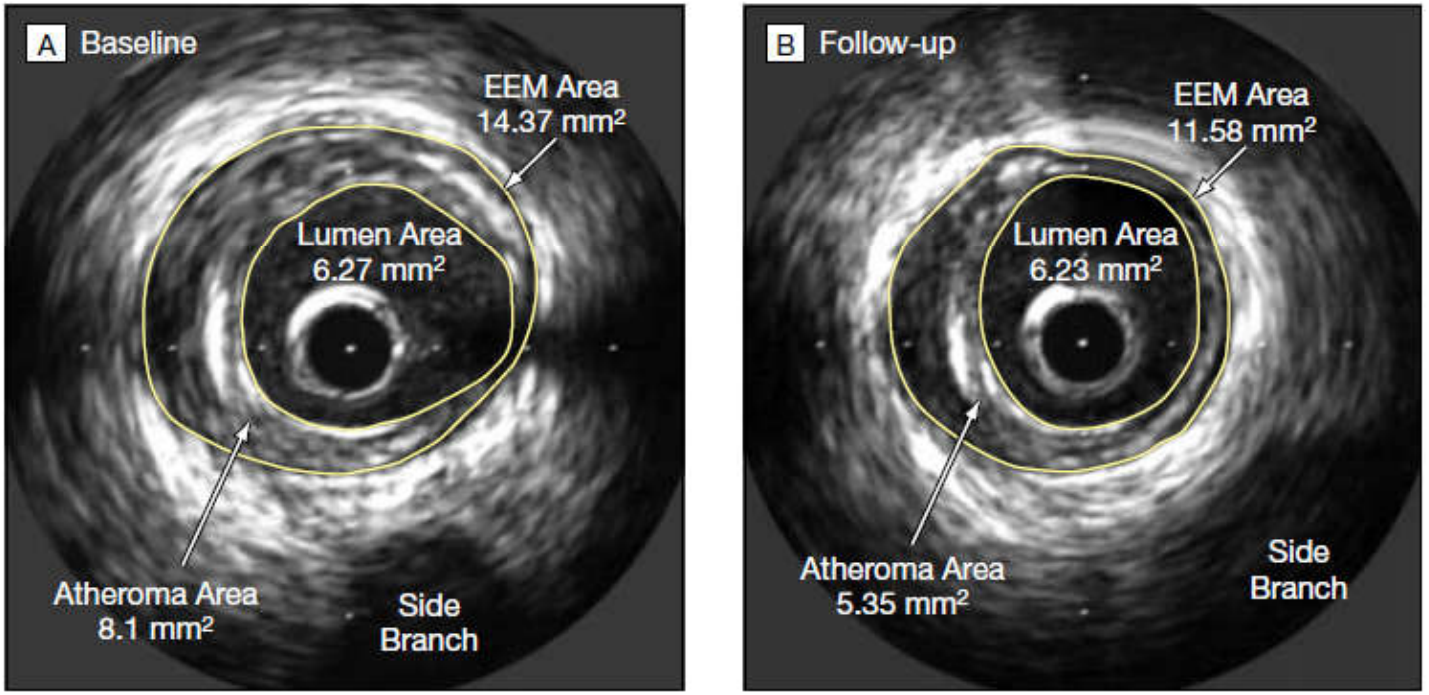
- Infusion of HDL or HDL analogs have shown regression of plaque in IVUS studies already after 5-6 weeks (Nissen et al 2003 JAMA)

- A large number of HDL or apoA1 analogues are presently being developed for infusion to treat atherosclerosis

Effect of Recombinant ApoA-I Milano on Coronary Atherosclerosis in Patients With Acute Coronary Syndromes

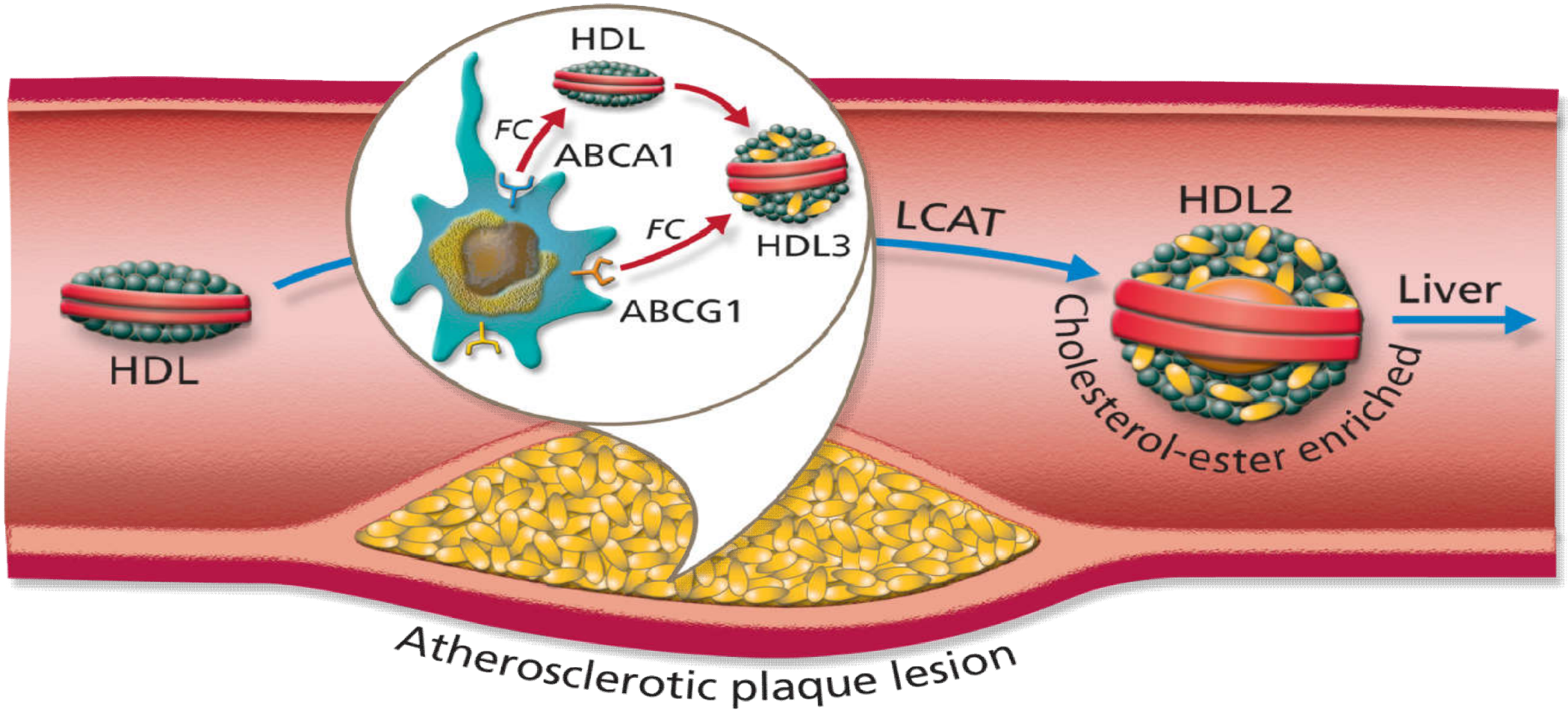
A Randomized Controlled Trial

Figure 4. Example of Atheroma Regression in a Patient Who Received High-Dose ETC-216



The atheroma area decreased from 8.1 to 5.35 mm² with virtually no change in the lumen area. EEM indicates external elastic membrane.

How fast can HDL remove cholesterol from plaque?



Results of the MILANO-PILOT Study

Effect of Infusion of ApoA-I_{Milano} HDL Mimetic on Coronary Atherosclerosis in Acute Coronary Syndrome Patients

Stephen J Nicholls MBBS PhD and Steven E Nissen MD

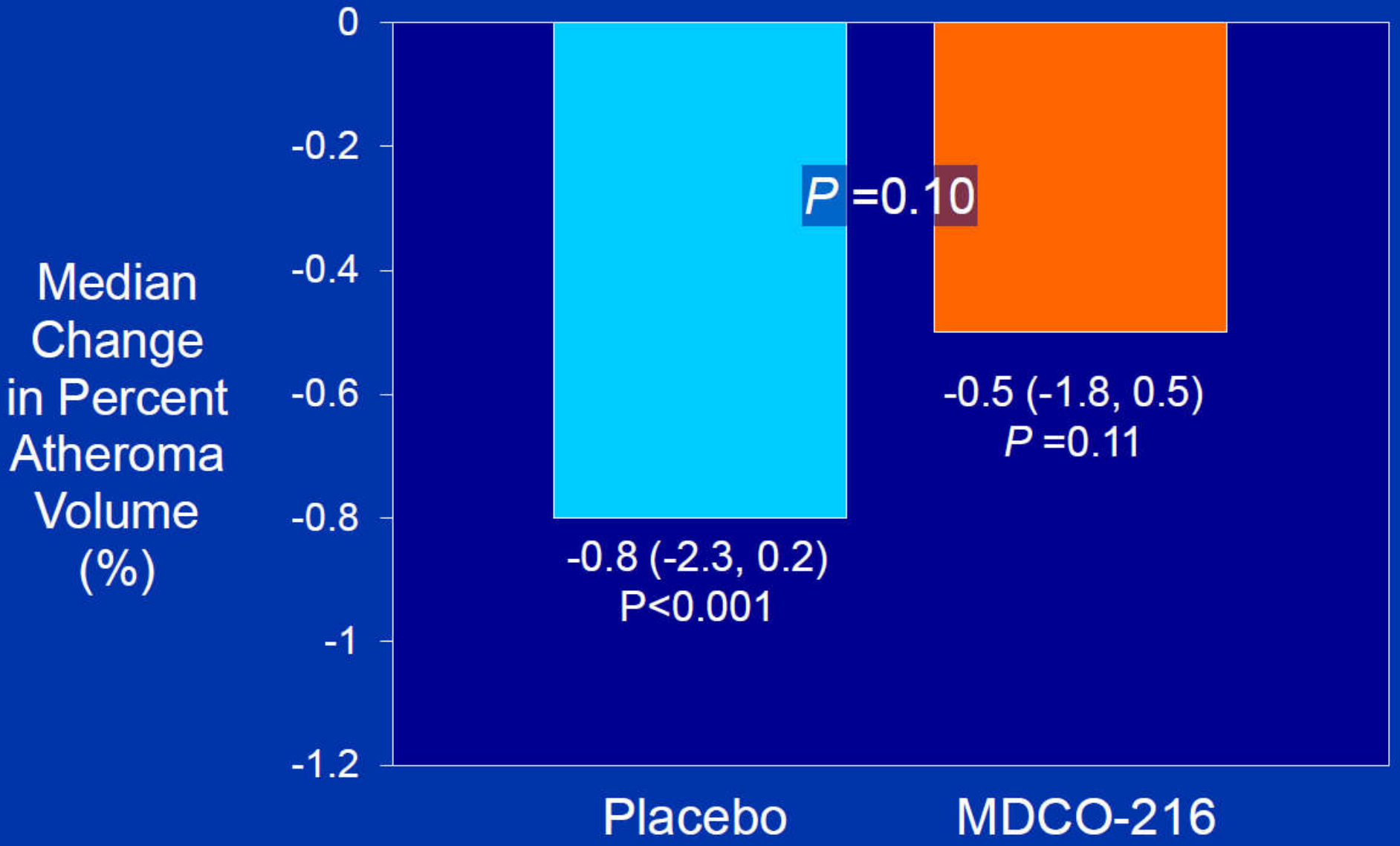
Disclosure

Consulting: AstraZeneca, Amgen, Anthera, Boehringer Ingelheim, CSL Behring, Eli Lilly, Esperion, Merck, Takeda, Roche, Kowa, LipoScience, Novartis, Sanofi-Regeneron.

Clinical Trials: Amgen, Anthera, AstraZeneca, Eli Lilly, Novartis, Cerenis, The Medicines Company, Resverlogix, InfraReDx, Roche, Sanofi-Regeneron, LipoScience.

The MILANO-PILOT study was sponsored by The Medicines Company.

Primary Endpoint: Percent Atheroma Volume



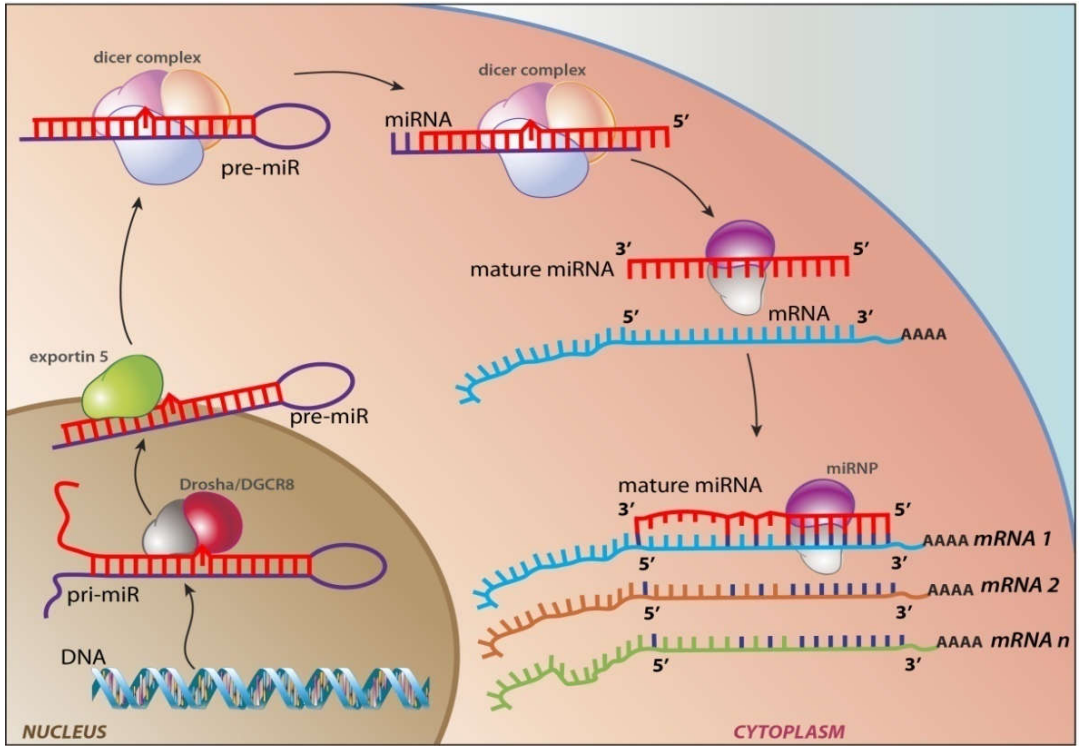
Results expressed as median (interquartile range)

The Safety and Tolerability of CSL112, a Reconstituted, Infusible, Plasma-Derived Human ApoA-I, After Acute Myocardial Infarction: The ApoA-I Event reducinG in Ischemic Syndromes I Trial (AEGIS-I)

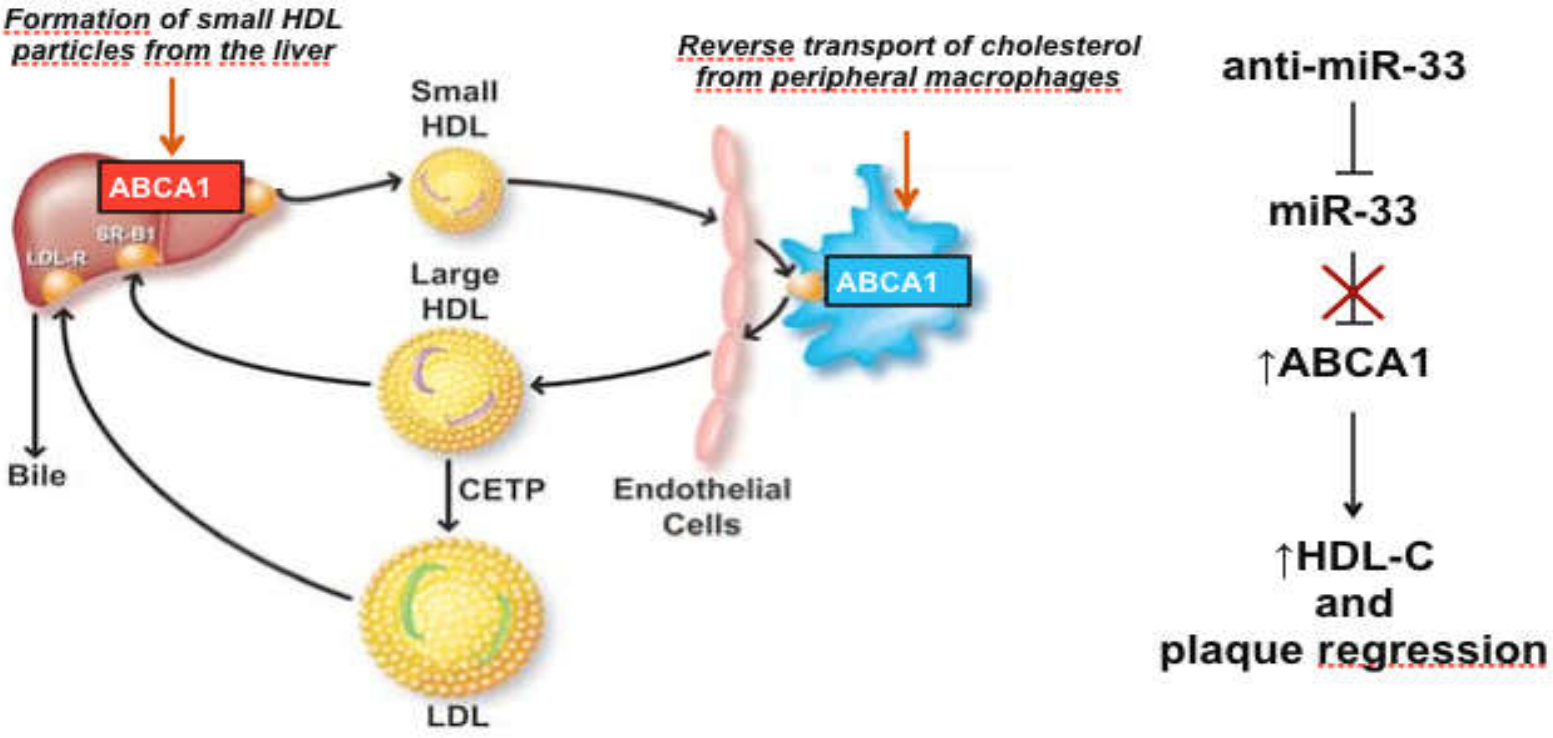
C. Michael Gibson, MS, MD
on behalf of the AEGIS-1 Investigators

miRNA: players in RCT?

- microRNAs are naturally occurring ~22 nt non-coding RNAs
- Regulate gene expression through hybridization to target messenger RNAs
- Highly conserved and evolutionarily selected to regulate pathways

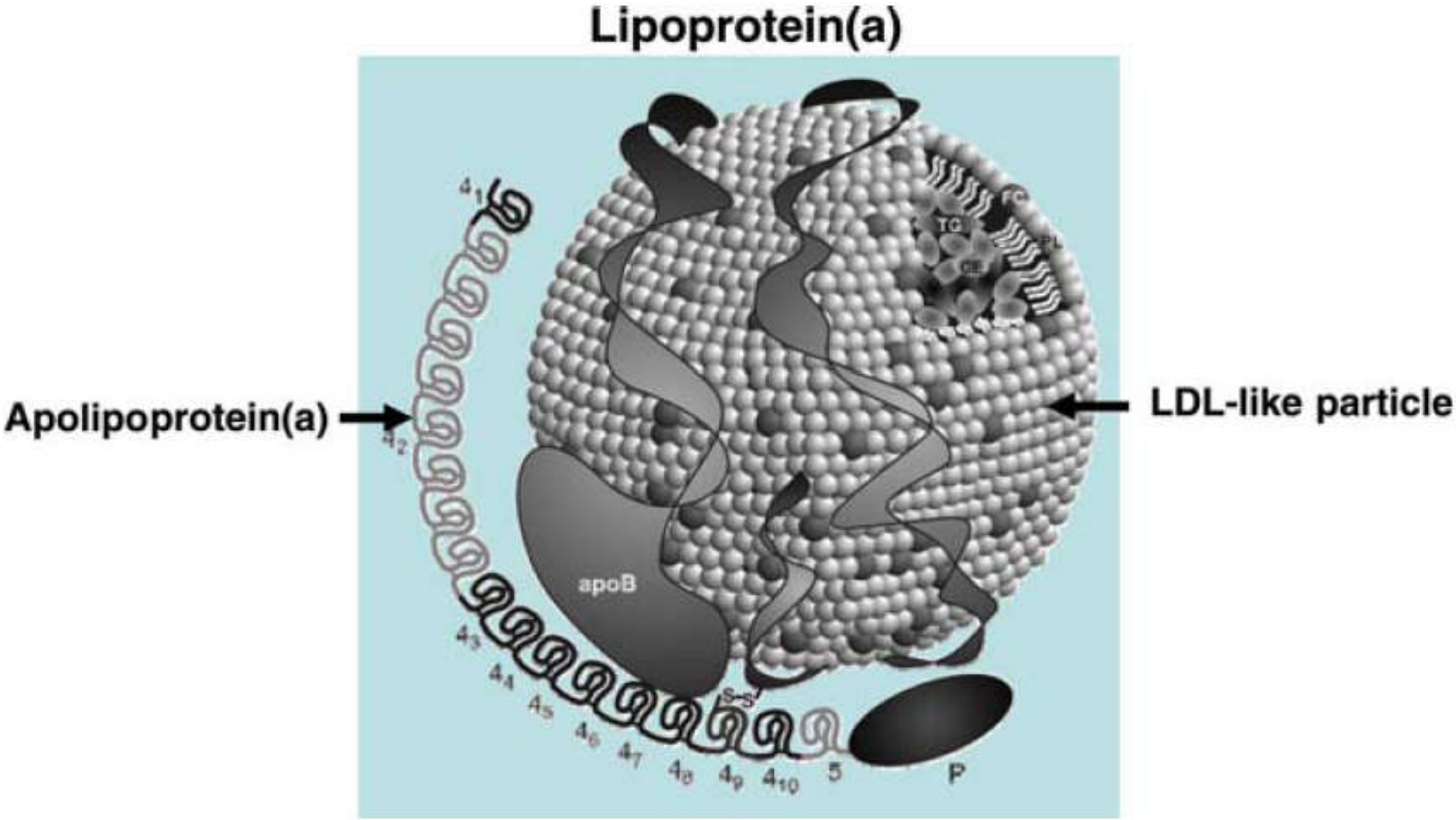


De-Repression of ABCA1 by anti-miR-33 is an Ideal Mechanism for Targeting Atherosclerosis



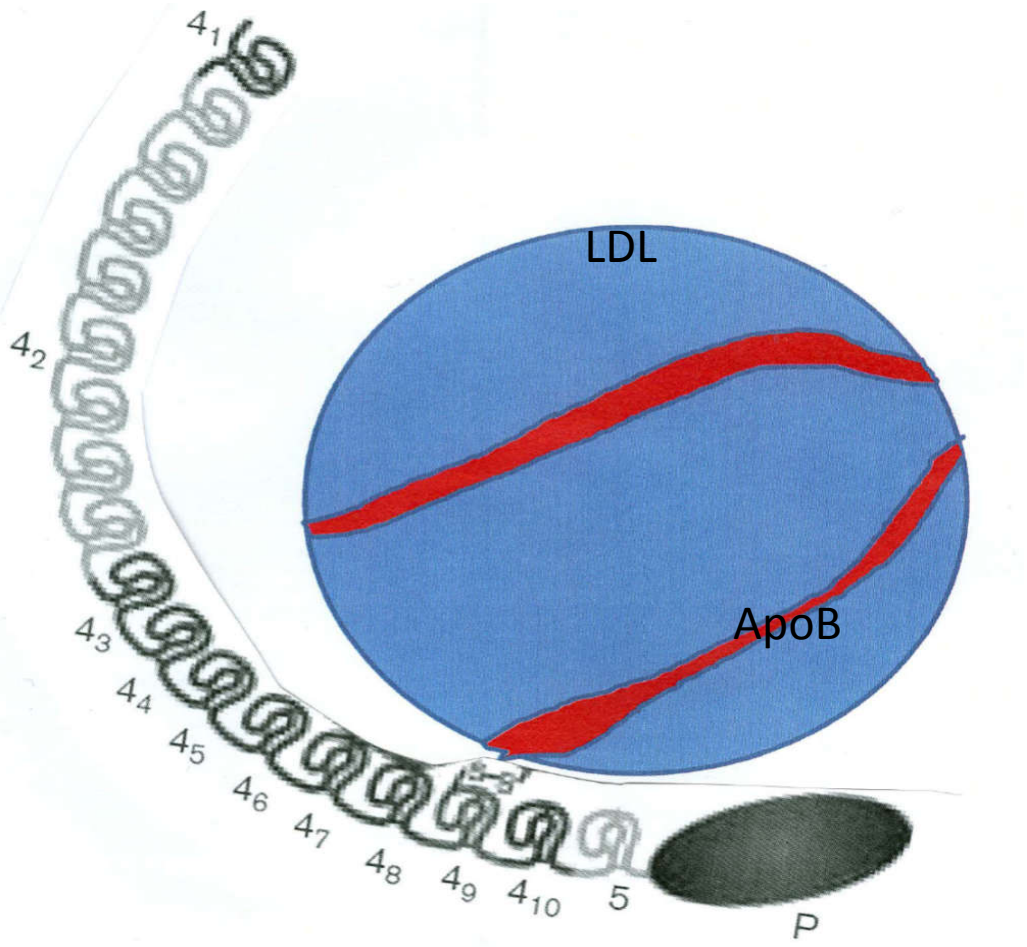
ΛΙΠΟΠΡΩΤΕΪΝΗ (a)

Λιποπρωτεΐνη Lp(a)

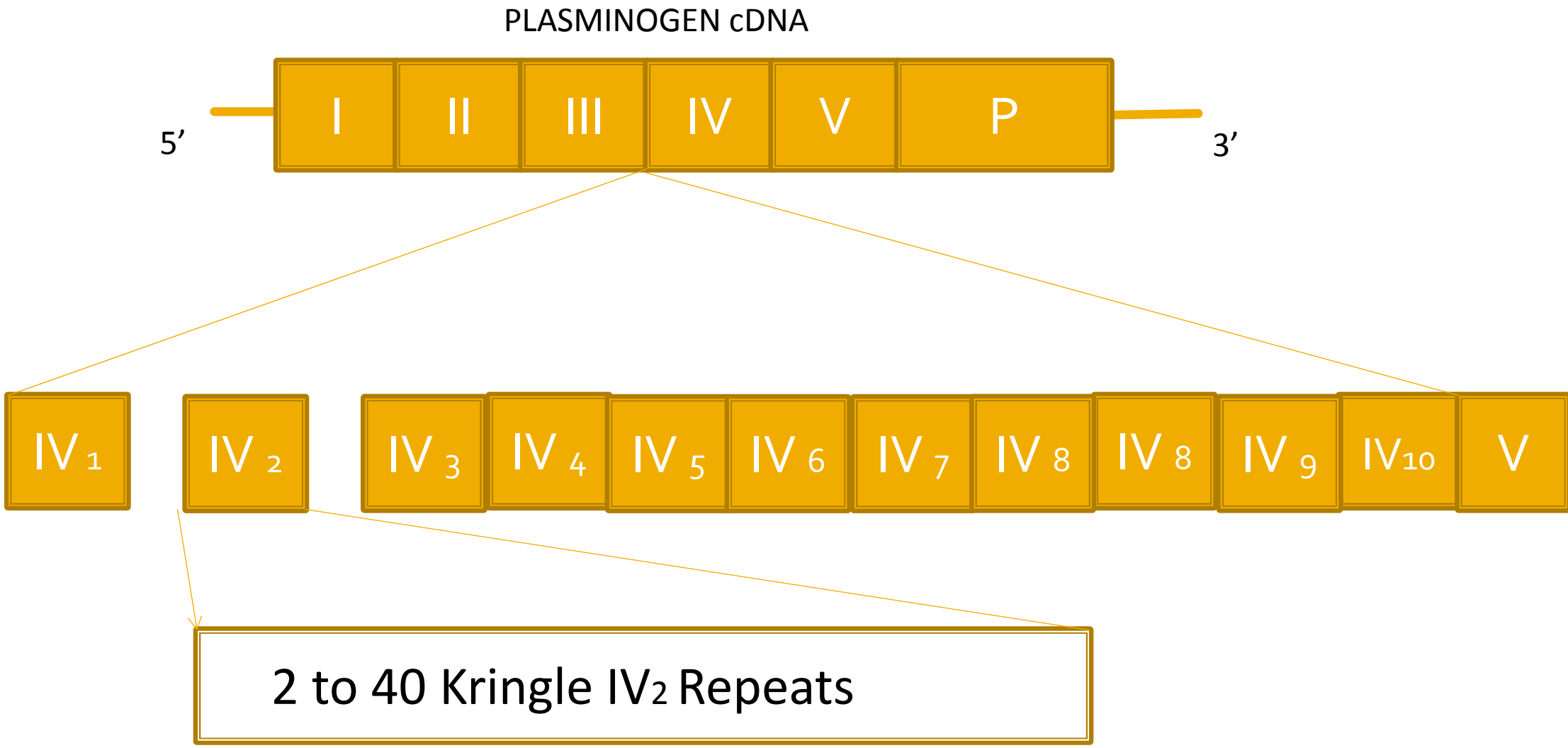


Structure of Lp(a)

Apo(a) with varying repeats of cringles



Homology between plasminogen and apo(a)



After Lackner et al1993

↑ Lp(a) → ↑ ΑΘΗΡΩΜΑΤΩΣΗΣ: ΕΠΙΔΗΜΙΟΛΟΓΙΚΑ ΔΕΔΟΜΕΝΑ

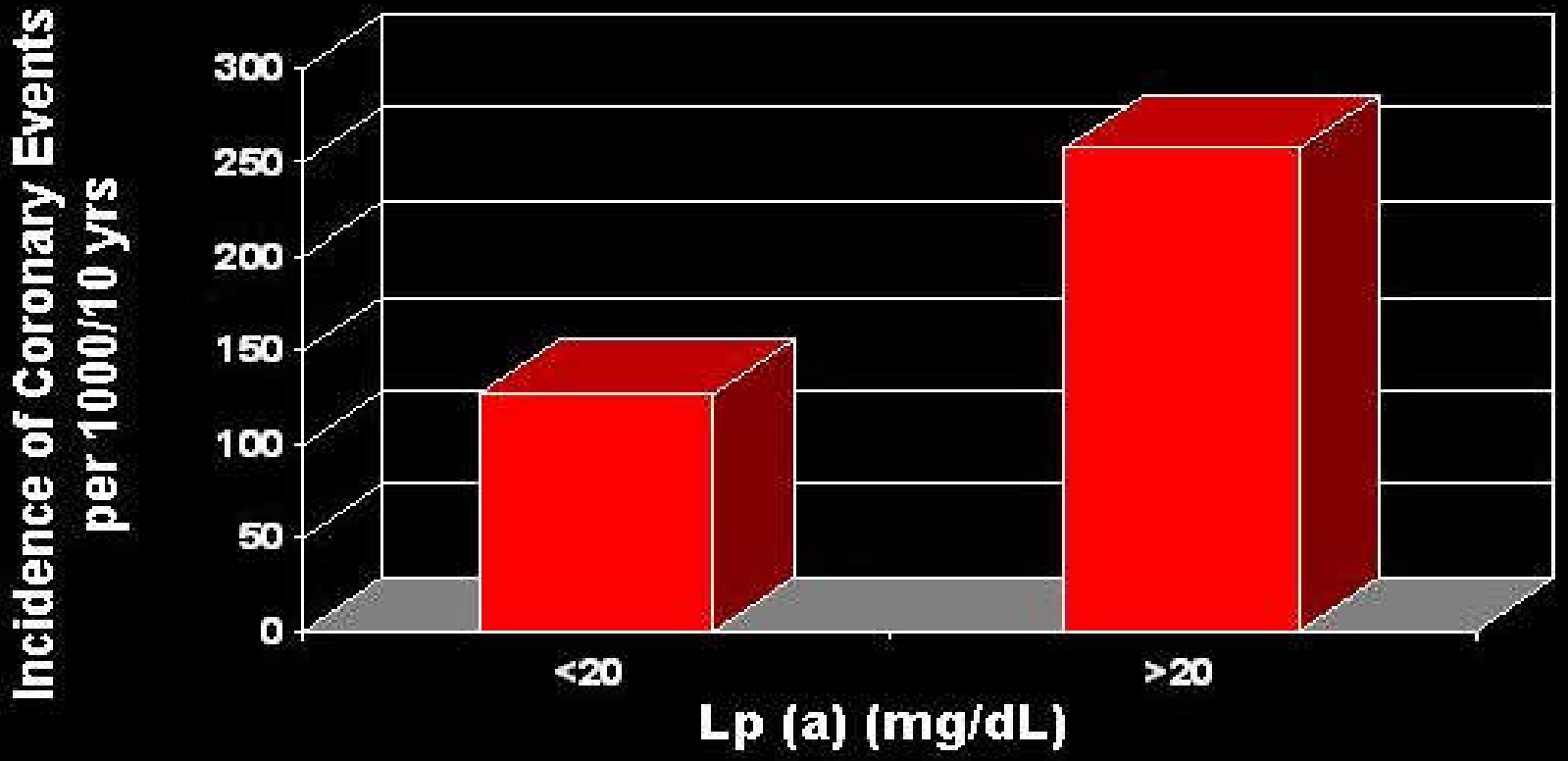
↑ Lp(a)

ΑΝΕΞΑΡΤΗΤΟΣ ΠΑΡΑΓΟΝΤΑΣ ΚΙΝΔΥΝΟΥ ΓΙΑ ΤΗΝ ΕΜΦΑΝΙΣΗ ΚΑΡΔΙΑΓΓΕΙΑΚΗΣ ΝΟΣΟΥ

JAMA 2009;301:2331-2339

Emerging Risk Marker: Lp (a)

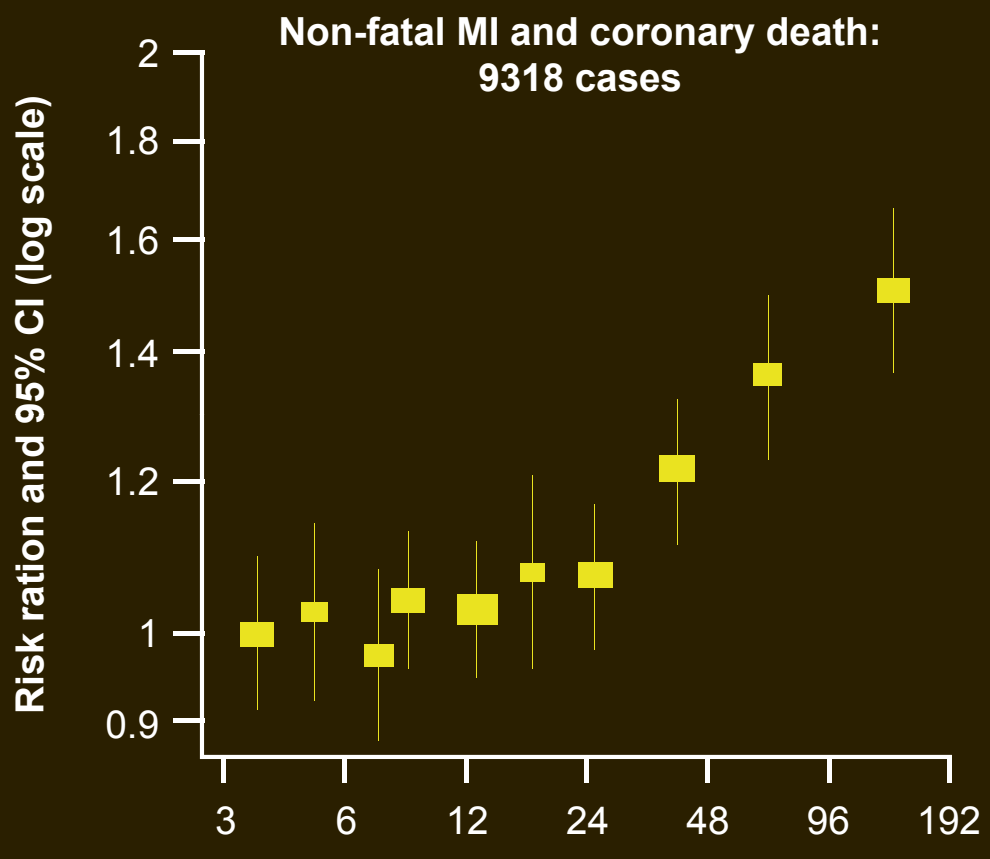
PROCAM Study: Estimated Incidence of Coronary Events by Lp (a)

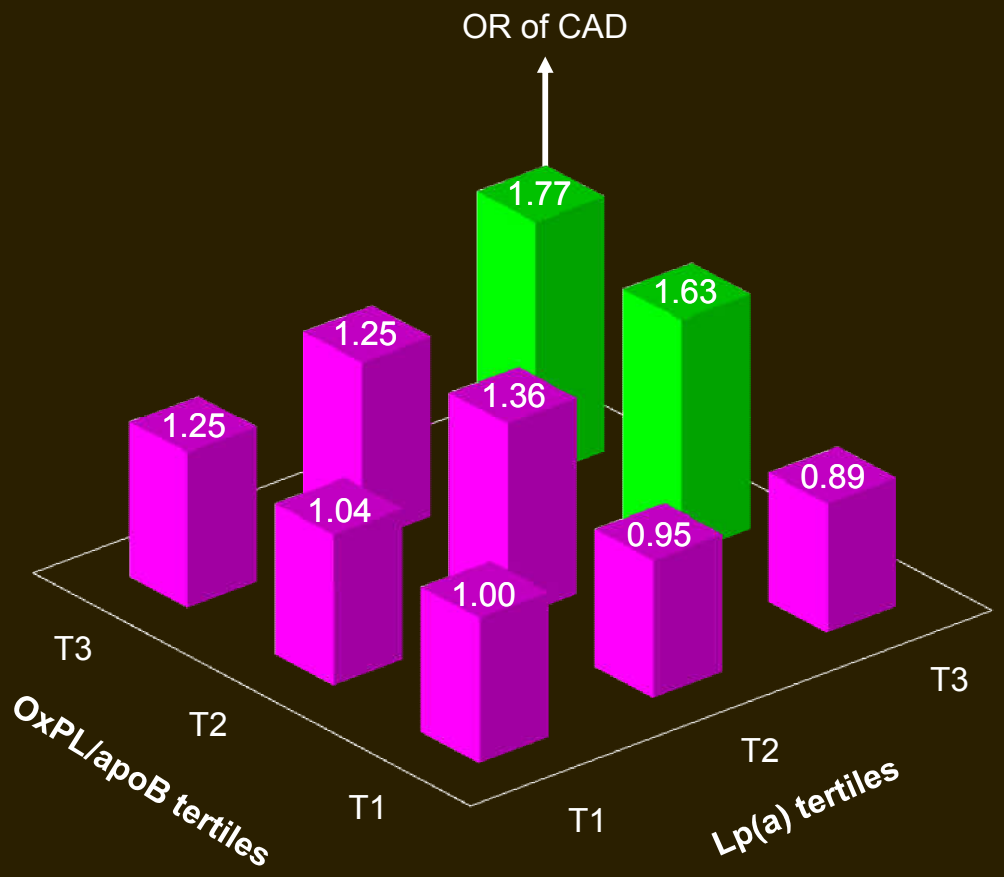


PROCAM = Münster Heart Study; Lp (a) = lipoprotein (a).

von Eckardstein A, et al. *J Am Coll Cardiol.* 2001;37:434-449.

Lp(a) as a cardiovascular risk factor: epidemiology

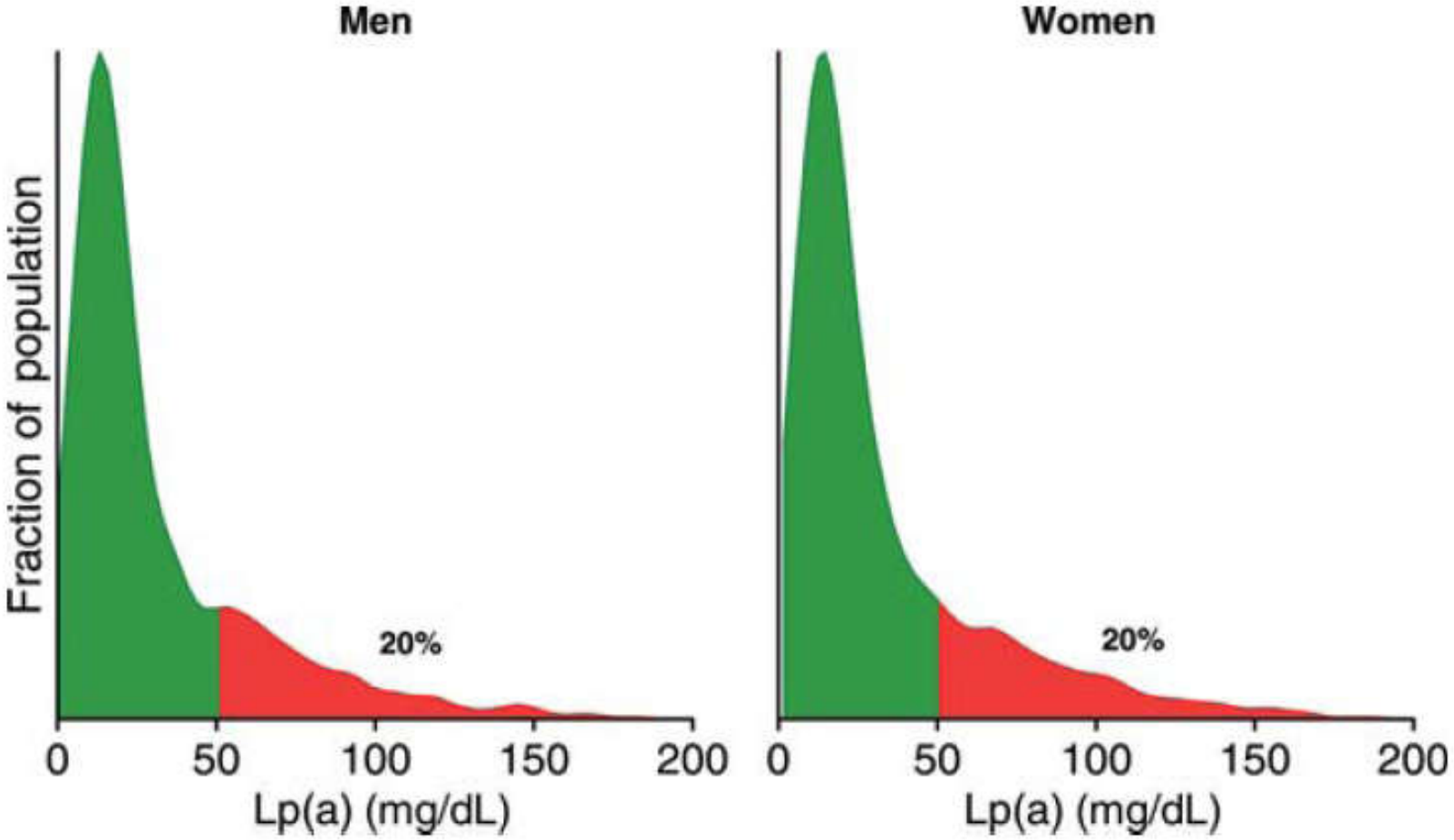




Epidemiology argument : YES

Tsimikas et al. *JACC* 2010
Nordestgaard BG, *et al.* Eur Heart J 2010;31:2844–53

Figure 2 Typical distributions of lipoprotein(a) levels in the general population



Is Lp(a) a cause or just secondary to other factors

Genetic analysis has given the answer!!
Mendelian randomisation studies strongly suggest that Lp(a) level is directly causing the increased risk.

Kamstrup et al JAMA 2009
Luke et al ATVB 2007
Helgadottir et al JACC 2012

Mendelian Randomization

ORIGINAL ARTICLE

Genetic Variants Associated with Lp(a) Lipoprotein Level and Coronary Disease

Robert Clarke, F.R.C.P., John F. Peden, Ph.D., Jemma C. Hopewell, Ph.D., Theodosios Kyriakou, Ph.D., Anuj Goel, M.Sc., Simon C. Heath, Ph.D., Sarah Parish, D.Phil., Simona Barlera, M.S., Maria Grazia Franzosi, Ph.D., Stephan Rust, Ph.D., Derrick Bennett, Ph.D., Angela Silveira, Ph.D., Anders Malarstig, Ph.D., Fiona R. Green, Ph.D., Mark Lathrop, Ph.D., Bruna Gigante, M.D., Karin Leander, Ph.D., Ulf de Faire, M.D., Udo Seedorf, Ph.D., Anders Hamsten, F.R.C.P., Rory Collins, F.R.C.P., Hugh Watkins, F.R.C.P., and Martin Farrall, F.R.C.Path., for the PROCARDIS Consortium*

CONCLUSIONS

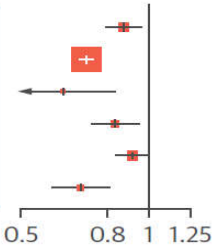
We identified two *LPA* variants that were strongly associated with both an increased level of Lp(a) lipoprotein and an increased risk of coronary disease. Our findings provide support for a causal role of Lp(a) lipoprotein in coronary disease.

Clarke R et al. *N Engl J Med* 2009;361:2518–28

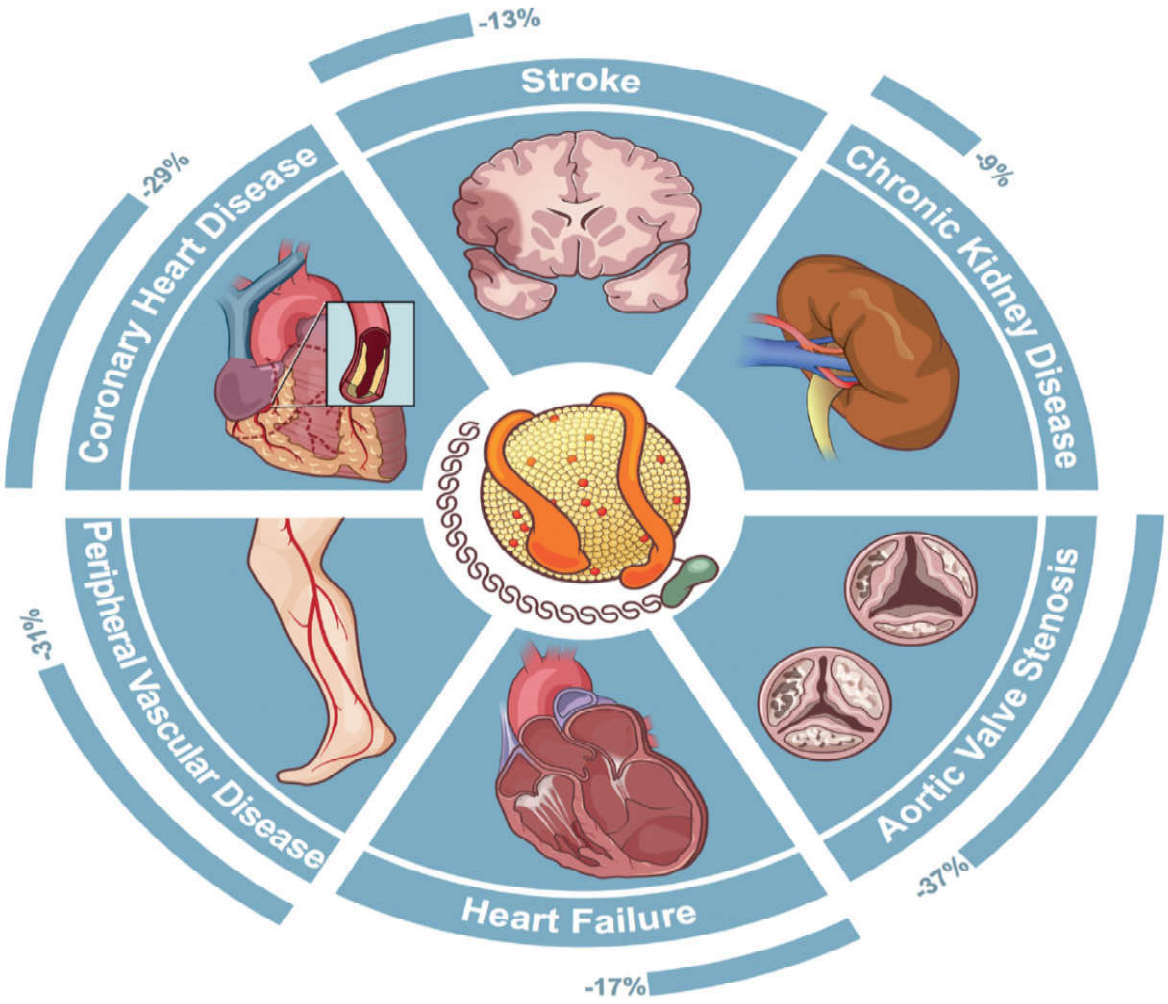
Phenotypic Characterization of Genetically Lowered Human Lipoprotein(a) Levels

FIGURE 2 Associations of Genetically Lowered Lp(a) With a Range of Diseases

Outcome	Cases	Controls	OR per SD Lower LPA	P-value
Cardiometabolic Disease: Significant Associations				
Stroke	2066	110272	0.87 [0.79; 0.96]	0.004
Coronary Heart Disease	46792	186109	0.71 [0.69; 0.73]	<0.0001
Aortic Valve Stenosis	193	112145	0.63 [0.47; 0.83]	0.0011
Heart Failure	2279	127690	0.83 [0.73; 0.94]	0.0045
Chronic Kidney Disease*	12385	117165	0.91 [0.83; 1.00]	0.043*
Peripheral Vascular Disease	698	111640	0.69 [0.59; 0.80]	<0.0001



CENTRAL ILLUSTRATION Impact of Genetically Mediated Lp(a) Reduction (1 SD) on Disease Risk



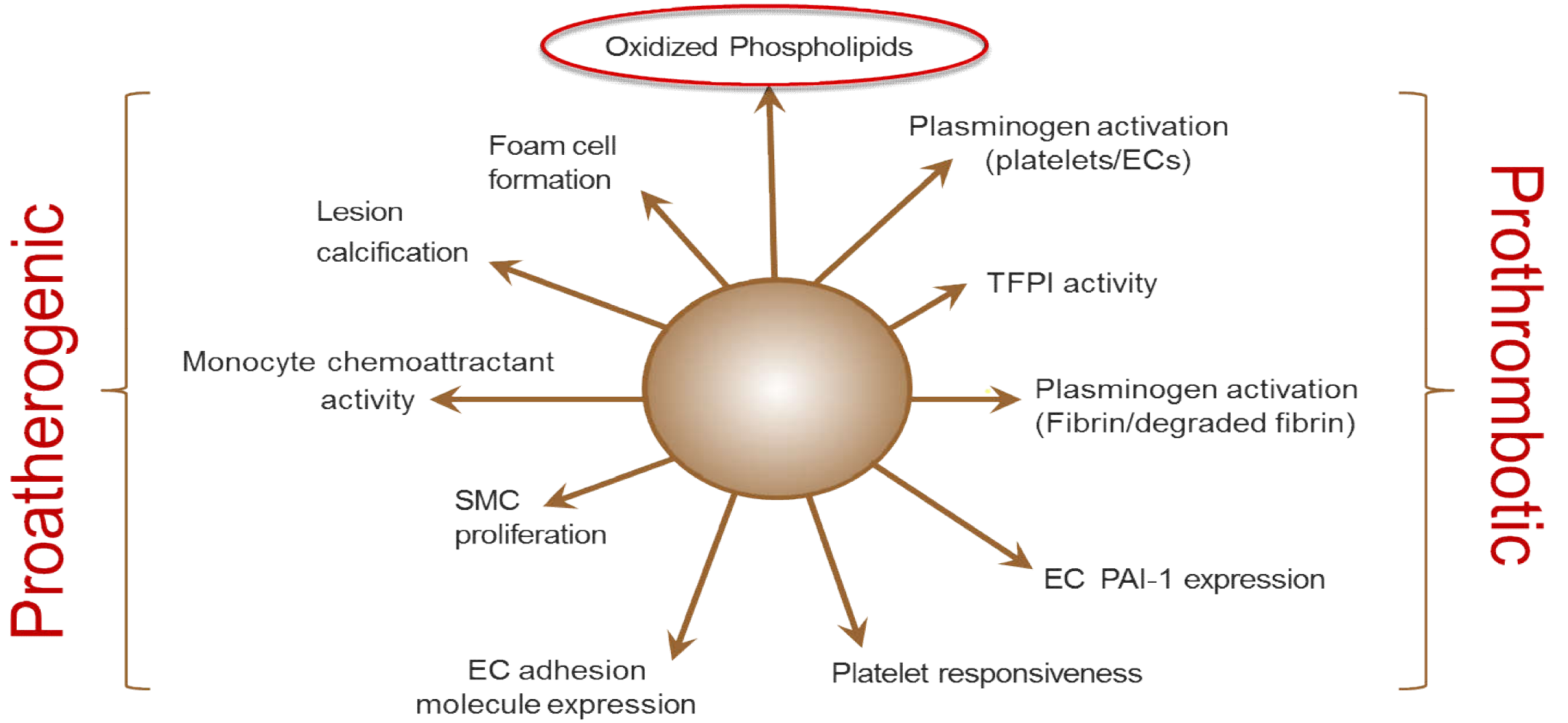
Emdin, C.A. et al. J Am Coll Cardiol. 2016;68(25):2761-72.

↑ Lp(a) → ↑ ΑΘΗΡΩΜΑΤΩΣΗΣ:
ΠΑΘΟΦΥΣΙΟΛΟΓΙΚΑ ΔΕΔΟΜΕΝΑ

Mechanisms for Lp(a) and atherosclerosis

- Prothrombotic
- Increased lipid deposition
- Proinflammatory

Proposed Pathogenic Mechanisms for Lp(a)



Spence and Koschinsky (2012) ATVB 32:1550-1551; Koschinsky & Marcovina (2004) Curr. Opin. Lipidol. 15: 167-74

↓ Lp(a) → ↓ ΑΘΗΡΩΜΑΤΩΣΗΣ: ΚΛΙΝΙΚΑ ΔΕΔΟΜΕΝΑ

Emerging Lp(a) therapies

Lp(a) lowering therapies	Lp(a) lowering effect	Possible mechanism of Lp(a) lowering	Best level of evidence
ASO 144367	86%	Inhibits synthesis of apo(a)	Transgenic Lp(a) mouse models
PCSK9 Inhibitors	12–30%	Unknown	Modest (180 patients) phase 2 multicenter randomized-controlled trials
; CETP inhibitor	40%	Unknown	Large (1623 patients) phase 3 randomized, placebo-controlled trials
Sobetirome; thyromimetic	20–40%	Increased bile acid synthesis and upregulation of LDL receptor via hepatic thyroid receptor ß receptor	Small animal studies, phase 1 human safety

Kolski B et al. Curr Opin Lipidology 2012;23(6): 560–568

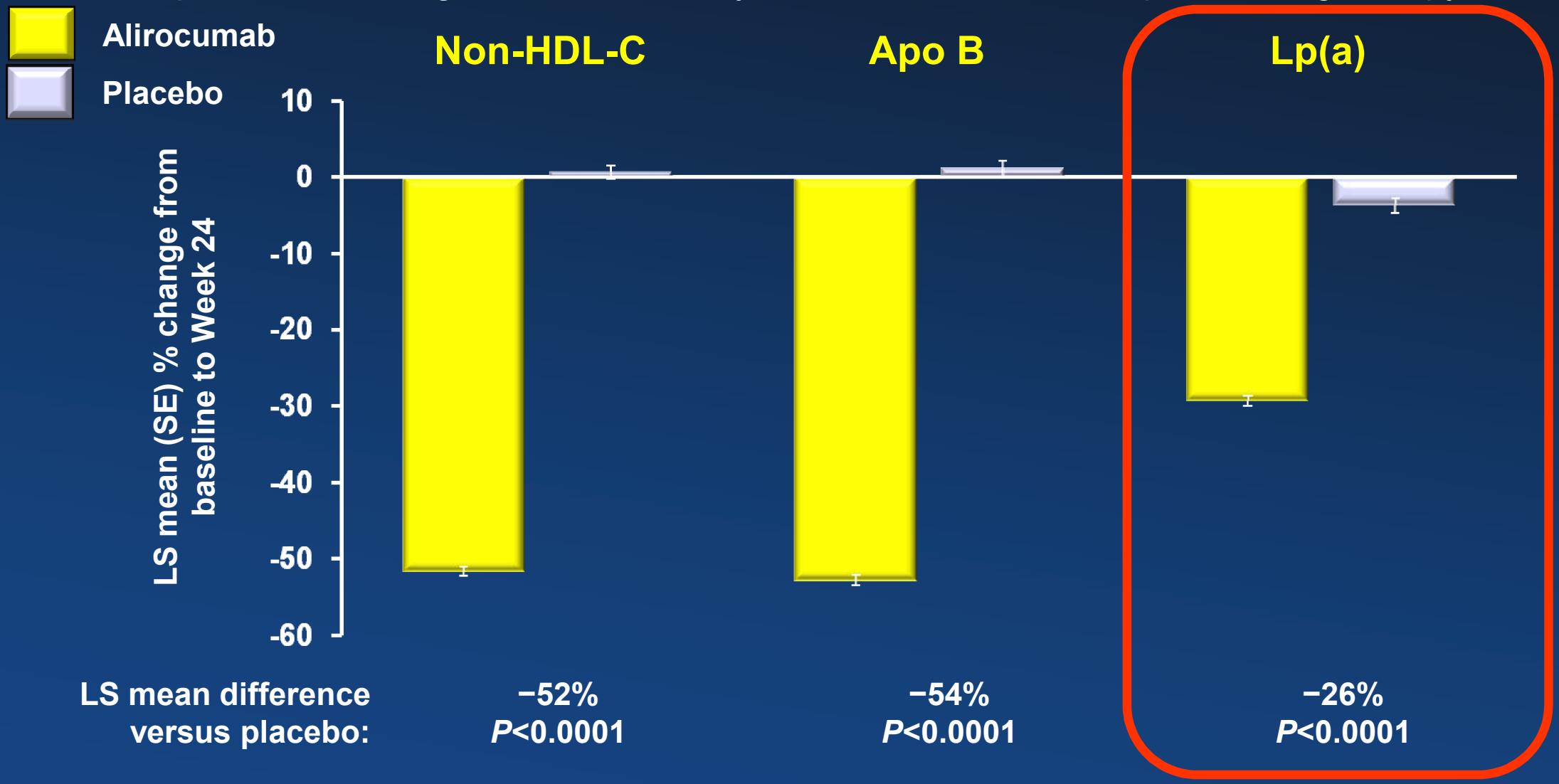
Intervention?

- No specific Lp(a) lowering agent....
- Lp(a) antisense ?

Therapy argument: Not yet

ODYSSEY LONG TERM: Significant Reductions in Secondary Lipid Parameters at Week 24

All patients on background of maximally-tolerated statin ± other lipid-lowering therapy



Adjusted mean (SE) shown for Lp(a).

Antisense therapy targeting apolipoprotein(a): a randomised, double-blind, placebo-controlled phase 1 study

Sotirios Tsimikas, Nicholas J Viney, Steven G Hughes, Walter Singleton, Mark J Graham, Brenda F Baker, Jennifer L Burkey, Qingqing Yang, Santica M Marcovina, Richard S Geary, Rosanne M Crooke, Joseph L Witztum

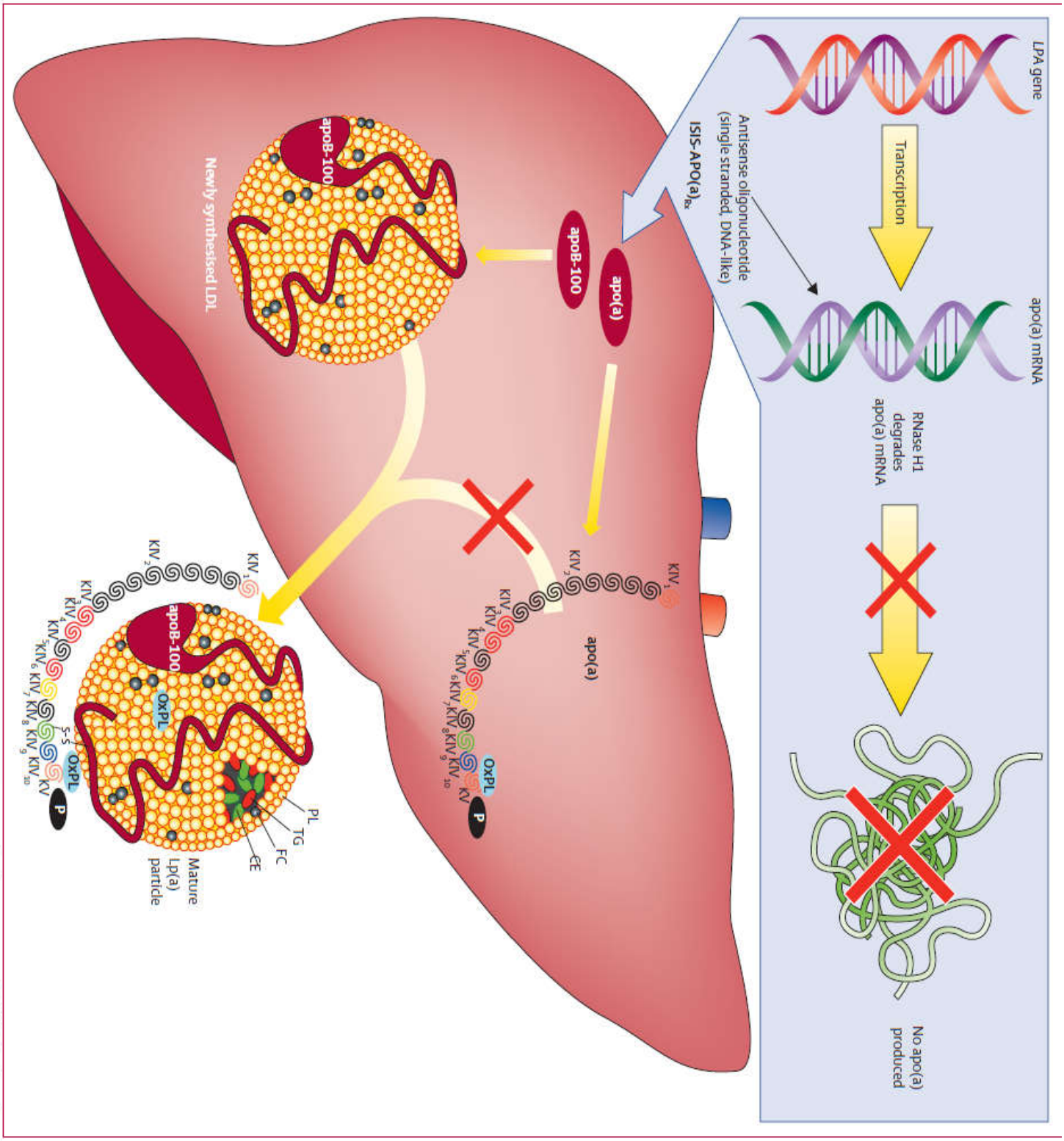
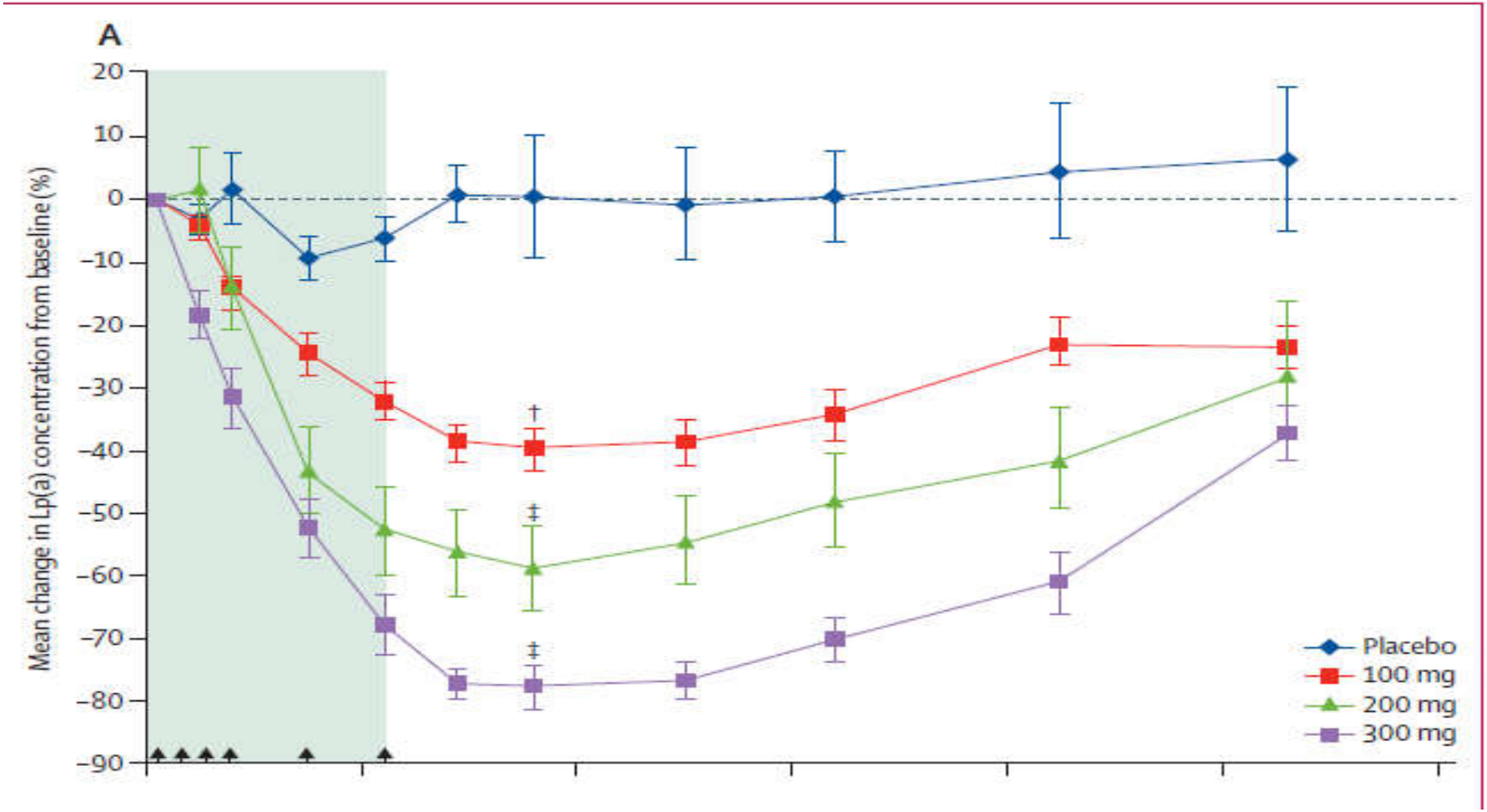


Figure 1: Mechanism by which ISIS-APO(a)$_{Rx}$ suppresses apo(a) protein synthesis

www.thelancet.com **Published online July 23, 2015**

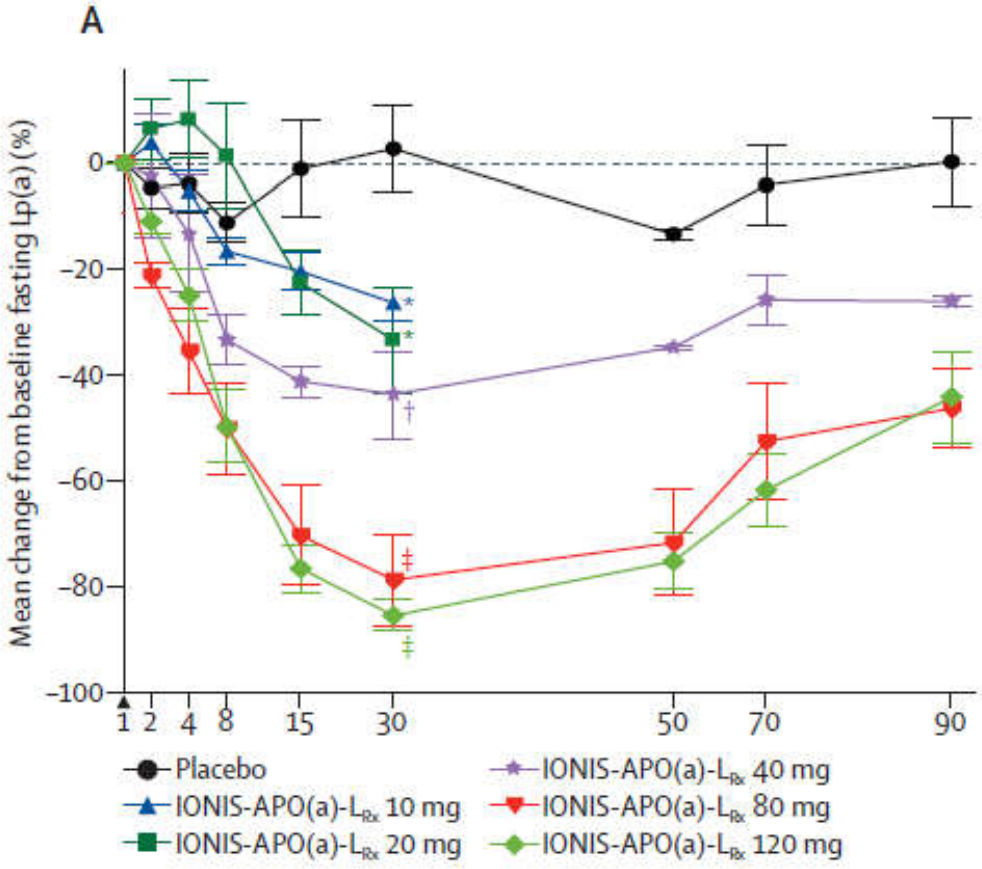
Antisense therapy targeting apolipoprotein(a): a randomised, double-blind, placebo-controlled phase 1 study

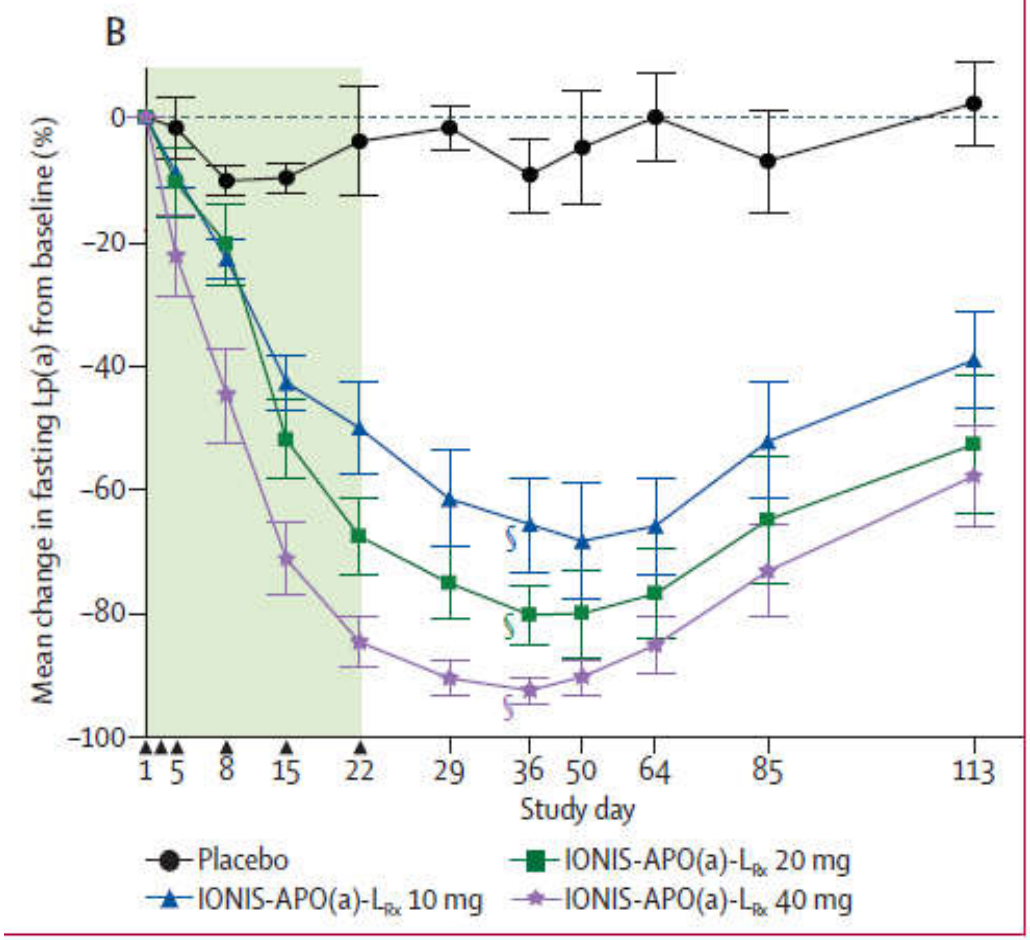
Sotirios Tsimikas, Nicholas J Viney, Steven G Hughes, Walter Singleton, Mark J Graham, Brenda F Baker, Jennifer L Burkey, Qingqing Yang, Santica M Marcovina, Richard S Geary, Rosanne M Crooke, Joseph L Witztum



Antisense oligonucleotides targeting apolipoprotein(a) in people with raised lipoprotein(a): two randomised, double-blind, placebo-controlled, dose-ranging trials

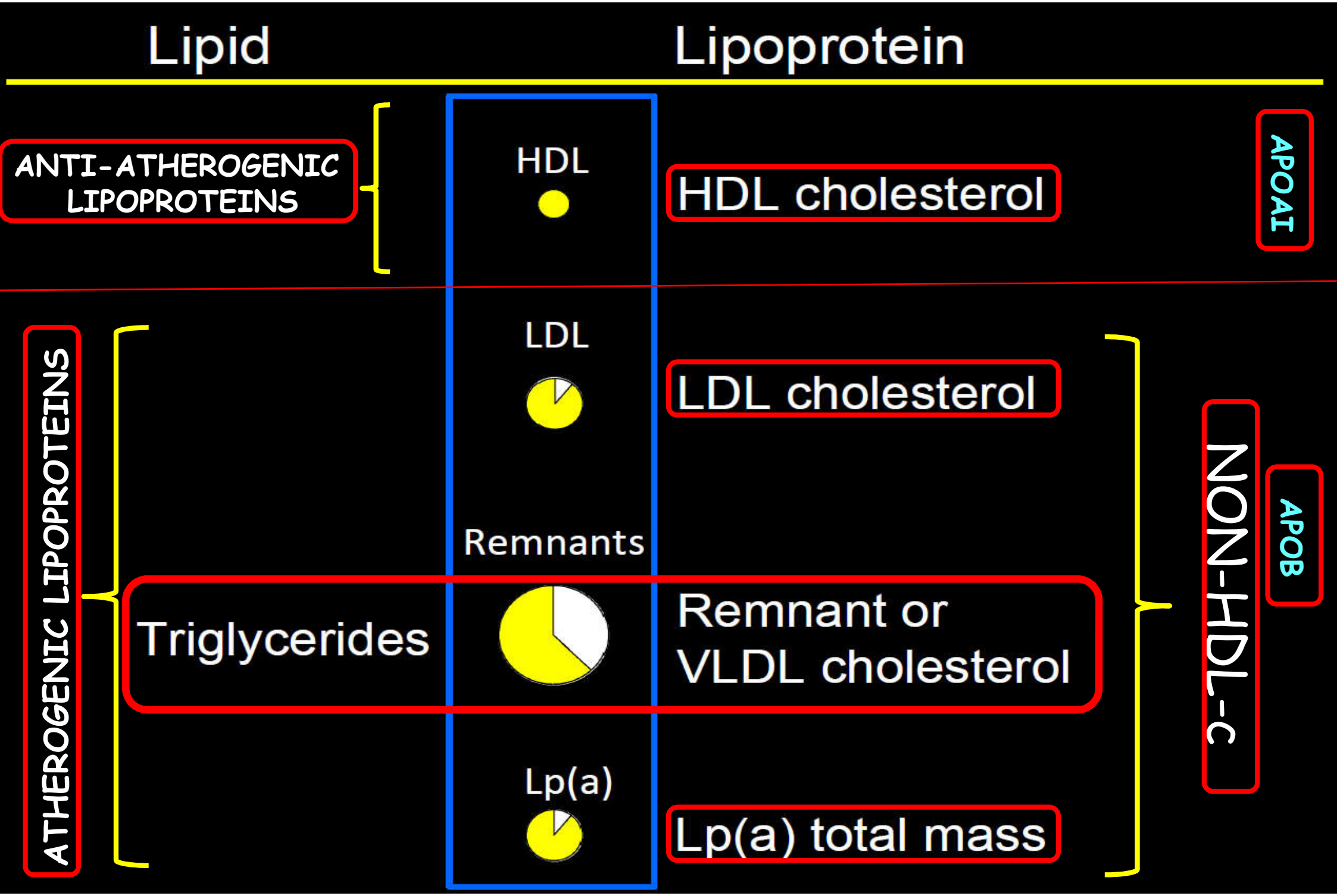
Nicholas J Viney, Julian C van Capelleveen, Richard S Geary, Shuting Xia, Joseph A Tami, Rosie Z Yu, Santica M Marcovina, Steven G Hughes, Mark J Graham, Rosanne M Crooke, Stanley T Crooke, Joseph L Witztum, Erik S Stroes, Sotirios Tsimikas



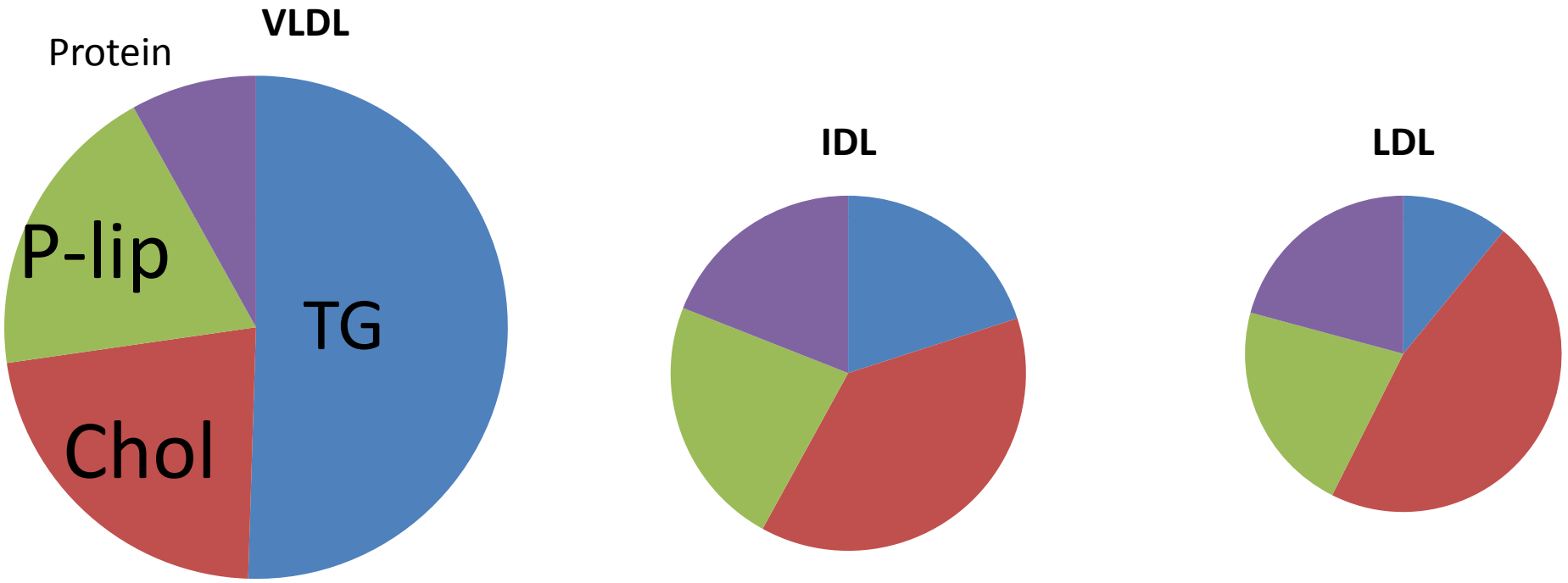


www.thelancet.com Published online September 21, 2016

NON-HDL ΧΟΛΗΣΤΕΡΟΛΗ ΚΑΙ ΑΡΟΒ


Lipid
Lipoprotein
ANTI-ATHEROGENIC LIPOPROTEINS
HDL
HDL cholesterol
APOAI
ATHEROGENIC LIPOPROTEINS
LDL
LDL cholesterol
Remnants
Triglycerides
Remnant or VLDL cholesterol
Lp(a)
Lp(a) total mass
NON-HDL-C
APOB

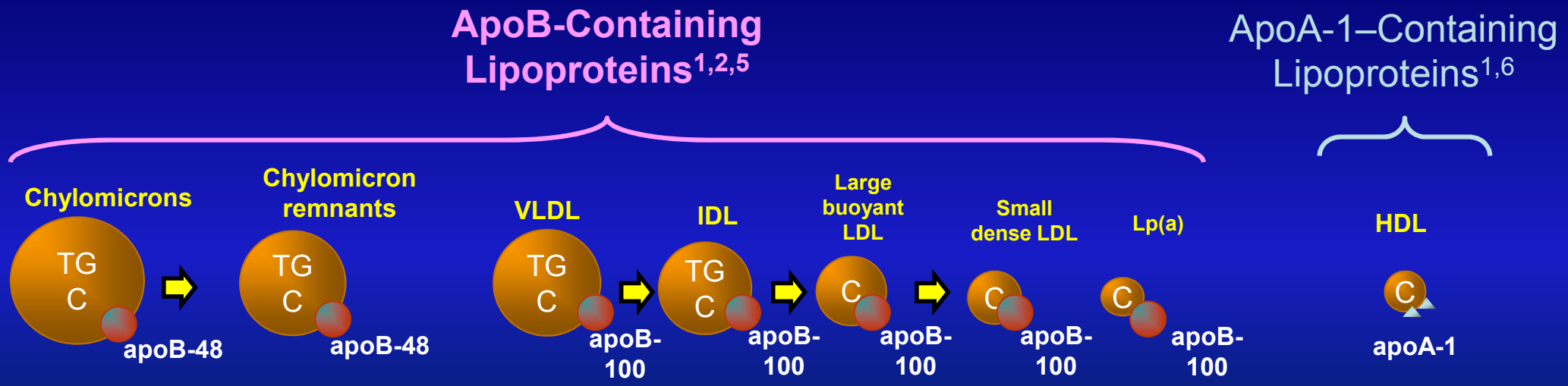
The atherogenic lipoproteins = non-HDL-C = T-CHOL – HDL-C



ApoB containing lipoproteins

APOB vs APOAI

- ApoB is the major apolipoprotein of all atherogenic lipoproteins, including VLDL, IDL, LDL, Lp(a), and chylomicrons[1,2]
  - **Typically, ~90% of total plasma apoB is carried by LDL particles[4]**

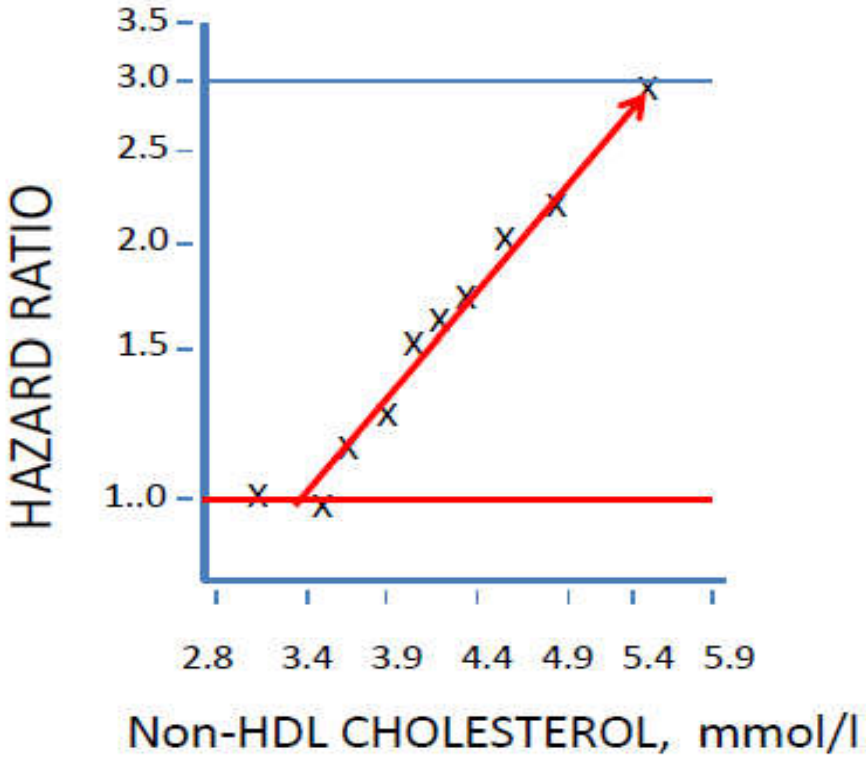


Adapted with permission from Walldius G et al.[3]

Apo = apolipoprotein; CHD = coronary heart disease; VLDL = very low-density lipoprotein; IDL = intermediate-density lipoprotein; Lp(a) = lipoprotein (a); TG = triglyceride; C = cholesterol.

1. NCEP ATP III Expert Panel. *Circulation*. 2002;106:3143–3421. **2**. Rana JS et al. *Curr Opin Cardiol*. 2010;25:622–626. **3**. Walldius G et al. *J Intern Med*. 2004;255:188–205. **4**. Mudd JO et al. *J Am Coll Cardiol*. 2007;50:1735–1741. **5**. Chapman MJ et al. *Eur Heart J Suppl*. 2004;6(suppl A):A43–A48. **6**. Barter P. In: Ballantyne CM. *Clinical Lipidology: A Companion to Braunwald's Heart Disease*. Saunders, an imprint of Elsevier Inc; 2009:387–395.

Predictive power of non-HDL-C



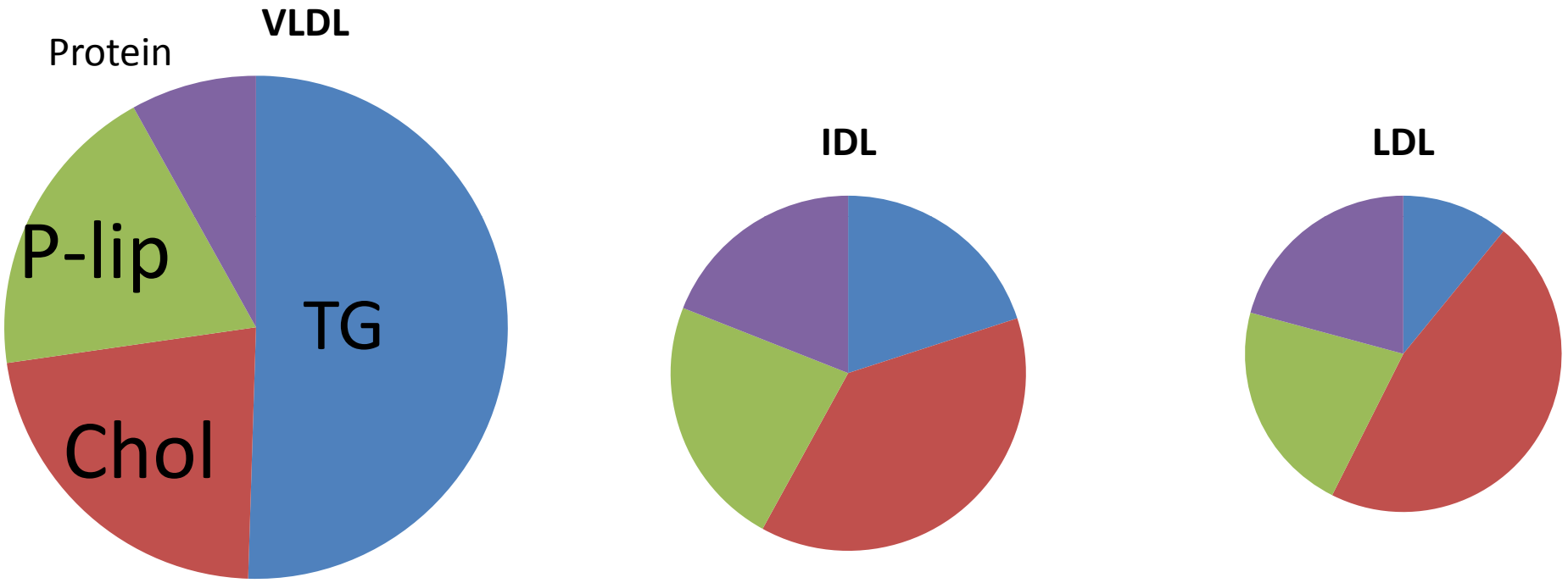
Adapted from,

Major Lipids, Apolipoproteins, and Risk of Vascular Disease

JAMA. 2009 November 11; 302(18): 1993–2000. doi:10.1001/jama.2009.1619.

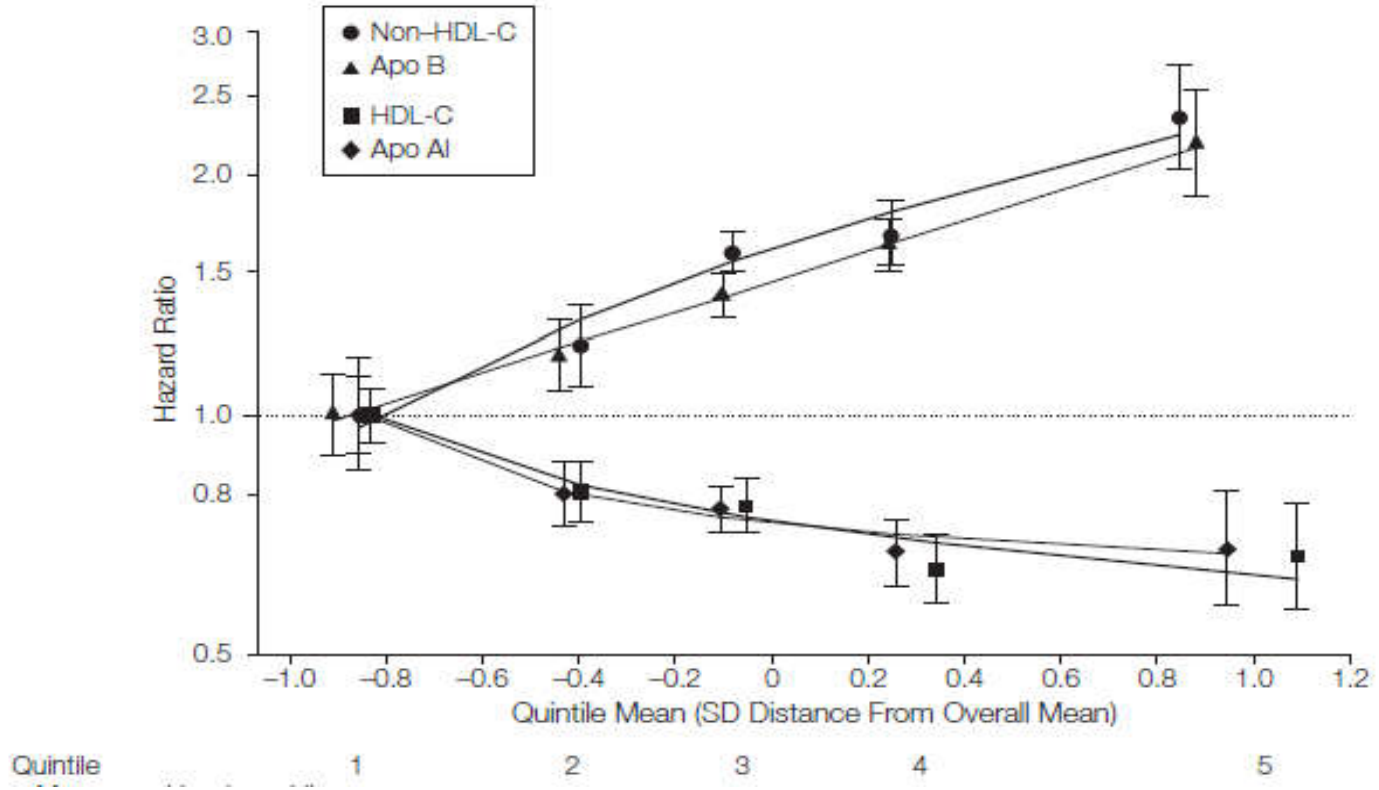
The Emerging Risk Factors Collaboration*

Plasma apoB is an alternative to non-HDL



ApoB containing lipoproteins

ApoB equivalent to non-HDL-C for risk estimation



Hazard ratio over quintiles for non-HDL, apoB, apoAI, HDL.

Major Lipids, Apolipoproteins, and Risk of Vascular Disease

The Emerging Risk Factors Collaboration*

JAMA. 2009;302(18):1993-2000

ΛΙΠΟΠΡΩΤΕΪΝΕΣ ΚΑΙ CVD

LDL

- ✓ΝΑΙ παράγοντας κινδύνου
- ✓ΝΑΙ Θεραπεία

ΠΛΟΥΣΙΕΣ ΣΕ ΤΡΙΓΛΥΚΕΡΙΔΙΑ ΛΙΠΟΠΡΩΤΕΪΝΕΣ & Lp(a)

- ✓ΝΑΙ παράγοντας κινδύνου
- ✓Θεραπεία;

HDL

- ✓Παράγοντας κινδύνου;
- ✓Θεραπεία;

ΙΝΣΤΙΤΟΥΤΟ ΜΕΛΕΤΗΣ, ΕΡΕΥΝΑΣ & ΕΚΠΑΙΔΕΥΣΗΣ
ΓΙΑ ΤΟ ΣΑΚΧΑΡΩΔΗ ΔΙΑΒΗΤΗ
ΚΑΙ ΤΑ ΜΕΤΑΒΟΛΙΚΑ ΝΟΣΗΜΑΤΑ

Επιστημονικός Υπεύθυνος: ΣΤΑΥΡΟΣ Ι. ΠΑΠΠΑΣ

Πανελλήνιες Εκπαιδευτικές Ημερίδες Πρωτοβάθμιας Φροντίδας Υγείας "Γ. Παπαδάκης"

17ο Έτος

Θα χορηγηθούν Μόρια Συνεχιζόμενης Ιατρικής Εκπαίδευσης (CME CREDITS)

13 - 17 Φεβρουαρού 2017
Ξενοδοχείο
DIVANI CARAVEL
Αθήνα

18ο Εκπαιδευτικό Σεμινάριο

«Διαταραχές της οξεοβασικής ισορροπίας και των ηλεκτρολυτών»

Χορηγούνται **4 μόρια** Συνεχιζόμενης Ιατρικής Εκπαίδευσης (C.M.E. CREDITS)

ΠΡΟΓΡΑΜΜΑ

Σάββατο 4 Μαρτίου 2017

Αθήνα, Ξενοδοχείο DIVANI CARAVEL

7ο Πανελλήνιο Συνέδριο

31 Μαρτίου - **02** Απριλίου

2017

Grand Serai Hotel

Ιωάννινα

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Βορειοδυτικής Ελλάδος

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Τμήματος Ιατρικής
Πανεπιστημίου Ιωαννίνων

5ο Εκπαιδευτικό Σεμινάριο:

Προκλήσεις & Διλήμματα στα Μεταβολικά Νοσήματα και την Εσωτερική Παθολογία

Χορηγούνται Μόρια Συνεχιζόμενης Ιατρικής Εκπαίδευσης από τον Πανελλήνιο Ιατρικό Σύλλογο.

19 & 20 Μαΐου 2017
Ξενοδοχείο Limneon
ΚΑΣΤΟΡΙΑ

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E-mail: info@conferre.gr, Website: www.conferre.gr

26ο ΕΚΠΑΙΔΕΥΤΙΚΟ ΣΕΜΙΝΑΡΙΟ

Ελληνική Εταιρεία Αθηροσκλήρωσης
Hellenic Atherosclerosis Society

ΧΑΛΚΙΔΙΚΗ
9-11 Ιουνίου 2017
Ξενοδοχείο Porto Carras

Θέμα:

«Τι νέο υπάρχει στην θεραπεία της υπερλιπιδαιμίας, του σακχαρώδη διαβήτη, της παχυσαρκίας και της υπέρτασης με έμφαση στην καθημερινή κλινική πράξη»

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www.atherosclerosis.gr

10ο ΘΕΡΙΝΟ ΣΧΟΛΕΙΟ

Η ΧΡΗΣΗ ΤΩΝ ΦΑΡΜΑΚΩΝ ΓΙΑ ΤΗΝ ΠΡΟΛΗΨΗ ΚΑΙ ΘΕΡΑΠΕΙΑ ΤΩΝ ΚΑΡΔΙΑΓΓΕΙΑΚΩΝ ΝΟΣΗΜΑΤΩΝ ΣΤΗΝ ΚΑΘΗΜΕΡΙΝΗ ΚΛΙΝΙΚΗ ΠΡΑΞΗ

Ενδείξεις-Αντενδείξεις-Αλληλεπιδράσεις
Ανεπιθύμητες ενέργειες - Κλινική χρήση

29 Ιουνίου - 01 Ιουλίου

Ξενοδοχείο **2017**
Royal Olympic,
Αθήνα

Υπό την αιγίδα των:

European Atherosclerosis Society

International Atherosclerosis Society

Conferre Ltd

Οργανωτικό - Συντονιστικό Γραφείο/Γραμματεία: Συνεδριακή ΕΠΕ/Conferre Ltd: "The art of Bringing People Together"
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E-mail: info@conferre.gr, Website: www.conferre.gr

27η Εκπαιδευτική Διημερίδα

Πρόληψη και Αντιμετώπιση του Καρδιαγγειακού Κινδύνου

22-23 Σεπτεμβρίου 2017

Ξενοδοχείο Electra Palace

Θεσσαλονίκη

www.atherosclerosis.gr

Ελληνική Εταιρεία Αθηροσκλήρωσης

Συμμετοχή Δωρεάν

Θα χορηγηθούν Μόρια Συνεχιζόμενης Ιατρικής Εκπαίδευσης

Ελληνική Εταιρεία Αθηροσκλήρωσης

Υπό την Αιγίδα των:

European Atherosclerosis Society
Ευρωπαϊκή Εταιρεία Αθηροσκλήρωσης

International Atherosclerosis Society
Διεθνής Εταιρεία Αθηροσκλήρωσης

7ο ΣΥΜΠΟΣΙΟ ΤΩΝ ΟΜΑΔΩΝ ΕΡΓΑΣΙΑΣ

1 & 2 Δεκεμβρίου 2017

Ξενοδοχείο Divani Caravel, Αθήνα

Θα χορηγηθούν Μόρια Συνεχιζόμενης Ιατρικής Εκπαίδευσης (CME-CPD credits)

Θεματικές Ενότητες

- Παθοφυσιολογία της αθηροσκλήρωσης
- Επιδημιολογία και πρόληψη της αθηροσκλήρωσης
- Μεταβολικό σύνδρομο
- Οικογενής υπερχοληστερολαιμία
- Υπέρταση
- Τρόπος ζωής, ψυχοκοινωνικοί παράγοντες και αθηροσκλήρωση
- Πρόληψη Αγγειακών εγκεφαλικών επεισοδίων

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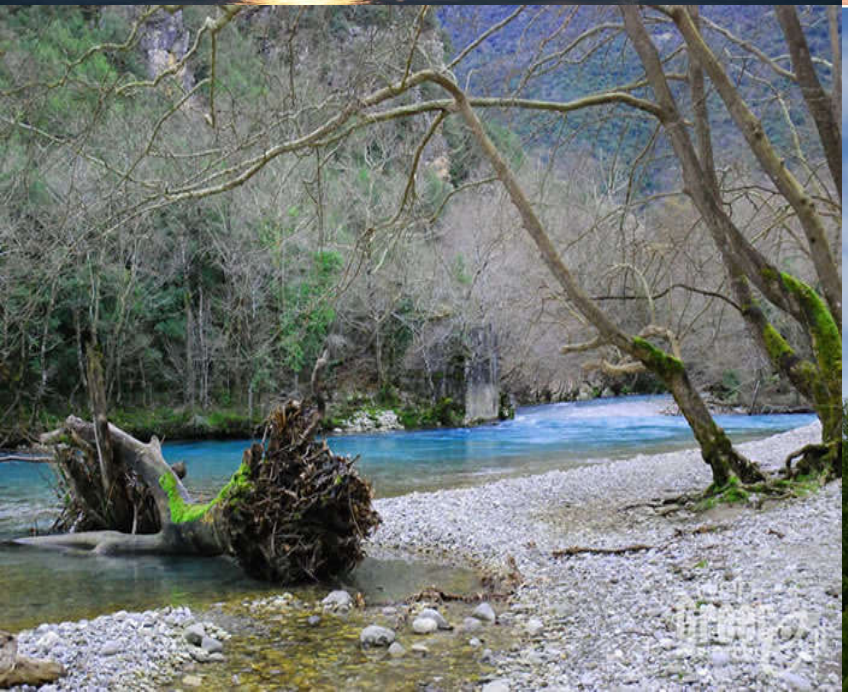
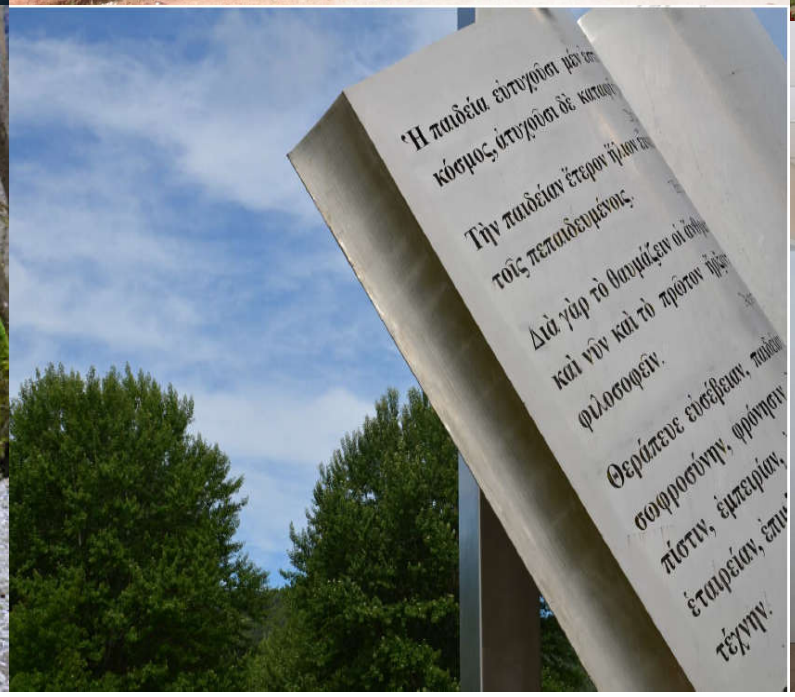
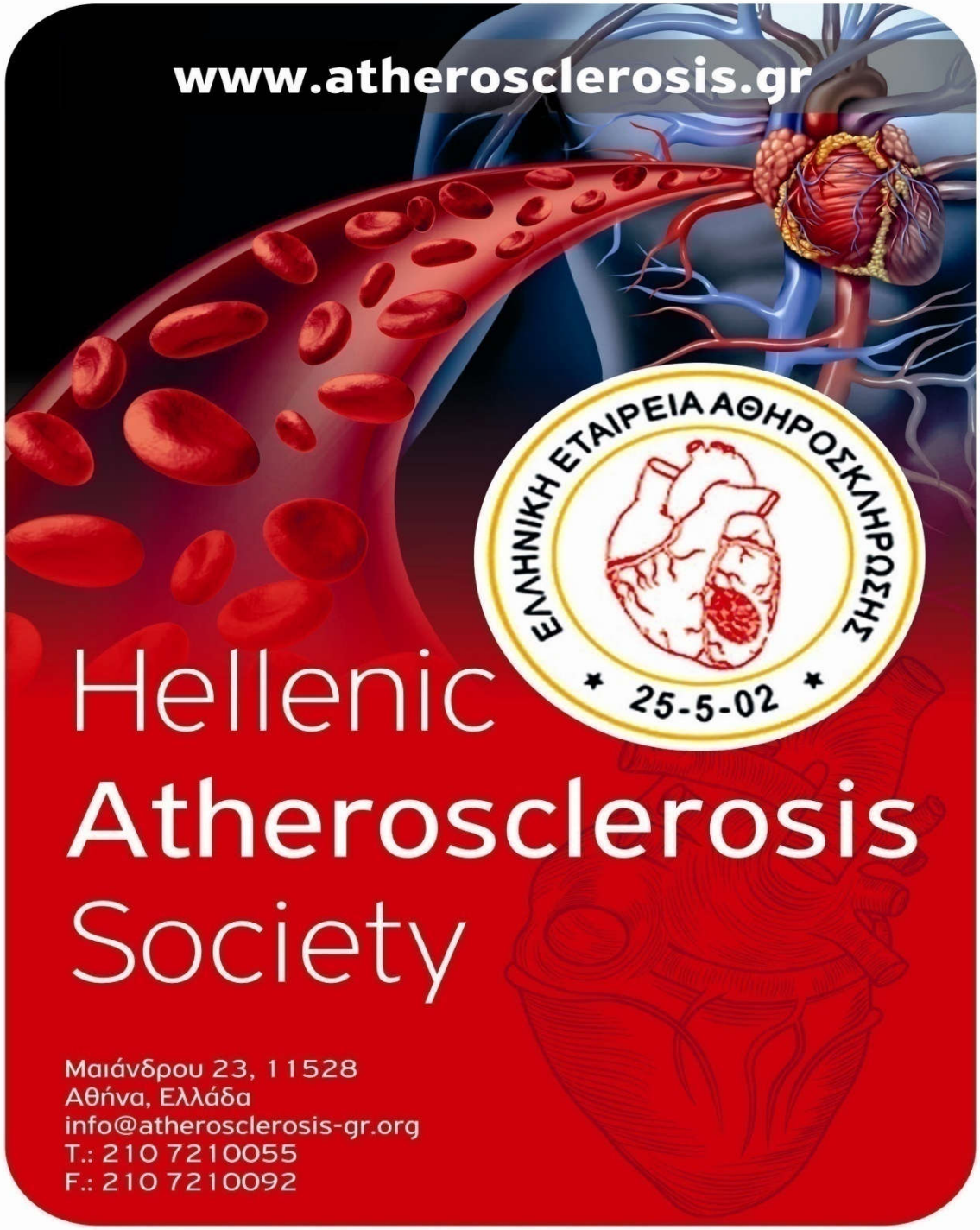
ΙΑΤΡΙΚΗ ΣΧΟΛΗ

Πανεπιστήμιο Ιωαννίνων



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25-5-02
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