Sterol Trafficking
The Lipoprotein Story

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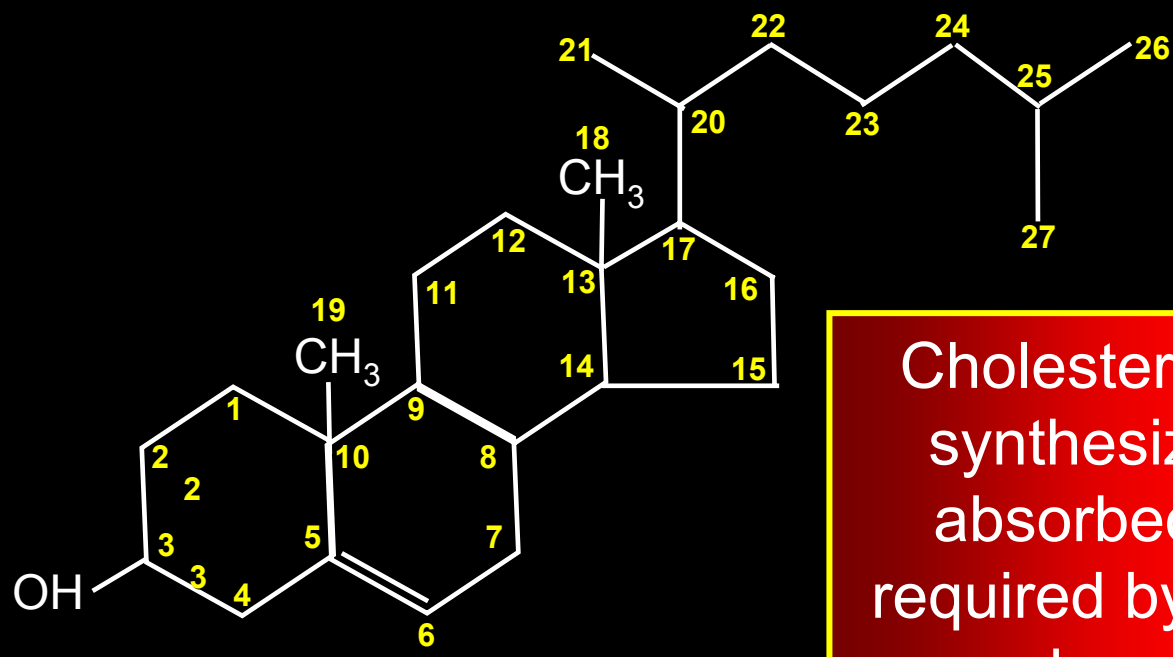
Cholesterol

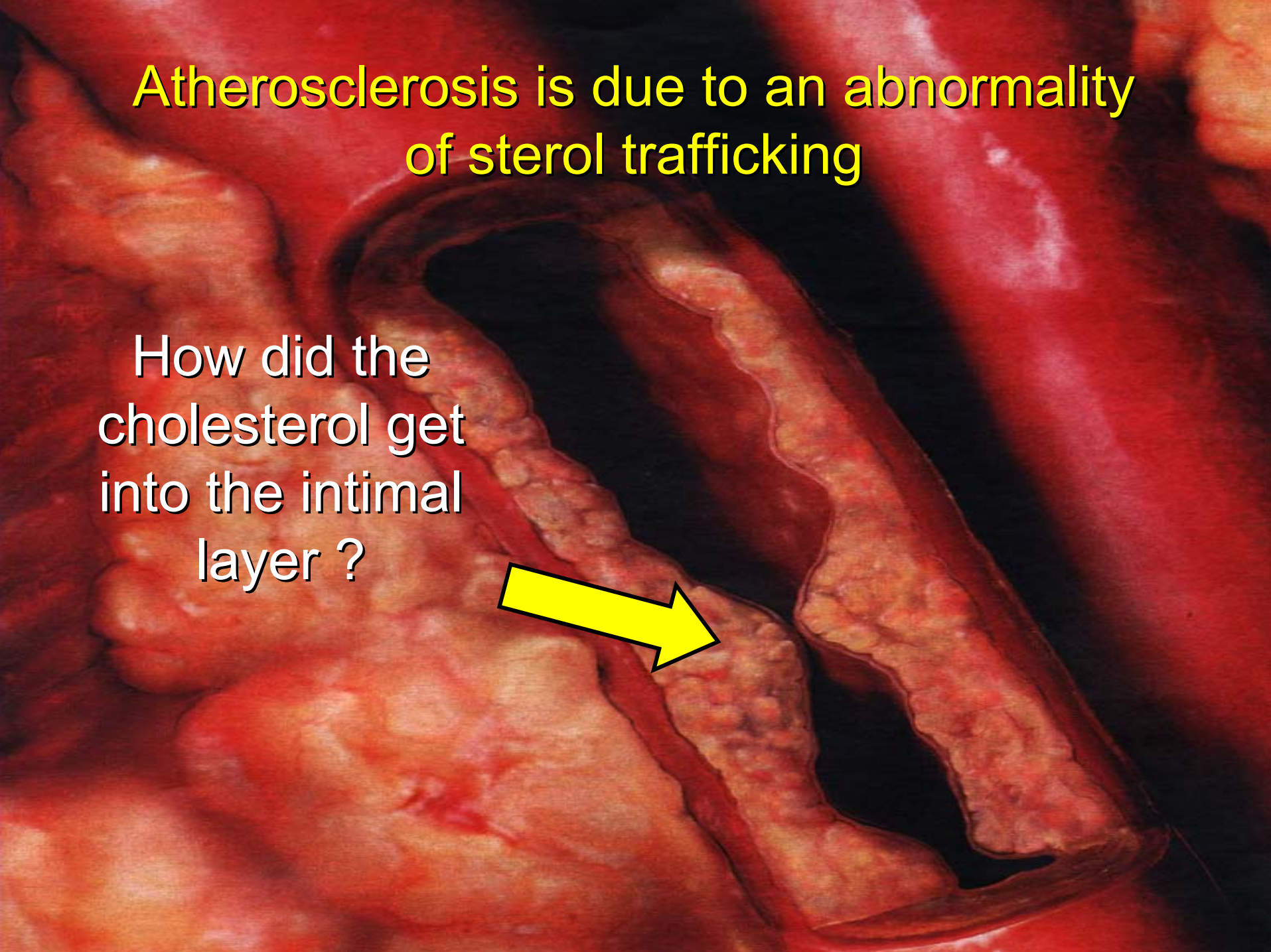


Cholesterol which can be synthesized de novo or absorbed intestinally is required by humans for cell membranes, steroid, bile acid and vitamin D production.

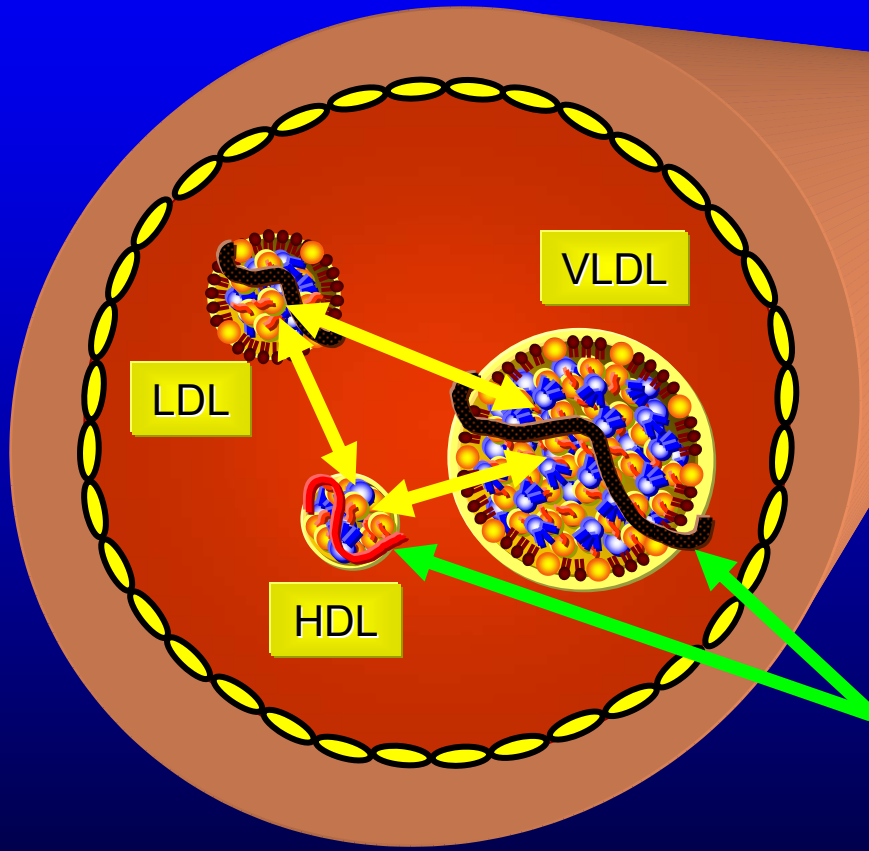
Braunwald E. Atlas of Heart Diseases. Brown WV. Volume X Atherosclerosis: Risk Factors and Treatment. Mosby, Current Medicine Inc. Philadelphia 1996

Atherosclerosis is due to an abnormality of sterol trafficking

How did the cholesterol get into the intimal layer ?



Normal Lipid Transportation



Lipids

Free & esterified sterols
Triglycerides
Phospholipids

Lipid Transfer Proteins

Apolipoproteins

"Lipid" movement is **lipoprotein** driven

LIPIDS

	mg/dL	Optimal	Near or above optimal	Borderline-high	High	Very High
LDL-C (calculated)	**112**	<100	100 - 129	130 - 159	160 - 189	≥190

	mg/dL		mg/dL		mg/dL
HDL-C	**37**	**Triglycerides**	**181**	**Total Cholesterol**	**185**
Desirable ≥ 40		Desirable <150		Desirable <200	

LDL-C cannot be reported if triglycerides are >400 mg/dL. LDL-C will be inaccurate if the sample is nonfasting.

The Particle or apoB Story

Apoprotein-related MOrtality RISk
AMORIS Study

- 175,553 patients from screening programs
  - 98,722 men and 76,831 women
- Examined relationship of apoproteins and lipids and prediction of fatal MI
- Mean Follow up 66-68 months

Wallidius G et al Lancet 2001;358:2026-2033

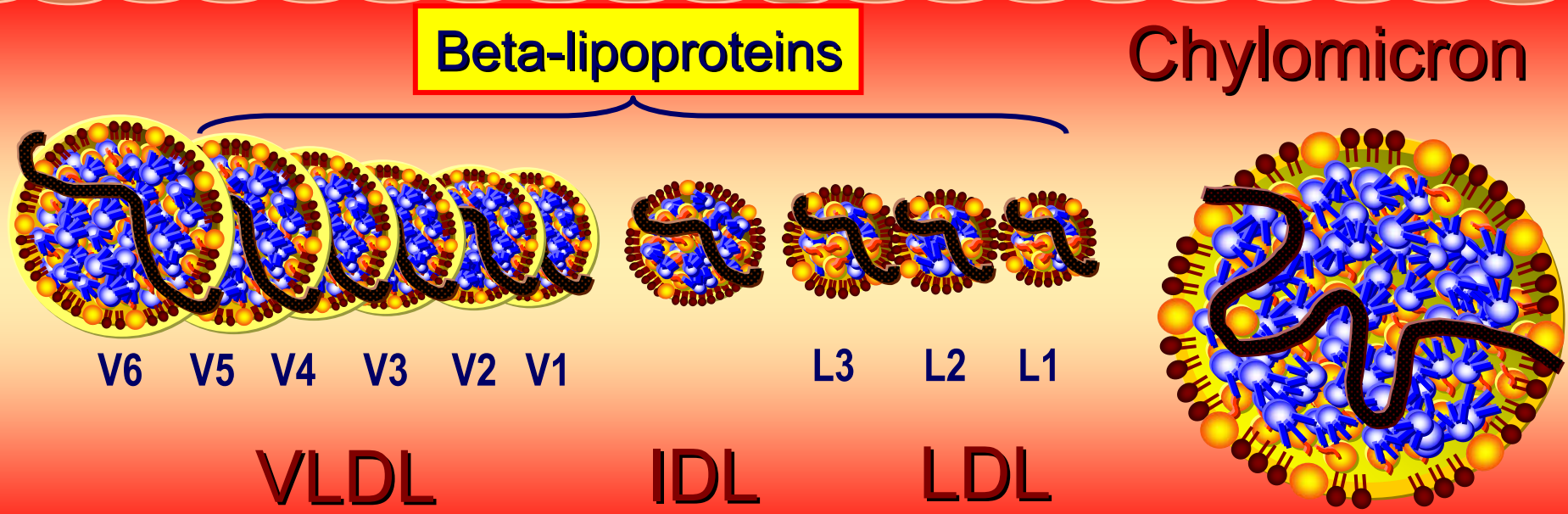
Apoprotein-related MOrtality RISk
AMORIS Study

- In multivariate analyses adjusted for age, TC and TG
- **Apolipoprotein B** was a stronger predictor of risk than LDL-C in both sexes

ApoB is obviously a marker of atherogenic lipoprotein particles

Wallidius G et al Lancet 2001;358:2026-2033

Lipoprotein Class & Subclass



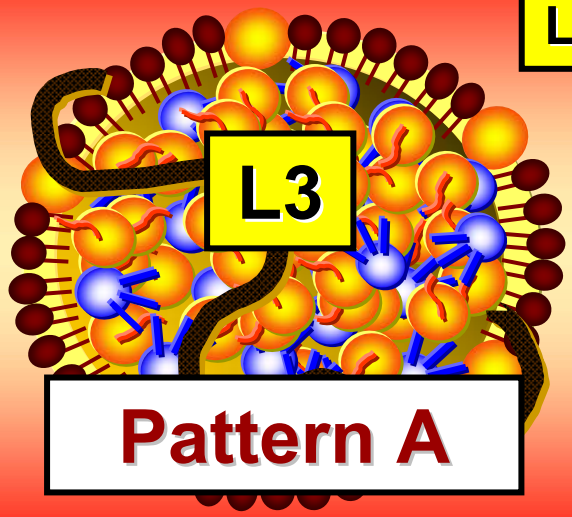
There is one molecule of apoB on each beta-lipoprotein particle

Arterioscler Thromb Vasc Biol 1998;18:1046-1053

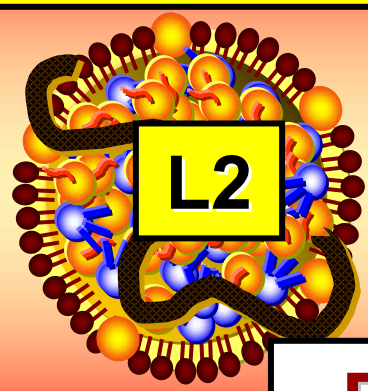
Handbook of lipoprotein Testing 2nd Ed 2000 AACC Press Washington DC

LDL Particle Subclass (NMR*)

LDL-P = # of LDL particles in a liter of plasma



Pattern A



Pattern B

- LDL particles are a heterogeneous mixture of particles of varying composition and size, each with a single molecule of apoB
- The larger, more buoyant particles are termed **Phenotype or Pattern A**
- The smaller, denser, less buoyant particles are termed **Phenotype or Pattern B**
- LDL-C is the sum of the cholesterol within all of the LDL particles per/dL of serum
- If present … nic

LDL-C = cholesterol content within all of the LDL particles in a deciliter (dL) of plasma

*Nuclear magnetic resonance spectroscopy

www.lipoprofile.com

Arterioscler Thromb Vasc Biol 1998;18:1046-1053

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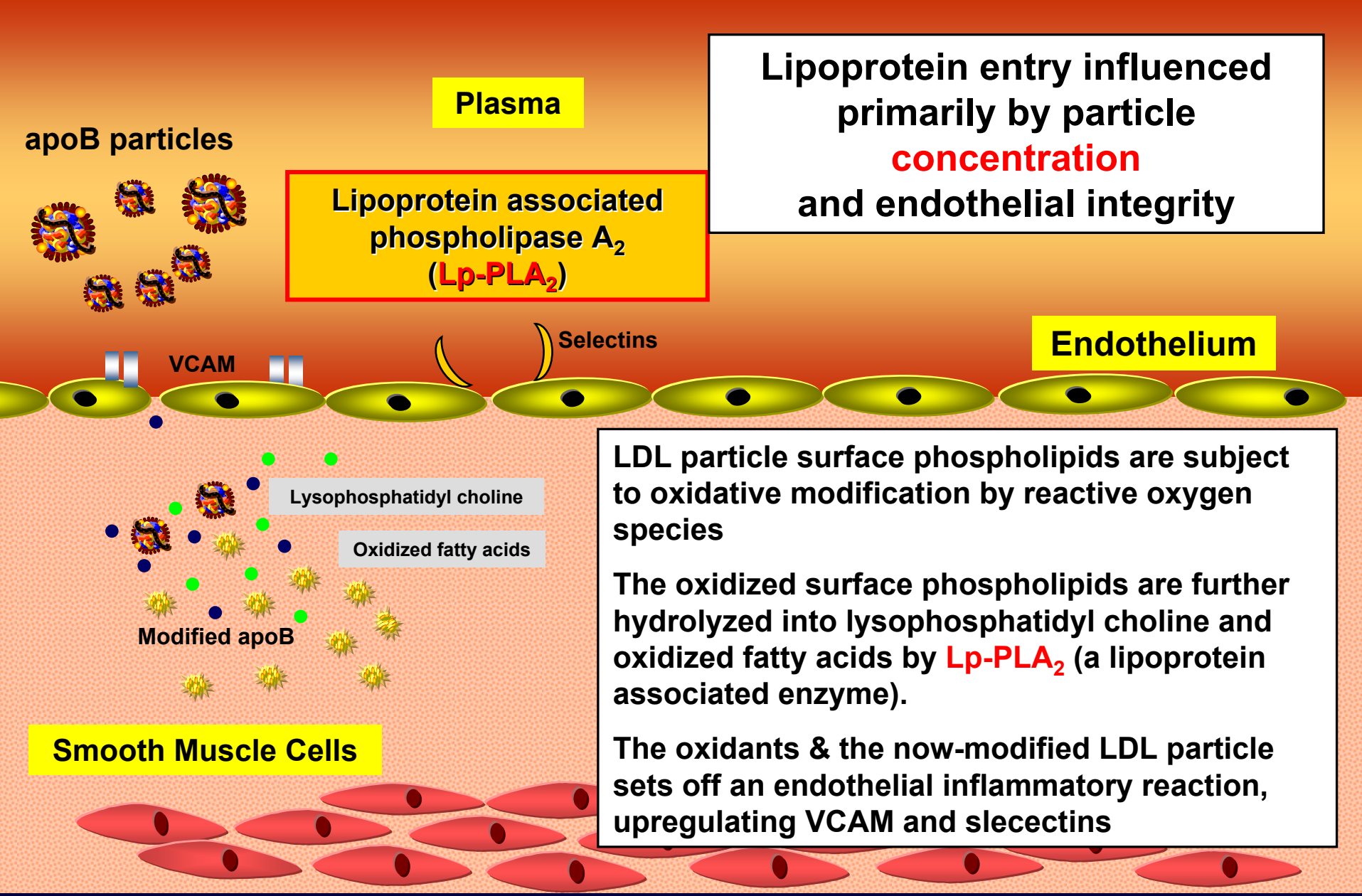
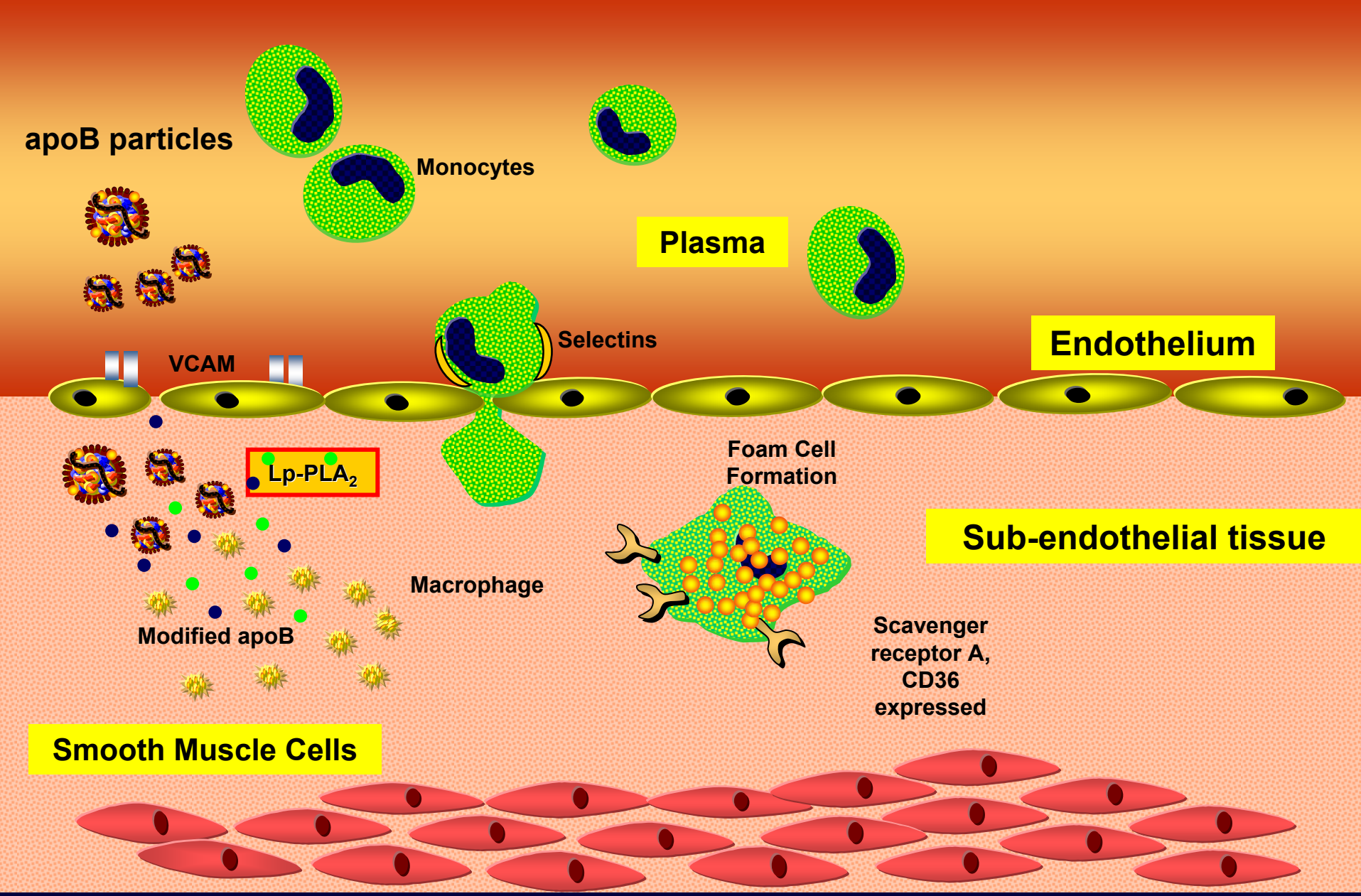


de Winther MPJ et al. *Arterioscler Thromb Vasc Biol*. 2005;25:904-914



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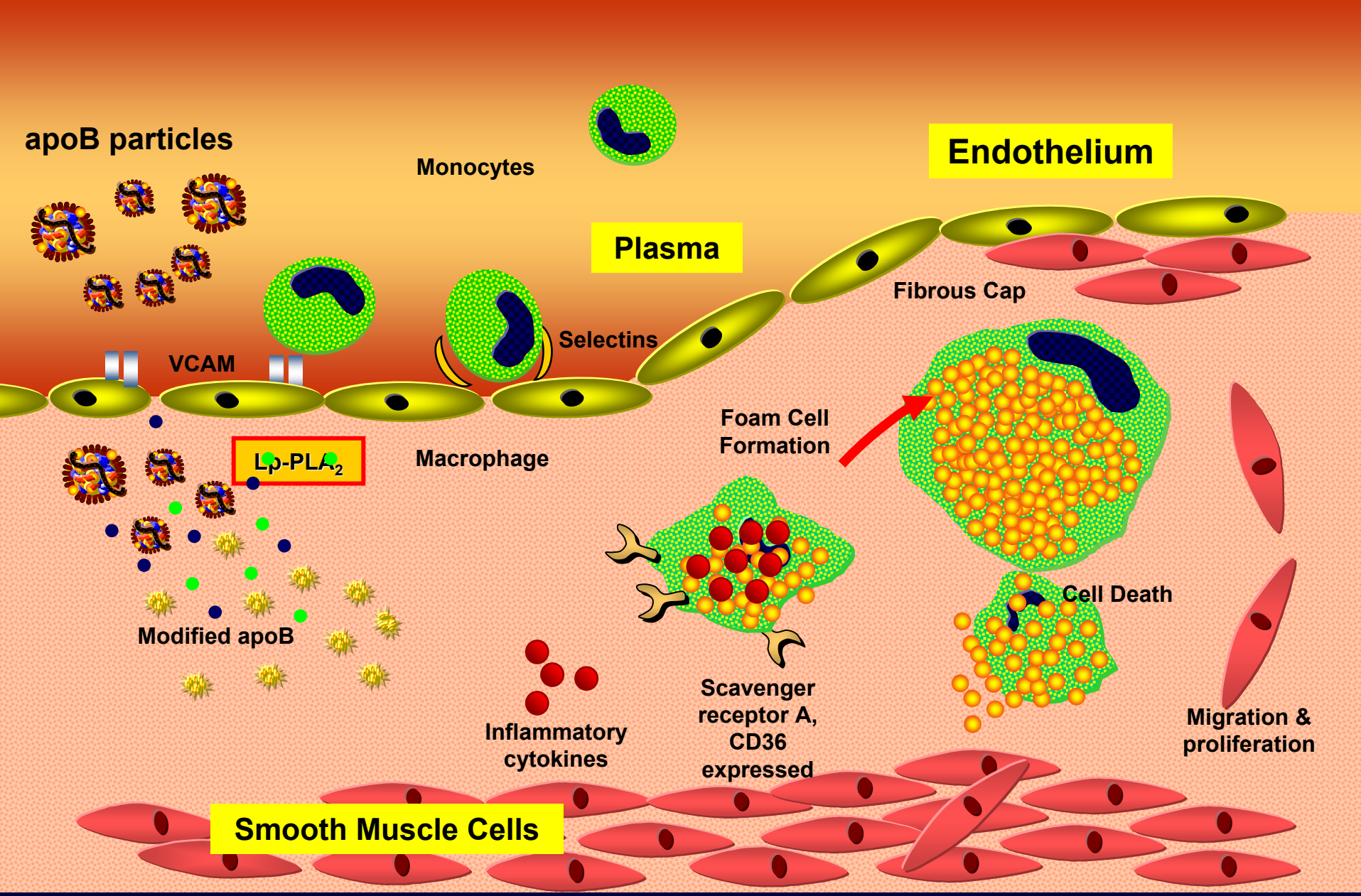

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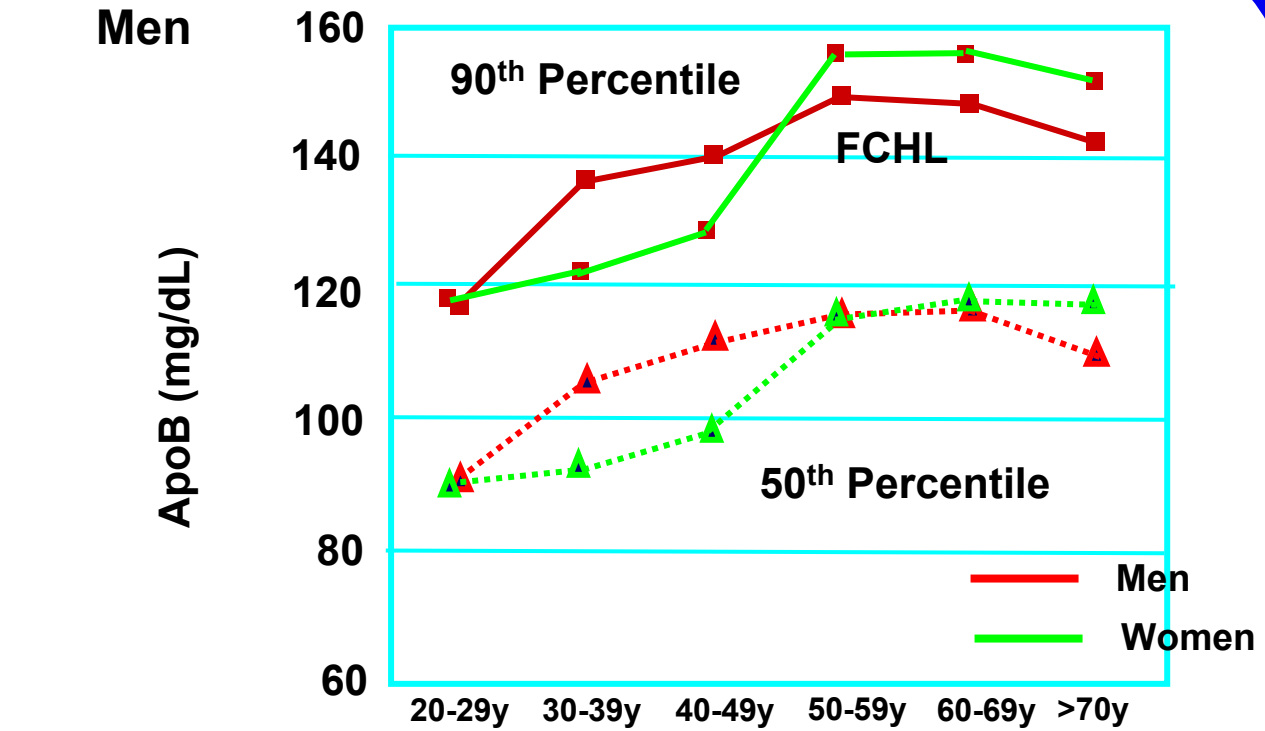
NHANES III: Apolipoprotein B Levels by Age, 50th and 90th Percentile



	20-29y	30-39y	40-49y	50-59y	60-69y	>70y
Mean	91	106	112	116	117	110
90th percentile	117	138	140	149	148	142

Carr M & Brunzell J J Clin Endo & Metab 2004;89:2601-2607

Journal of Internal Medicine 2006; 259: 247–258 doi:10.1111/j.1365-2796.2006.01616.x

REVIEW

Apo B versus cholesterol in estimating cardiovascular risk and in guiding therapy: report of the thirty-person/ten-country panel

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From the [1]Heart Research Institute, Camperdown, Sydney, NSW, Australia; [2]Baylor College of Medicine, Houston, TX, USA; [3]Department of Endocrinology and Nutrition, Facultad de Medicina y Hospital Clinico Universitario, Valencia, Spain; [4]St Franciscus Gasthuis, Rotterdam, the Netherlands; [5]Hôpital de la Pitié, Paris, France; [6]Centre Hospitalier Universitaire de Québec, Ste-Foy, Québec, Canada; [7]Radboud University Nijmegen Medical Center, Nijmegen, the Netherlands; [8]Division of Cardiovascular and Endocrine Science, Department of Medicine, Manchester Royal Infirmary, University of Manchester, Manchester, UK; [9]Aarhus Amtssygehus University Hospital, Aarhus C, Denmark; [10]University of British Columbia, St Paul's Hospital, Vancouver, BC, Canada; [11]Wake Forest University School of Medicine, Winston-Salem, NC, USA; [12]Université de Laval, Laval, Québec, Canada; [13]University of Texas Health Science Center, San Antonio, TX, USA; [14]Royal Free and University College Medical School, London, UK; [15]Clinical Epidemiology Unit, Department of Medicine, Karolinska Institute, Stockholm; [16]CALAB Research, Stockholm, Sweden; [17]Children's Hospital Oakland Research Institute, Oakland, CA; [18]The Johns Hopkins Medication Institutions, Baltimore, MD; [19]University of Washington, Seattle, WA, USA; [20]Glasgow Royal Infirmary, Glasgow, UK; [21]University of Rochester, Rochester, NY, USA; [22]All India Institute of Medical Sciences, New Delhi, India; [23]Northwestern University, Chicago, IL, USA; [24]Isfahan Cardiovascular Research Center, Isfahan, Iran; [25]Mike Rosenbloom Laboratory for Cardiovascular Research, McGill University Health Sciences Centre, Montreal, Québec, Canada; [26]Metabolic and Atherosclerosis Research Center, Cincinnati, OH, USA; [27]Monash University, Victoria, Australia; and [28]King Gustaf V Research Institute and Karolinska Institute, Stockholm, Sweden

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All of the national and transnational screening and therapeutic guidelines are based on total or LDL cholesterol.

This presumes that cholesterol is the most important lipoprotein-related proatherogenic risk variable.

On the contrary, risk appears to be more directly related to the number of circulating atherogenic particles that contact and enter the arterial wall than to the measured concentration of cholesterol in these lipoprotein fractions.

Each of the atherogenic lipoprotein particles contains a single molecule of apolipoprotein (apo) B and therefore the concentration of apo B provides a direct measure of the number of circulating atherogenic lipoproteins.

Evidence from fundamental, epidemiological and clinical trial studies indicates that apo B is superior to any of the cholesterol indices to recognize those at increased risk of vascular disease and to judge the adequacy of lipid-lowering therapy.

Barter PJ et al. J Intern Med 2006;249:247-258

The apoA-I Story

ApoA-I

Apoprotein-related MOrtality RISk
AMORIS Study

- In multivariate analyses adjusted for age, TC and TG
- **Apolipoprotein B** was a stronger predictor of risk than LDL-C in both sexes
- **Apolipoprotein A-I** was protective

Wallidius G et al Lancet 2001;358:2026-2033

Apoprotein-related MOrtality RISk
AMORIS Study

- In multivariate analyses adjusted for age, TC and TG
- **Apolipoprotein B** was a stronger predictor of risk than LDL-C in both sexes
- **Apolipoprotein A-I** was protective
  - The values for **Apo B** and the **ApoB/ApoA-I** ratio were strongly and positively related to risk of fatal MI in men and women

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The evidence also indicates that the **apo B/apo A-I ratio is superior to any of the conventional cholesterol ratios** in patients without symptomatic vascular disease or diabetes to evaluate the lipoprotein- related risk of vascular disease.

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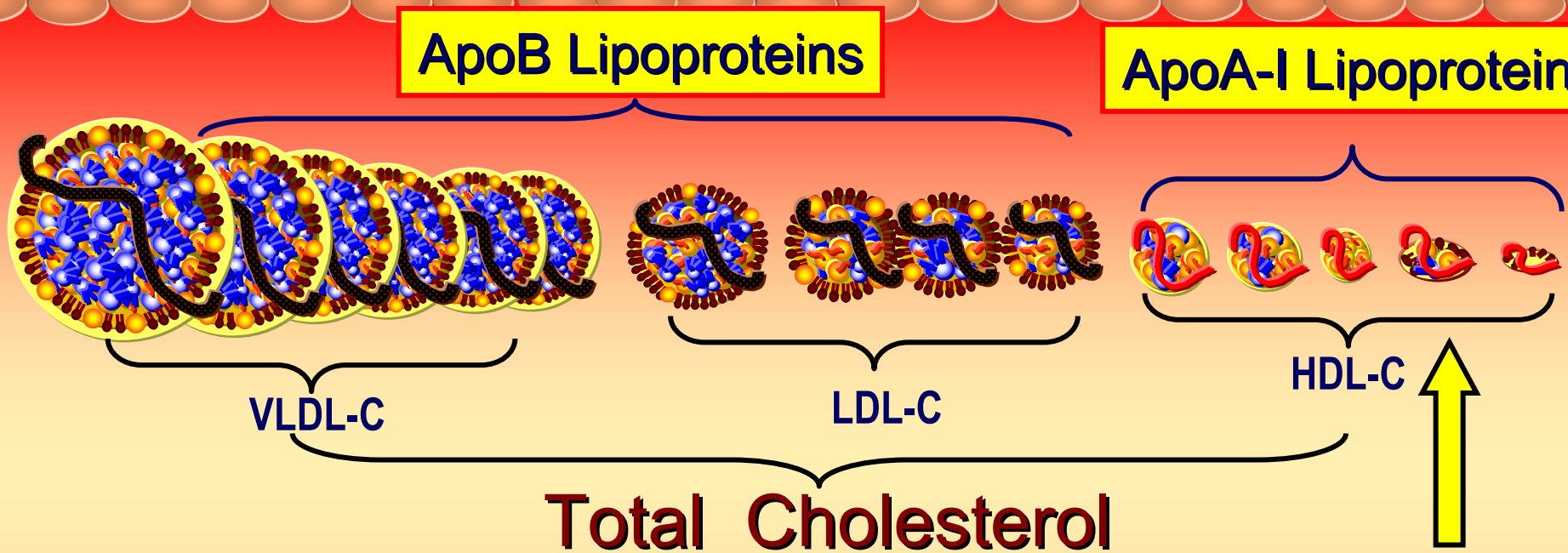
Apolipoprotein B & A-I Surrogates



TC > 200 mg/dL is an apoB surrogate

HDL-C is the lipid apoA-I surrogate

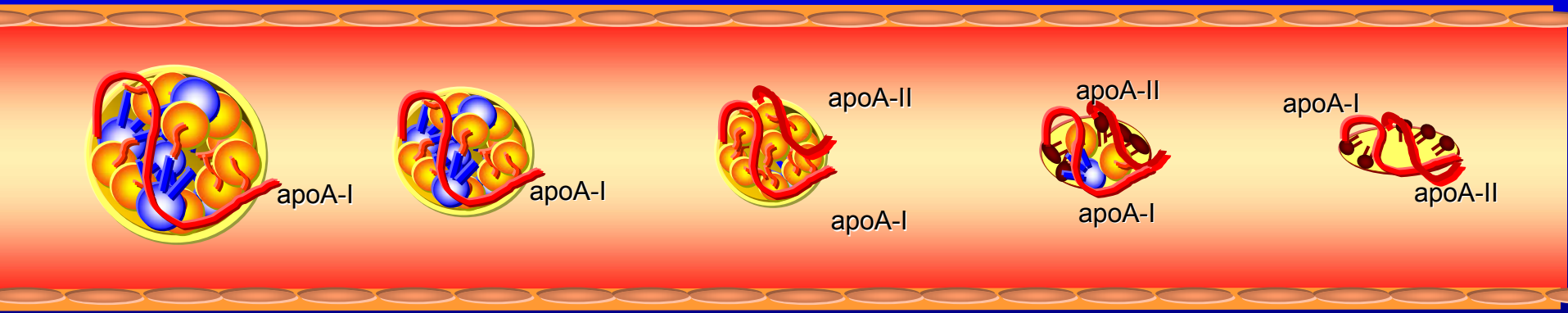
TC/HDL-C ~ apoB/apoA-I ratio

Handbook of lipoprotein Testing 2nd Ed 2000 AACC Press Washington DC

HDL Subpopulations by GGE & NMR

Nuclear Magnetic Resonance Subpopulation Nomenclature

HDL5	HDL4	HDL3	HDL2	HDL1
10-13 nm	8.8-10 nm	8.2-8.8 nm	7.8-8.2 nm	7.3-7.7 nm



HDL_{2b}	HDL_{2a}	HDL_{3a}	HDL_{3b}	HDL_{3c}
10.6 nm	9.2 nm	8.4 nm	8.0 nm	7.6 nm

Gel Electrophoresis Subpopulation Nomenclature

Barter, Philip et al. Atherosclerosis 2003;168:195-211

HDL-cholesterol Concentration

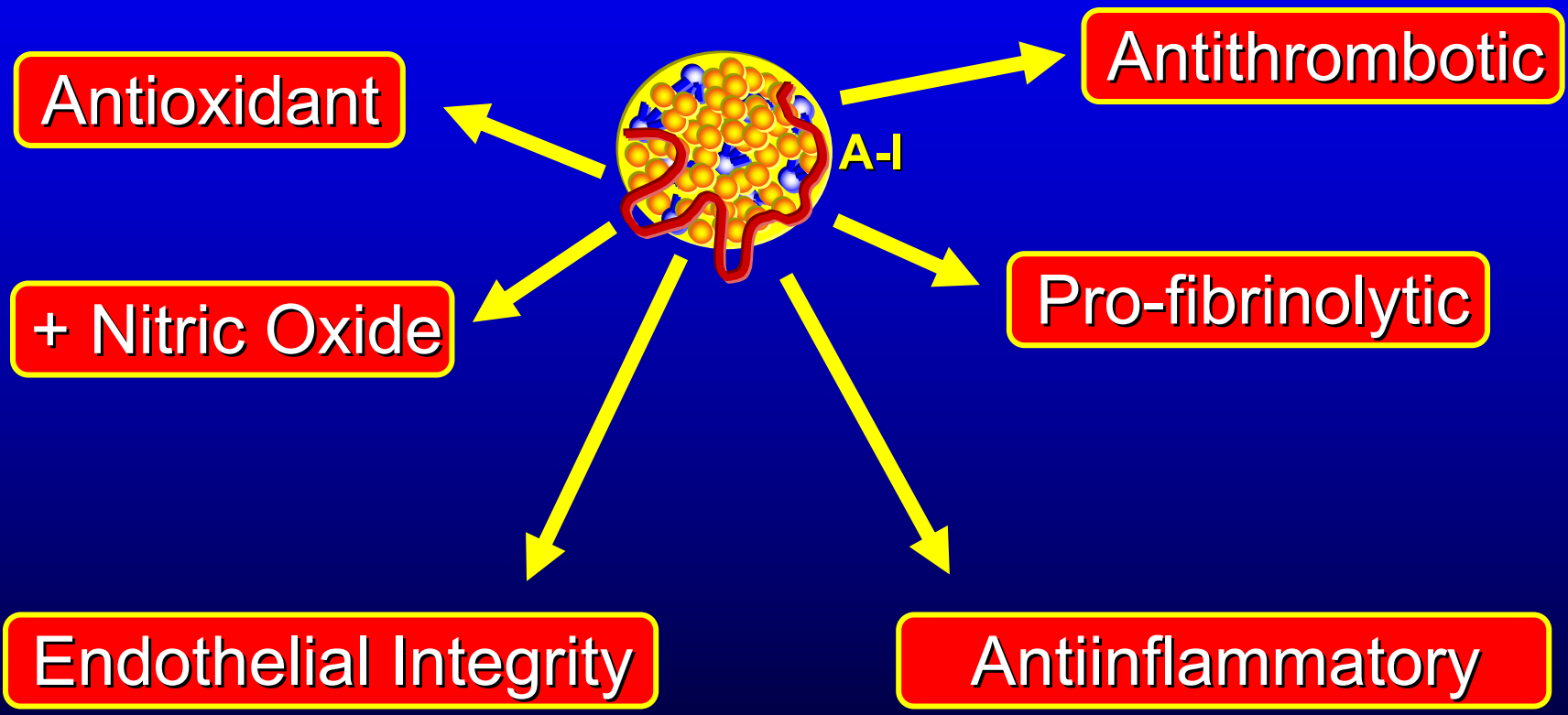
HDL5	HDL4	HDL3	HDL2	HDL1
HDL_{2b}	HDL_{2a}	HDL_{3a}	HDL_{3b}	HDL_{3c}

HDL-P reflects the number of HDL particles

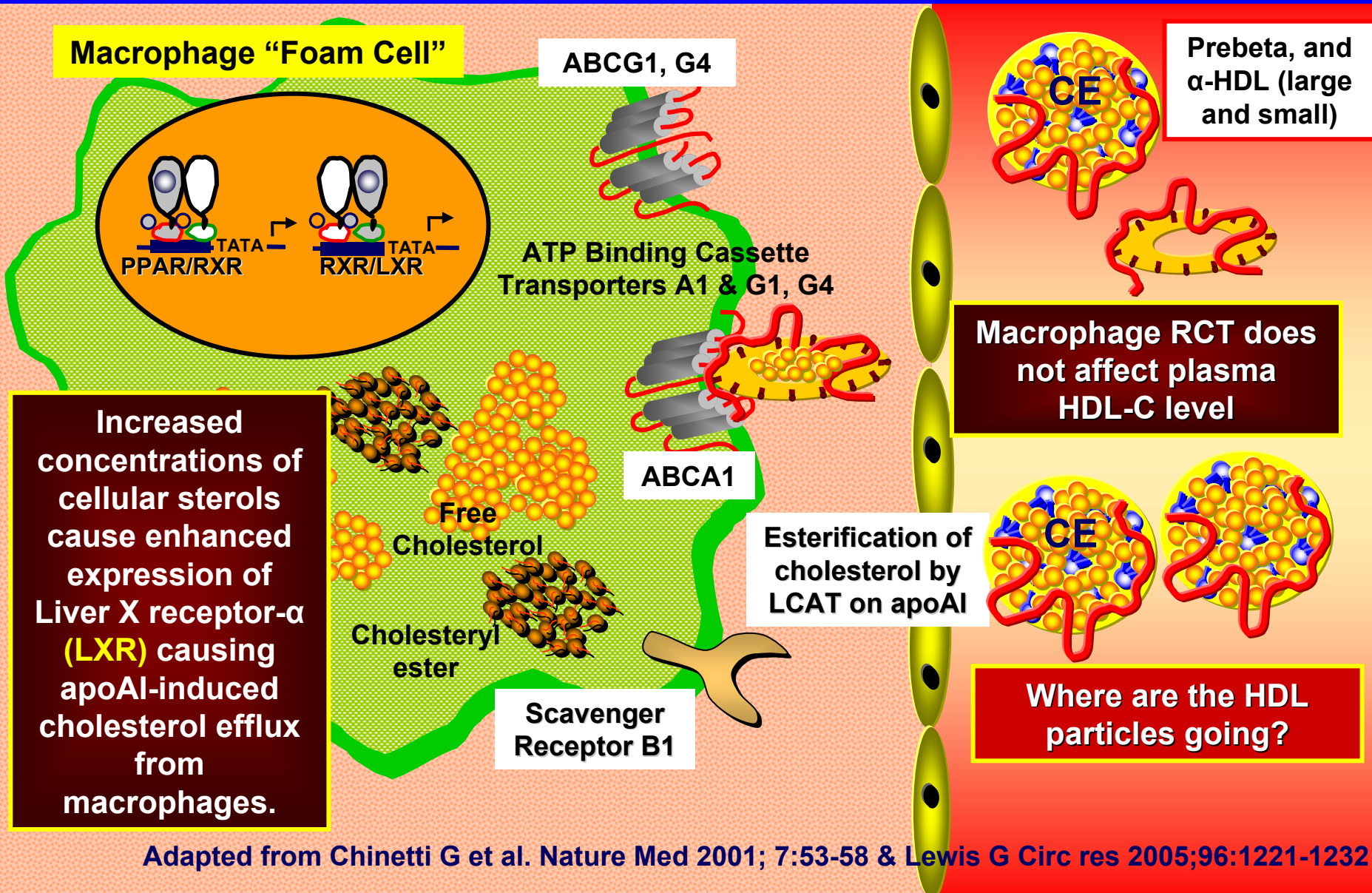
HDL-C primarily reflects cholesterol levels within large, cholesterol-rich particles and lacks sensitivity to detect small cholesterol-poor particles

Kontush A & Chapman J. Pharm Rev. 2006;58:342-374

HDL Functionality and Vascular Protection



Macrophage Reverse Cholesterol Transport



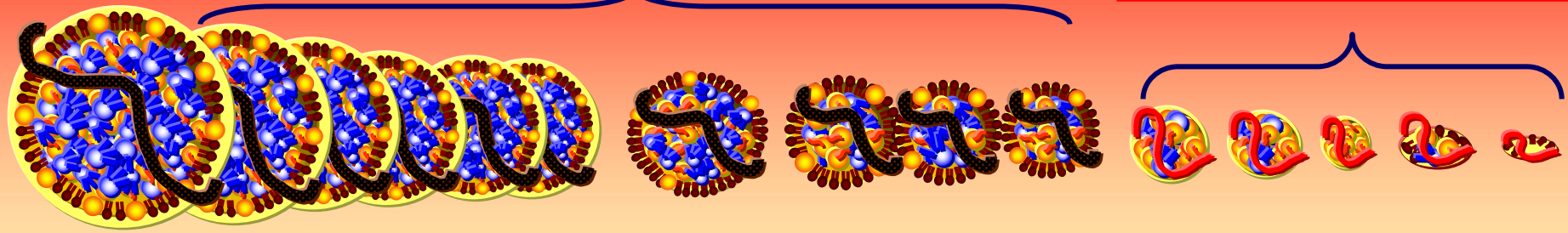
Adapted from Chinetti G et al. Nature Med 2001; 7:53-58 & Lewis G Circ res 2005;96:1221-1232

Interpreting the Lipid Profile and Understanding NCEP ATP-III Goals

Lipoprotein & Lipid Concentrations

ApoB-lipoproteins

ApoAI-lipoproteins



V6 V5 V4 V3 V2 V1

L3 L2 L1

H5 H4 H3 H2 H1

VLDL-C

TG/5

IDL-C + LDL-C

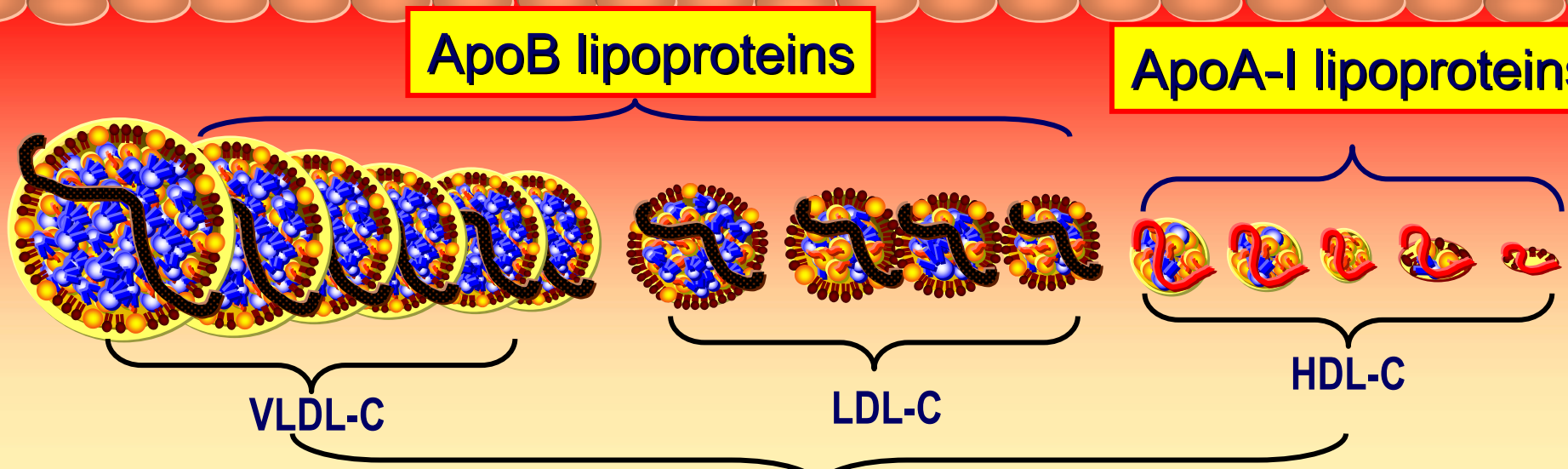
HDL-C

Reported LDL-C TC – (HDL-C + TG/5)

Total Cholesterol

What are the Lipid Surrogates of apoB and apoA-I

Apolipoprotein B Surrogates



TC > 200 mg/dL is an apoB surrogate

LDL-Cholesterol is a better apoB surrogate

Handbook of lipoprotein Testing 2nd Ed 2000 AACC Press Washington DC

National Cholesterol Education Program

Adult Treatment Panel III NCEP-ATP III

Goals of Therapy

- **Normalize LDL-C** (depending on risk)
  - 130 mg/dl in moderate risk patients (10-20% 10 year risk)
  - <100 mg/dl in high risk patients (>20% 10 year risk)
  - Option for < 70 in very high risk patients

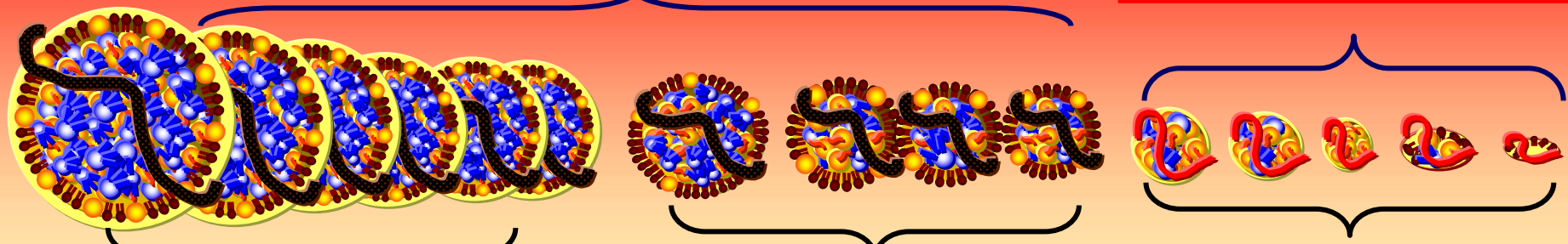
LDL-C is a surrogate of apoB

NCEP JAMA 2001;285:2486 Final Report Circulation 2002;106:3143-3421

Apolipoprotein B Surrogates

ApoB-lipoproteins

ApoAI-lipoproteins



VLDL-C

LDL-C

HDL-C

ApoB-Cholesterol

Non HDL-C

Non HDL-C = TC – HDL-C

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Apo B versus cholesterol in estimating cardiovascular risk and in guiding therapy: report of the thirty-person/ten-country panel

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Abstract. Barter PJ, Ballantyne CM, Carmena R, Castro Cabezas M, John Chapman M, Couture P, de Graaf J, Durrington PN, Faergeman O, Frohlich J, Furberg CD, Gagne C, Haffner SM, Humphries SE, Jungner I, Krauss RM, Kwiterovich P, Marcovina S, Packard CJ, Pearson TA, Srinath Reddy K, Rosenson R, Sarrafzadegan N, Sniderman AD, Stalenhoef AF, Stein E, Talmud PJ, Tonkin AM, Walldius G, Williams KMS (Heart Research Institute, Sydney, NSW, Australia; Baylor College of Medicine, Houston, TX, USA; Hospital Clinico Universitario, Valencia, Spain; St Franciscus Gasthuis, Rotterdam, the Netherlands; Hôpital de la Pitié, Paris, France; Centre Hospitalier Universitaire de Québec, Québec, Canada; Radboud University Nijmegen Medical Center, Nijmegen, the Netherlands; University of Manchester, Manchester, UK; Aarhus Amtssygehus University Hospital, Aarhus C, Denmark; University of British Columbia, St Paul's Hospital, Vancouver, BC, Canada; Wake Forest University School of Medicine, Winston-Salem, NC, USA; Université de Laval, Laval, Québec, Canada; University of Texas Health Science Center, San Antonio, TX, USA; Royal Free and University College Medical School, London, UK; Karolinska Institute, Stockholm; CALAB Research, Stockholm, Sweden; Children's Hospital Oakland Research Institute, Oakland, CA; The Johns Hopkins Medication Institutions, Baltimore, MD; University of Washington, Seattle, WA, USA; Glasgow Royal Infirmary, Glasgow, UK; University of Rochester,

Non-HDL cholesterol is not a clinically accurate surrogate for apo B. The two are highly correlated but only moderately concordant. Thus, at any level of non-HDL cholesterol, there will be considerable variation in apo B levels.

The converse is also true: at any level of apo B, there will be substantial variation in non-HDL cholesterol.

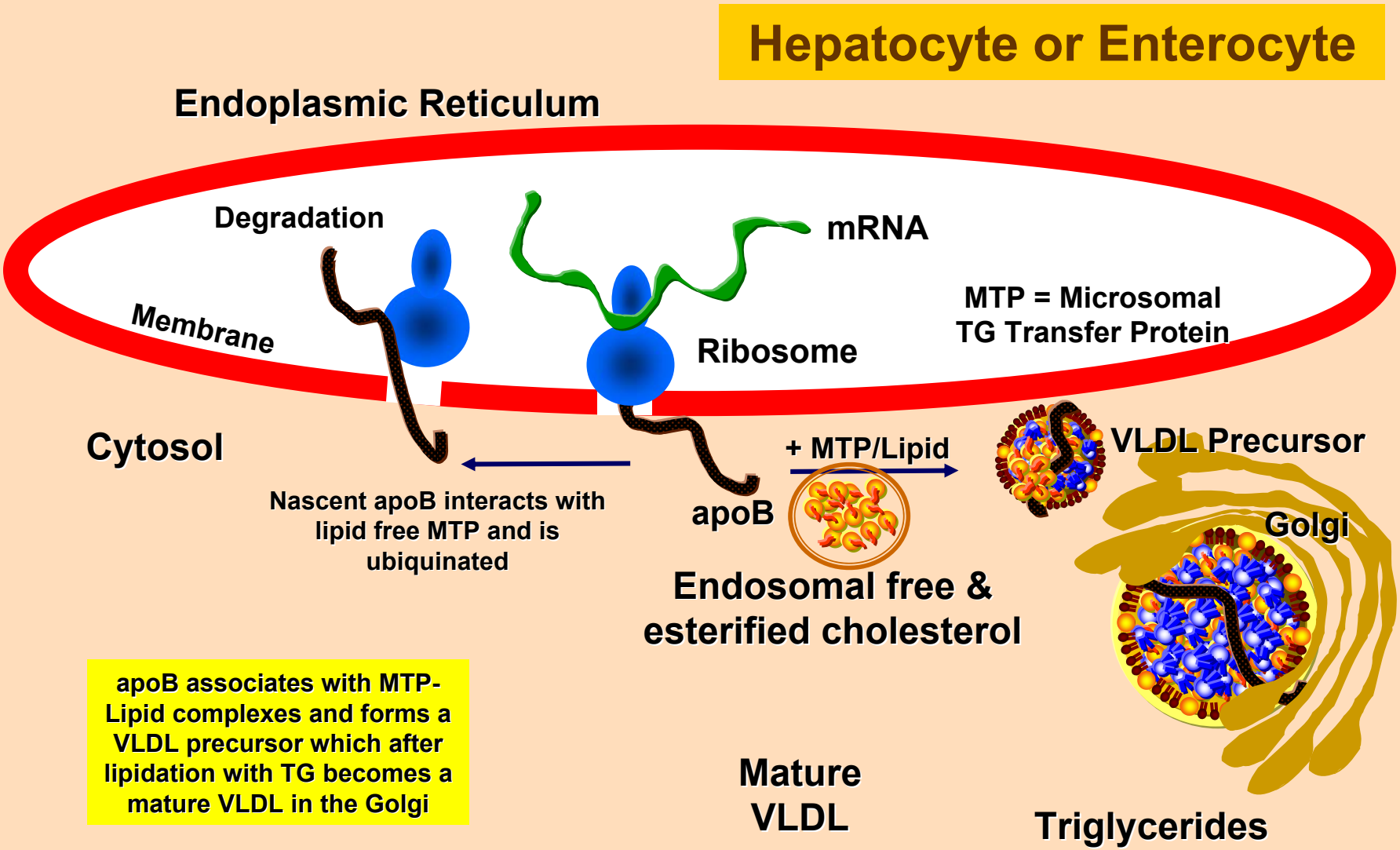
Non- HDL cholesterol is the sum of the cholesterol in VLDL, IDL, LDL and Lp(a). Of the total plasma apo B, approximately 90% are IDL and LDL particles with almost the remainder VLDL particles.

Not so for VLDL cholesterol, which can easily range from 10% to 25% or more of non-HDL cholesterol, with the result that there is much greater variance in VLDL cholesterol as a percentage of non-HDL cholesterol than there is of VLDL apo B as a percentage of total apo B.

Barter PJ et al. J Intern Med 2006;249:247-258

The apoB Story

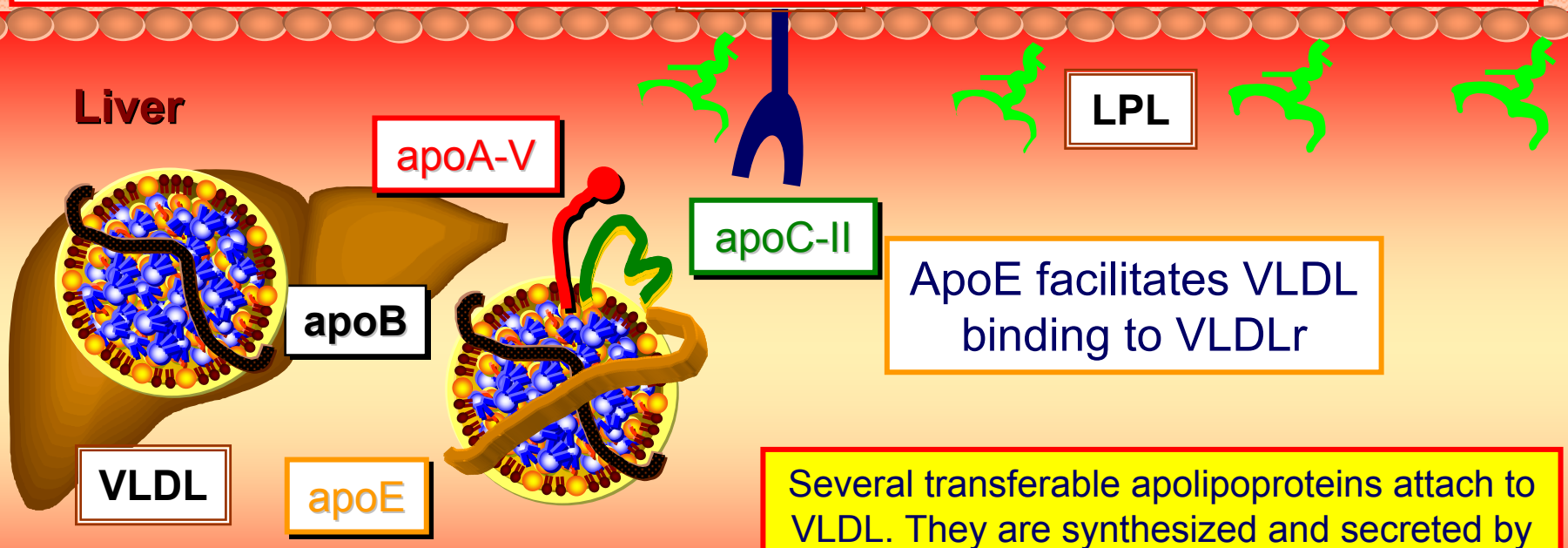
Lipidation of Apolipoprotein B



Whitfield AJ et al. Clin Chem 2004;50:1725-1732

VLDL Lipolysis

ApoA-V facilitates the binding of ApoC-II to lipoprotein lipase (LPL)

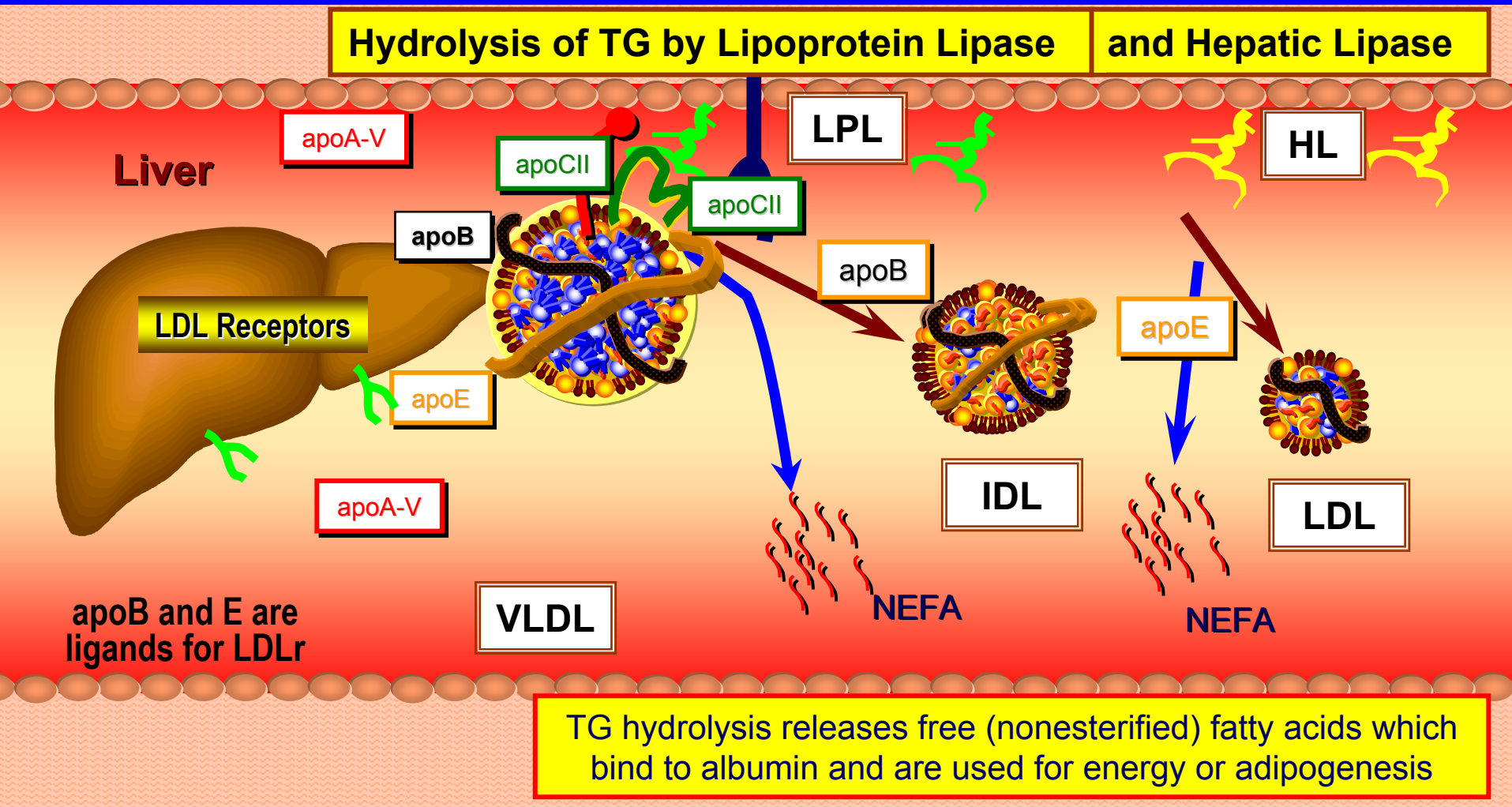


ApoE facilitates VLDL binding to VLDLr

Several transferable apolipoproteins attach to VLDL. They are synthesized and secreted by the liver and often trafficked on HDL particles

Blood Vessel Intima

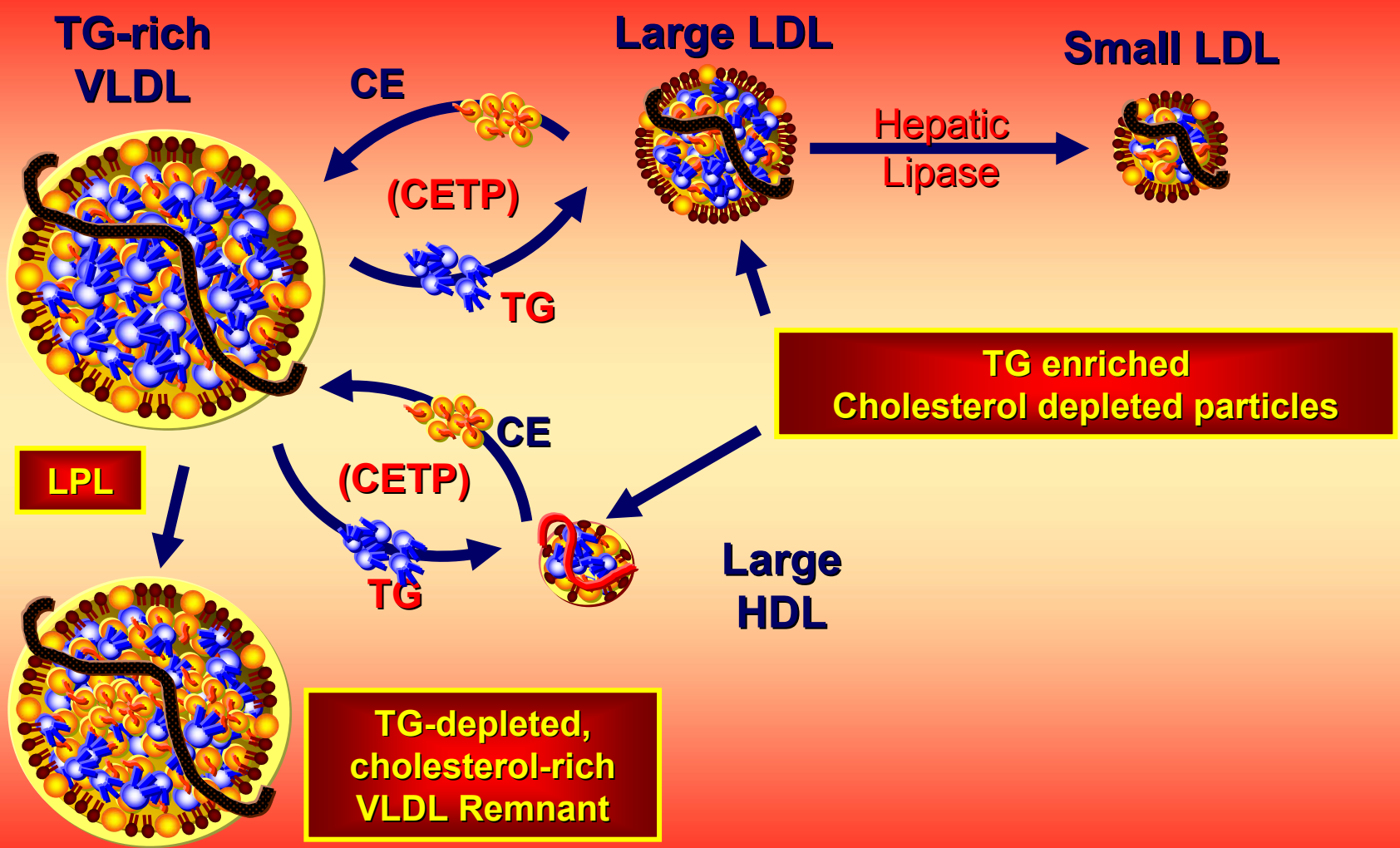
VLDL Lipolysis



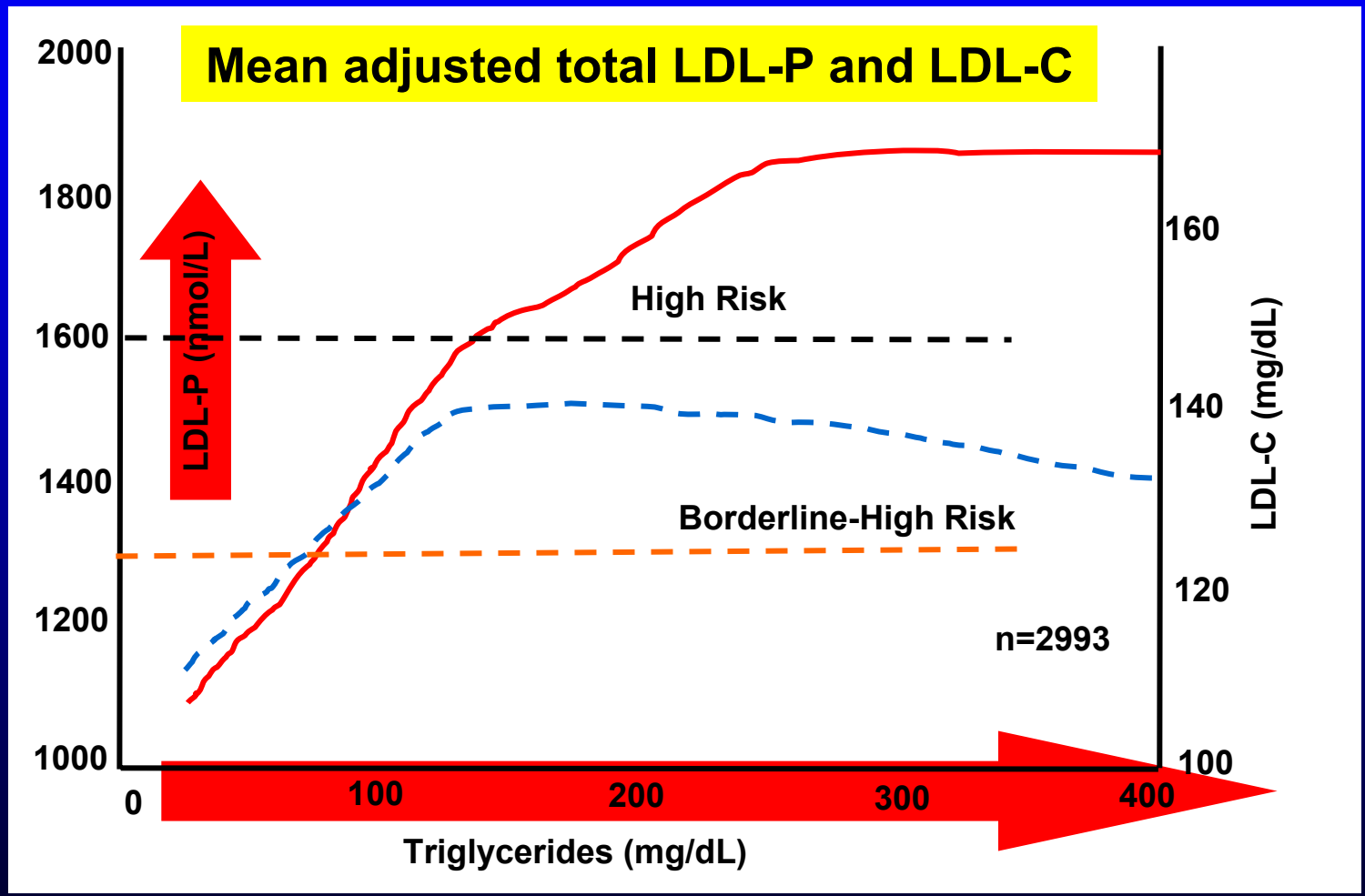
The apoB Story

TG/HDL Axis Abnormalities

Lipoprotein Abnormalities in TG/HDL Axis Disorders

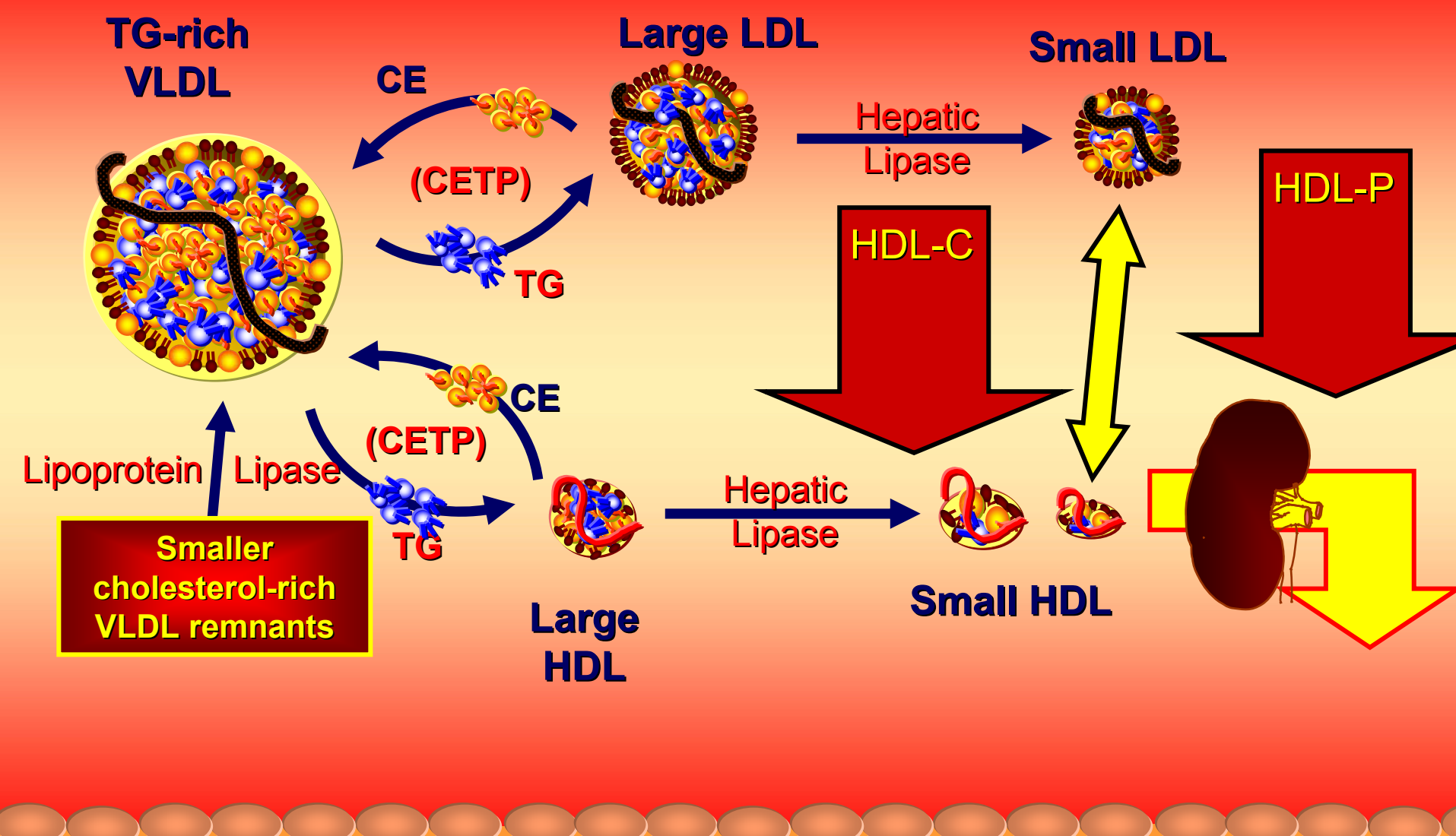


Framingham Offspring Study
LDL-P and Metabolic Syndrome



Kathiresan S, Otvos JD, Sullivan LM et al. *Circulation*. 2006;113:20-29.

HDL Particle Abnormalities in TG/HDL Axis Disorders

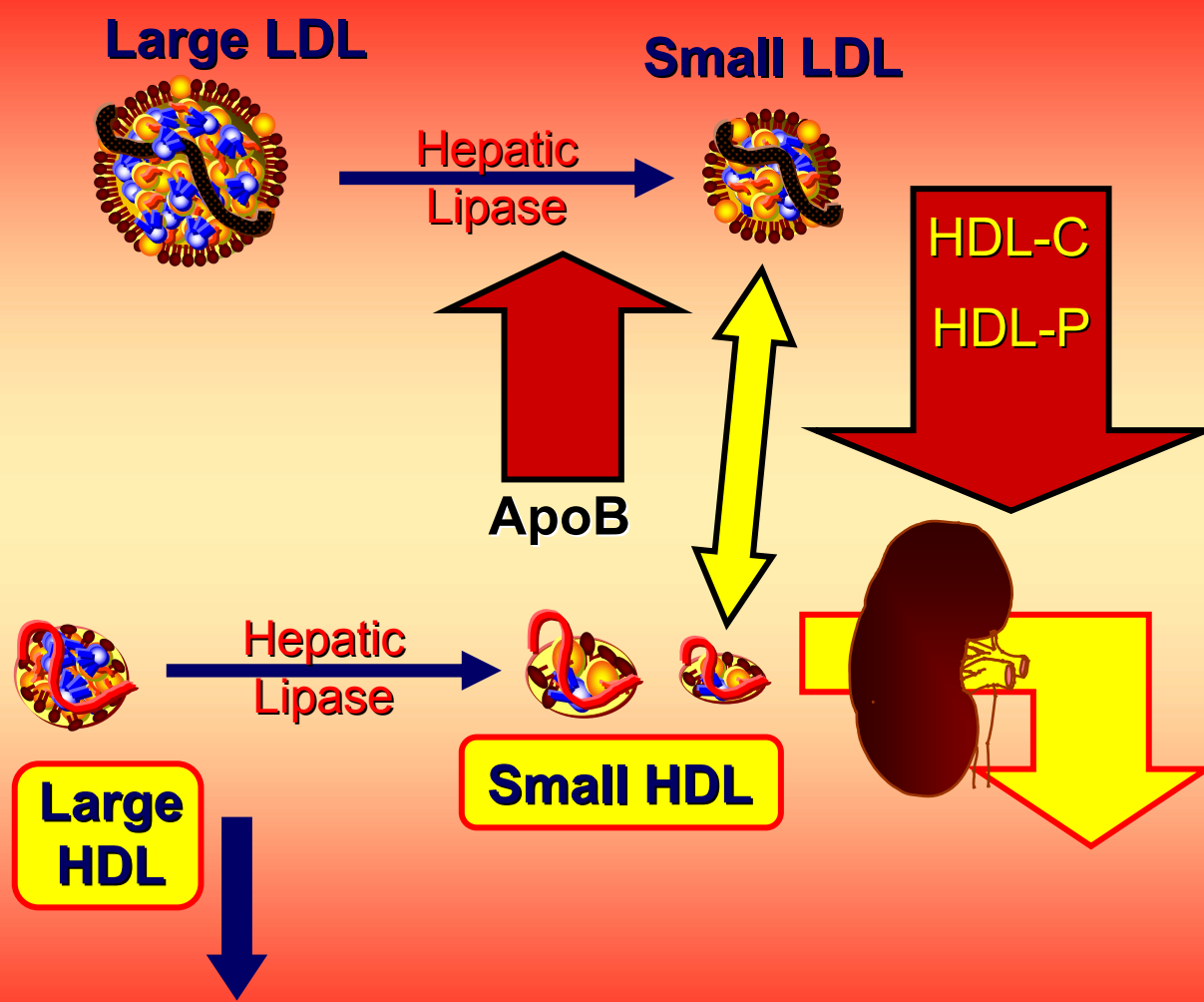


HDL Particle Abnormalities in TG/HDL Axis Disorders

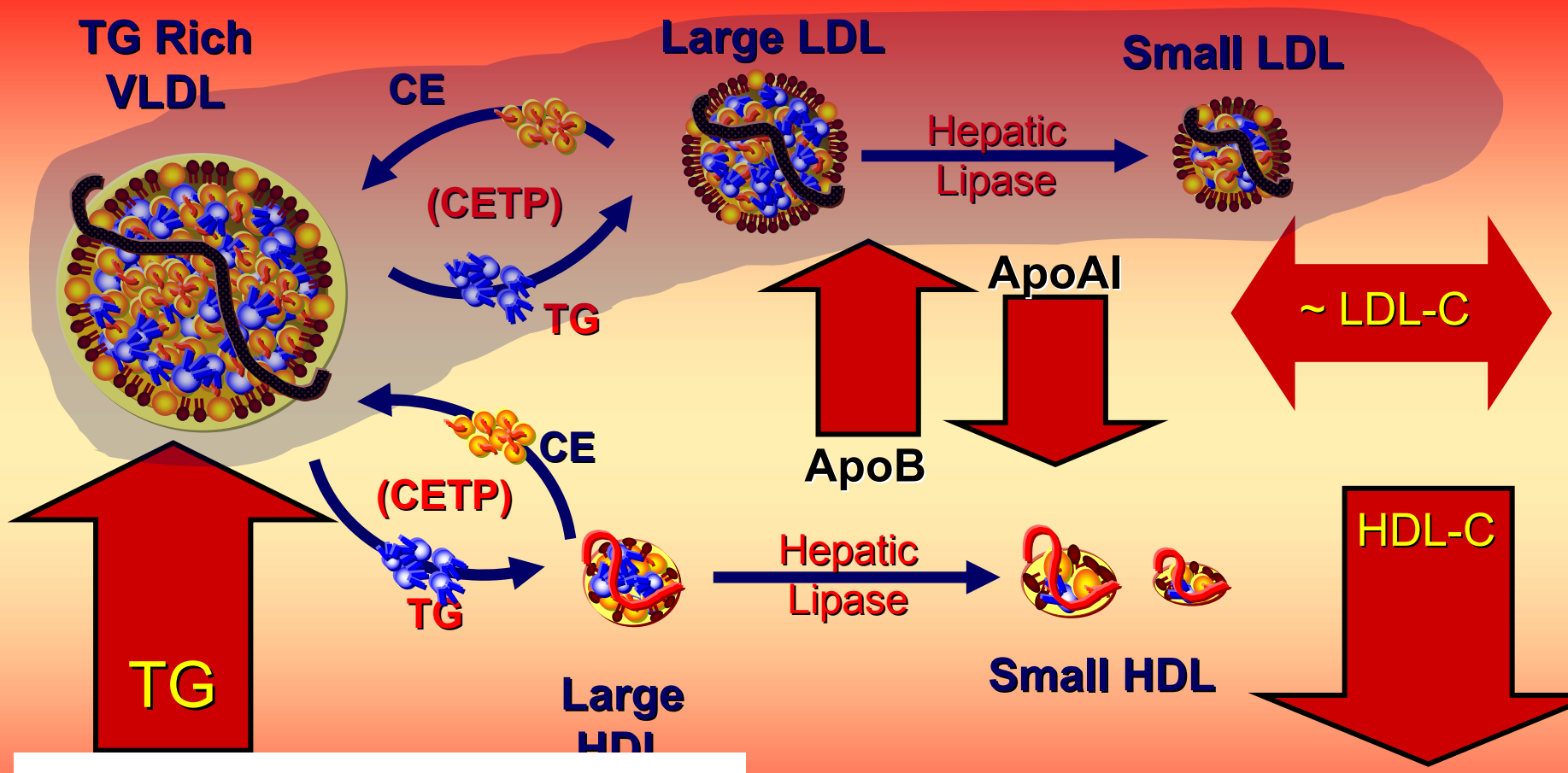
TG/HDL Axis disorders will lack HDL particles (↓ HDL-P or apoAI)

Of those HDLs that remain the predominant species will be small

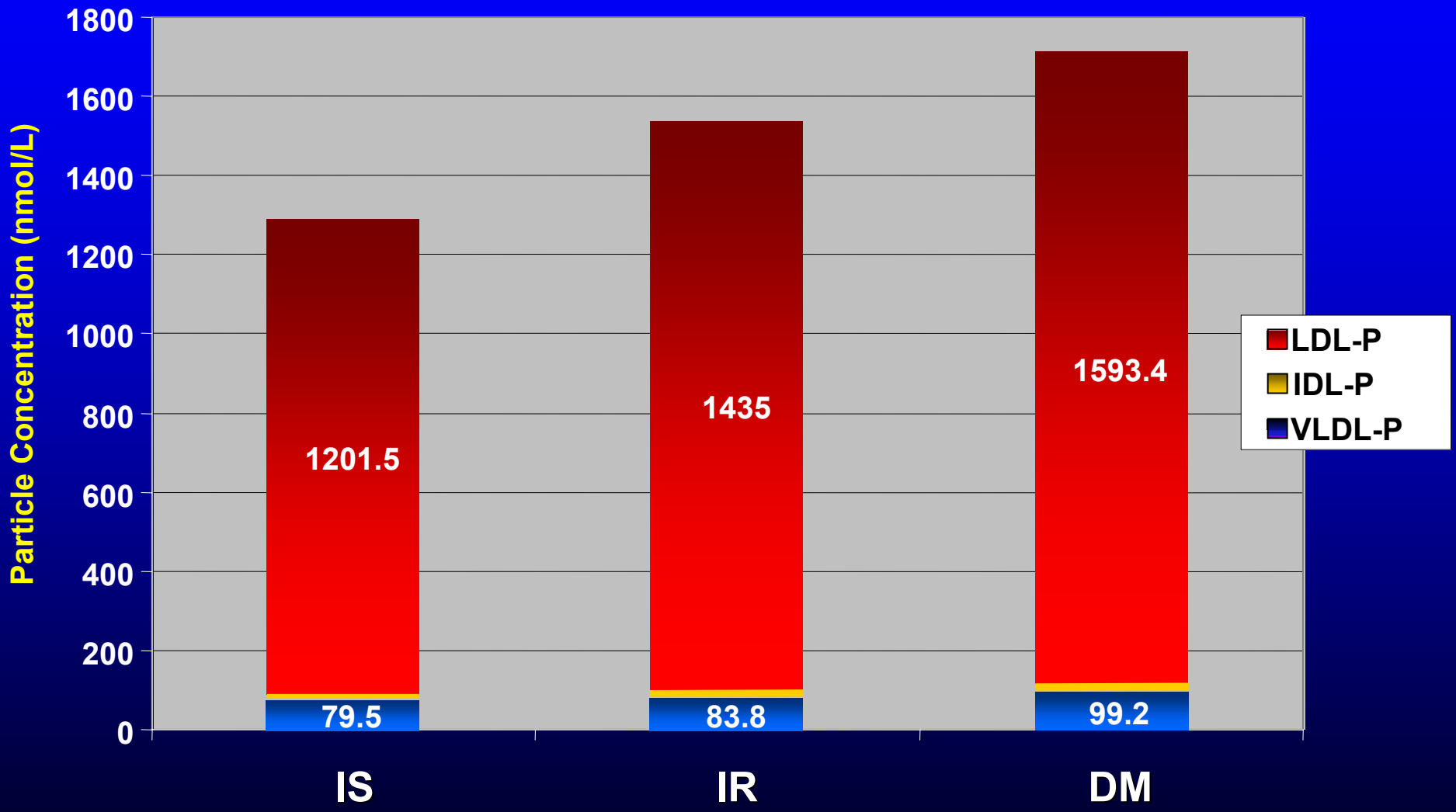
The apoB or LDL-P will be elevated



Lipoprotein Abnormalities of Type 2 Diabetes

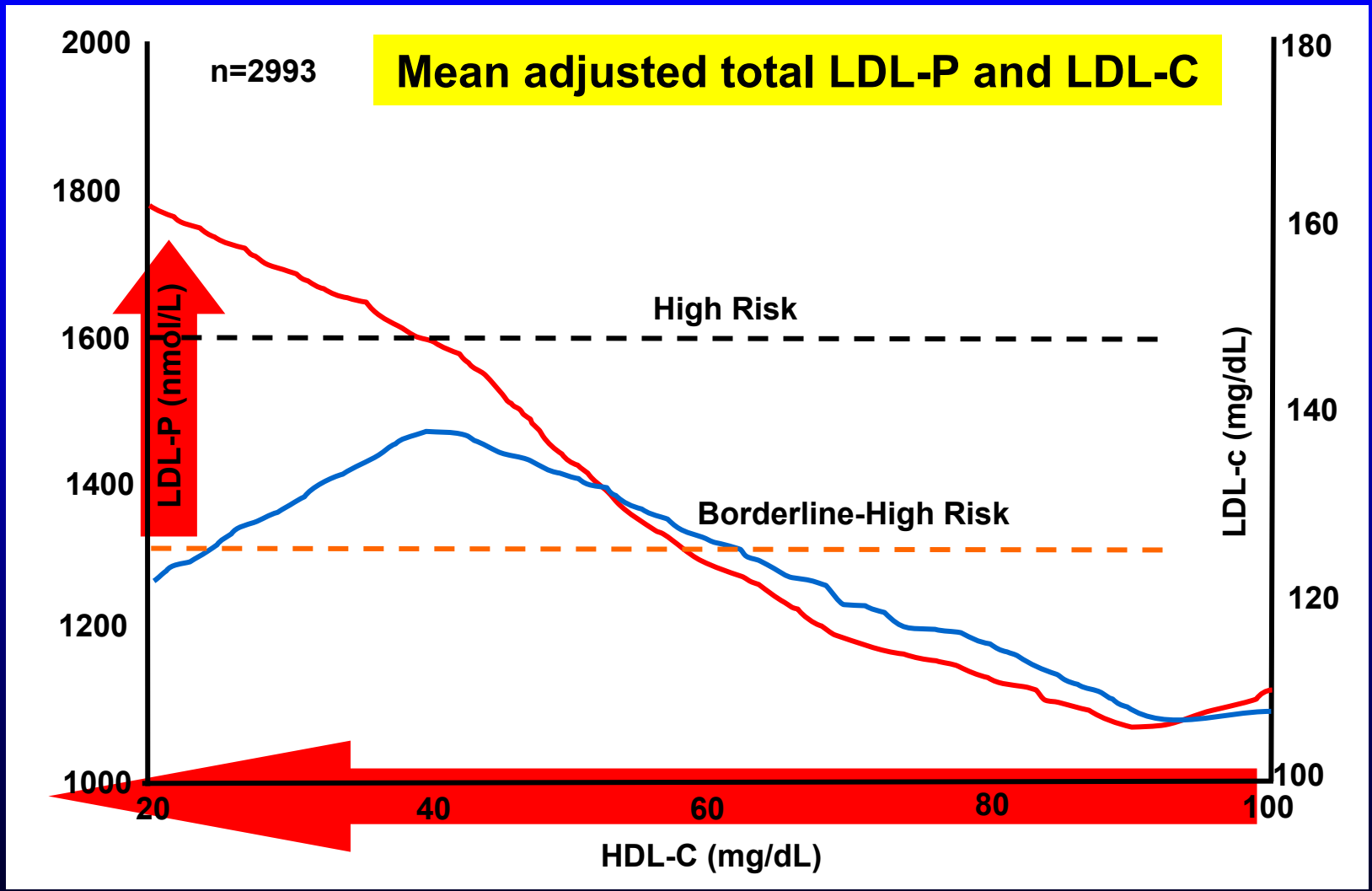


NMR Lipoprotein Particle Concentrations In IS, IR, and Type 2 Diabetic Subjects



Garvey et al. *Diabetes* 2003;52(2):453-462

Framingham Offspring Study
LDL-P and Metabolic Syndrome



Kathiresan S, Otvos JD, Sullivan LM et al. *Circulation*. 2006;113:20-29.

National Cholesterol Education Program

Adult Treatment Panel III NCEP-ATP III

Treatment of Triglycerides

What is the NCEP ATP III **goal for TG therapy,** if baseline TG is 200-500 mg/dL?

Elevated TG is simply a surrogate of apoB or LDL-P

NCEP JAMA 2001;285:2486 Final Report Circulation 2002;106:3143-3421

National Cholesterol Education Program

Adult Treatment Panel III NCEP-ATP III

Treatment of Triglycerides

What is the NCEP ATP III **goal for TG therapy,** if baseline TG is 200-500 mg/dL?

1) Normalize LDL-C

2) Normalize the non HDL-C value

↓ **ApoB**

NCEP JAMA 2001;285:2486 Final Report Circulation 2002;106:3143-3421

The LipoScience Story

Particles

LDL Particle Numbers

	nmol/L	Optimal	Near or above optimal	Borderline High	High	Very High
LDL-P (LDL Particle Number)	**1654**	under 1000	Under 1300	1300 - 1599	1600 - 2000	Over 2000

	nmol/L	Low	Moderate	Borderline High	High
Small LDL-P	**1354**	under 1000	Under 1300	1300 - 1599	1600 - 2000

Patient Goals:

High Risk Patients:

- primary goal: LDL-P < 1000 nmol/L
- secondary goal: small LDL particle number < 850 nmol/L

Moderately High Risk Patients:

- primary goal: LDL-P < 1300 nmol/L
- secondary goal: small LDL particle number < 850 nmol/L

Metabolic Syndrome Markers

These markers increase the risk of developing Type 2 diabetes mellitus

		Large (Pattern) A	Small (Pattern) A
LDL particle size	**19.1**	23.0 – 20.6	20.5 – 18.0

		Low Risk	Intermediate	High Risk
Large HDL-P	**3.1**	> 9.0	4.0-9	< 4.0

		Low Risk	Intermediate	High Risk
Large VLDL-P	**6.1**	> 0.5	0.5 – 5.0	> 5.0

Small LDL size (≤ 20.5 nm) ✓

Low Large HDL-P (< 4.0 umol/L) ✓

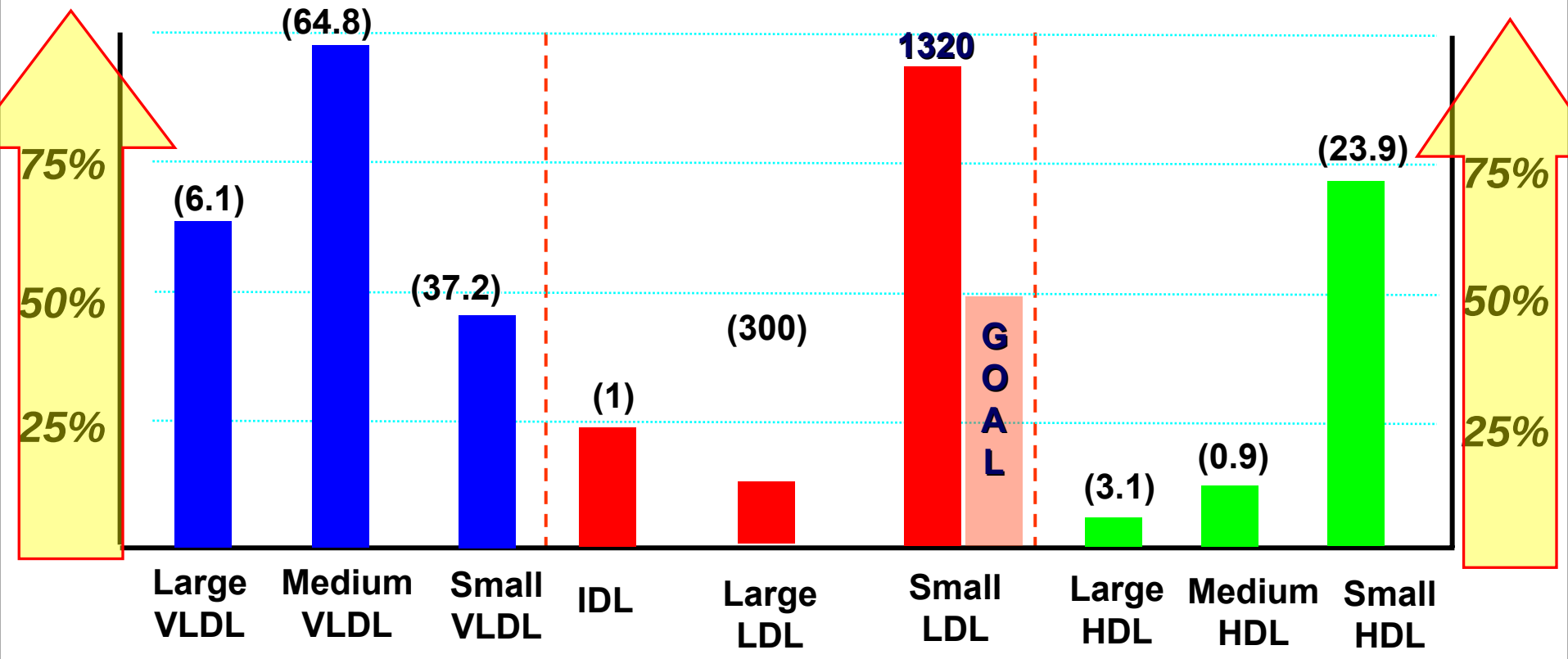
High Large VLDL-P (> 5.0 nmol/L) ✓

SUBCLASS LEVELS

VLDL Subclasses
Low values are Desirable
(especially large VLDL)

LDL Subclasses
Low Values are Desirable
(especially small LDL)

HDL Subclasses
High Values are Desirable
(especially large HDL)



LP subclass particle numbers are given in parentheses above each bar. The height of the bar is the percentile indicating if the value is "high" or "low" based on a reference population consisting of >6900 subjects enrolled in the Multi-Ethnic Study of Atherosclerosis (MESA)

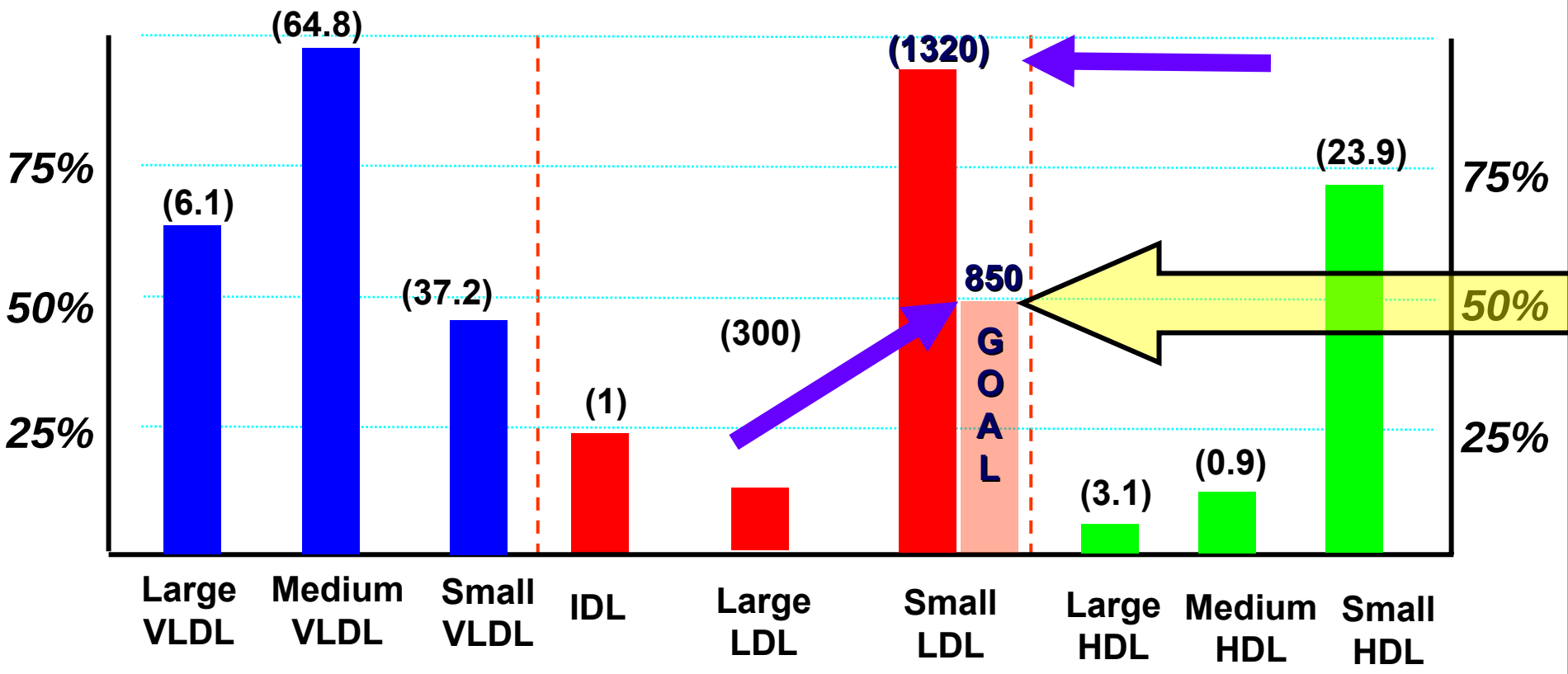
The concentration of small LDL particles (in nmol/L) is given in parentheses above the percentile bar. The suggested treatment goal for the high-risk and moderately high-risk patients is < 850 nmol/L (<50th percentile)

SUBCLASS LEVELS

VLDL Subclasses
Low values are Desirable
(especially large VLDL)

LDL Subclasses
Low Values are Desirable
(especially small LDL)

HDL Subclasses
High Values are Desirable
(especially large HDL)



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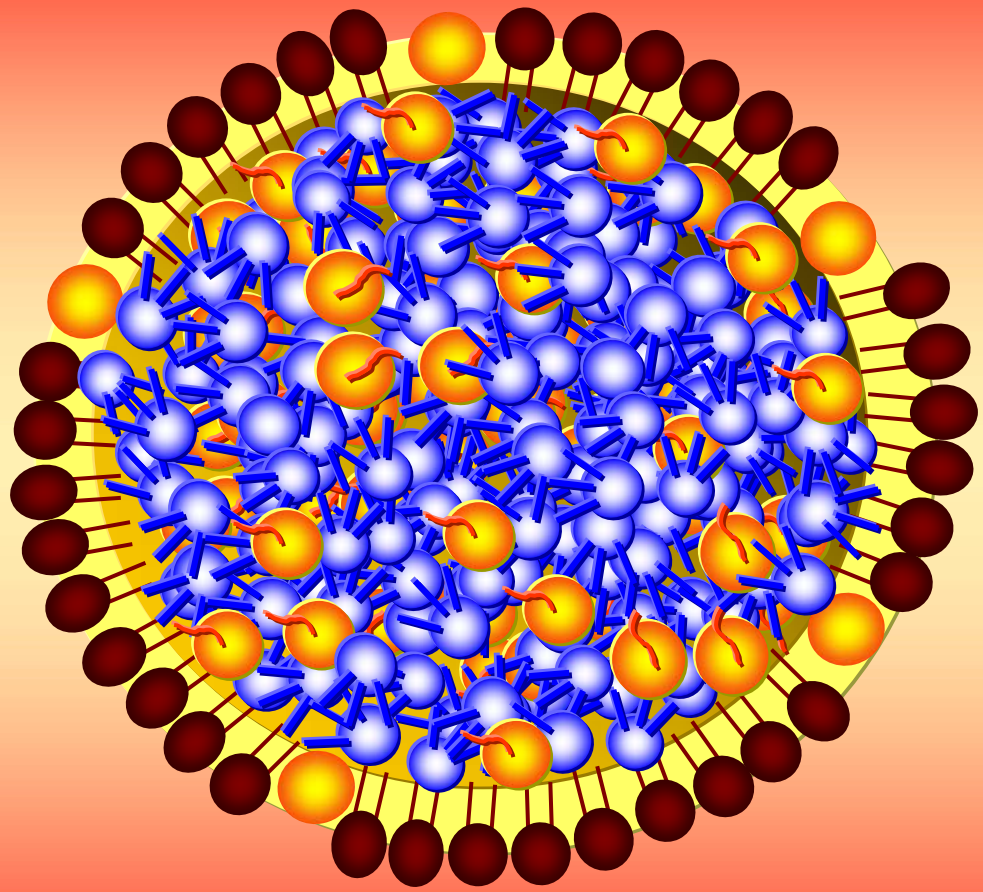
The apoB Story

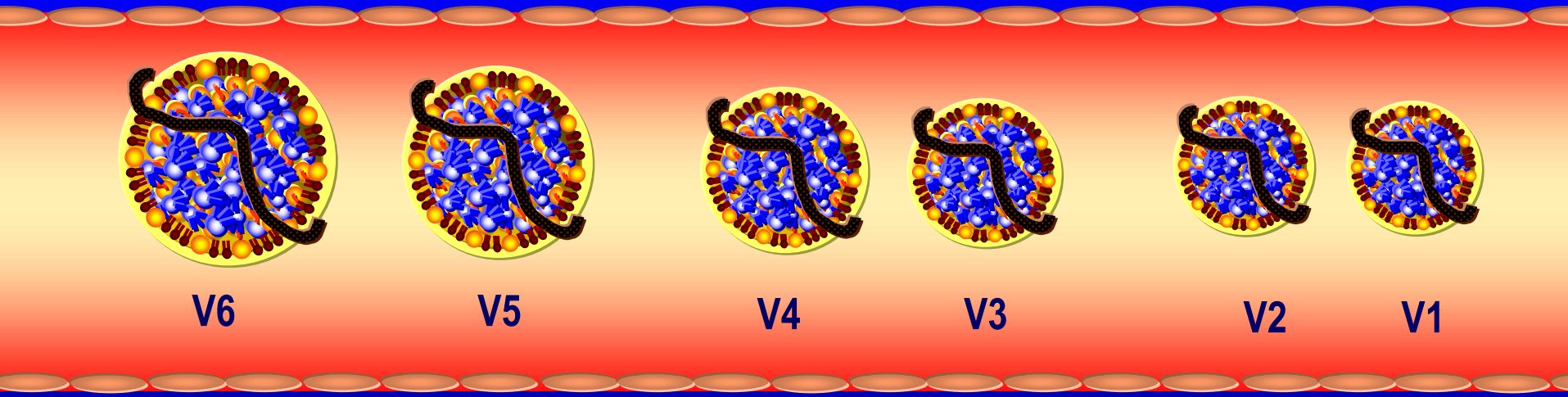
VLDL

Very Low Density Lipoprotein (VLDL)



- The primary TG transporting lipoprotein
- Size, depending on TG content varies from 350 Å (35 nm) to 700 Å (70 nm)
- Normal particle composition is 80% TG and 20% cholesterol **(or a 5 to 1 ratio)**
- VLDL-C ~ TG/5

VLDL Size or Subclass



Nuclear Magnetic Resonance Spectroscopy

6 particles: (V6, V5 largest ------ V1 smallest)

Using the NMR LipoProfile

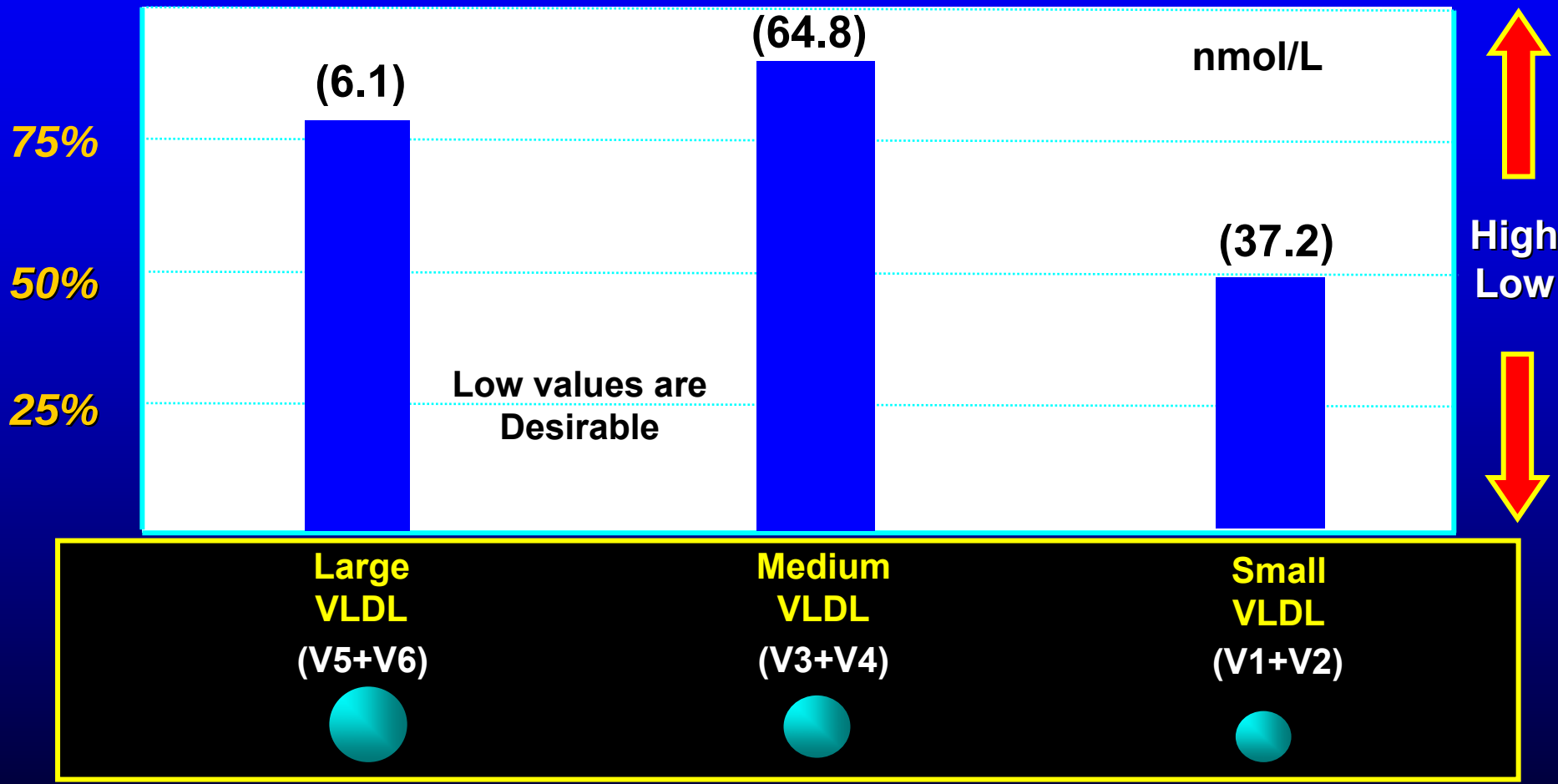
Large VLDL-P (Large VLDL Particle Number)

- Large VLDL subclass particles in nanomoles per liter

< 0.5	0.5 – 5.0	> 5.0
Low Risk	Intermediate	High Risk
< 25th Percentile		> 75th Percentile

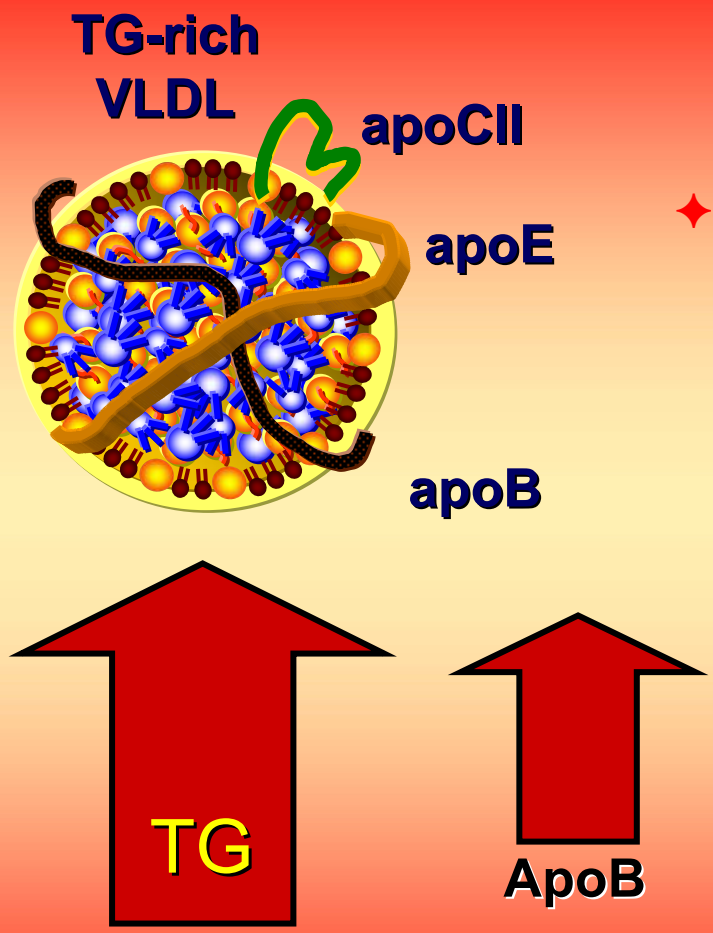
Using the NMR LipoProfile

VLDL Subclasses



LP subclass particle concentrations re given in parentheses above each bar. The height of the bar is the percentile indicating if the value is “high” or “low” based on a reference population consisting of >6900 subjects in Multi-Ethnic Study of Atherosclerosis (MESA)

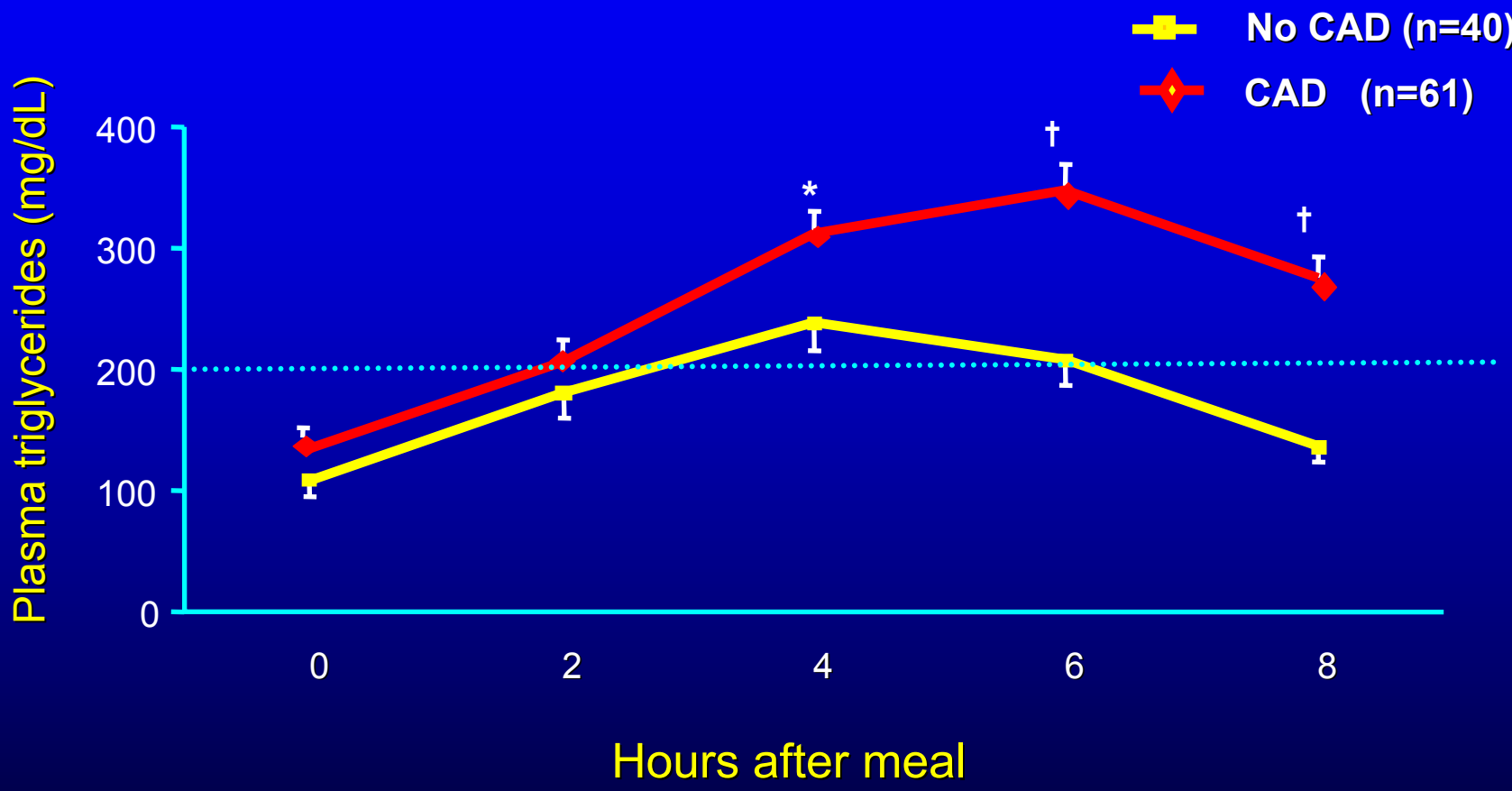
Rheological Abnormalities in TG/HDL Axis Disorders



- **Increased hepatic production of large TG-rich VLDL particles is also associated with**
  - **Increased blood viscosity**
  - **Decreased arterial flow-mediated dilation (endothelial dysfunction)**
  - **Increased hypercoagulability**

Triglyceride Cholesteryl ester

Postprandial Triglyceride Levels
in Subjects With and Without Coronary Artery Disease



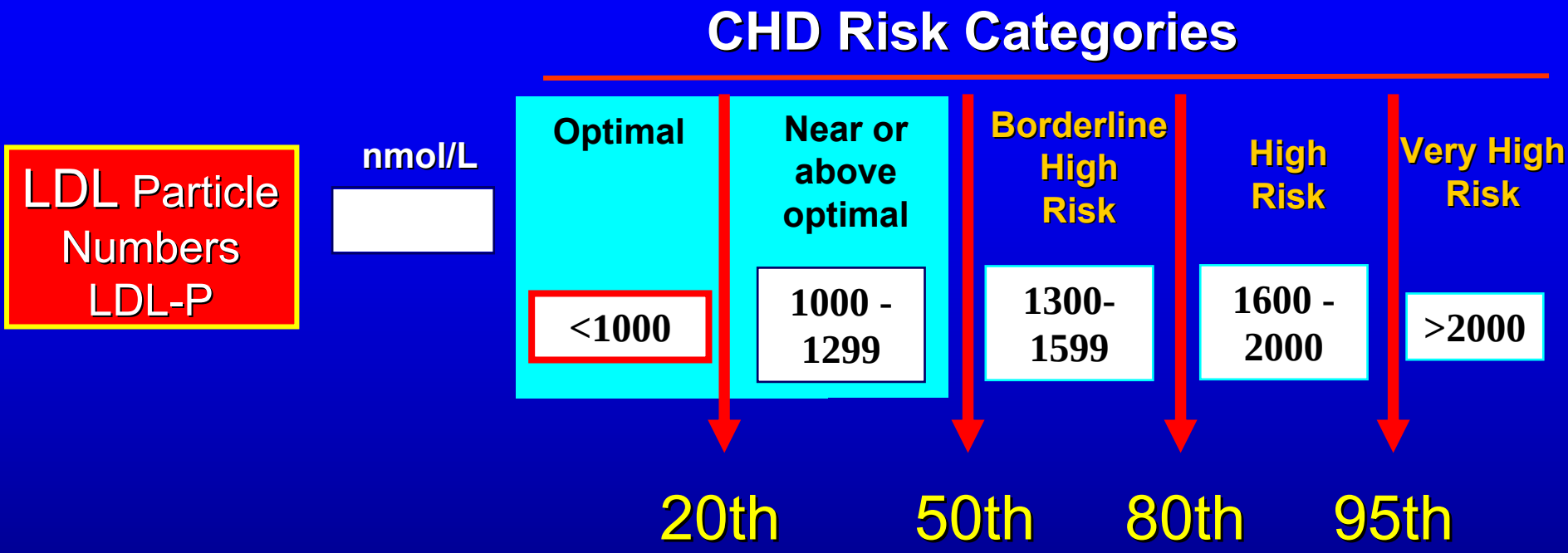
*P=0.025; †$P \leq 0.001$.

Patsch JR et al. *Arterioscler Thromb*. 1992;12:1336-1345.

The apoB Story

LDL

Using NMR LipoProfile

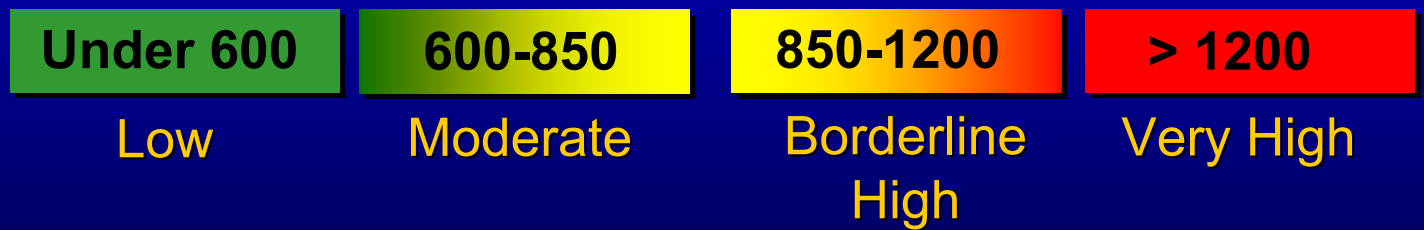


Risk categories for LDL particles correspond to NCEP risk categories for LDL-C
(20^{th}, 50^{th}, 80^{th}, & 95^{th} percentile cut points)

Using the NMR LipoProfile

Small LDL-P (Small LDL Particle Number)

- The total number of small LDL particles in nanomoles per liter is a significant source of CHD risk in many metabolic syndrome and diabetic patients
  - The treatment goal for small LDL-P is < 850 nmol/L (50^{th} percentile)



Quantitating LDL Particles

LDL-P (LDL Particle Number)

- The total number of LDL particles in nanomoles per liter
  - 1 nmol/L = 6 X 10^{14} particles/L.
  - 600,000,000,000,000 (six hundred trillion)
  - Thus with an ideal LDL-P of 1000 nmol/L there would be
    - 600,000,000,000,000,000 (six hundred quadrillion) per liter
  - In 5 liters of plasma there would be
    - 3,000,000,000,000,000,000 (3 quintillion LDL particles)

Under 1000	1000-1299	1300-1599	1600-2000	> 2000
Optimal	Near Optimal	Borderline High	High	Very High

www.lipoprofile.com

LDL Particle Subclass (NMR*)

LDL Particle Numbers

	nmol/L	Optimal	Near or above optimal	Borderline High	High	Very High
LDL-P (LDL Particle Number)	**1654**	under 1000	Under 1300	1300 - 1599	1600 - 2000	Over 2000

	nmol/L	Low	Moderate	Borderline High	High
Small LDL-P	**1354**	< 600	600-849	850-1200	> 1200

Patient Goals:

High Risk Patients:

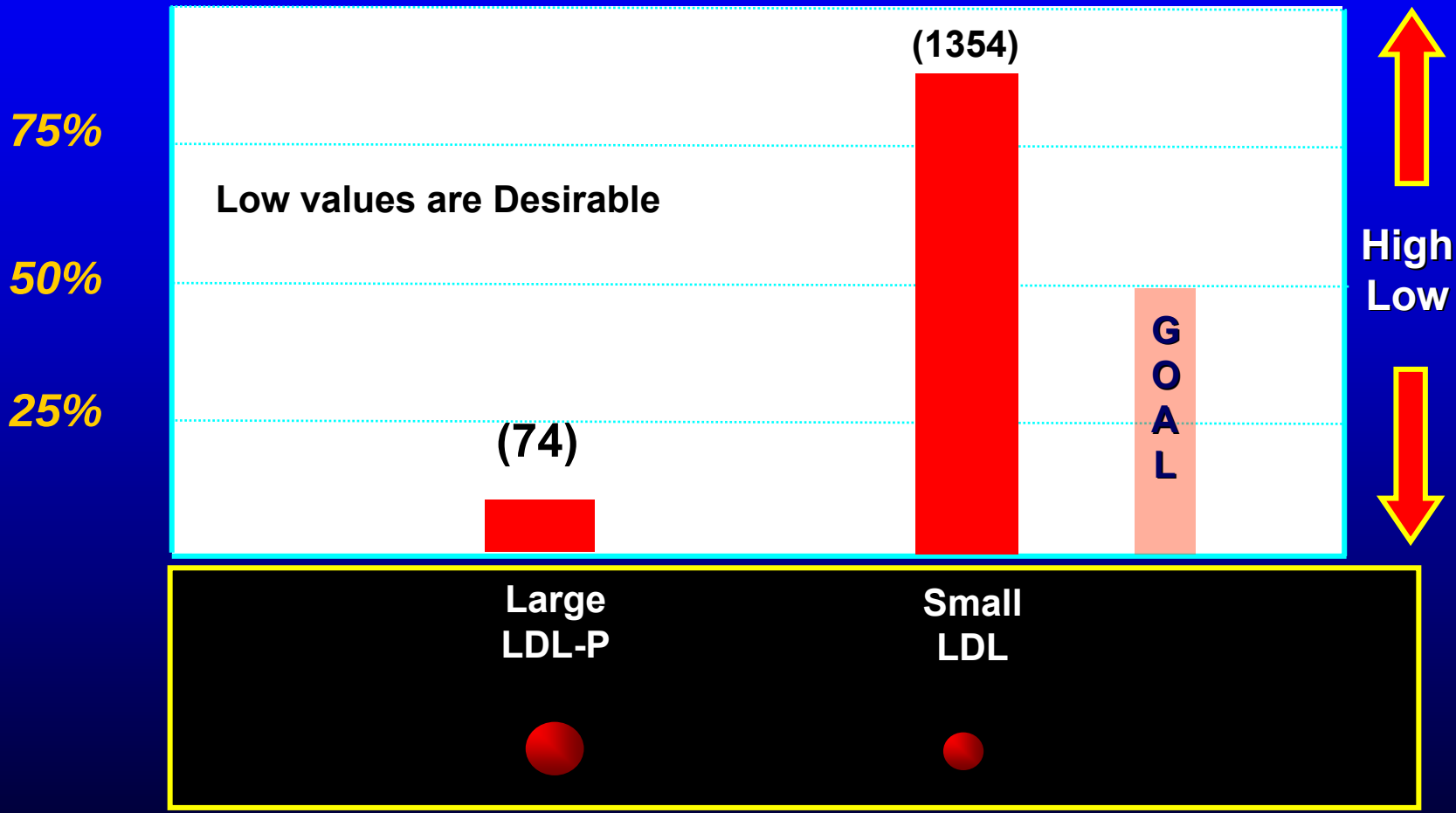
- primary goal: LDL-P < 1000 nmol/L
- secondary goal: small LDL particle number < 850 nmol/L

Moderately High Risk Patients:

- primary goal: LDL-P < 1300 nmol/L
- secondary goal: small LDL particle number < 850 nmol/L

Using the NMR LipoProfile

LDL Subclasses



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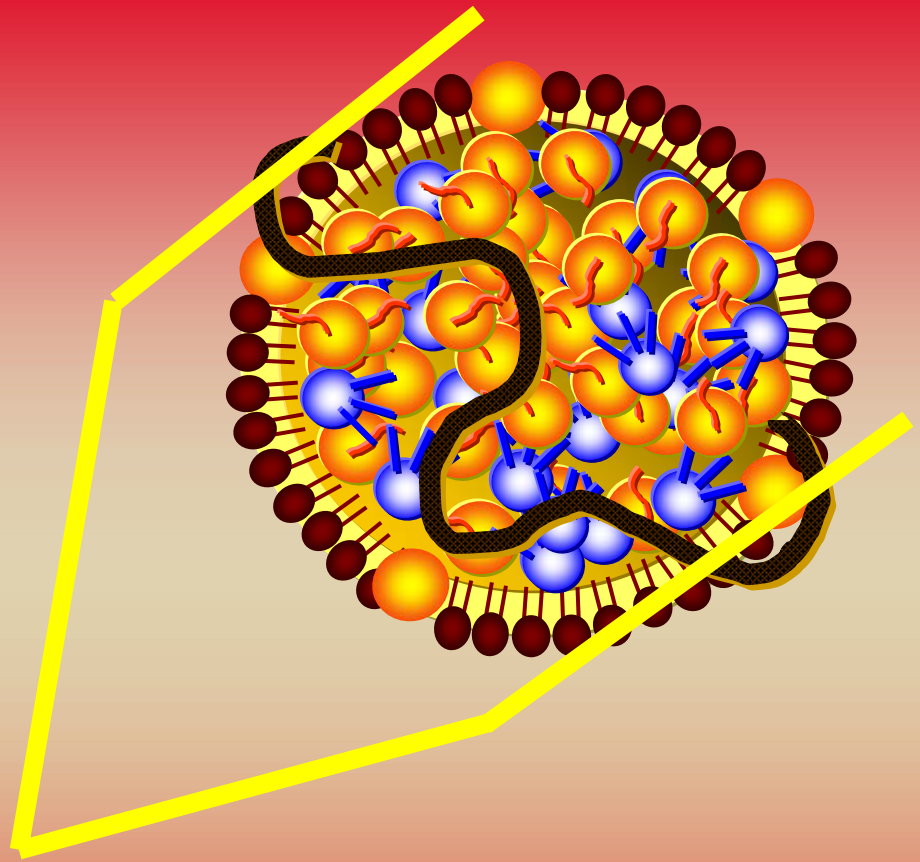
LDL Particle Size



LDL Particle Size

Does size make an LDL particle Atherogenic?

Using the NMR LipoProfile

LDL Particle Size

- Average diameter (nm) of the patient's LDL particles.
- A predominance of small LDL particles is associated with metabolic syndrome and insulin resistance

23.0 – 20.6	20.5 – 18.0
Large (Pattern A)	Small (Pattern B)

LDL Sizes are referenced to those measured by electron microscopy and are 5 nm smaller than gradient gel electrophoresis estimates

LDL-C Often Fails to Reflect the Number of LDL Particles (LDL-P)

- LDL particles can be large or small, and the amount of cholesterol and triglycerides contained within these particles varies widely.

It takes 40-70% more of smaller LDL particles compared to large to carry X amount of cholesterol

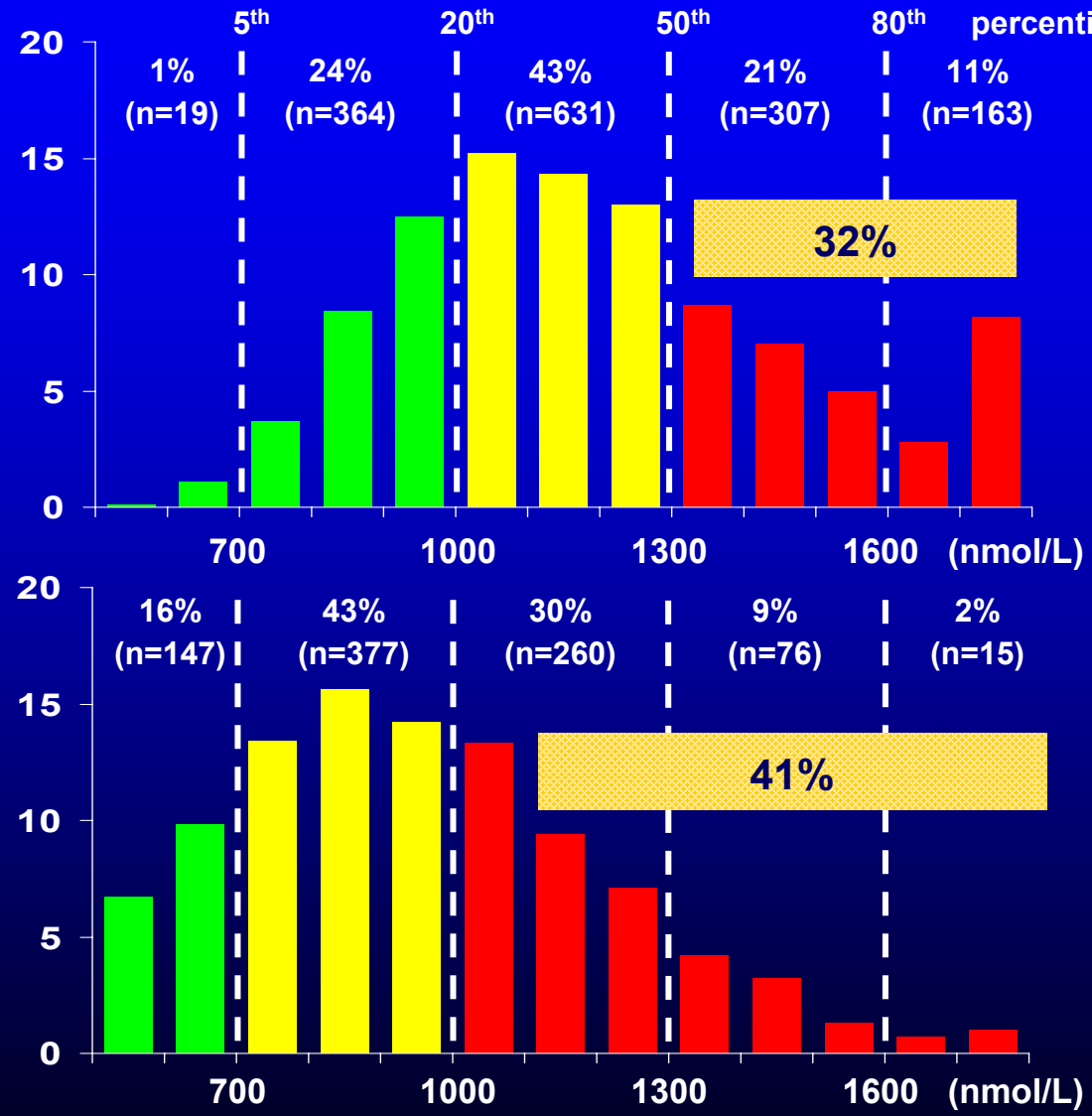
LDL-C = whatever (mg/dL)

LDL-P = X | LDL-P = 2X | LDL-P = 3X | LDL-P = 6X | LDL-P = 12X

LDL-P in nmol/L

Otvos JD, Jayarajah E, Cromwell, WC. *AJC* 2002;90(8A):22i-29i

LDL Particle Number Distribution in T2DM Subjects



LDL-C
71-99 mg/dL
(n=1,484)

LDL-C
≤ 70 mg/dL
(n=871)

AHA Scientific Sessions, 2005

Multi-Ethnic Study of Atherosclerosis (MESA)

- Previous studies have shown that individuals with predominantly small LDL particles (pattern B) have greater cardiovascular risk than those with predominantly large LDL (pattern A).
- However, these studies examined only the distribution of LDL subclasses or LDL size phenotype (large or small) rather than particle concentrations of LDL subclasses.
- Thus, they did not adequately control for the inverse correlation between small and large LDL particle concentrations (LDL-p) and potential confounding due to their differing associations with other lipoproteins, lipids, and traditional cardiovascular risk factors

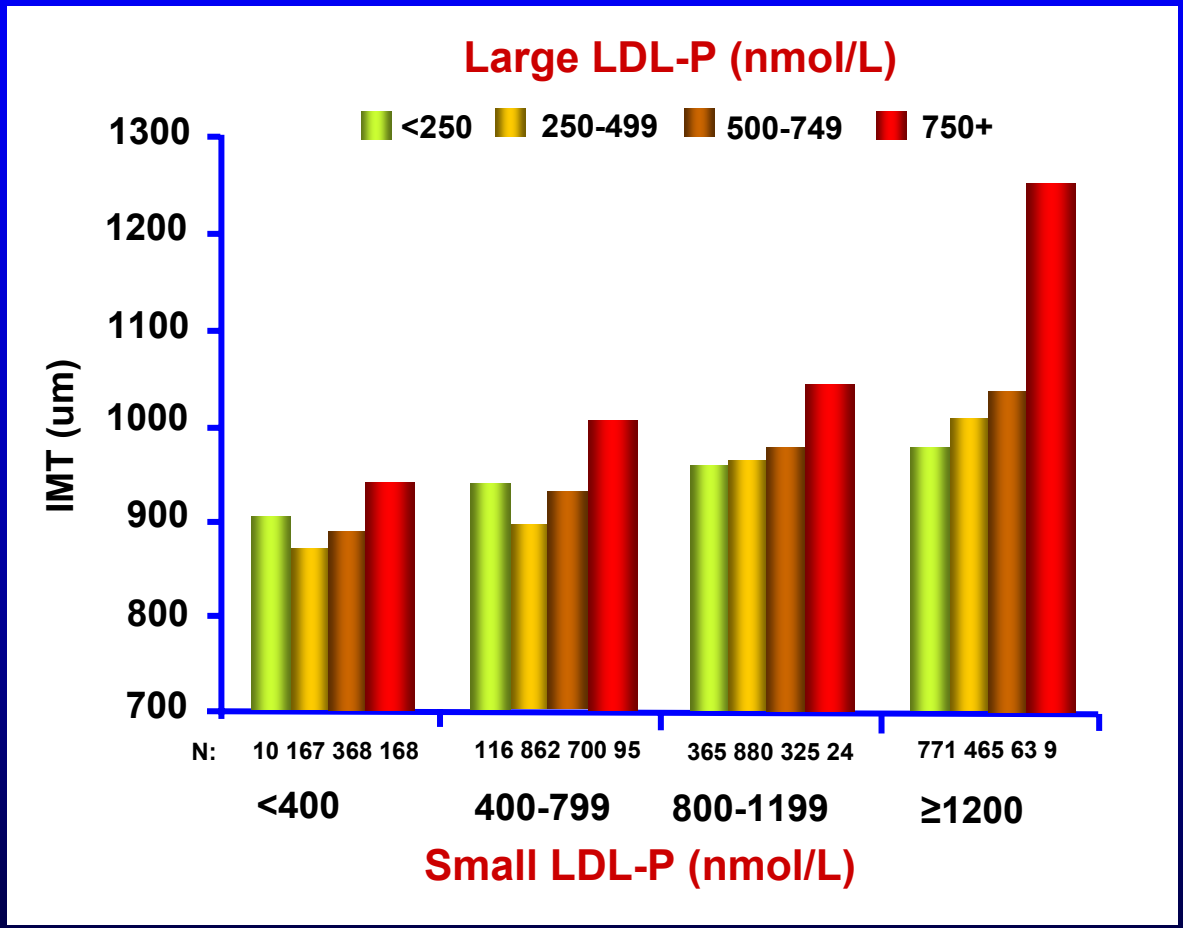
Mora S, Szklo S, Otvos JD et al. Atherosclerosis 2006;

Multi-Ethnic Study of Atherosclerosis (MESA)

- Contrary to current opinion, both small and large LDL were significantly associated with subclinical atherosclerosis independent of each other, traditional lipids, and established risk factors, with **no association between LDL size and atherosclerosis** after accounting for the concentrations of the two subclasses.

Mora S, Szklo S, Otvos JD et al. Atherosclerosis 2006;

Multi-Ethnic Study of Atherosclerosis (MESA)



Mean IMT (*y*-axis) for increasing levels of large LDL particle concentration

(LDL-p) are shown across increasing levels of small LDL-p.

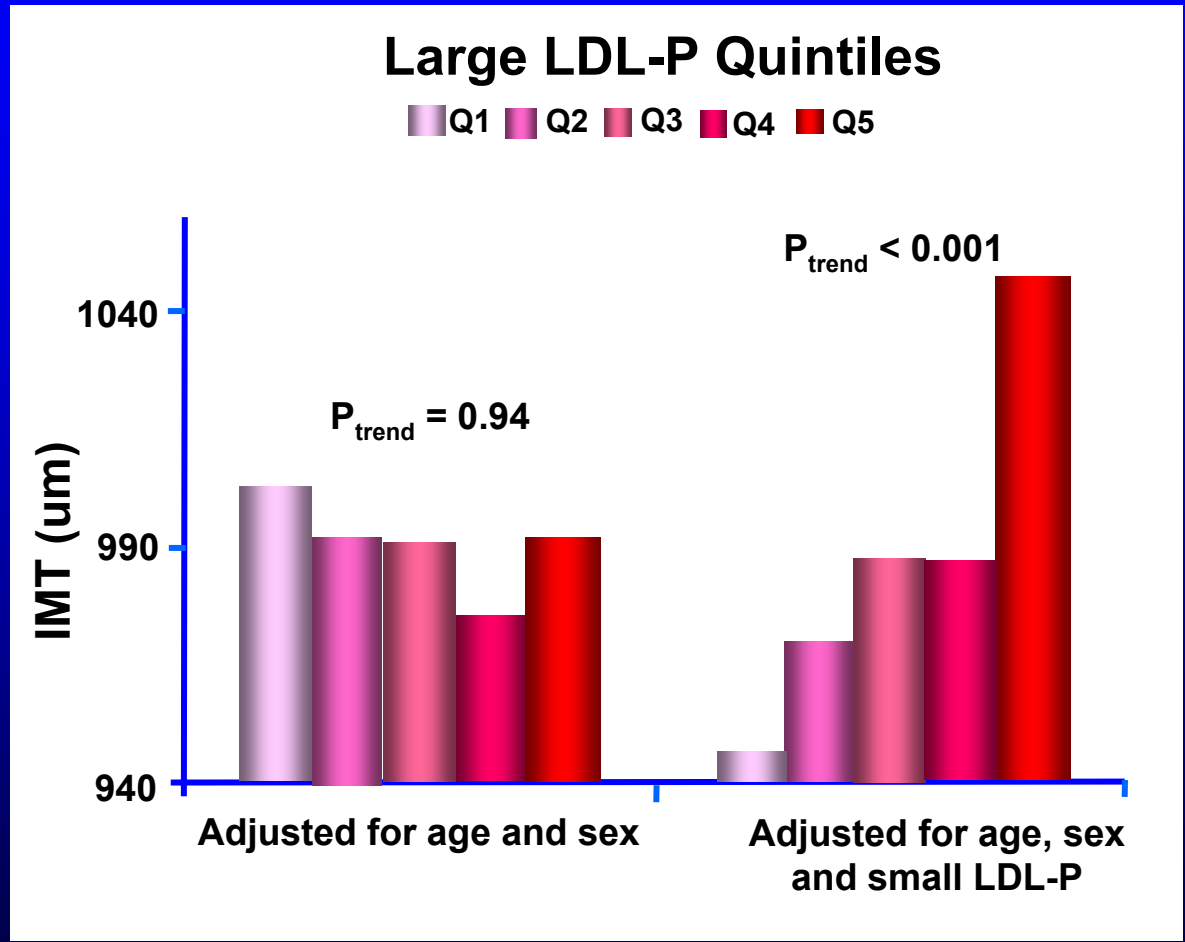
Increasing concentrations of large LDL were positively associated with carotid IMT within any category of small LDL-p

Mora S, Szklo S, Otvos JD et al. Atherosclerosis 2006;

Multi-Ethnic Study of Atherosclerosis (MESA)

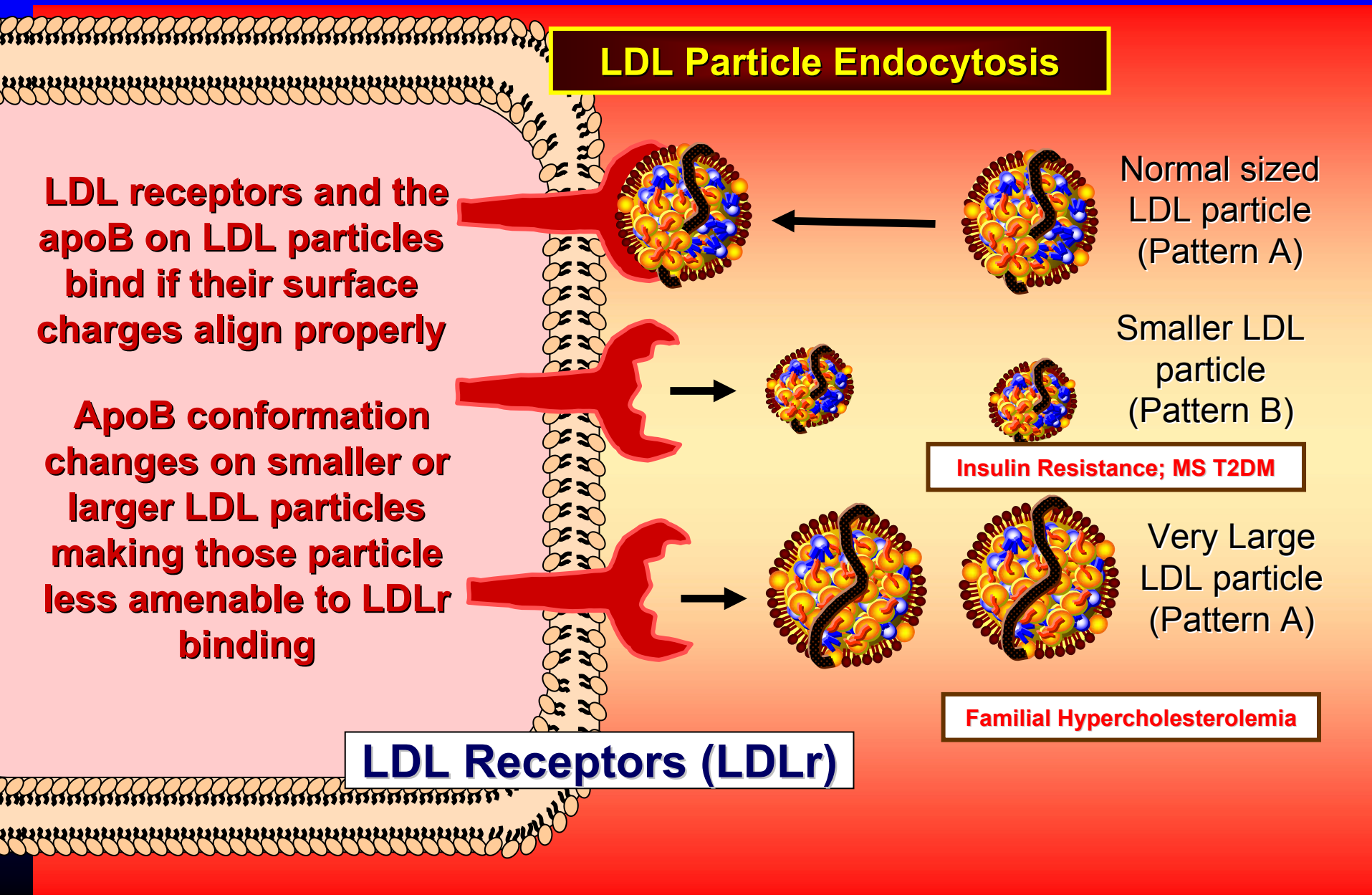
When adjusted for age & sex but not small LDL-P, there was no association between large LDL-P and IMT

After adjusting for small LDL-P there was significant association between large LDL-P & IMT



Mora S, Szklo S, Otvos JD et al. Atherosclerosis 2006;

LDL Receptor & LDL Particles

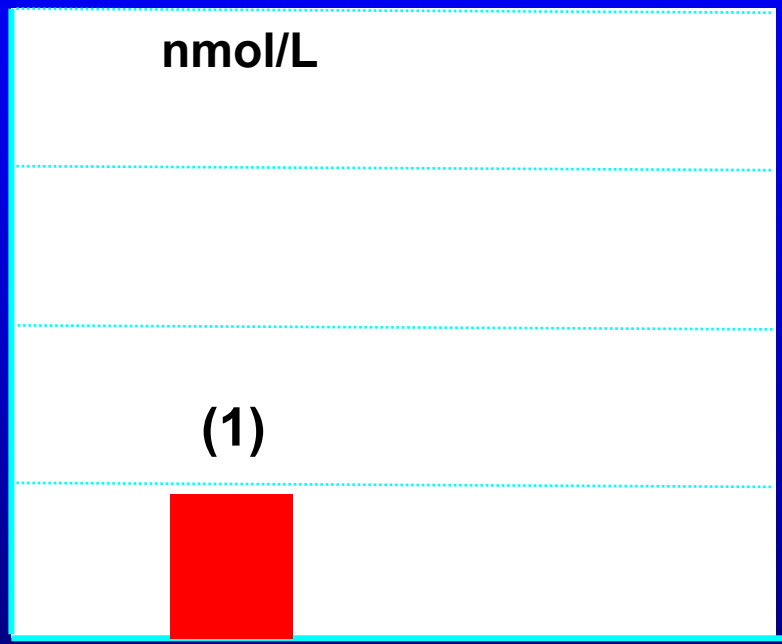


The apoB Story

IDL

Using the NMR LipoProfile

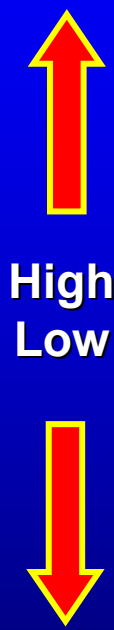
IDL

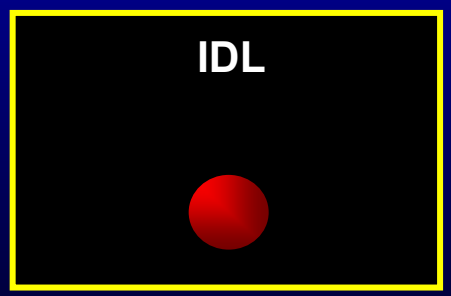


Low values are Desirable

If present in increased numbers IDL particles are very atherogenic particles

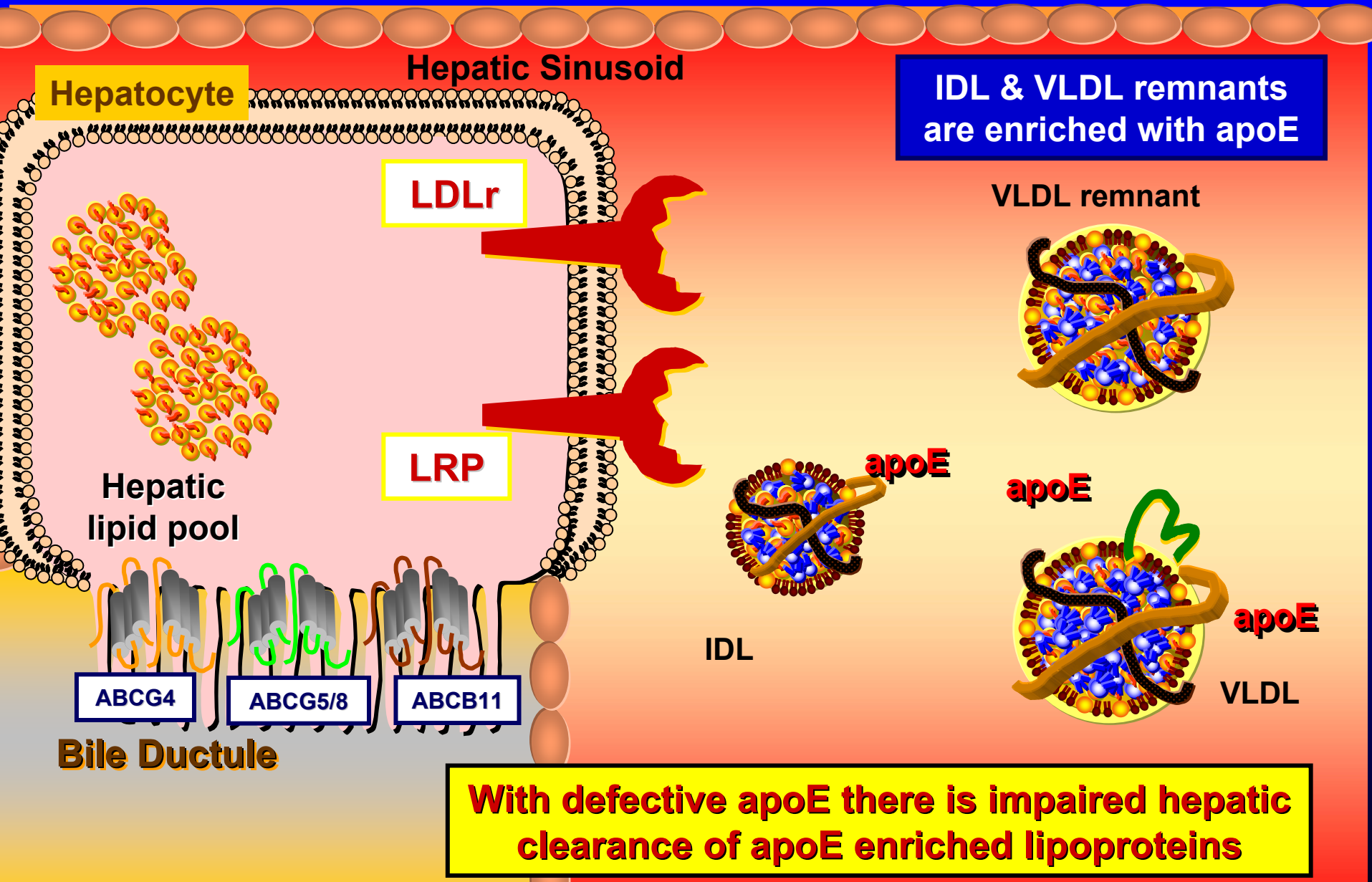
Very high IDL is typical of Fredrickson's Type III Hyperlipidemia





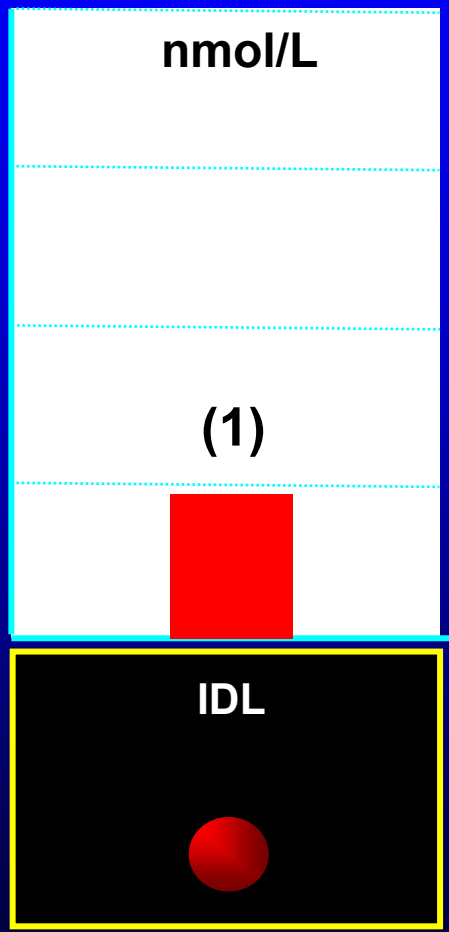
LP subclass particle concentrations re given in parentheses above each bar. The height of the bar is the percentile indicating if the value is "high" or "low" based on a reference population consisting of >6900 subjects in Multi-Ethnic Study of Atherosclerosis (MESA)

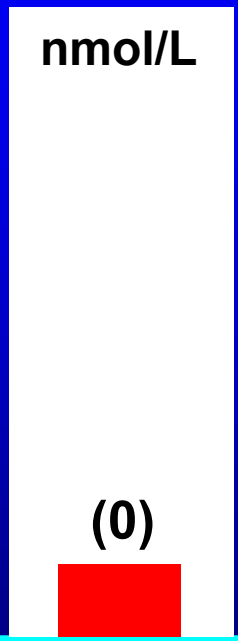
Type III Dyslipoproteinemia



Using the NMR LipoProfile

IDL





75%

50%

25%

Low values are Desirable

If present in increased numbers IDL particles are very atherogenic particles

Very high IDL is typical of Fredrickson's Type III Hyperlipidemia

High
Low

Is it possible to have an IDL of zero?

Yes: they have very short half lives and are post-prandial lipoproteins

LP subclass particle concentrations re given in parentheses above each bar. The height of the bar is the percentile indicating if the value is "high" or "low" based on a reference population consisting of >6900 subjects in Multi-Ethnic Study of Atherosclerosis (MESA)

The HDL Particle Story

Using the NMR LipoProfile

Large HDL-P (Large HDL Particle Number)

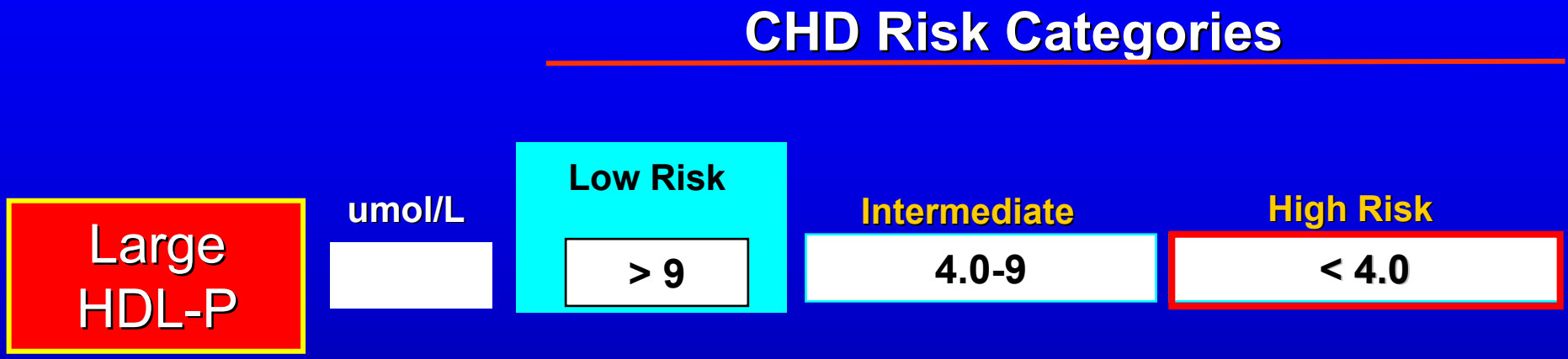
- Large HDL subclass particles in micromoles per liter
  - 1 umol/L = 6 X 10^{17} particles/L
  - 600,000,000,000,000,000 (600 quadrillion)

>9.0	9.0 – 4.0	< 4.0
Low Risk	Intermediate	High Risk
> 75th Percentile		< 25th Percentile

Drug Naive patients

www.lipoprofile.com

Using the NMR LipoProfile

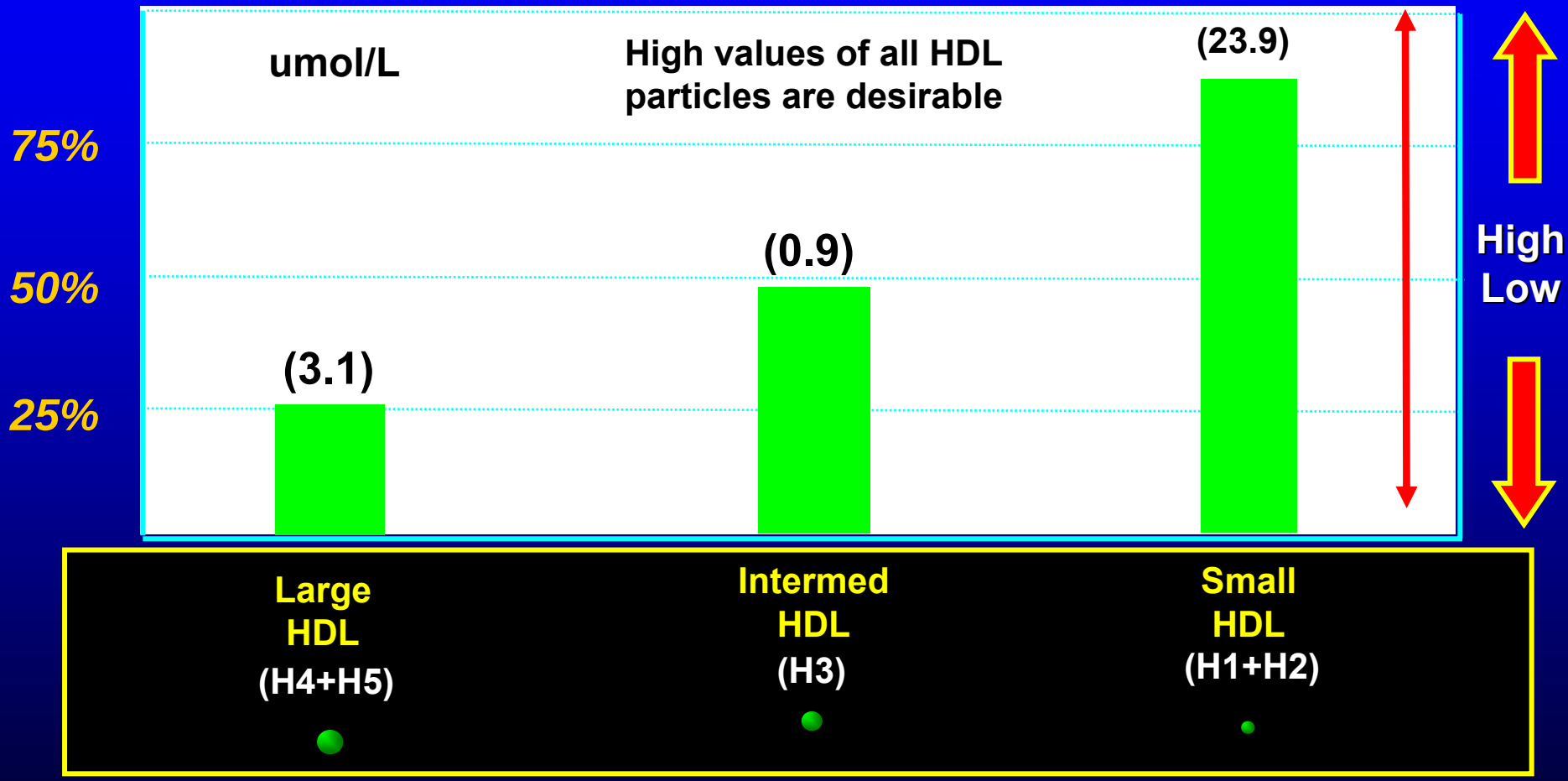


In drug naive patients, large HDL is associated with less risk

Levels < 4.0 umol/L (30th percentile) indicate higher risk and > 9 umol/L (75th percentile) lower risk

Using the NMR LipoProfile

HDL Subclasses



LP subclass particle concentrations re given in parentheses above each bar. The height of the bar is the percentile indicating if the value is “high” or “low” based on a reference population consisting of >6900 subjects in Multi-Ethnic Study of Atherosclerosis (MESA)

National Cholesterol Education Program

Adult Treatment Panel III NCEP-ATP III

Treatment of Low HDL-C

- **Low HDL-C: is defined as <40 mg/dL**
  No specific goal defined for raising HDL-C

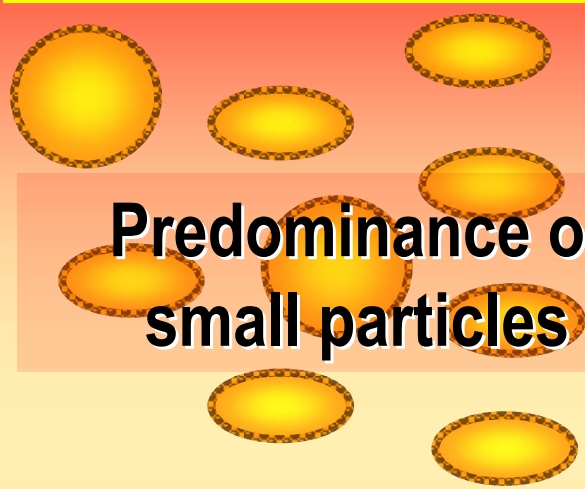
- Targets of therapy:
  - Normalize LDL-C in all
  - Those with TG 200–499 mg/dL: achieve **non–HDL-C goal** as secondary priority

↓ **ApoB**

JAMA 2001;285 :2331-2338

Drug Effect on HDL-C vs HDL-P

Patient on Fenofibrate



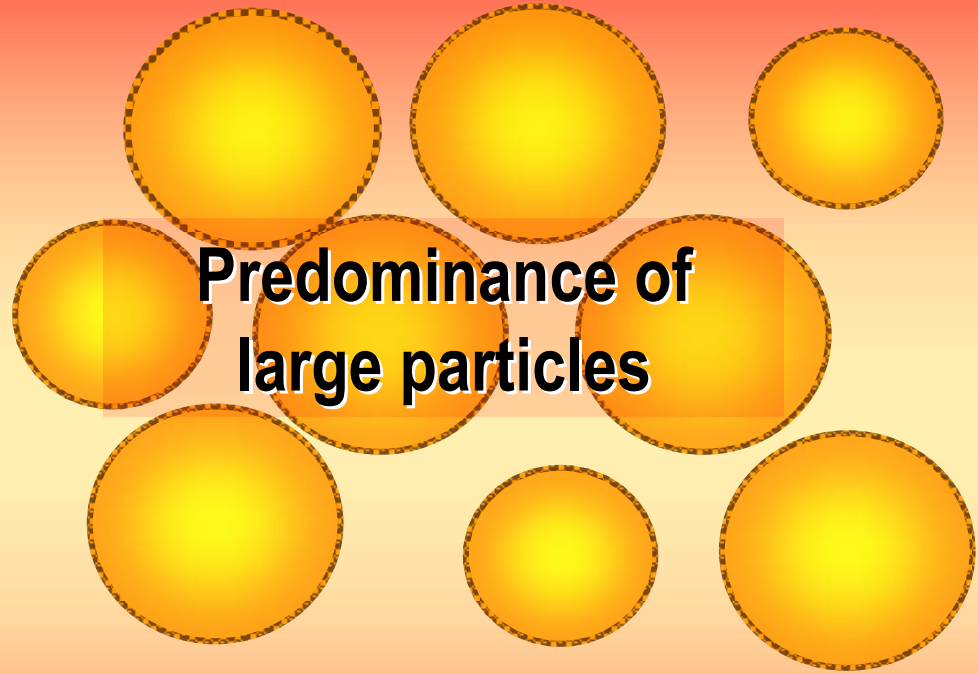
Predominance of small particles

HDL-P = X

HDL-C = Y

↑ Biliary Cholesterol

Patient on Niacin



Predominance of large particles

HDL-P = X

HDL-C > Y

Veterans Affairs HDL Intervention Trial (VA-HIT)

Explaining the Beneficial Effect of Gemfibrozil

Variable	Baseline (SD)	Change	P *
HDL Particles, μmol/L	25.1 (4.6)	+10%	<0.001
Large HDL, μmol/L	2.7 (1.7)	-15%	0.71
Small HDL, μmol/L	20.4 (5.2)	+21%	<0.001
Ave. HDL size, nm	8.5 (0.3)	-0.1 nm	0.68

Otvos J et al Circulation 2006:113 on line

Summary

Particles

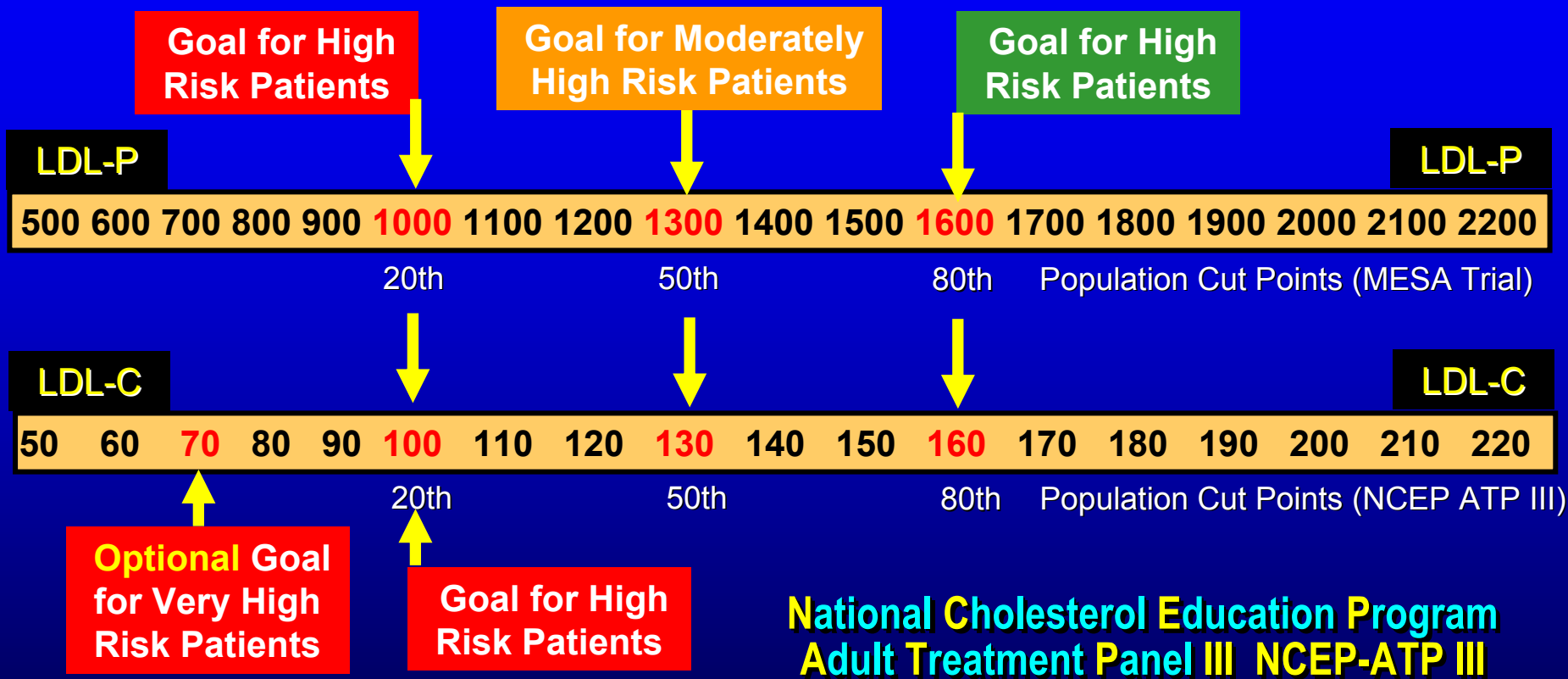
Lipoprotein Analysis

NMR LIPOPROFILE®

The NMR LipoProfile technology directly measures the lipoprotein particles responsible for coronary heart disease (CHD). The NMR LipoProfile test enhances clinical management of CHD risk by identifying patients whose true risk is higher or lower than assessed by cholesterol testing. Treatment of at-risk patients is improved by directing therapy to reduce overall numbers of LDL particles, the primary causal agents of atherosclerosis.

LipoProfile Panel: reports key lipoprotein risk factors not supplied in a lipid panel. Highlighted boxes indicate which CHD risk categories apply to the patient, guided by recommendations of the National Cholesterol Education Program (NCEP) and recent research results.

Using the NMR LipoProfile



National Cholesterol Education Program Adult Treatment Panel III NCEP-ATP III Goals of Therapy

LDL-C is used as a surrogate of apoB or LDL-P

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