

Low Density Lipoprotein (LDL) Biology & Pathobiology

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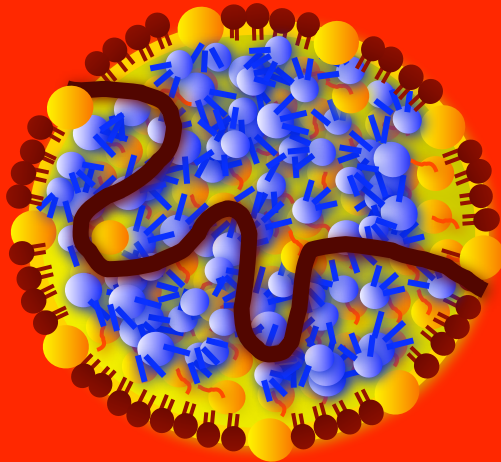
North Jersey Institute of Menopausal Lipidology

Wayne, New Jersey

Apolipoprotein B Lipoproteins

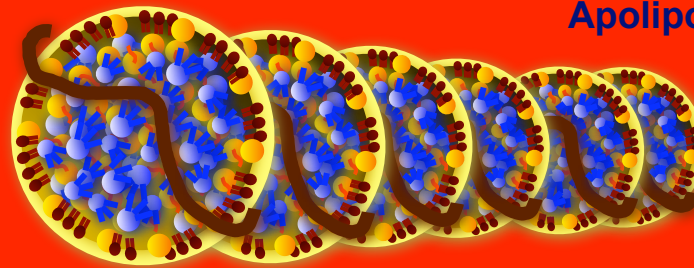
ApoB Lipoproteins

Apolipoprotein
B 48



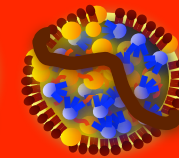
Chylomicron

Apolipoprotein B 100

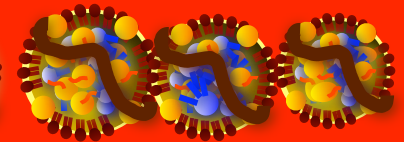


V6 V5 V4 V3 V2 V1

VLDL



IDL



L3 L2 L1

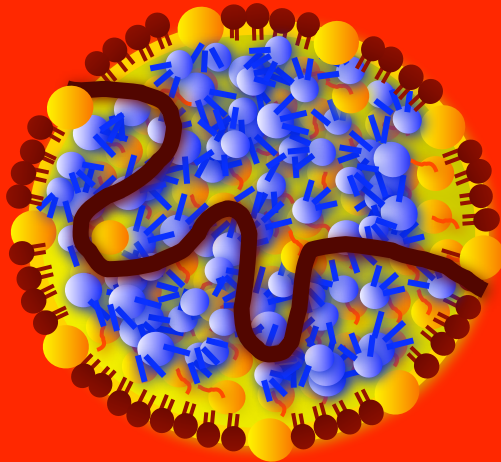
LDL

There is one molecule of apoB on each beta-lipoprotein particle. The apoB on a chylomicron is a truncated version (48% of the molecular weight) of the apoB on a lipoprotein of hepatic origin

Apolipoprotein B Lipoproteins

ApoB Lipoproteins

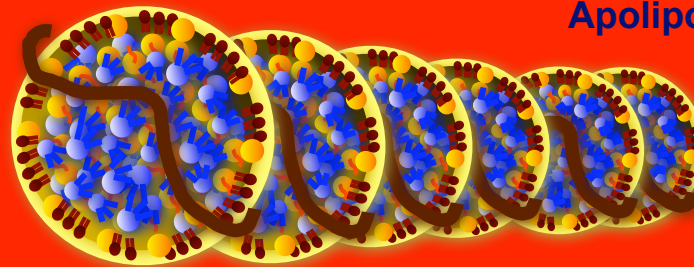
Apolipoprotein
B 48



Chylomicron

1 hour

Apolipoprotein B 100

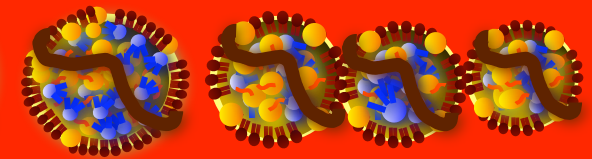


V6 V5 V4 V3 V2 V1

VLDL

Half
Life

2-4 hours



L3

L2

L1

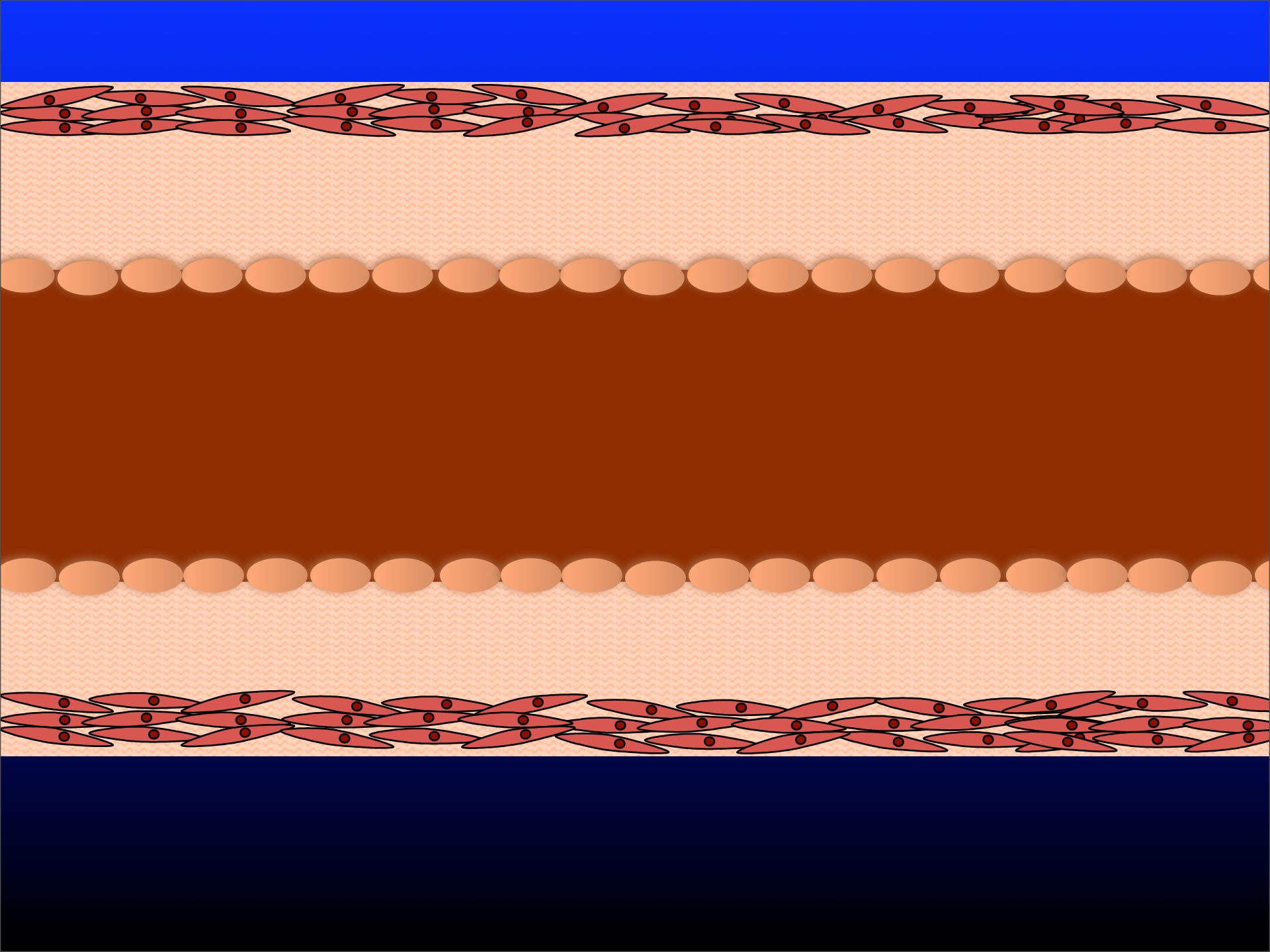
IDL

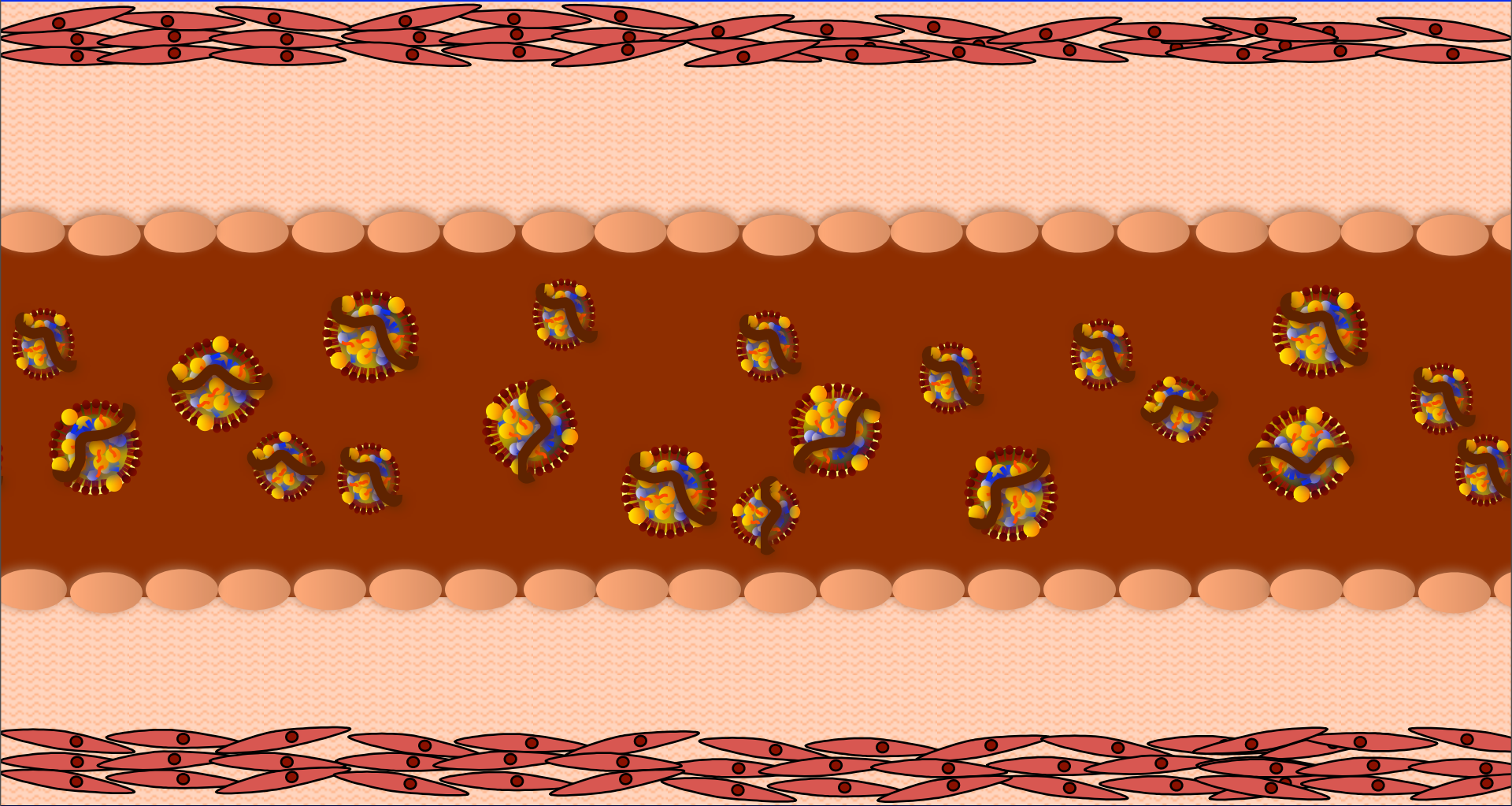
LDL

1-2 hours

2-3 days

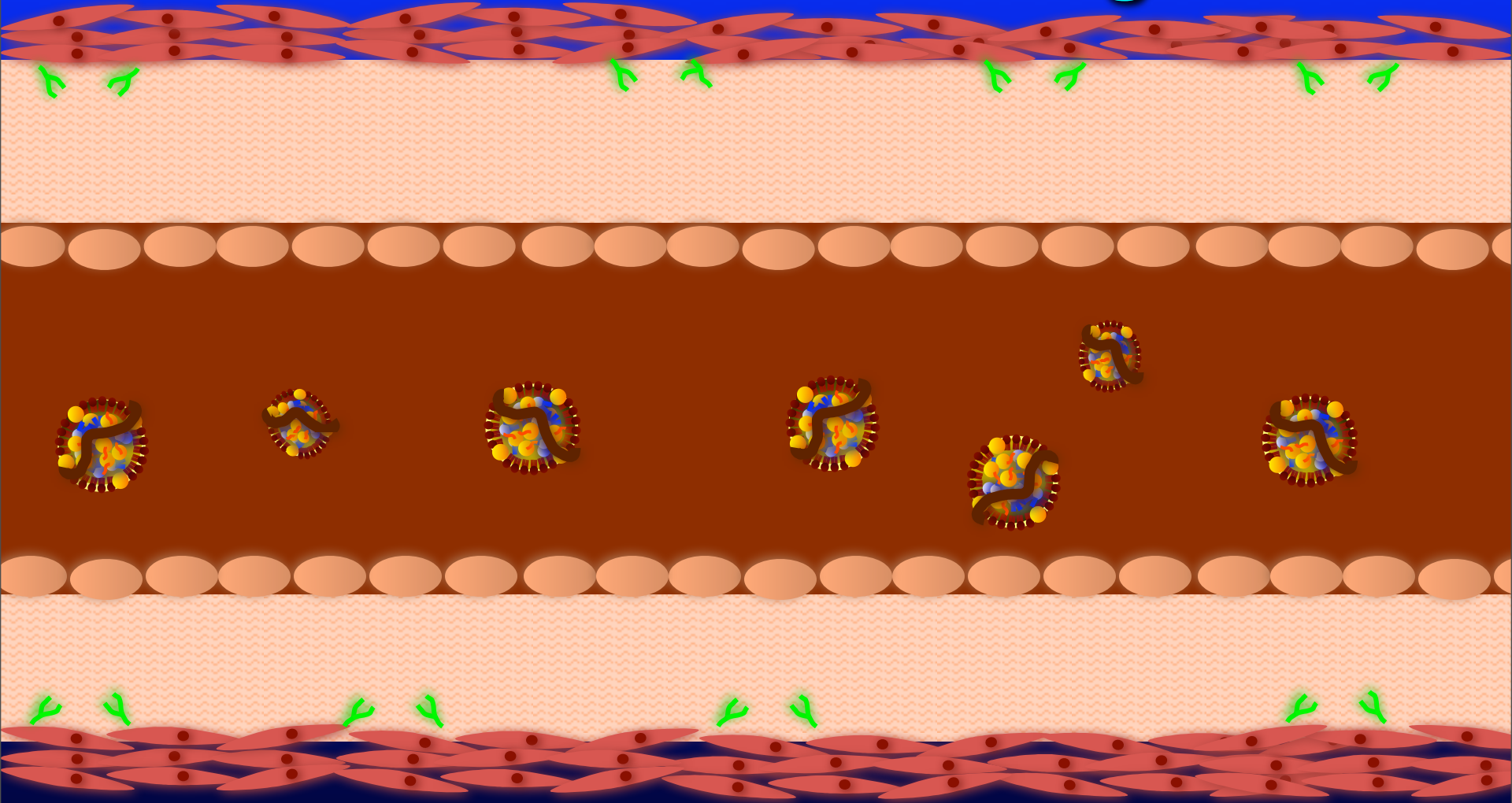
There is one molecule of apoB on each beta-lipoprotein particle. The apoB on a chylomicron is a truncated version (48% of the molecular weight) of the apoB on a lipoprotein of hepatic origin



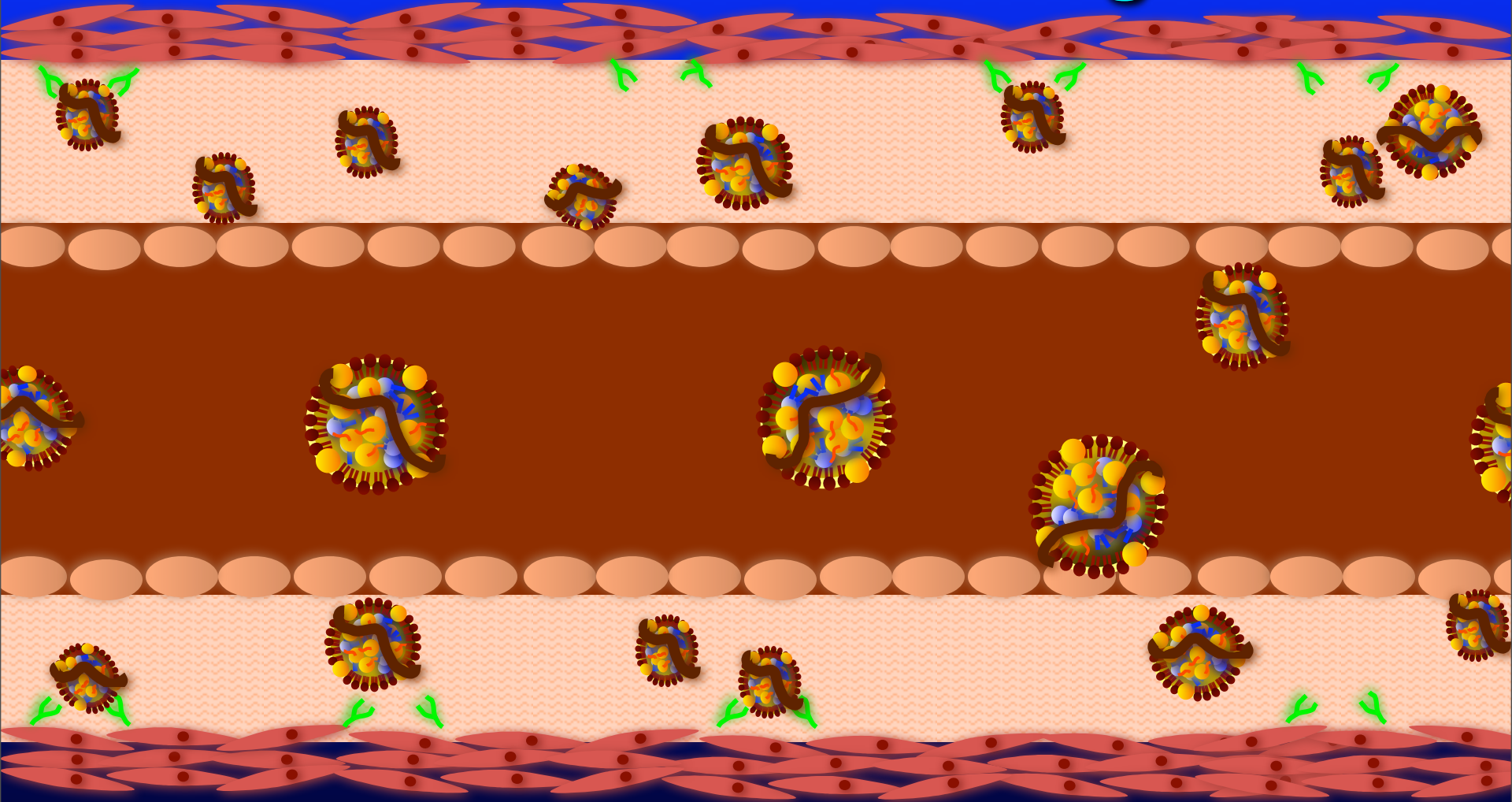


Low Density Lipoproteins (LDL) with their load of Cholesterol esters and Triglycerides circulate

LDL Particles and Atherogenesis



LDL Particles and Atherogenesis



Low Density Lipoproteins (LDL) invade the endothelium and enter the intimal layer. Particle number not size is the determining factor on arterial entry. The particles are quickly attached to intimal proteoglycans.

Low Density Lipoprotein Cholesterol (LDL-C)

Low Density Lipoprotein Cholesterol (LDL-C)

✦ Friedewald formula

LDL-C =

Total Cholesterol - ([HDL-C] + [VLDL-C])

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TC is determined analytically

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Low Density Lipoprotein Cholesterol (LDL-C)

✦ Friedewald formula

LDL-C =

Total Cholesterol - ([HDL-C] + [VLDL-C])

TC is determined analytically

HDL-C is determined analytically

VLDL-C is estimated by TG/5

Friedewald Equation

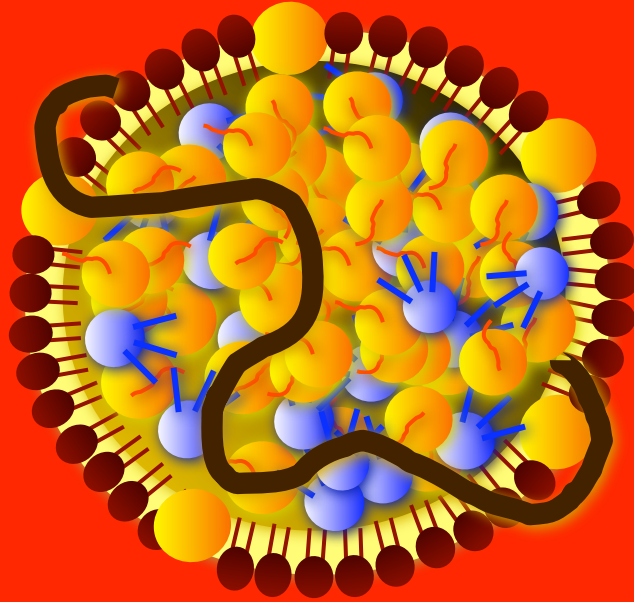
Friedewald Equation

- ✦ Using the Friedewald equation makes three assumptions
 - All TG-rich lipoproteins are VLDL particles (no chylomicrons are present)
 - All serum TG are in VLDL particles, with none in any other lipoproteins
 - The relative proportion of cholesterol in VLDL is constant at 20% of VLDL mass

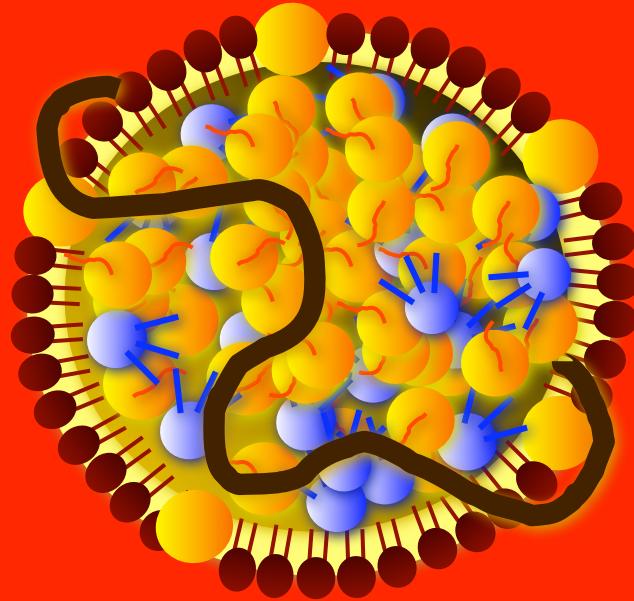
Friedewald Equation

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 - All TG-rich lipoproteins are VLDL particles (no chylomicrons are present)
 - All serum TG are in VLDL particles, with none in any other lipoproteins
 - The relative proportion of cholesterol in VLDL is constant at 20% of VLDL mass
- ✦ These assumptions which are only partially true are increasingly unreliable when TG levels > 250 and completely unreliable at TG > 400 and in individuals with Type III hyperlipidemia

Low Density Lipoprotein Particle



Low Density Lipoprotein Particle



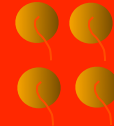
Free
Cholesterol



Triglycerides

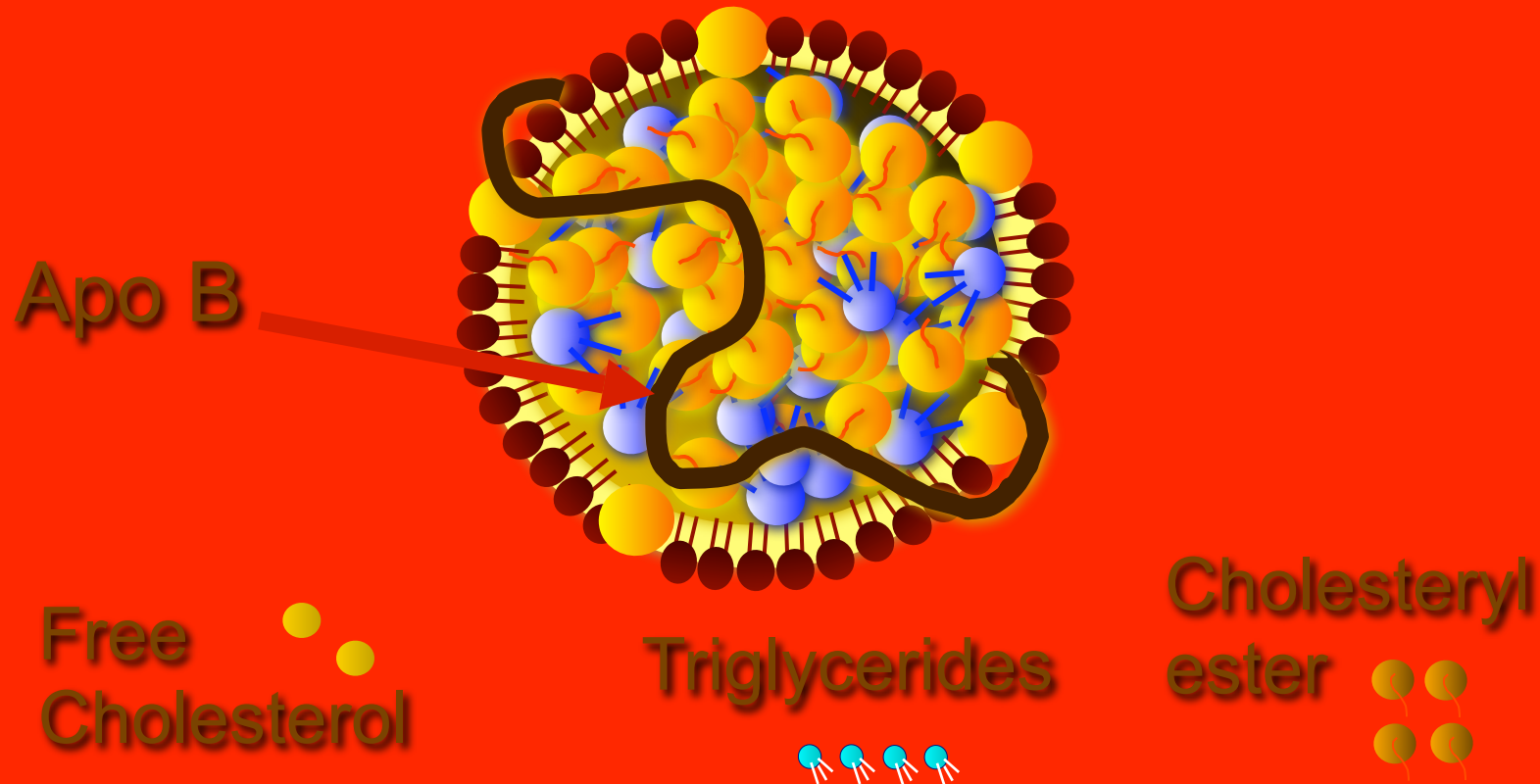


Cholesteryl
ester



A beta-lipoprotein with a composition of
of $> 90\%$ cholesterol and $< 10\%$ TG

Low Density Lipoprotein Particle

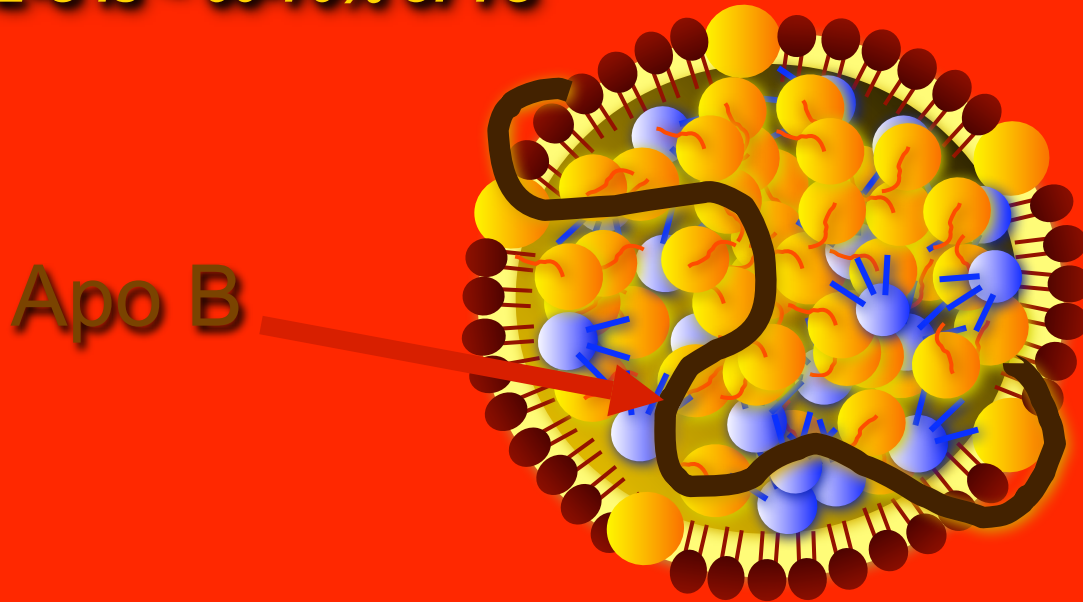


A beta-lipoprotein with a composition of
of $> 90\%$ cholesterol and $< 10\%$ TG

Low Density Lipoprotein Particle

LDL-C is ~ 60-70% of TC

LDL-C



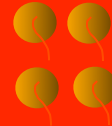
Free
Cholesterol



Triglycerides



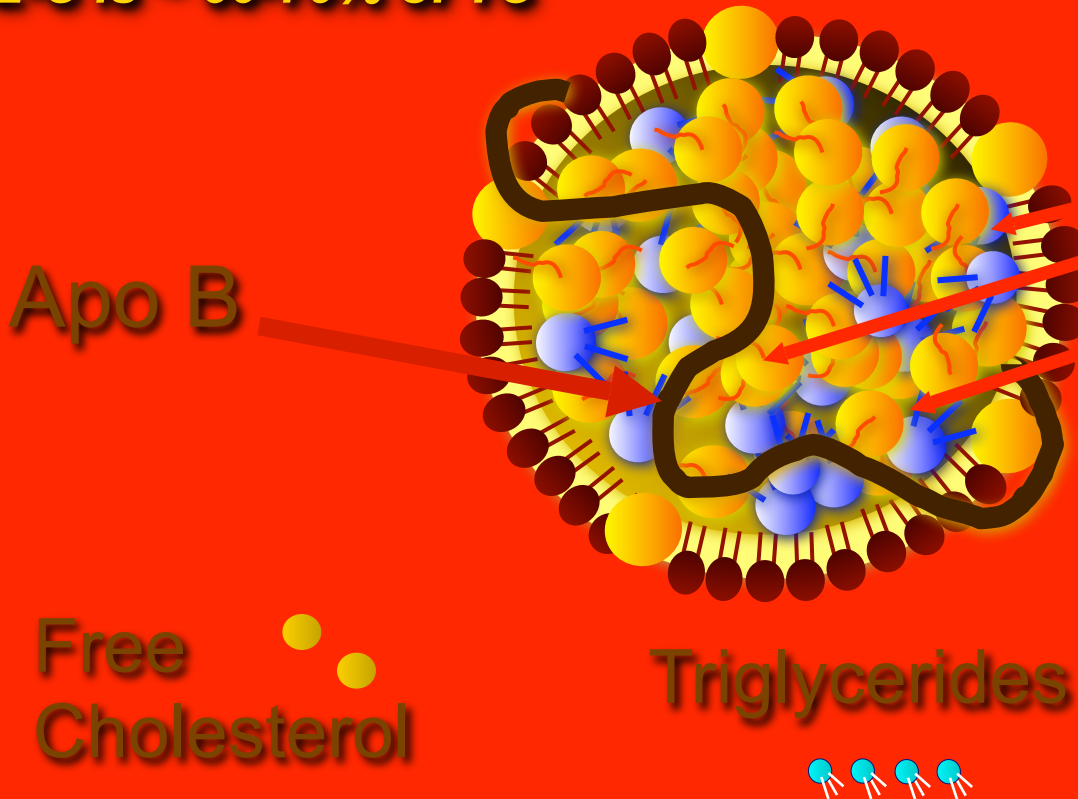
Cholesteryl
ester



A beta-lipoprotein with a composition of
of > 90% cholesterol and < 10% TG

Low Density Lipoprotein Particle

LDL-C is ~ 60-70% of TC



LDL-C

Cholesteryl
content of LDL
particle

Desirable is
< 100 mg/dl

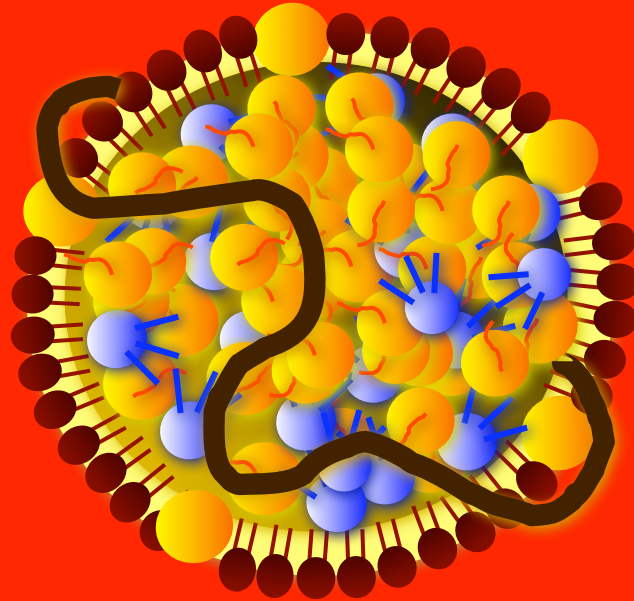
Cholesteryl
ester

✦ Friedewald formula

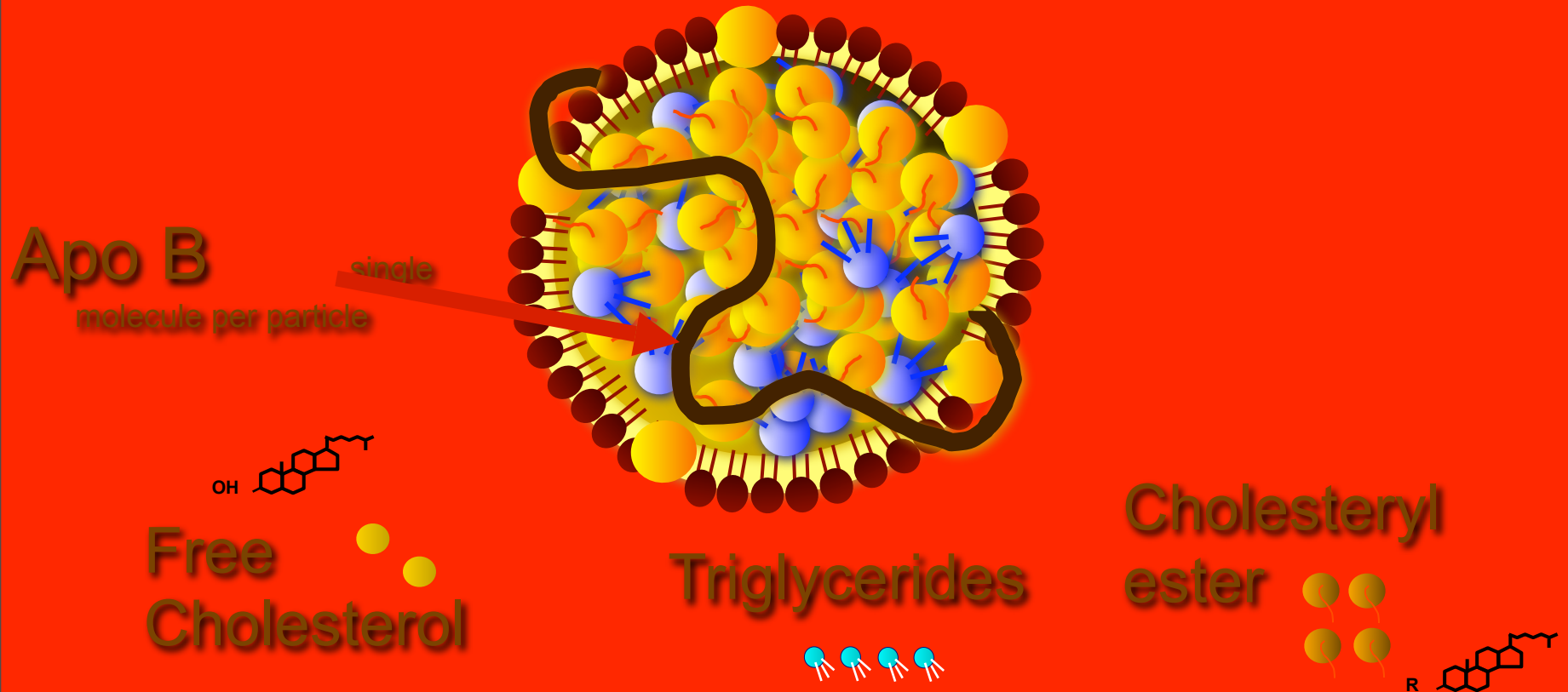
TG/5

$$\bullet \text{ LDL-C} = \text{Total Cholesterol} - ([\text{HDL-C}] + [\text{VLDL-C}])$$

Low Density Lipoprotein Particle



Low Density Lipoprotein Particle



A beta-lipoprotein with a composition of
of $> 90\%$ cholesterol and $< 10\%$ TG

Low Density Lipoprotein Particle

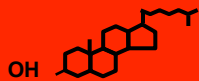
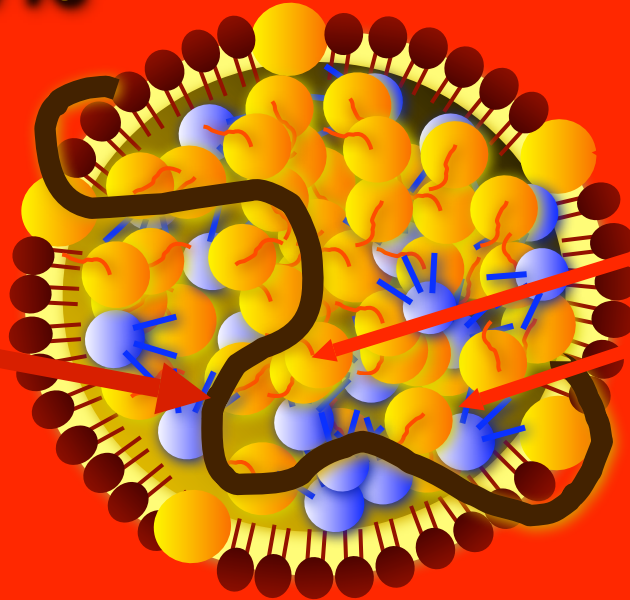
LDL-C is ~ 60-70% of TC

Desirable is < 100-120 mg/dl

LDL-C

Cholesterol & cholesteryl ester content of LDL particle

Apo B
molecule per particle



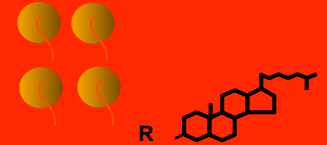
Free Cholesterol



Triglycerides



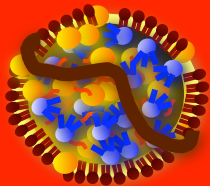
Cholesteryl ester



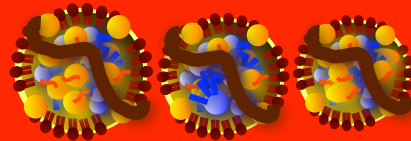
LDL-cholesterol

LDL cholesterol (LDL-C) is the cholesterol trafficked within all of the low and intermediate density lipoproteins in a deciliter of plasma

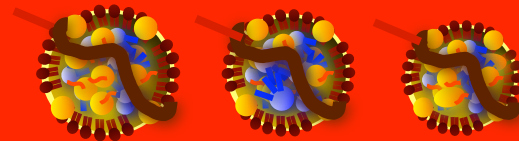
IDL



LDL

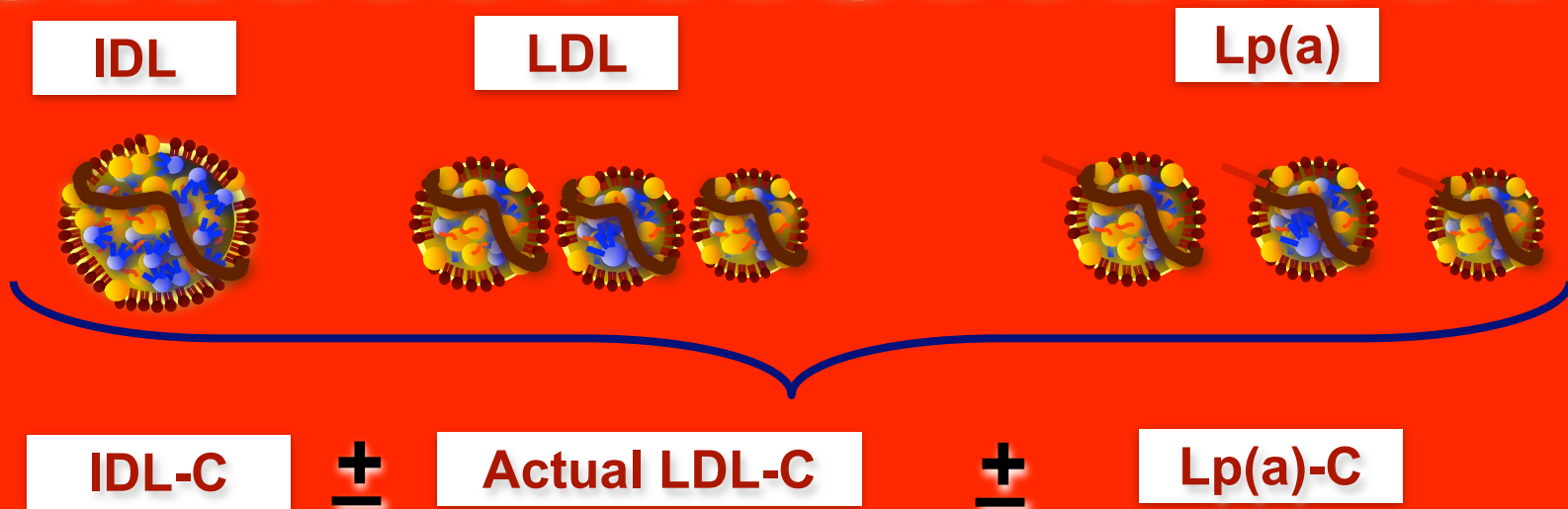


Lp(a)



LDL-cholesterol

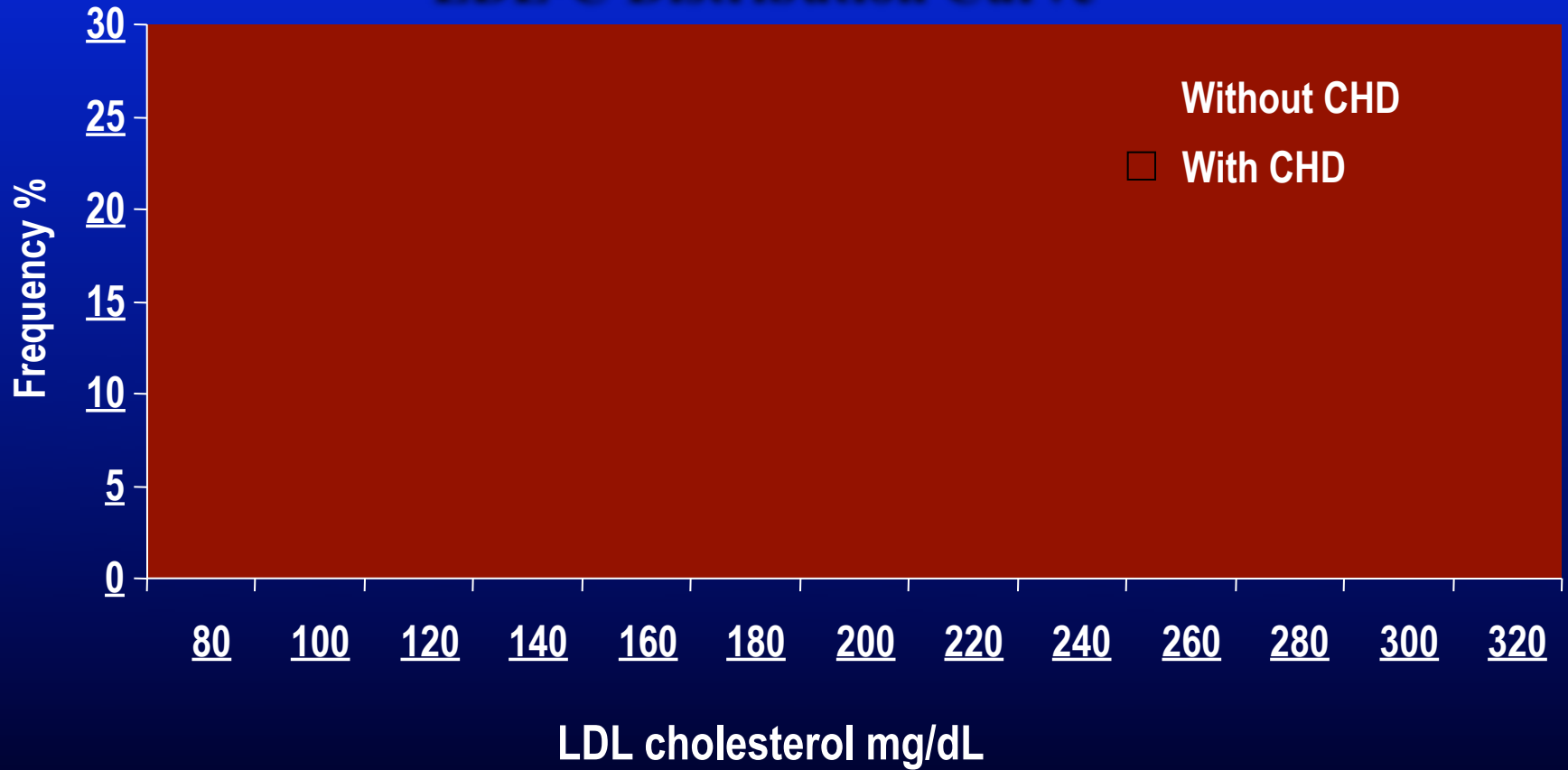
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Calculated or Direct LDL-Cholesterol

Can LDL-C Levels Predict CVD in Individual Patients?

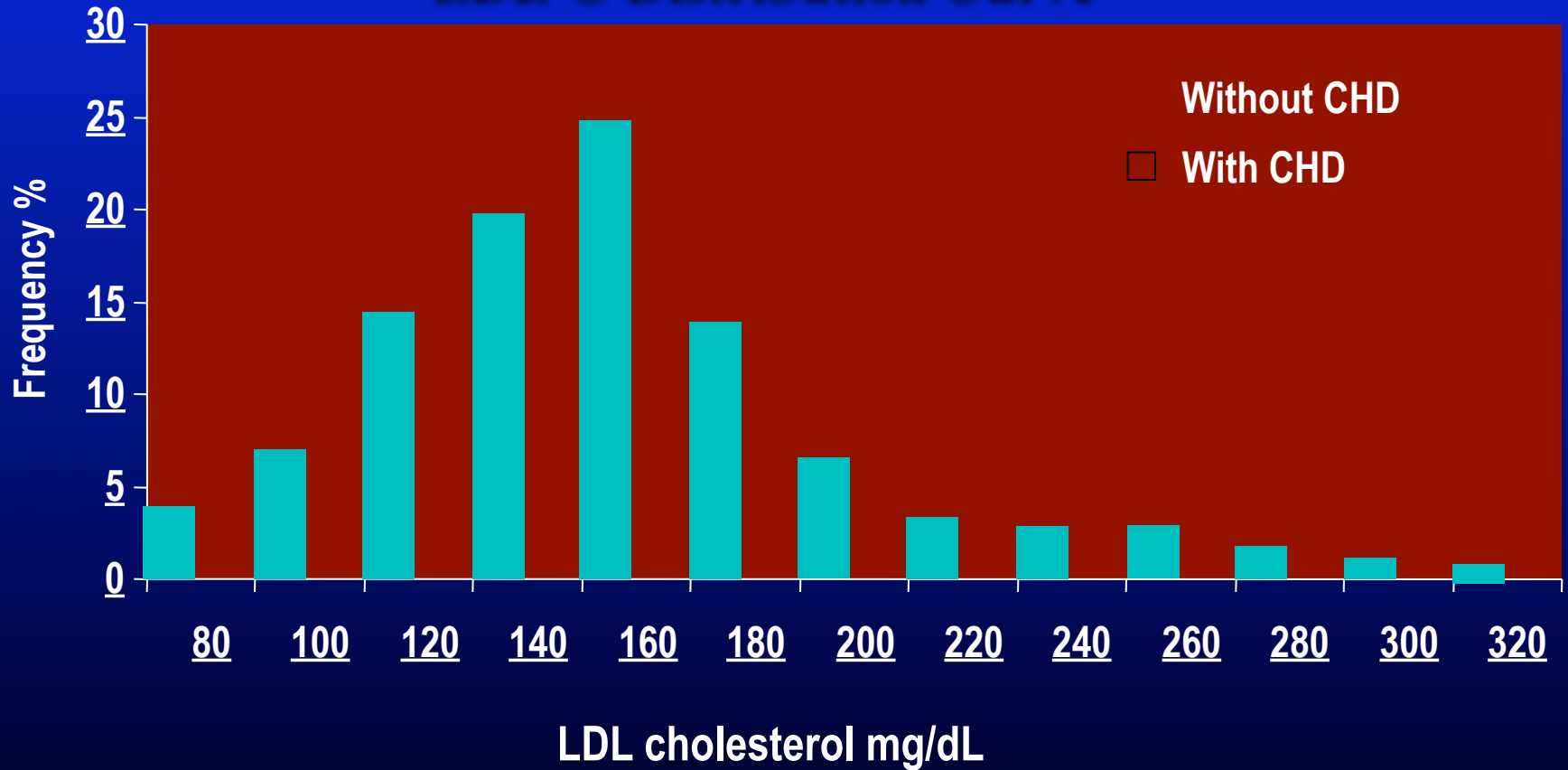
LDL-C Distribution Curve



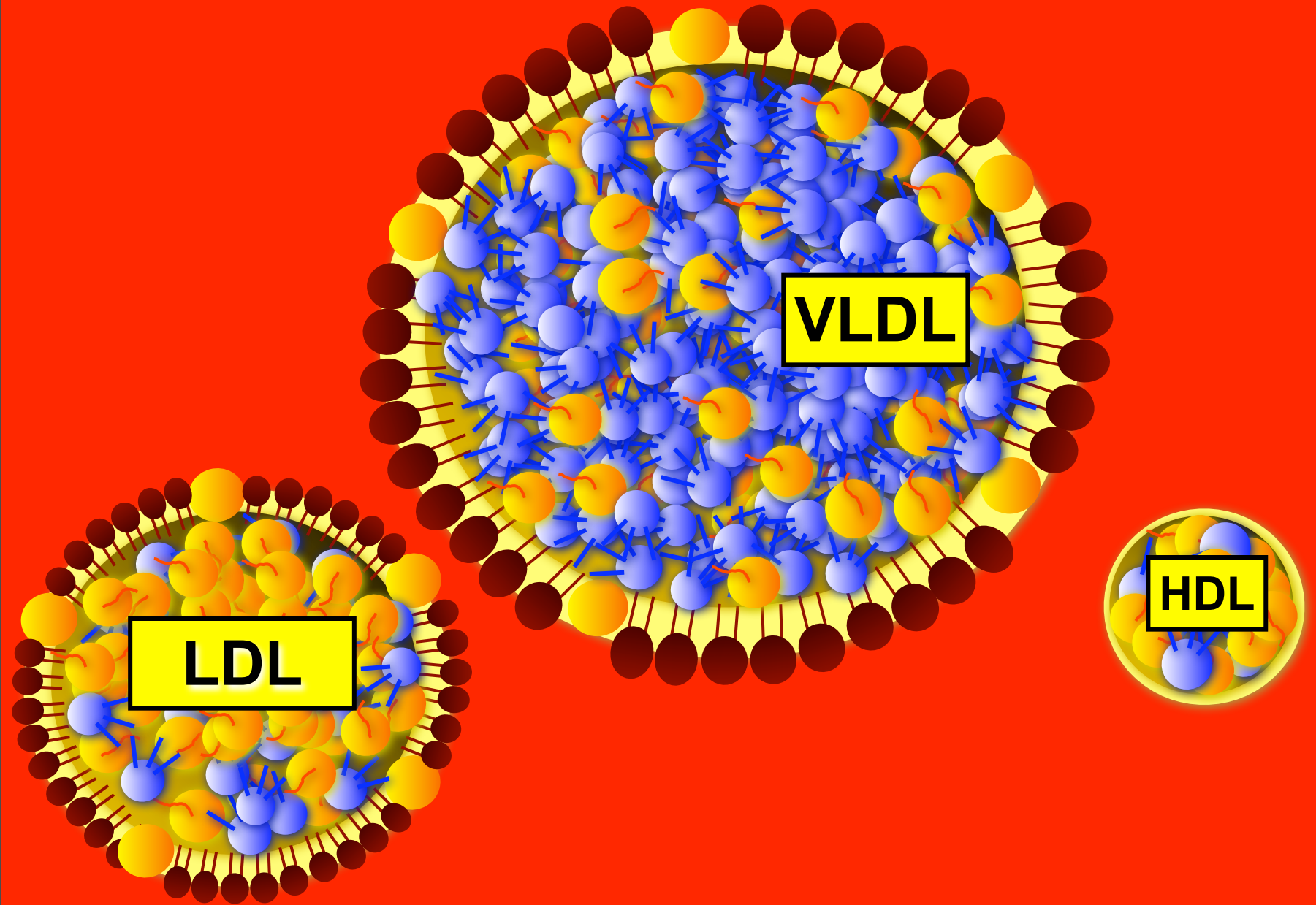
Kannel W. *Am J Cardiol.* 1995;76:69C-77C

Can LDL-C Levels Predict CVD in Individual Patients?

LDL-C Distribution Curve



Kannel W. *Am J Cardiol.* 1995;76:69C-77C

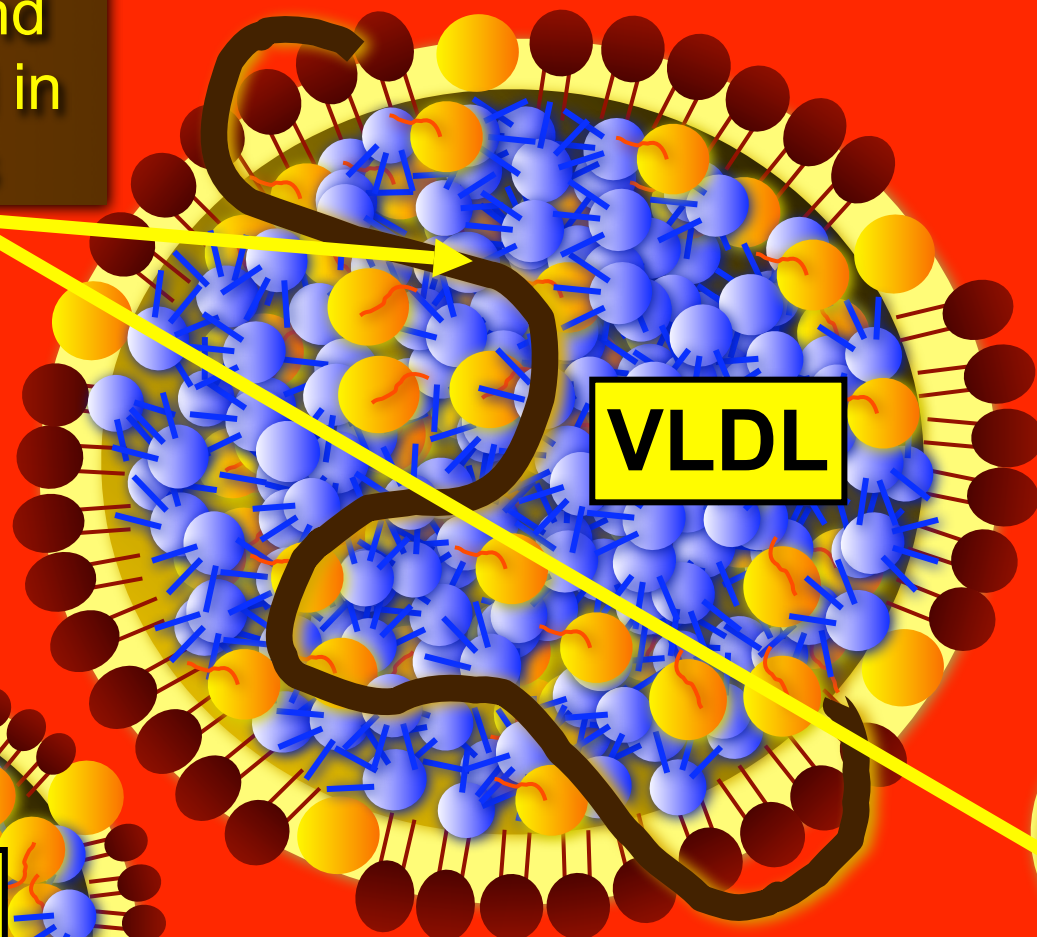
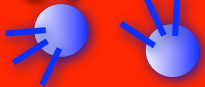


Cholesterol and TG are carried in Lipoproteins

Cholesterol ester



Triglycerides



VLDL

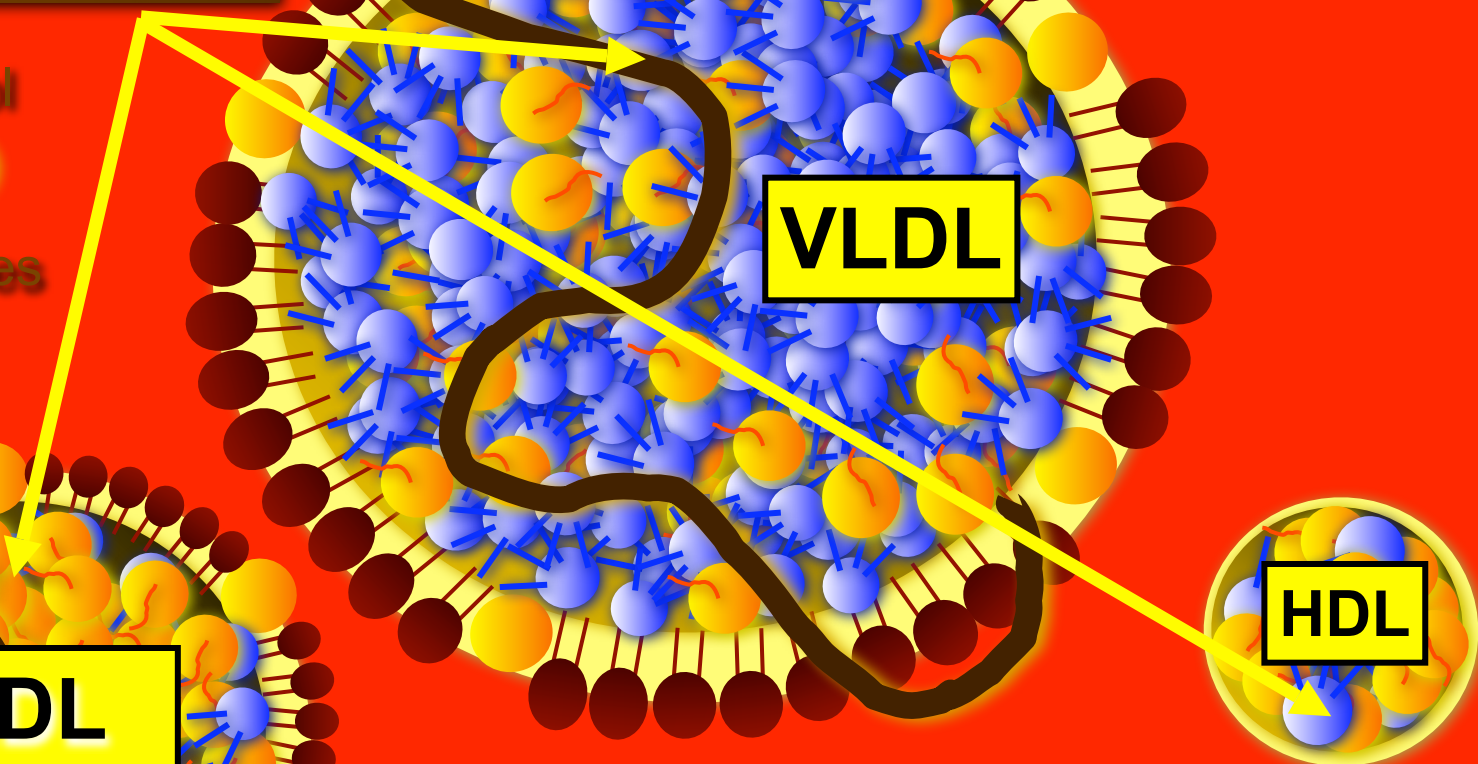


LDL



HDL

Apolipoprotein B

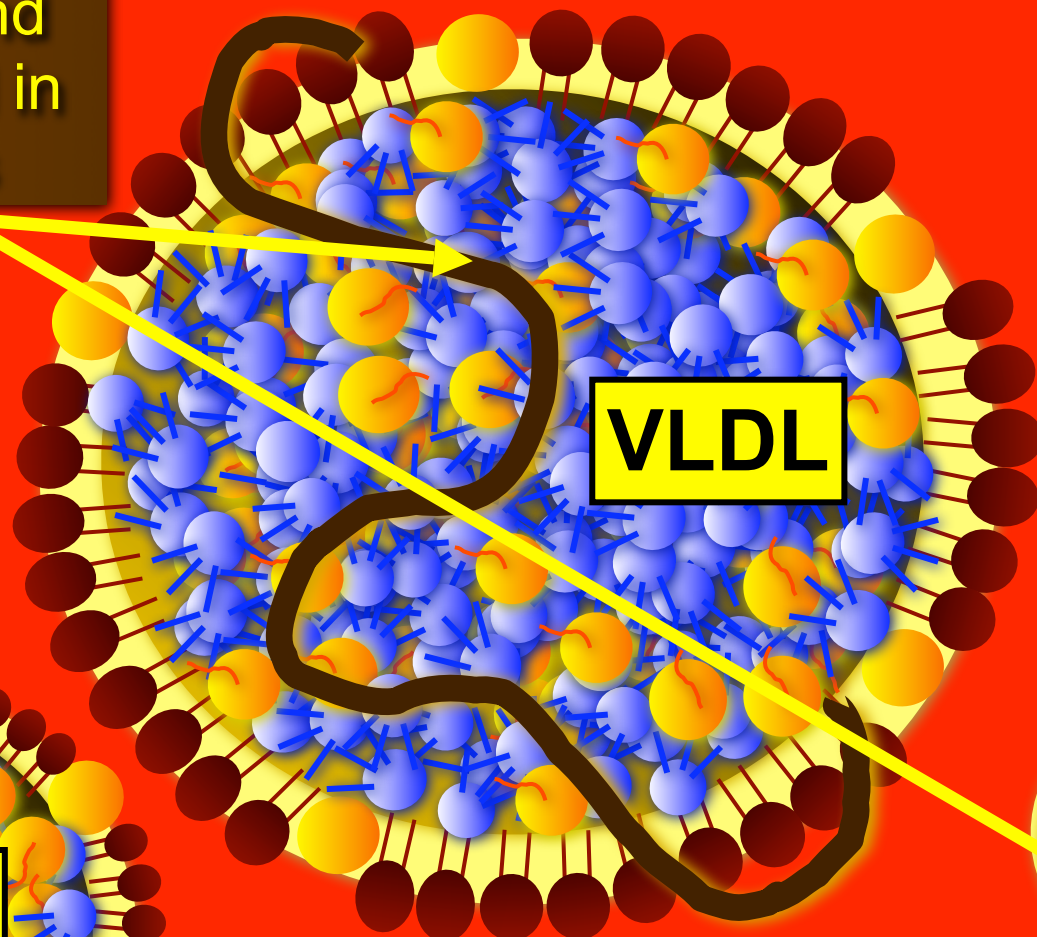
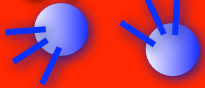


Cholesterol and TG are carried in Lipoproteins

Cholesterol ester



Triglycerides



VLDL



LDL



HDL

Apolipoprotein B

Apolipoprotein A-I

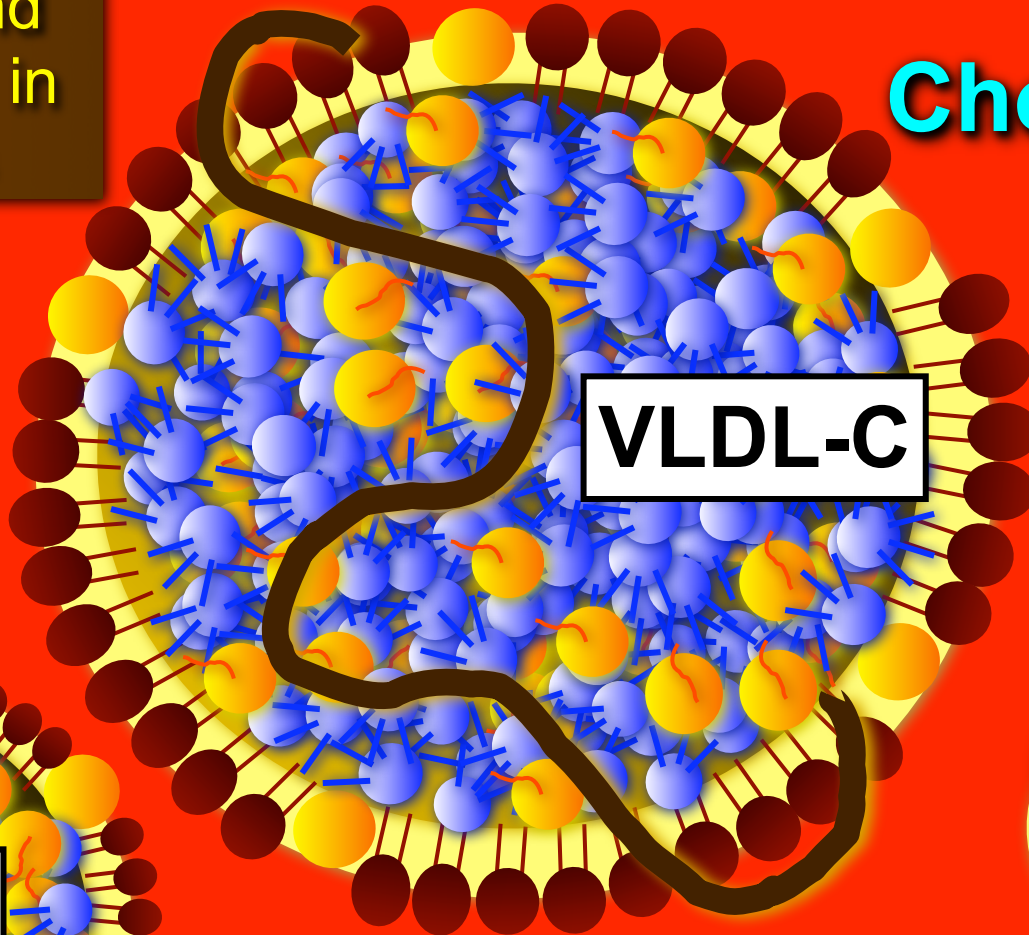
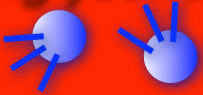
Cholesterol and
TG are carried in
Lipoproteins

**Total
Cholesterol**

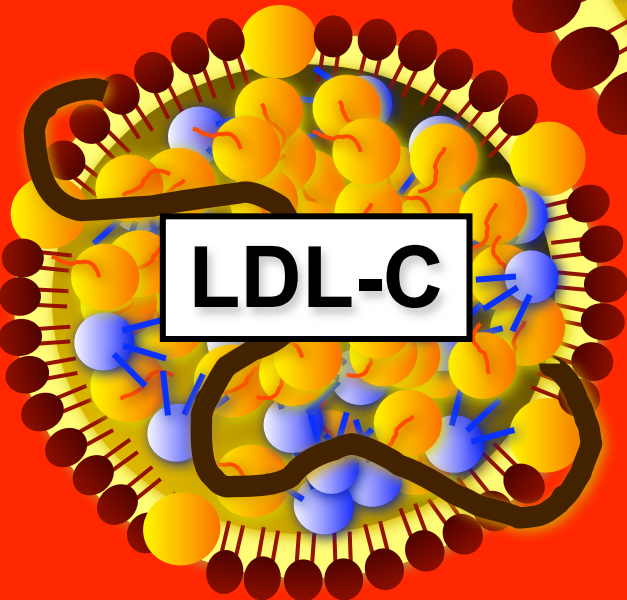
Cholesterol
ester



Triglycerides



VLDL-C



LDL-C

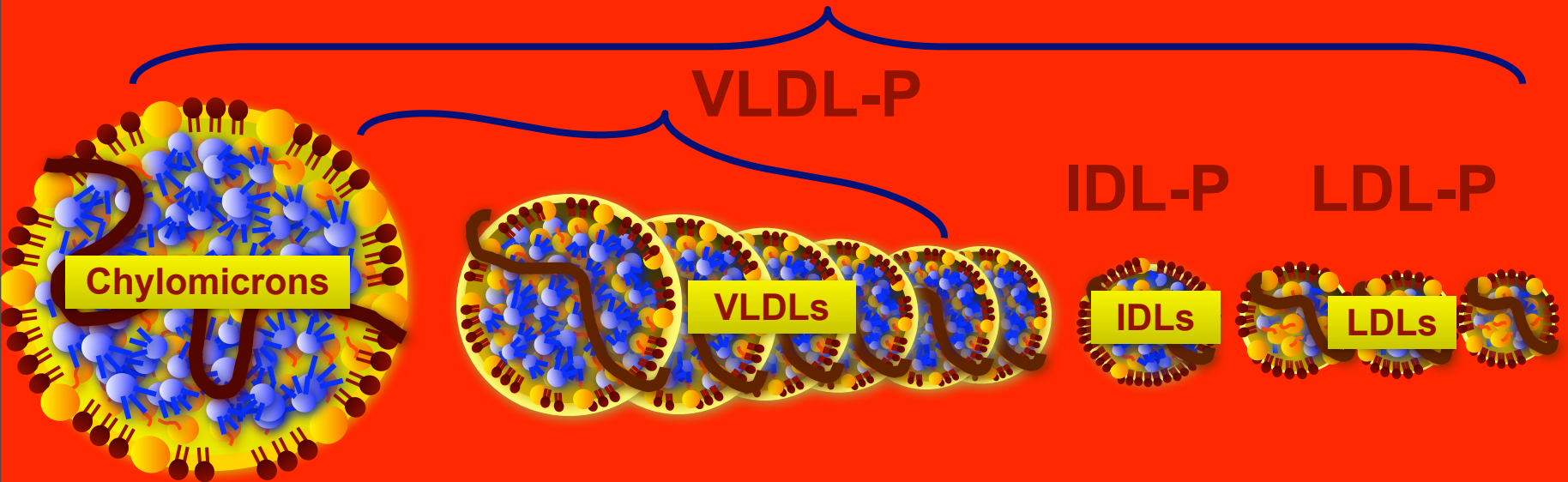


HDL-C

$$TC = LDL-C + HDL-C + VLDL-C$$

Lab Analysis of ApoB Lipoproteins

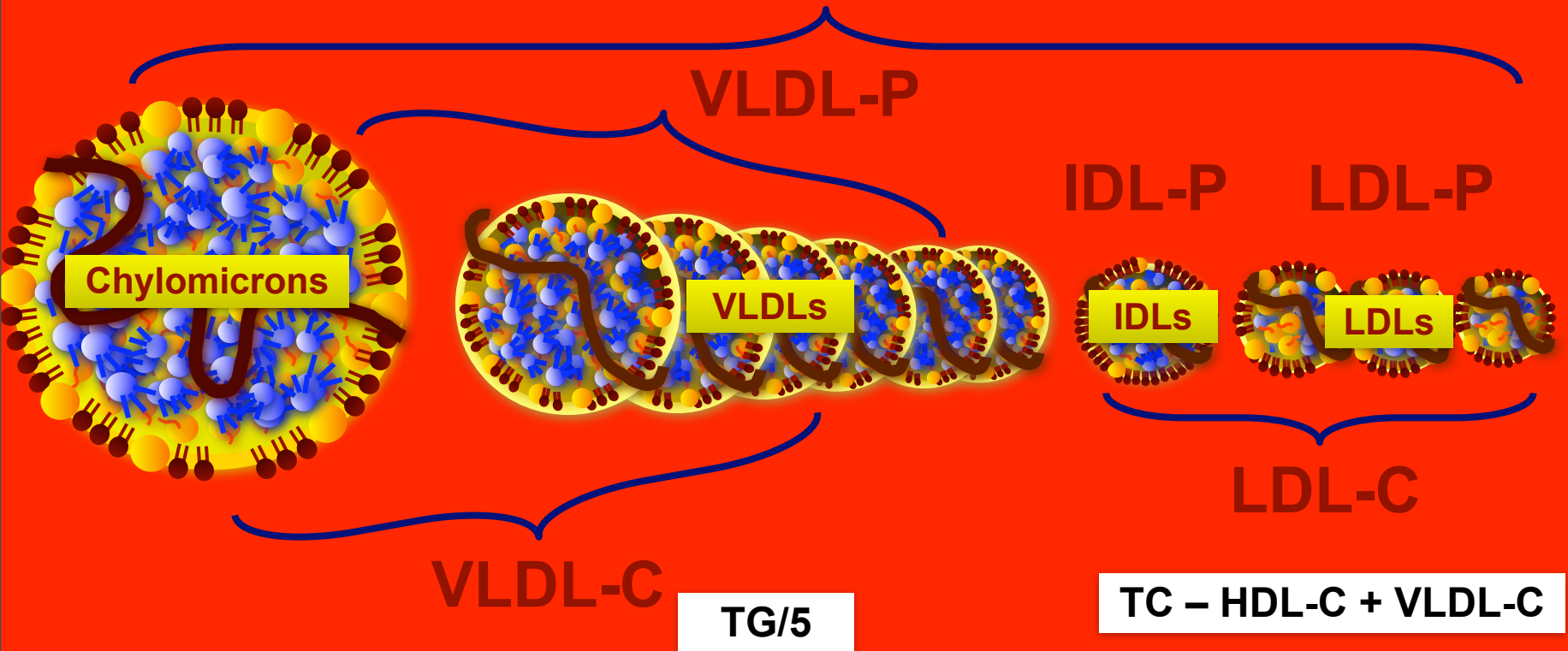
ApoB Concentration



ApoB Lipoproteins

Lab Analysis of ApoB Lipoproteins

ApoB Concentration

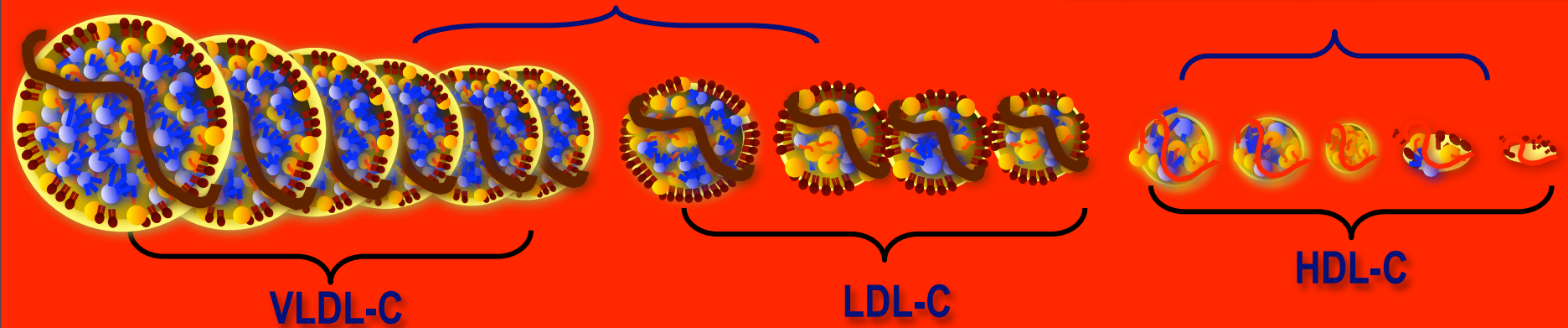


ApoB Lipoproteins

Apolipoprotein B Surrogates

ApoB lipoproteins

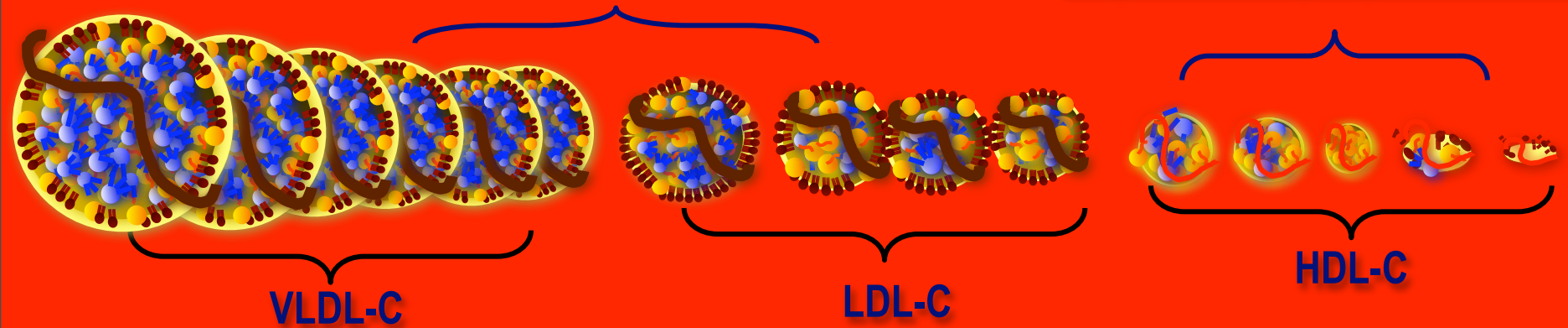
ApoA-I lipoproteins



Apolipoprotein B Surrogates

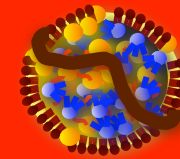
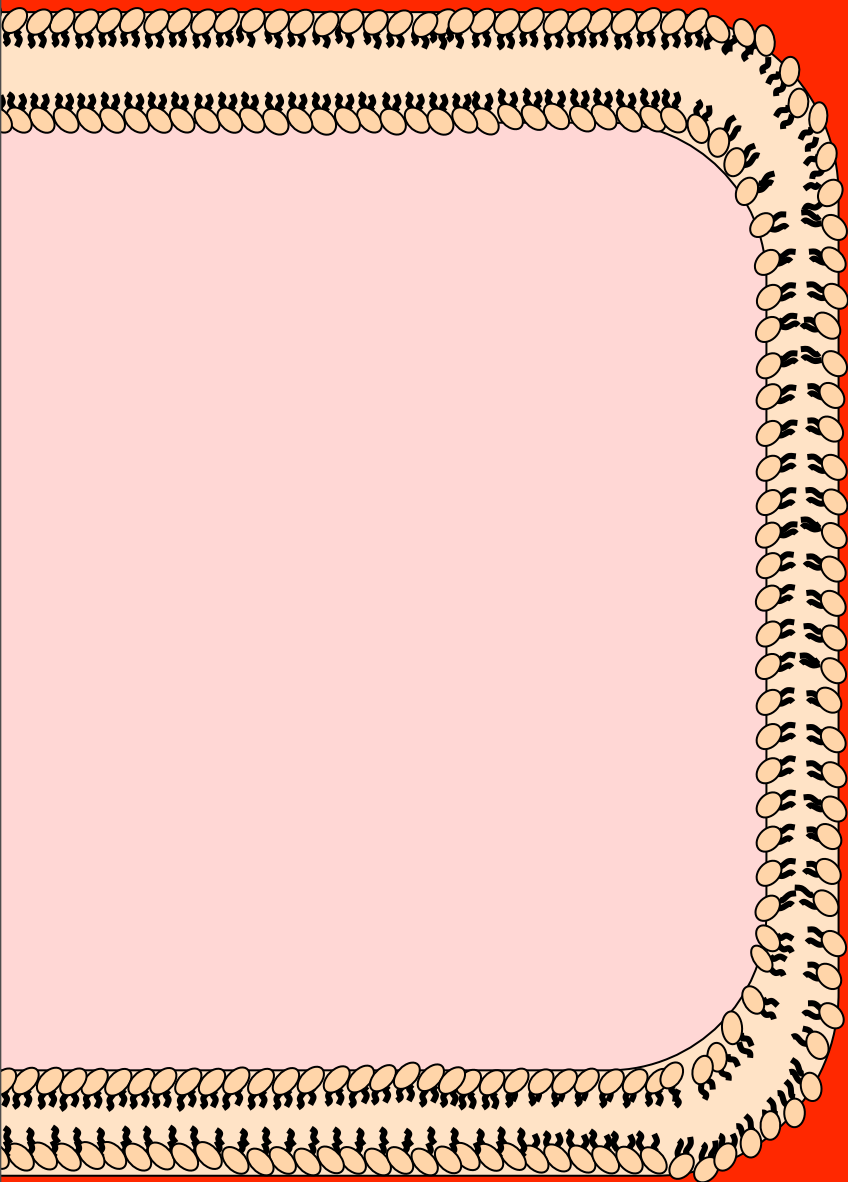
ApoB lipoproteins

ApoA-I lipoproteins

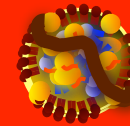


Since LDL-P makes up more than 90-95% of apoB particles, **Non HDL-C** is in effect an LDL-P surrogate

LDL Receptor & LDL Particles



**Normal sized
LDL particle
(Pattern A)**

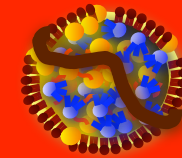
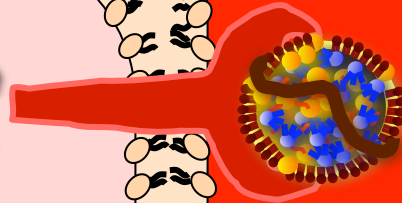


**Smaller LDL
particle
(Pattern B)**

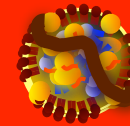
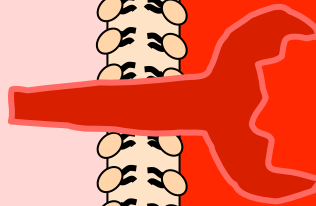
LDL Receptor & LDL Particles

LDL Particle Endocytosis

LDL receptors and the apoB on LDL particles bind if their surface charges align properly



Normal sized LDL particle (Pattern A)



Smaller LDL particle (Pattern B)

LDL Receptors (LDLr)

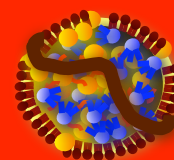
LDL Receptor & LDL Particles

LDL Particle Endocytosis

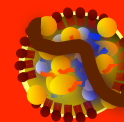
LDL receptors and the apoB on LDL particles bind if their surface charges align properly

ApoB conformation changes on smaller or larger LDL particles making those particles less amenable to LDLr binding

LDL Receptors (LDLr)



Normal sized LDL particle (Pattern A)

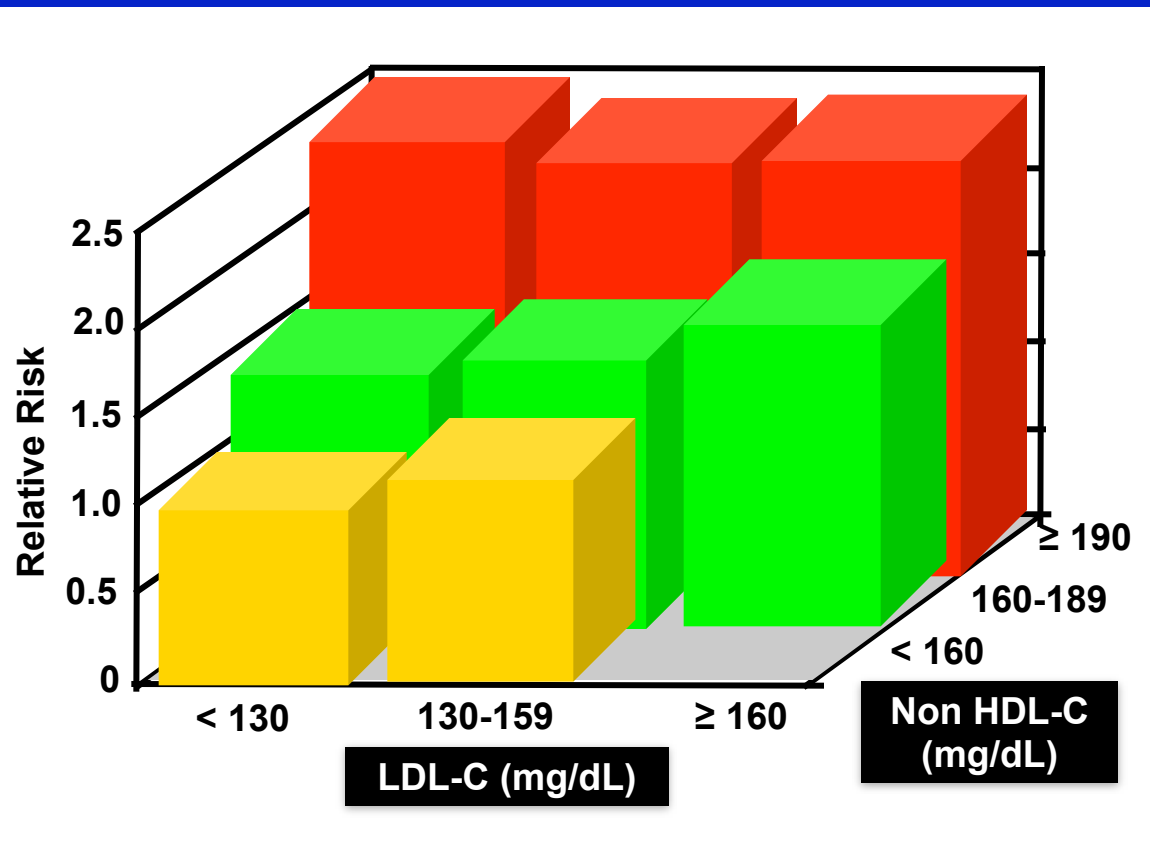


Smaller LDL particle (Pattern B)

Insulin Resistance; MS T2DM
Cardiometabolic Risk

Framingham Heart Study: Non HDL-C and VLDL-C and Their Risk Predictive Values in Coronary Heart Disease

Framingham Heart Study: Non HDL-C and VLDL-C and Their Risk Predictive Values in Coronary Heart Disease



Within non HDL cholesterol levels, no association was found between LDL-C and the risk for incident CHD.

In contrast, a strong positive and graded association between non-HDL-C and risk for CHD incidence occurred within every level of LDL-C

That is, non HDL-C appears to be a better predictor of CHD incidence.

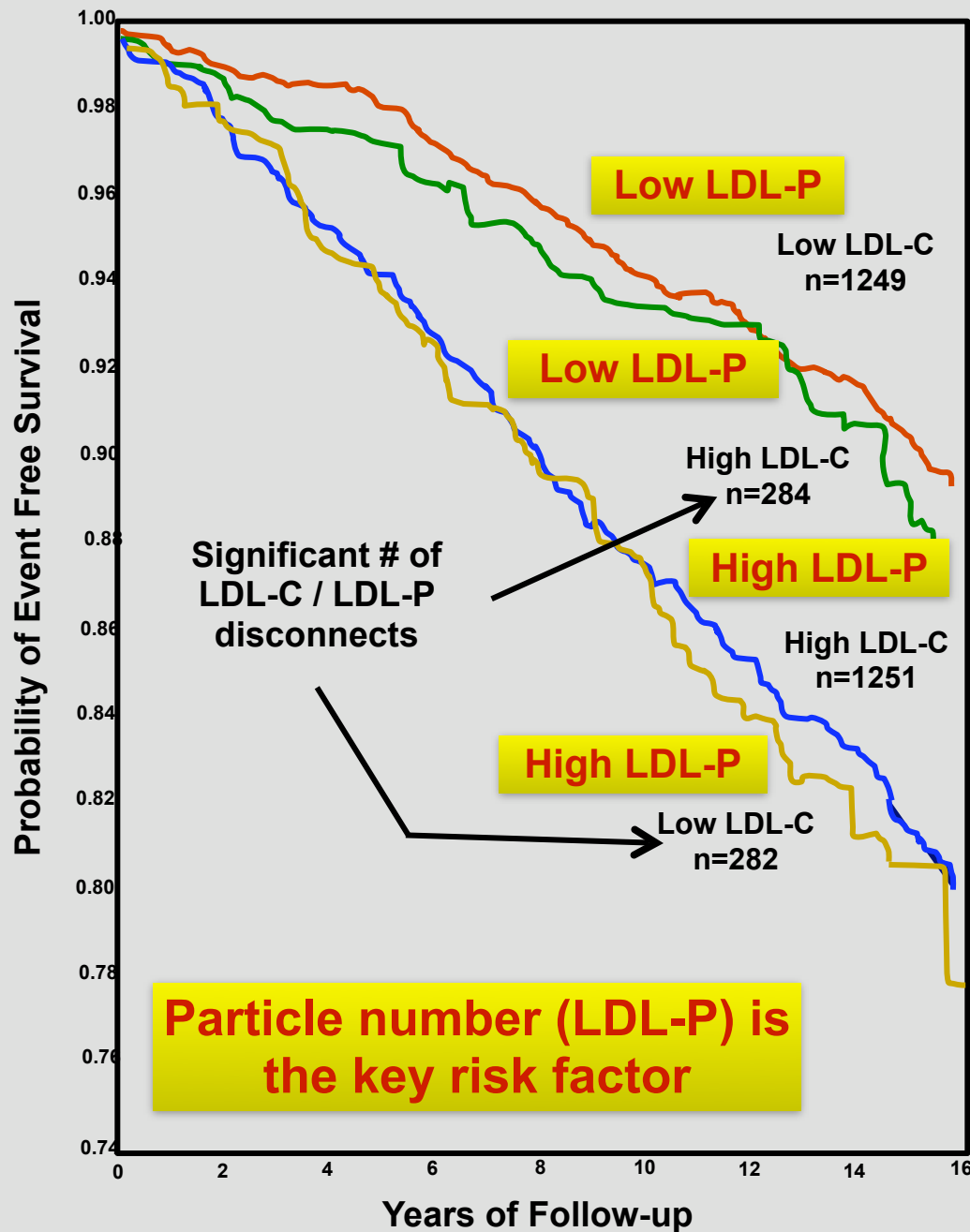
Framingham Heart Study Offspring Cohort

Event-free survival among participants with low-density lipoprotein cholesterol (LDL-C) and LDL particle number (LDL-P) above or below the median.

Median values were 131 mg/dL for LDL-C and 1414 nmol/L for LDL-P.

LDL-P was strongly associated with increased CVD risk in both men and women ($p < 0.0001$)

When data for men and women were combined, LDL-P was approximately twice as strongly related to CVD incidence as LDL-C



Framingham Heart Study: Offspring Cohort

Framingham Heart Study: Offspring Cohort

- ▶ **The graph makes a very simple point**
- ▶ **When LDL-C and LDL-P are both high there is risk and when the two indices are both low, risk is low**

Framingham Heart Study: Offspring Cohort

- ▶ **The graph makes a very simple point**
- ▶ **When LDL-C and LDL-P are both high there is risk and when the two indices are both low, risk is low**
- ▶ **The issue is what happens when the two indices are discordant:**
 - ▶ **When LDL-P is low, even though LDL-C is high, risk is low. Similarly when LDL-P is high and LDL-C is low, risk is high**

Framingham Heart Study: Offspring Cohort

- ▶ **The graph makes a very simple point**
- ▶ When LDL-C and LDL-P are both high there is risk and when the two indices are both low, risk is low
- ▶ The issue is what happens when the two indices are discordant:
 - ▶ When LDL-P is low, even though LDL-C is high, risk is low. Similarly when LDL-P is high and LDL-C is low, risk is high

Risk follows LDL-P, not LDL-C

Framingham Heart Study: Offspring Cohort

▶ This ratio provides the approximate number of cholesterol molecules per LDL particle.

**Cholesterol Molecules
per LDL Particle**

=

LDL-C (mol/L)

LDL-P (mol/L)

To convert mg to mols: multiply the mg/dL mass concentrations by 0.0259
mmol = 10^{-3} mol nmol = 10^{-9} mol

Framingham Heart Study: Offspring Cohort

- ▶ This ratio provides the approximate number of cholesterol molecules per LDL particle.

**Cholesterol Molecules
per LDL Particle**

=

LDL-C (mol/L)

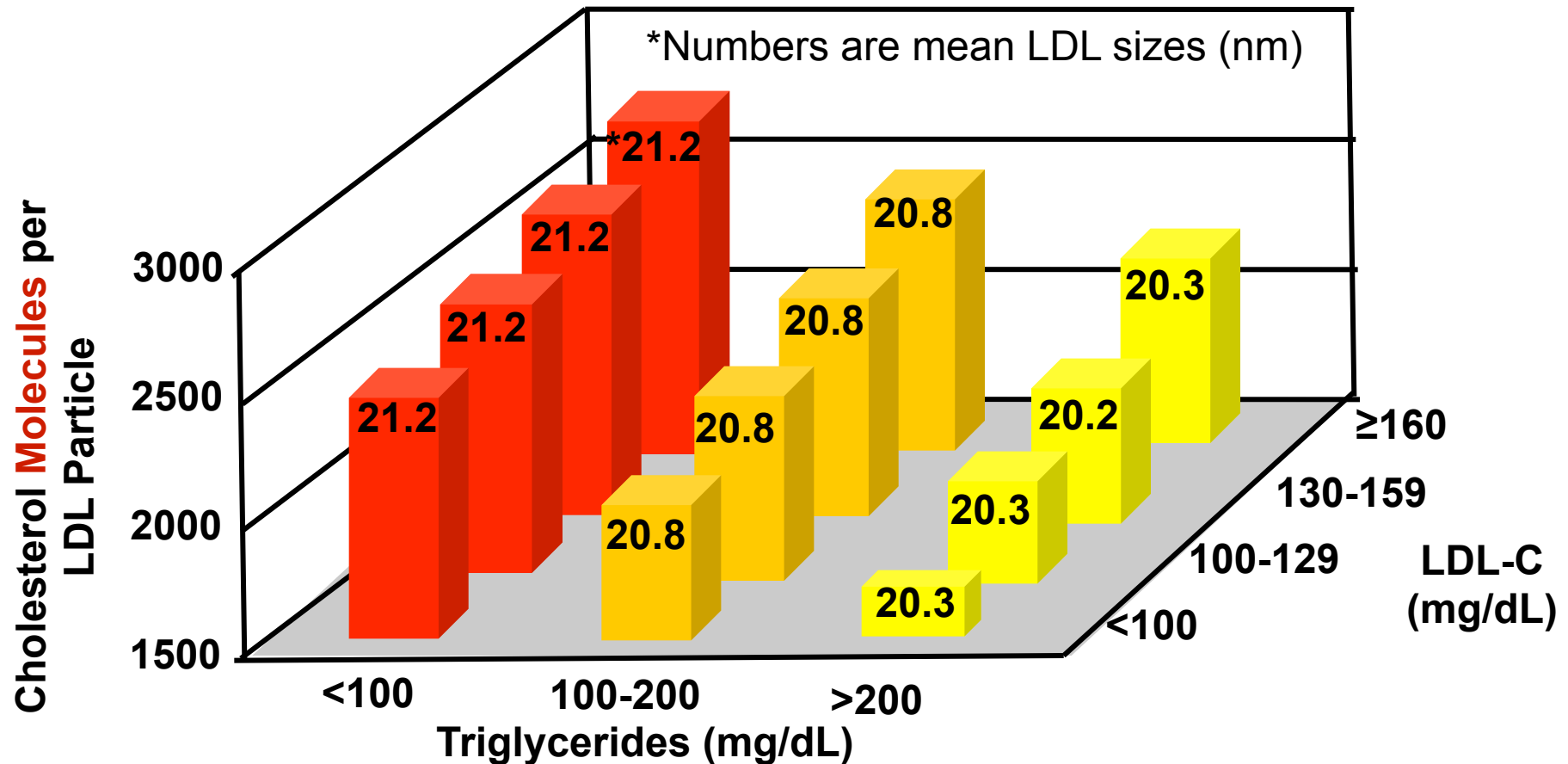
LDL-P (mol/L)

- ▶ Estimates of the cholesterol content of the LDL particles of individual subjects were obtained by dividing LDL-C (in mmol/L units), by LDL-P (nmol/L).

To convert mg to mols: multiply the mg/dL mass concentrations by 0.0259

mmol = 10^{-3} mol nmol = 10^{-9} mol

Framingham Heart Study: Offspring Cohort



Cholesterol content of low-density lipoprotein (LDL) particles in subgroups defined by levels of LDL cholesterol (LDL-C) and triglycerides

Racial & Gender Differences in Lipoproteins

Studies of a Targeted Risk Reduction Intervention Through Defined Exercise Study

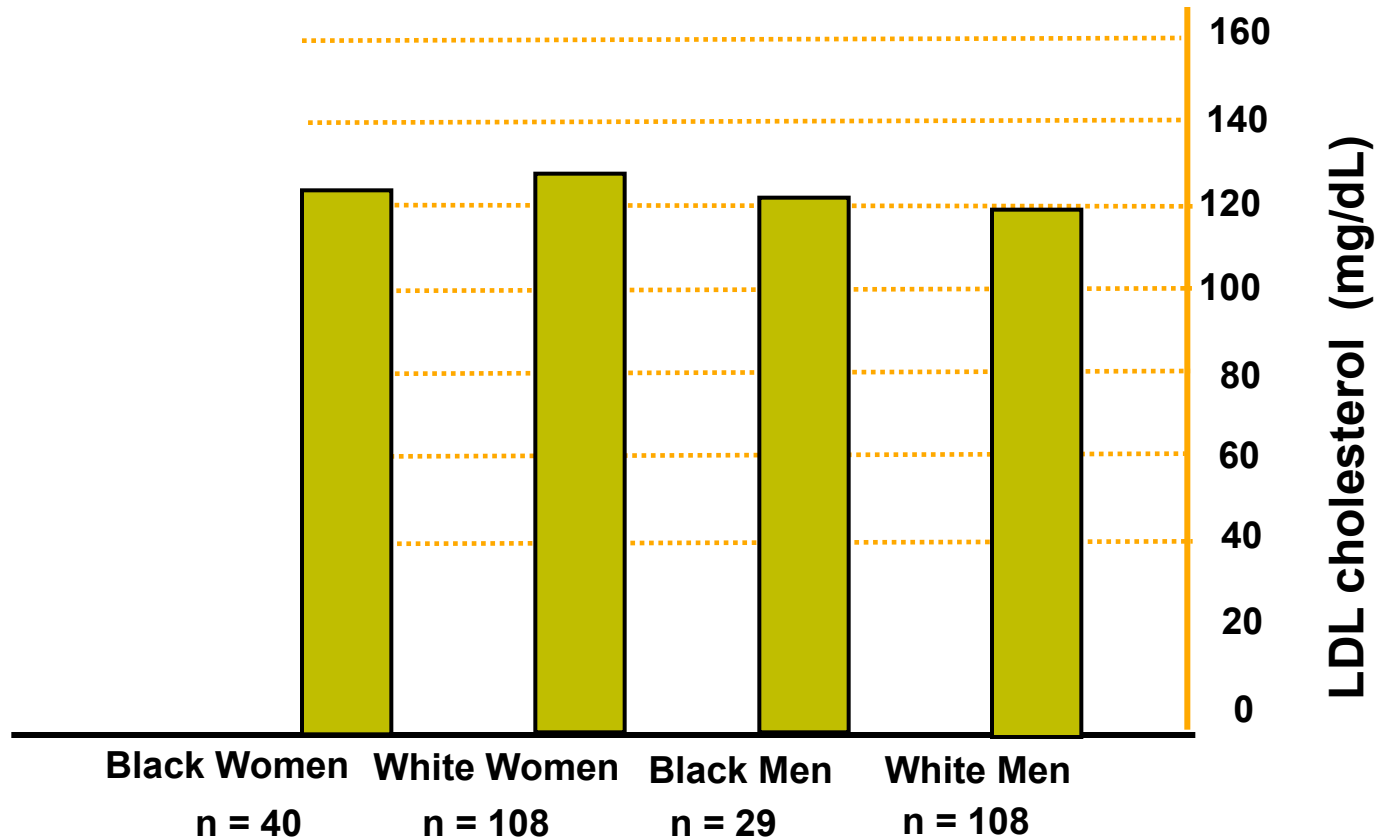
Black Women	White Women	Black Men	White Men
n = 40	n = 108	n = 29	n = 108

Data represents means adjusted
for differences in age and BMI

Johnson JL et al. *Atherosclerosis* 2004;176:371-37

Racial & Gender Differences in Lipoproteins

Studies of a Targeted Risk Reduction Intervention Through Defined Exercise Study

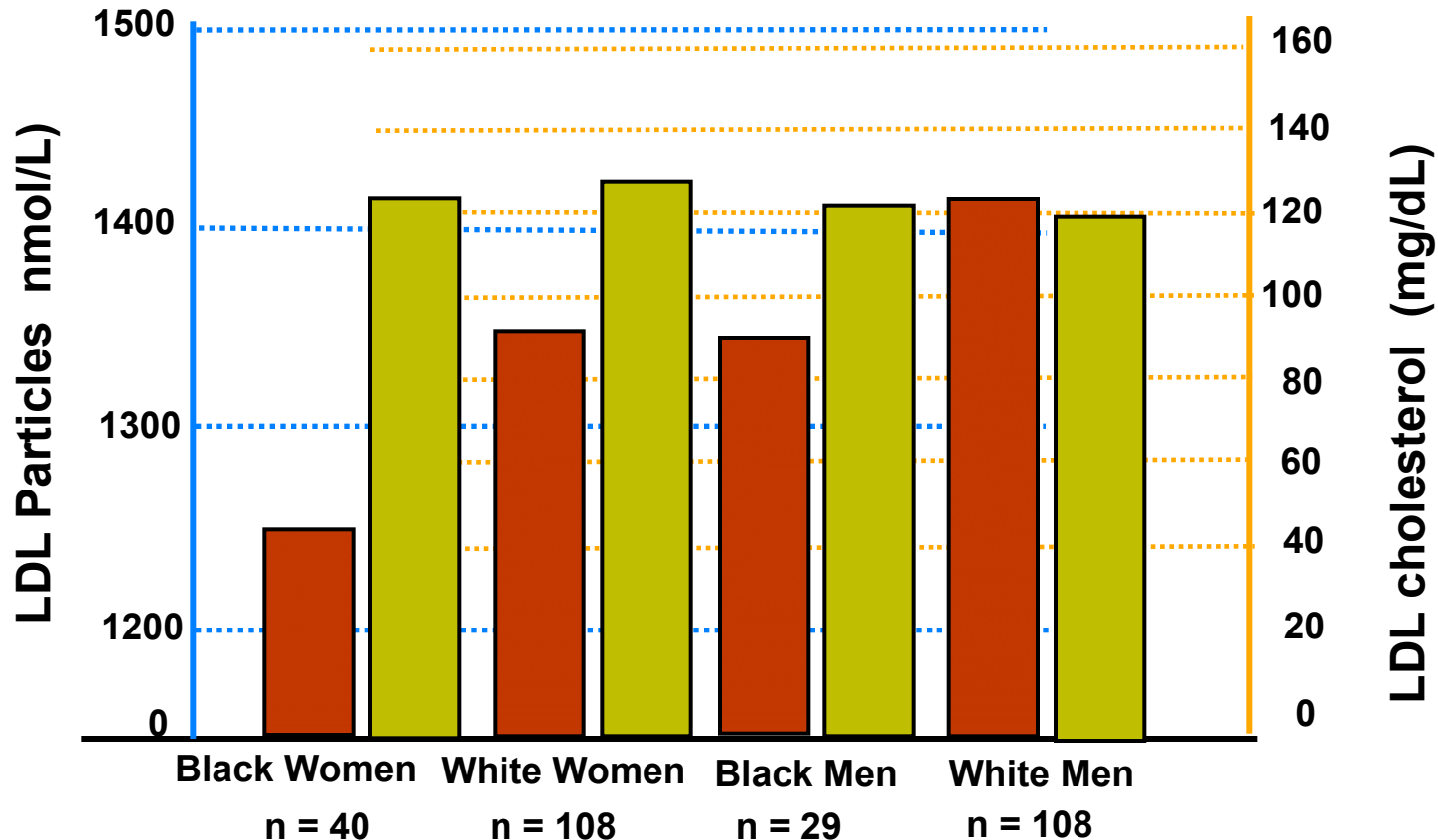


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Racial & Gender Differences in Lipoproteins

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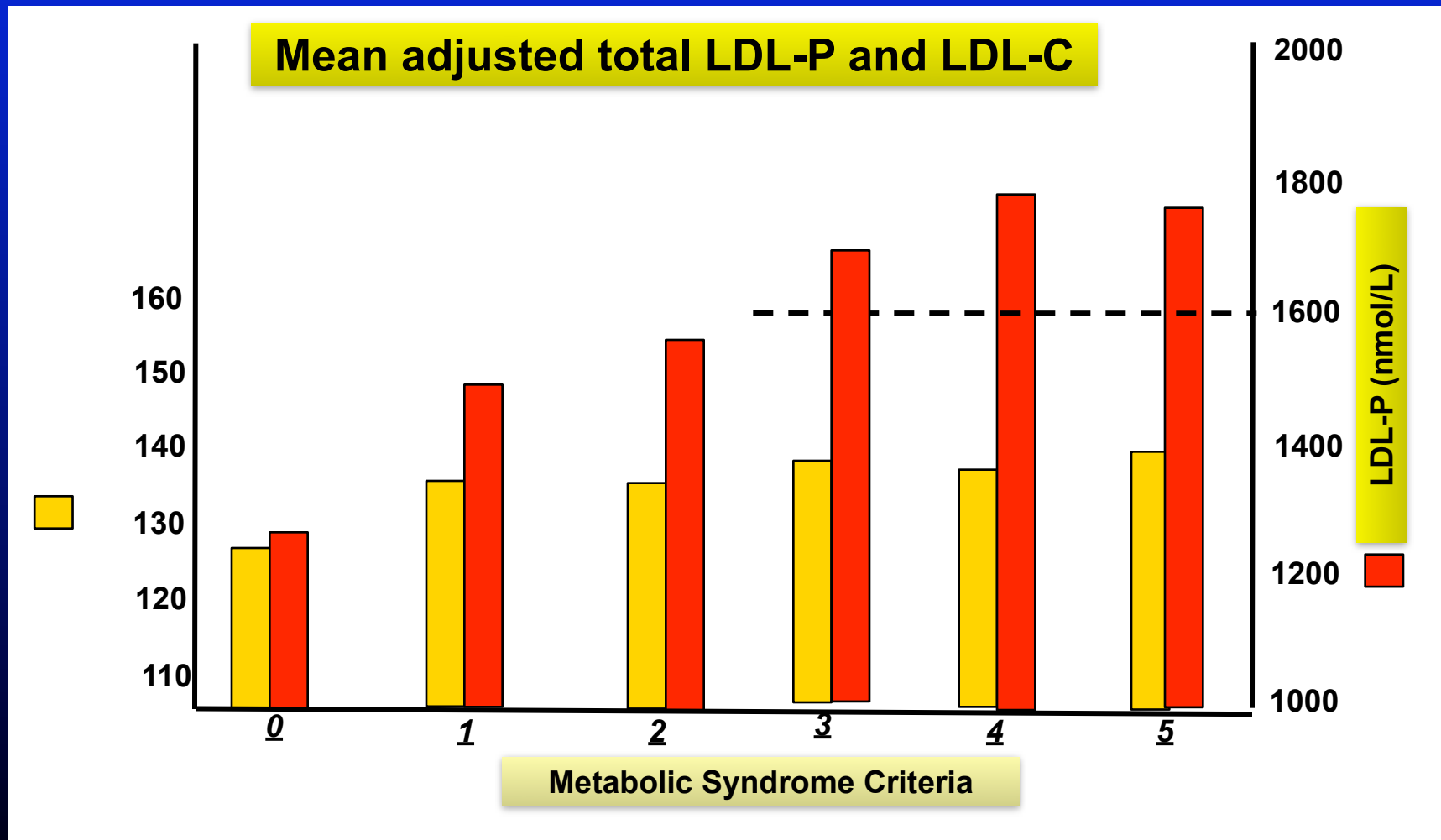


Despite similar levels of LDL-C there is an imbalance in LDL particle (LDL-P) concentration in the four groups

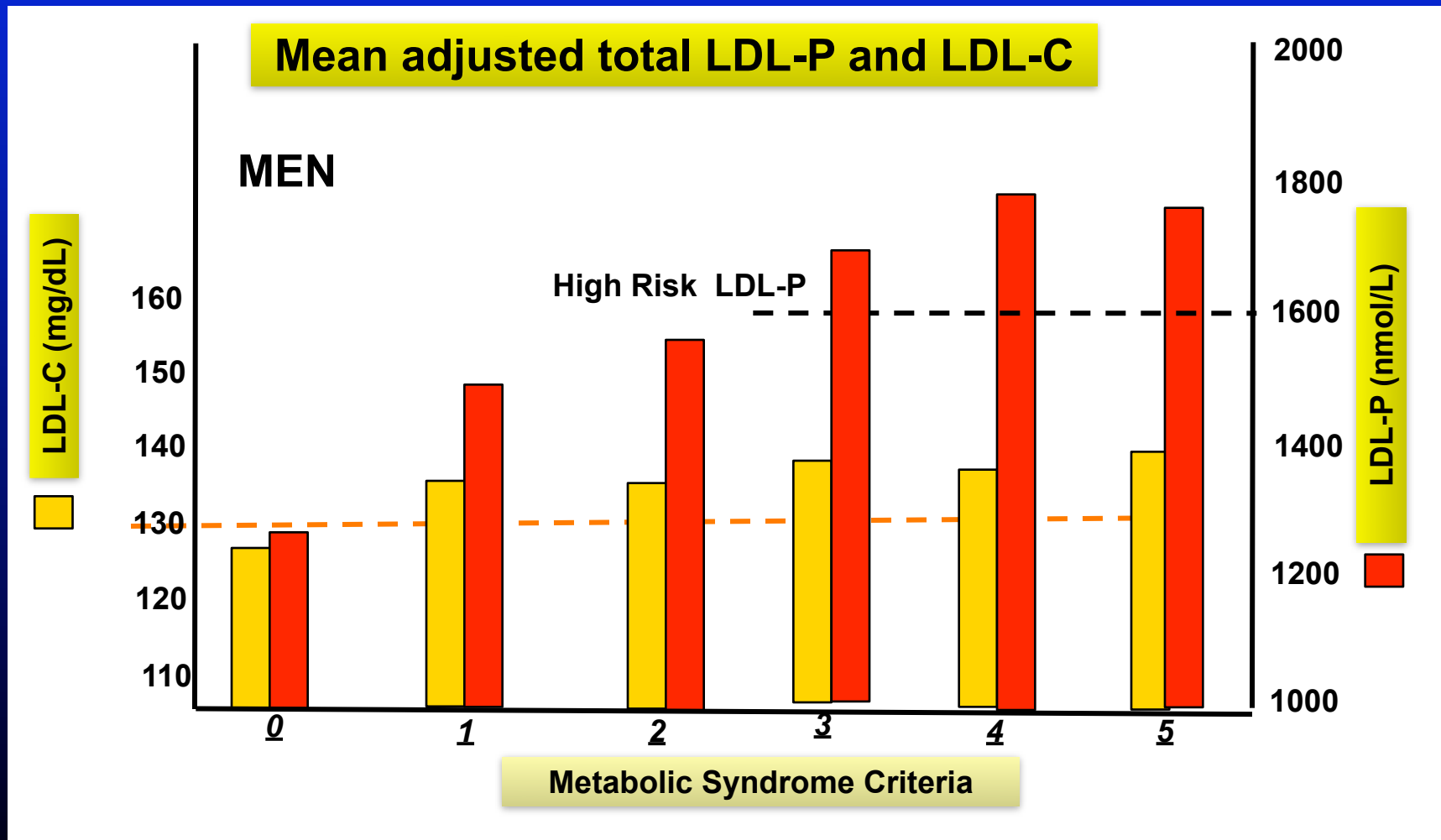
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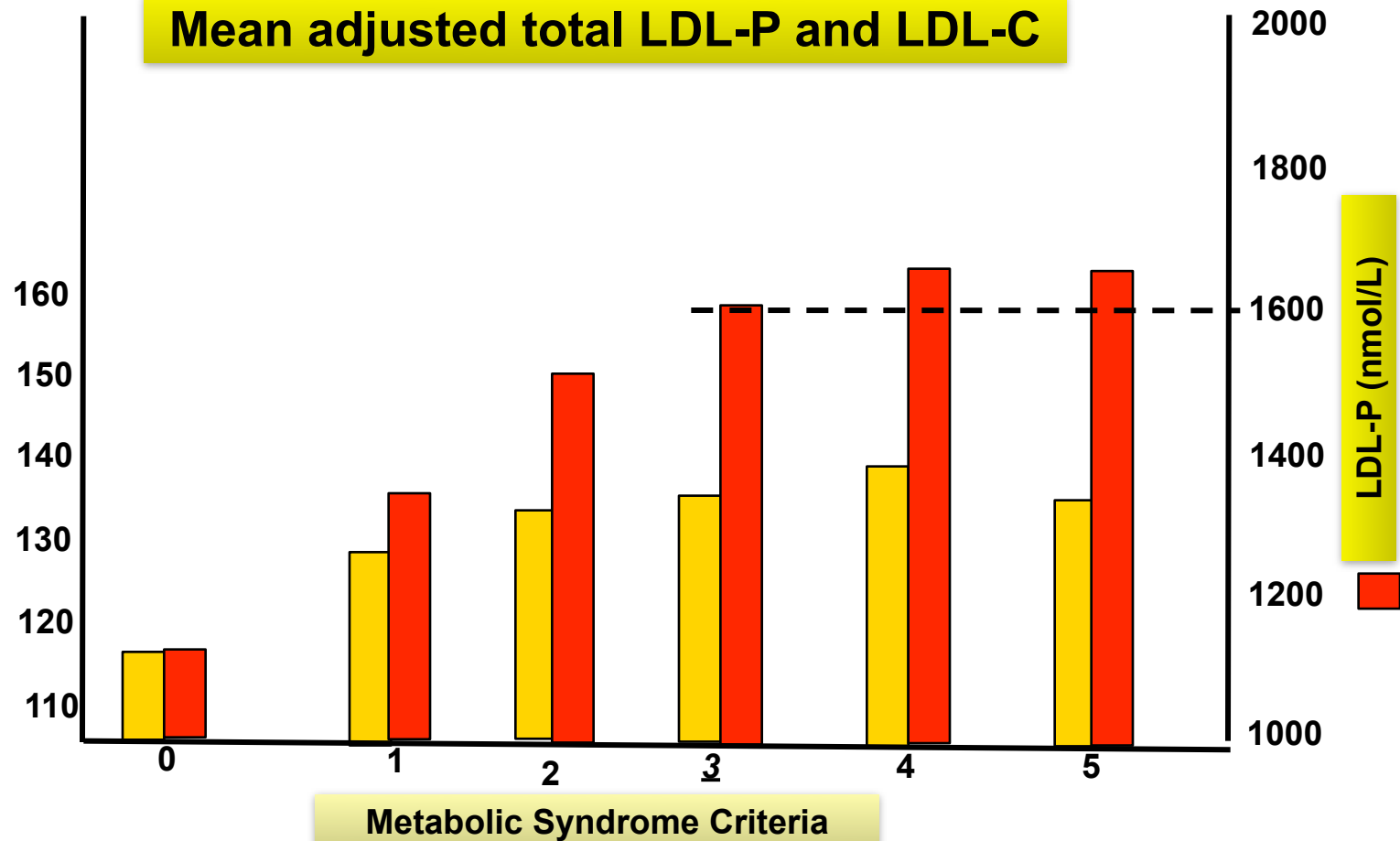
Framingham Offspring Study LDL-P and Metabolic Syndrome



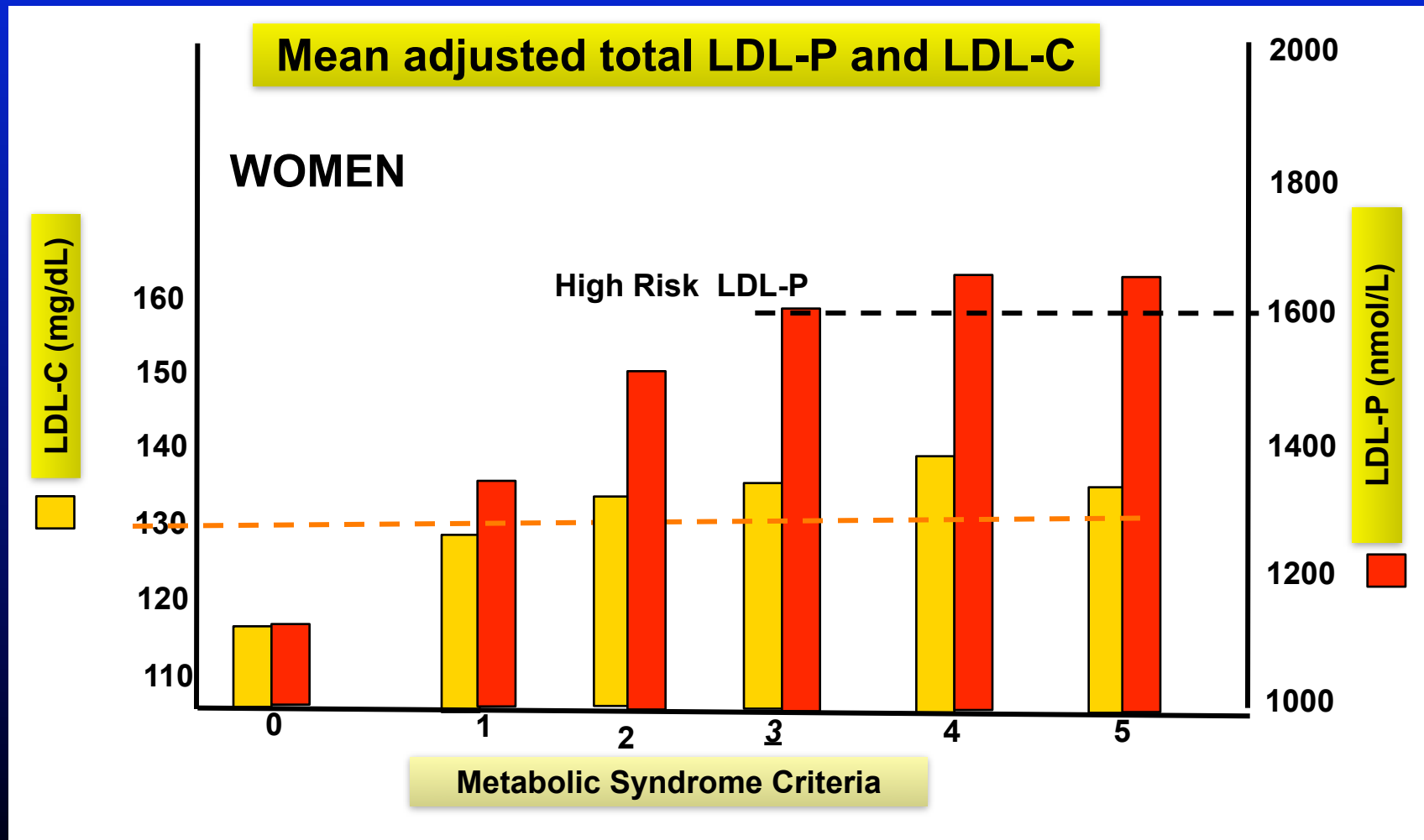
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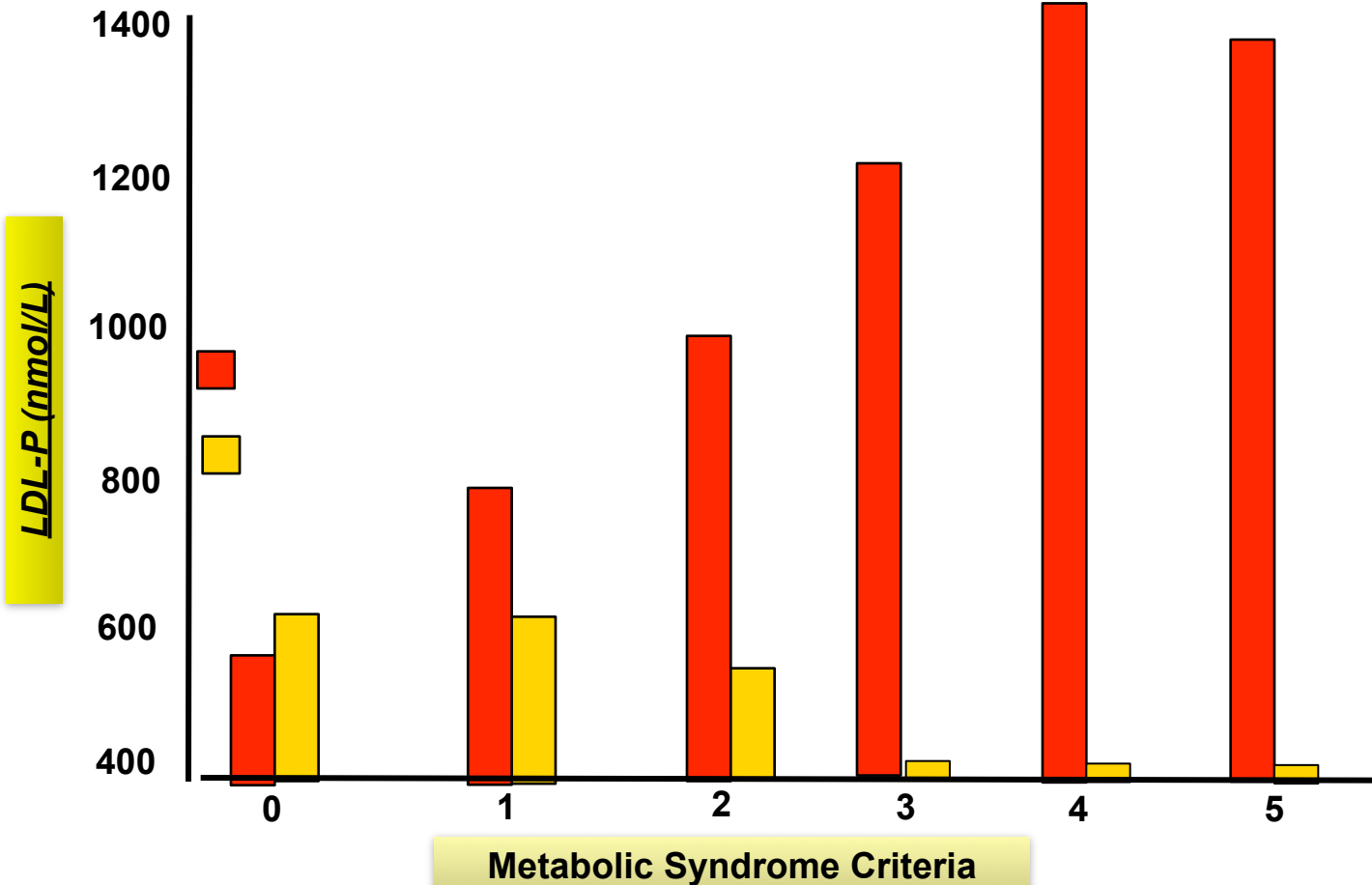


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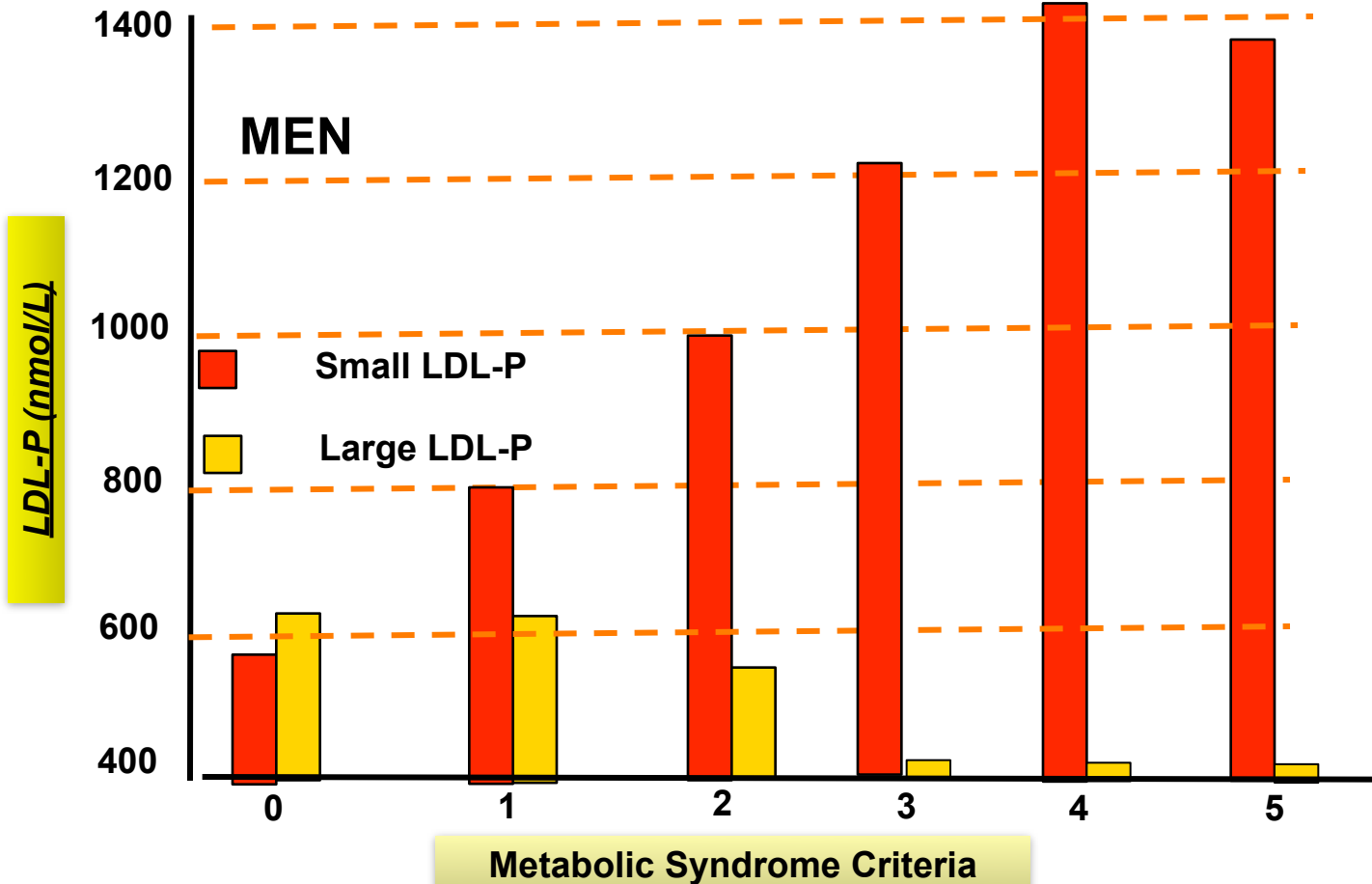
Framingham Offspring Study LDL-P and Metabolic Syndrome

Small and Large LDL-P



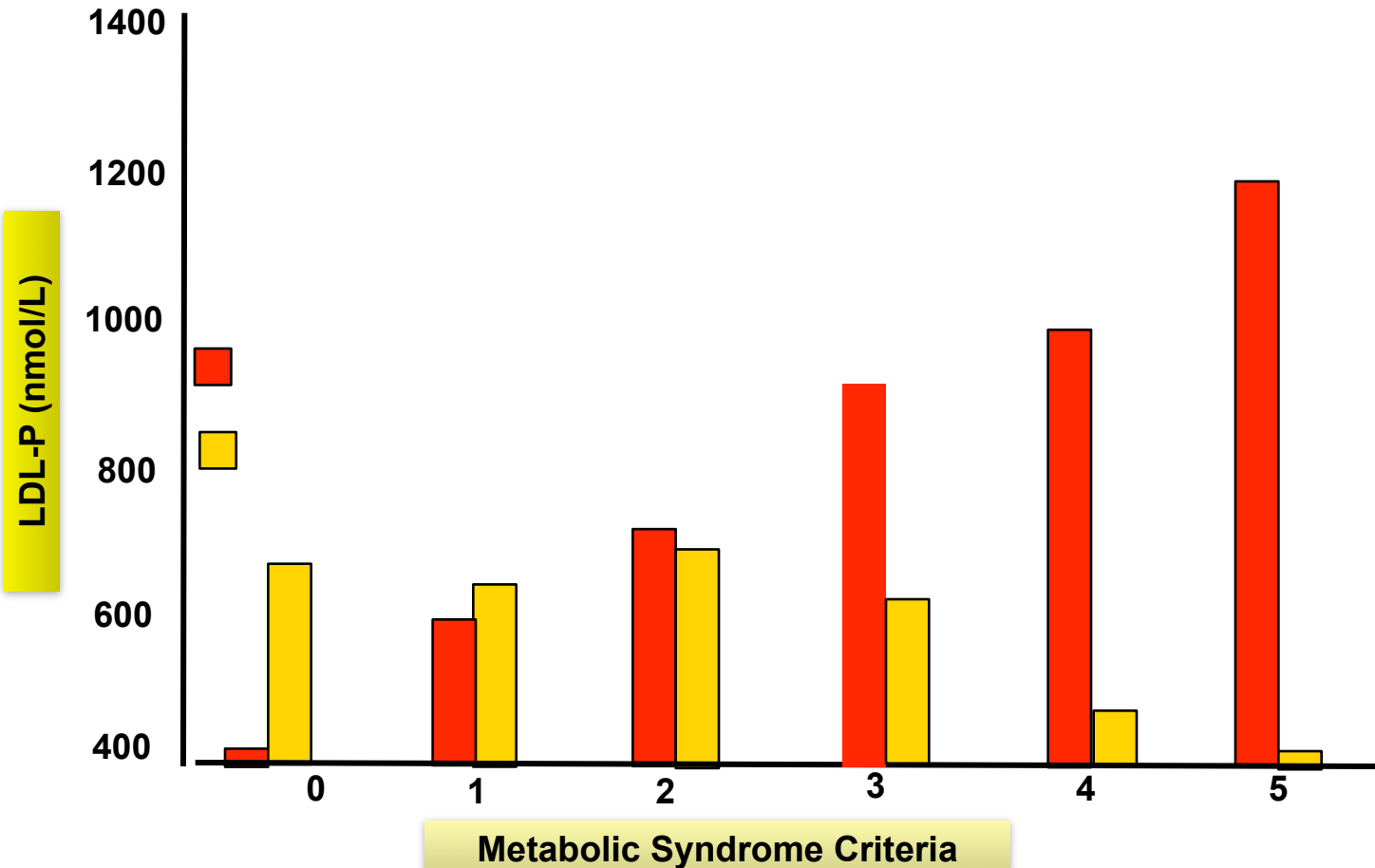
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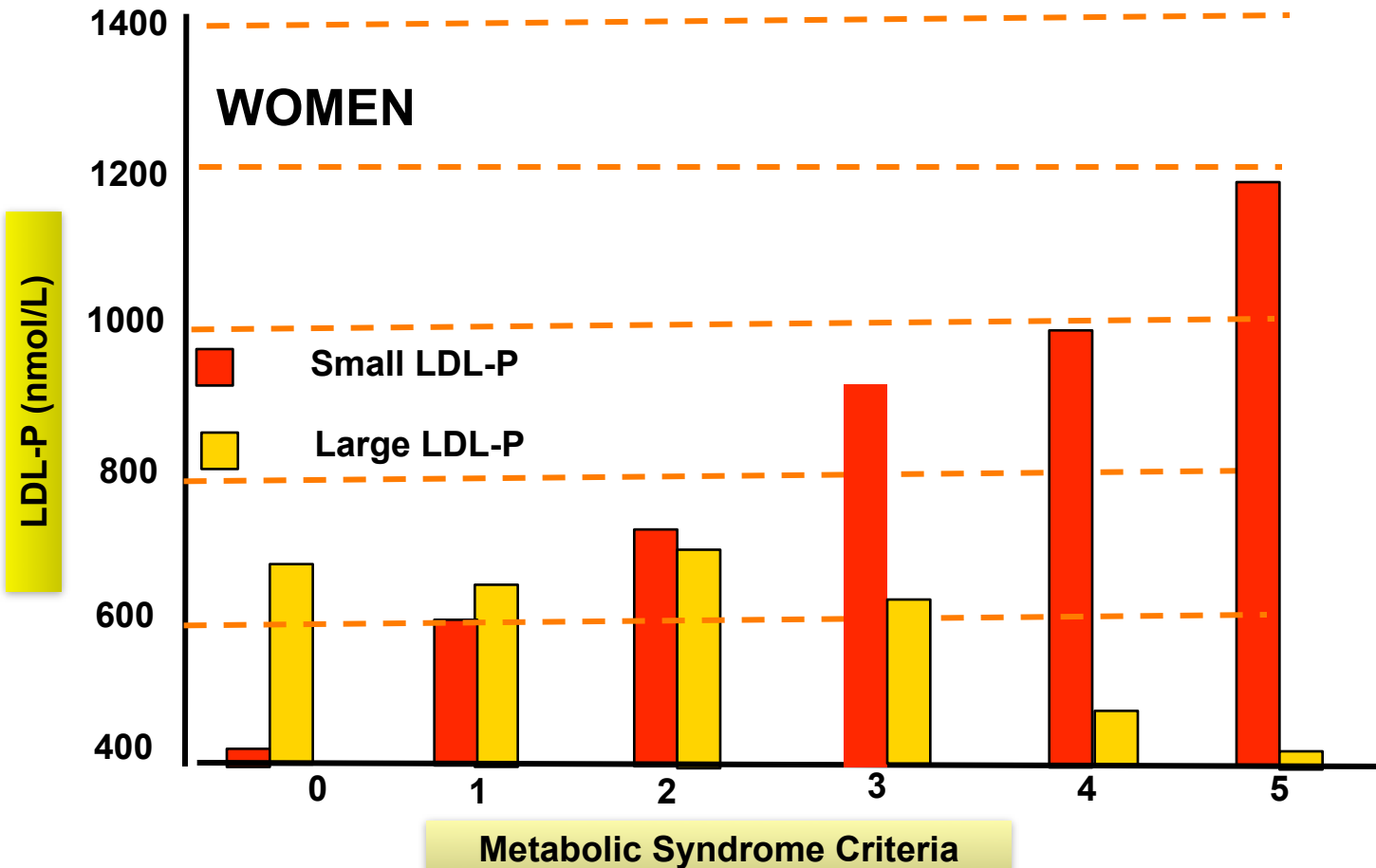
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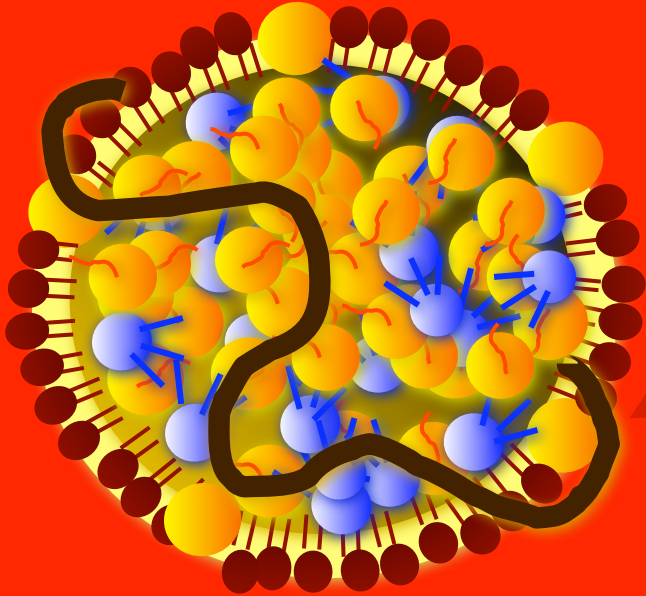


Framingham Offspring Study LDL-P and Metabolic Syndrome

Small and Large LDL-P



LDL Particle Concentration

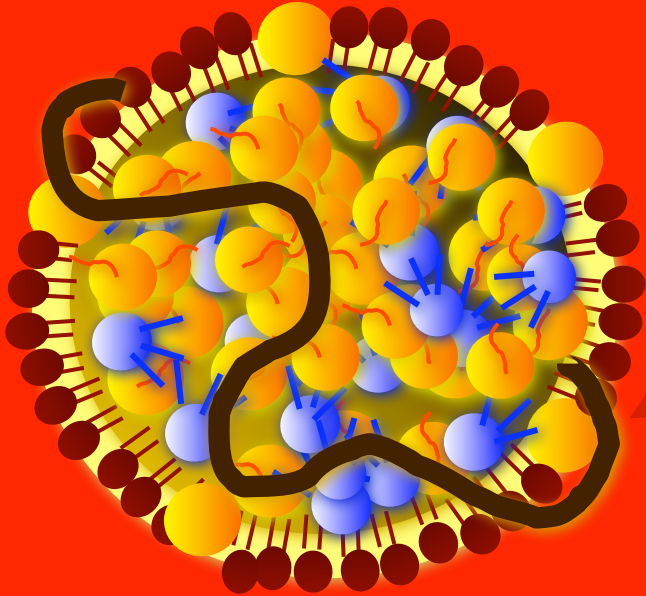


Apolipoprotein B

single molecule per particle

Because of their 3 day half Life
95% of apoB particles are LDLs

LDL Particle Concentration



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single molecule per particle

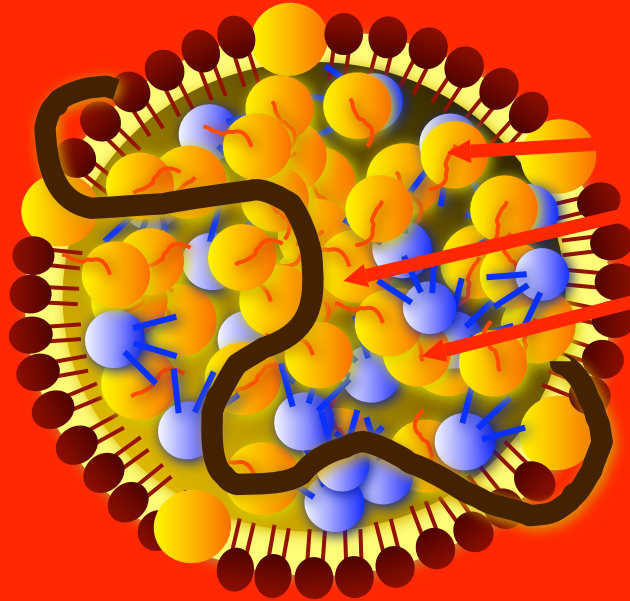
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LDL-P is estimated by measuring apoB

LDL-P Measured by NMR spectroscopy
or Centrifugation & Staining

Low Density Lipoprotein Particle

**LDL-P
or ApoB**

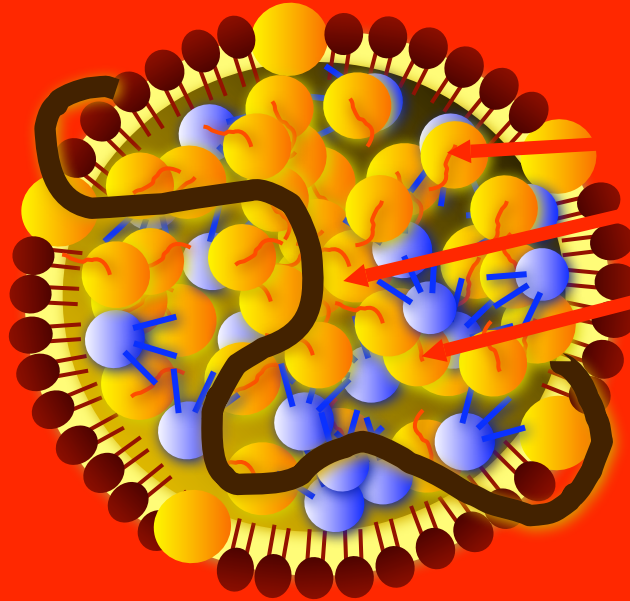


**Cholesterol
ester content of
LDL particle**

LDL-C

Low Density Lipoprotein Particle

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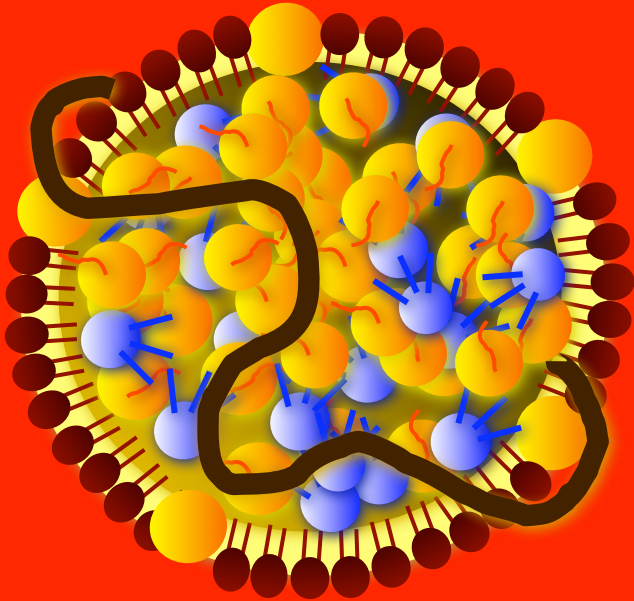
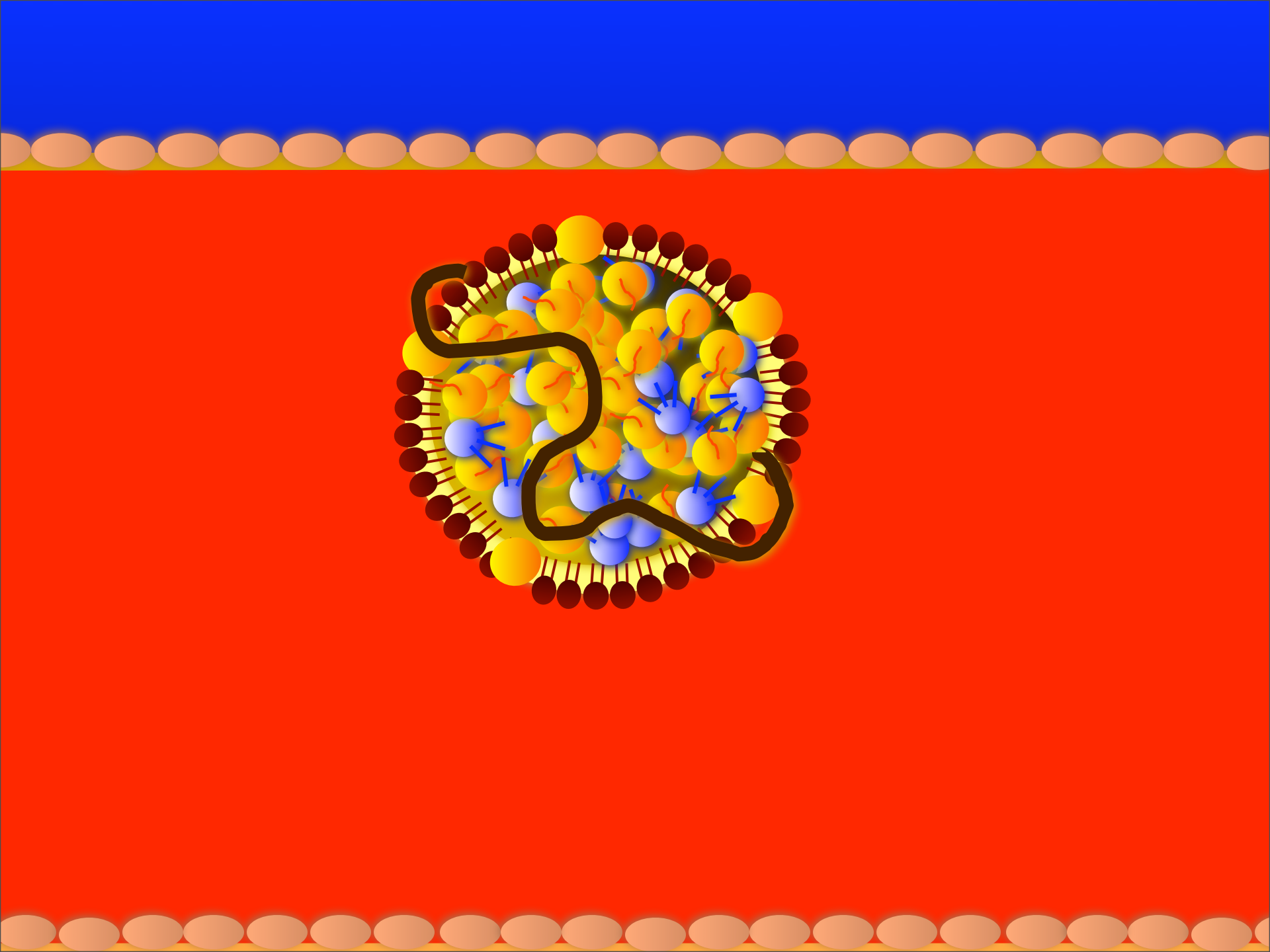


**Cholesterol
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LDL-C

Never confuse LDL-C with LDL-P (particle concentration)

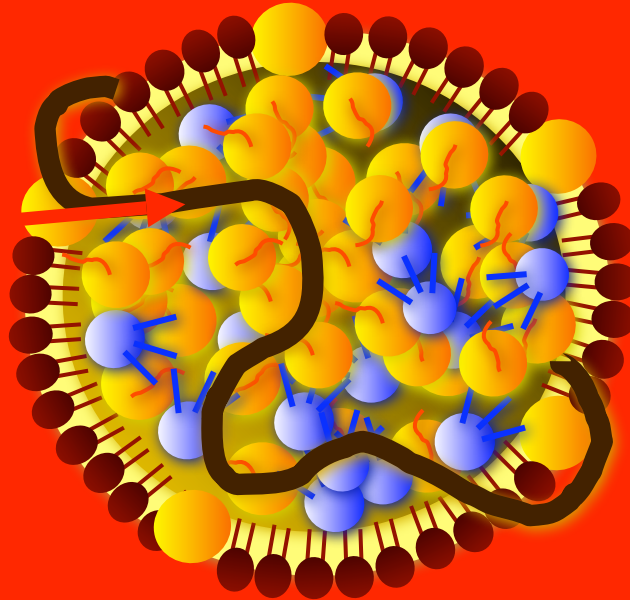
**The number of particles vs the cholesterol
content inside the particle**



LDL Particle Concentration

Estimated by
Apo B-100
concentration

Normal is
100-120 mg/dl

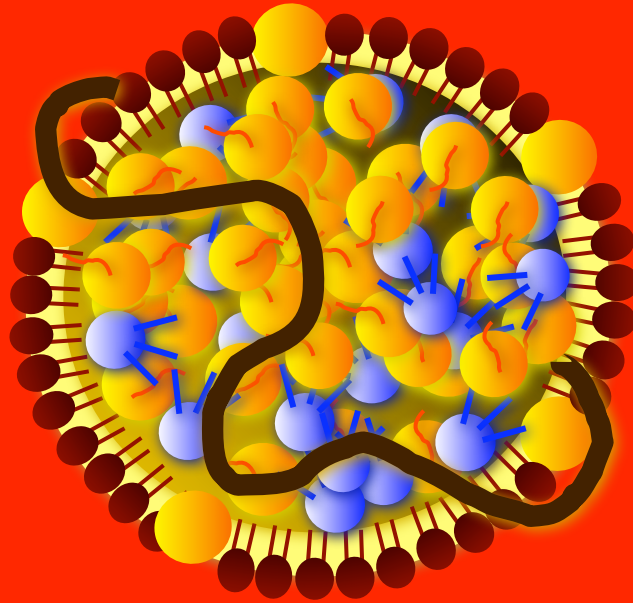


Most
Accurately
measured by
NMR
spectroscopy

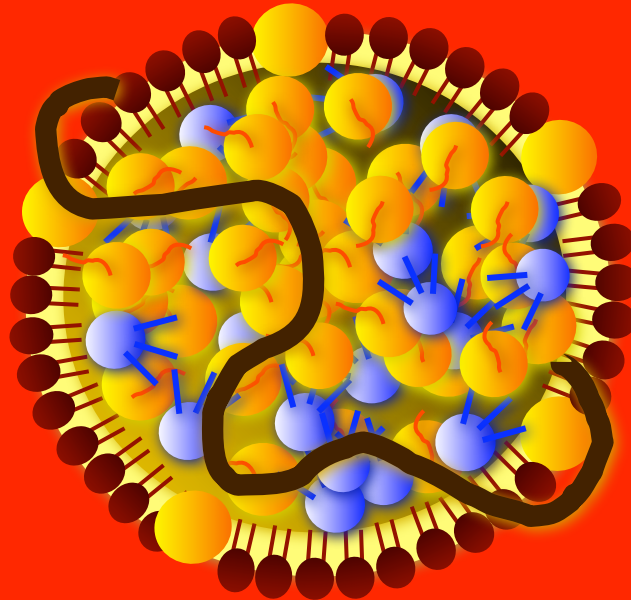
Normal is
< 1100 $\mu\text{mol/L}$

LDL particle concentration is the single
best predictor that we have of CHD risk

LDL Particle Concentration



LDL Particle Concentration



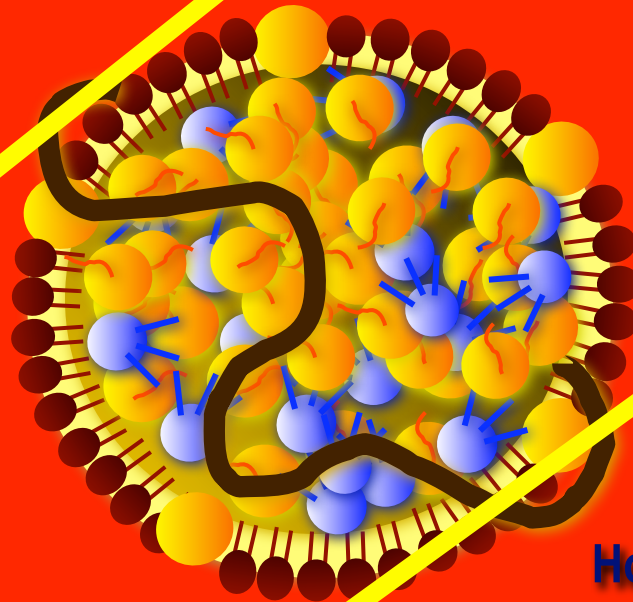
Most Accurately Measured by NMR spectroscopy

Normal is < 1000 $\mu\text{mol/L}$

Lipoprotein Particle Size



Lipoprotein Particle Size



The smaller the size of an apoB particle the more susceptible it is to oxidation and the less likely to it is to be cleared by hepatic LDL receptors

However, LDL particle size has no independent ability to predict CV events

LDL Particle Size

It is LDL-P, not LDL size that correlates with risk?

LDL Particle Subclass

LDL Particle Subclass

- ✦ LDL particles are a **heterogeneous mixture of particles** of varying composition and size, each with a single molecule of apoB

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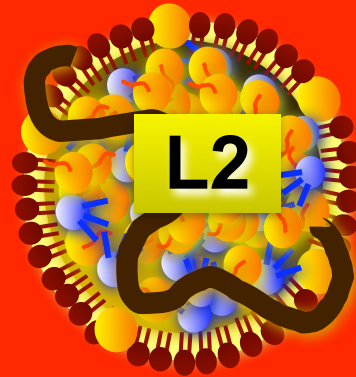
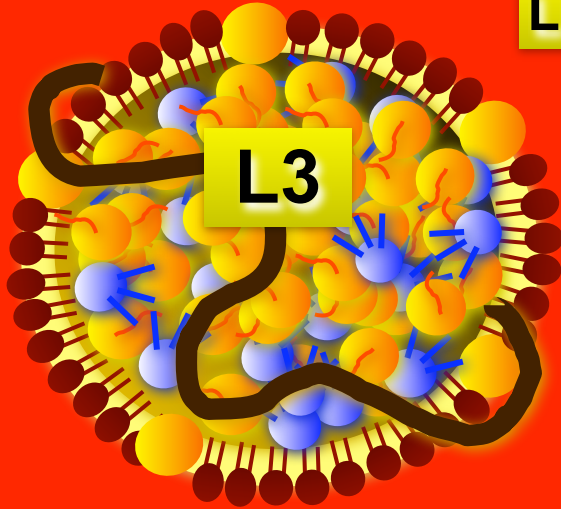
LDL Particle Subclass (NMR*)

*Nuclear magnetic resonance spectroscopy

Arterioscler Thromb Vasc Biol 1998;18:1046-1053
Handbook of Lipoprotein Testing 2000 AACC Press

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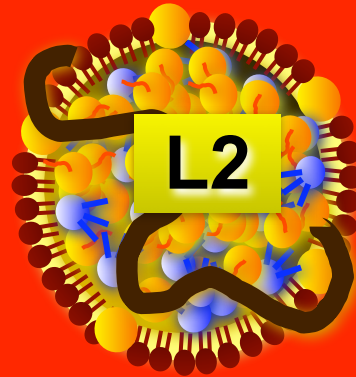
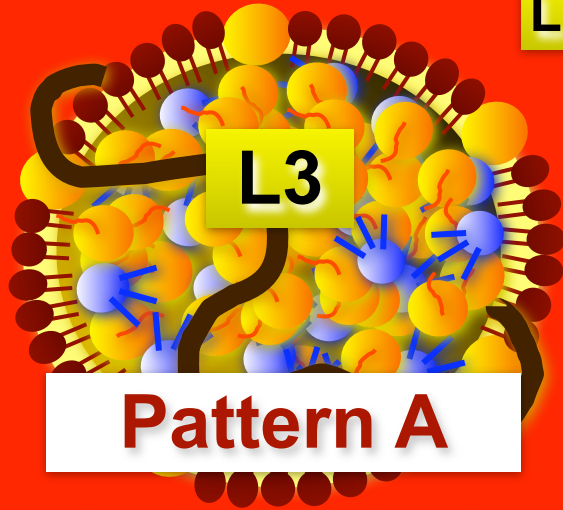
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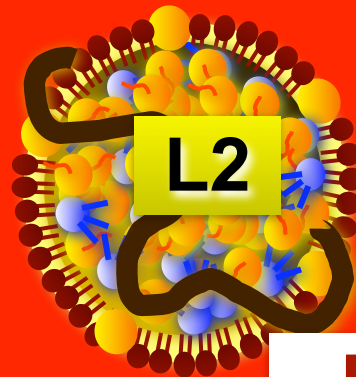
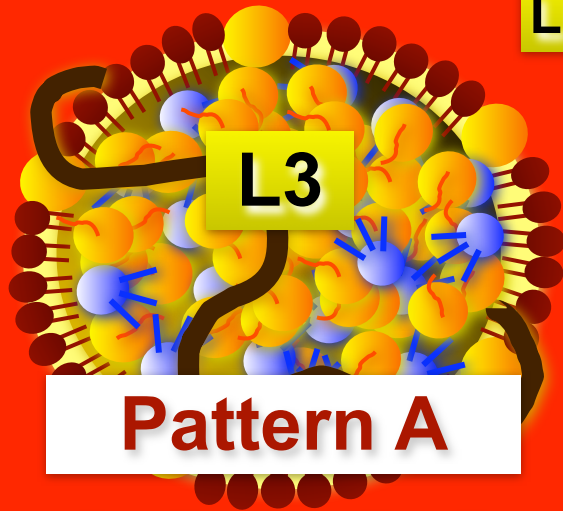
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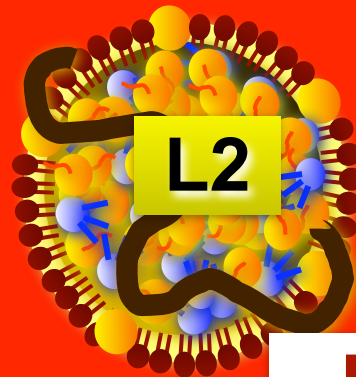
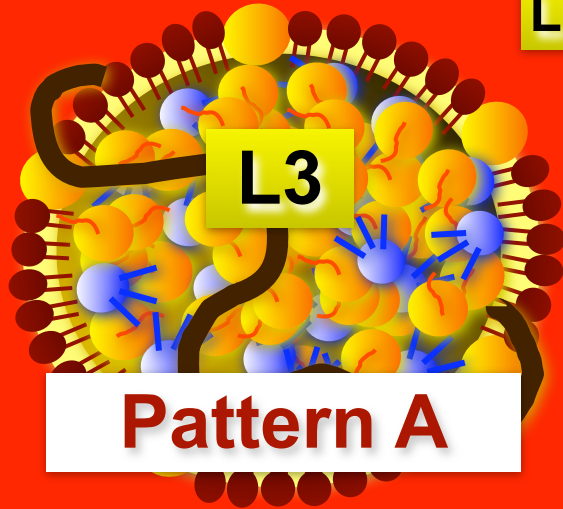
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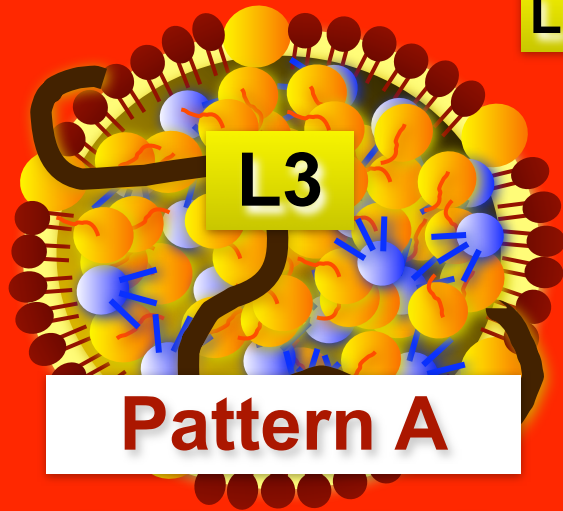


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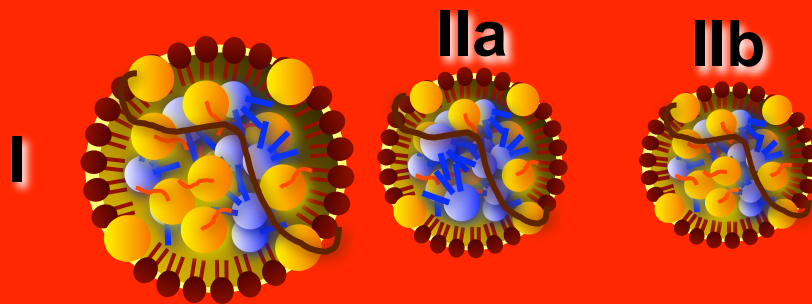
LDL Particle Subclass

NMR classification

L3

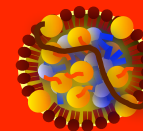
L2

L1

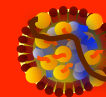


Gel Fractionation classification

Not drawn to scale



IIIa+b



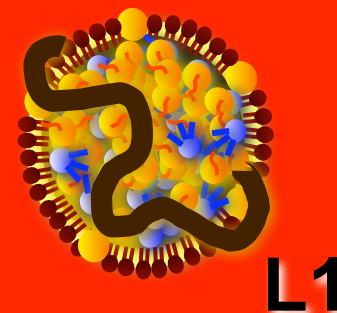
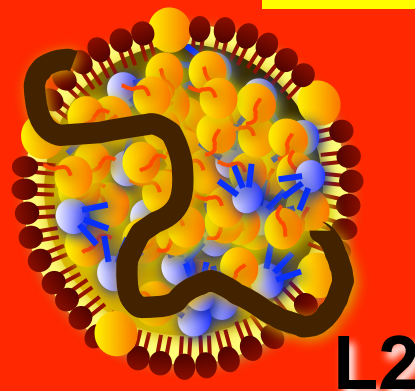
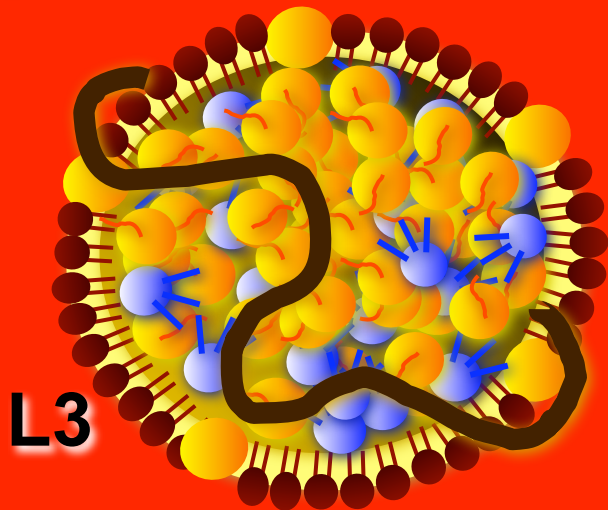
IVa



IVb

LDL Particle Subclass

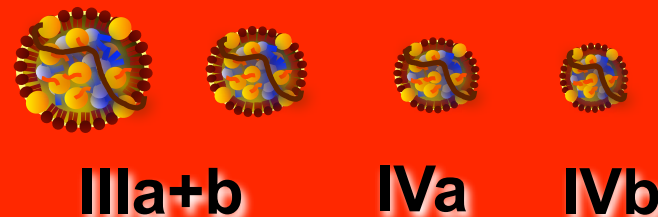
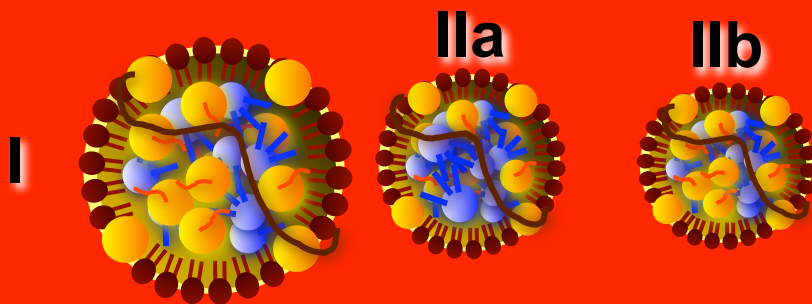
NMR classification



Pattern A

Pattern B

Not drawn to scale



Gel Fractionation classification

IIIa+b

IVa

IVb

LDL-P (LDL Particle Number)

LDL-P (LDL Particle Number)

- ✦ The total number of LDL particles in nanomoles per liter

Under 1000

Optimal

1000-1299

Near
Optimal

1300-1599

Borderline
High

1600-2000

High

> 2000

Very High

LDL-P (LDL Particle Number)

- ◆ The total number of LDL particles in nanomoles per liter
 - 1 nmol/L = 6×10^{14} particles/L. Plasma volume ~ 2.7 L
 - 600,000,000,000,000 (six hundred trillion)

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- 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 2.7 liters of plasma there would be $.6 \times 10^{18}$ particles
 - **600 quadrillion** – or put another way:
 - 0.6,000,000,000,000,000,000 (.6 quintillion LDL particles)

Under 1000

1000-1299

1300-1599

1600-2000

> 2000

Optimal

Near
Optimal

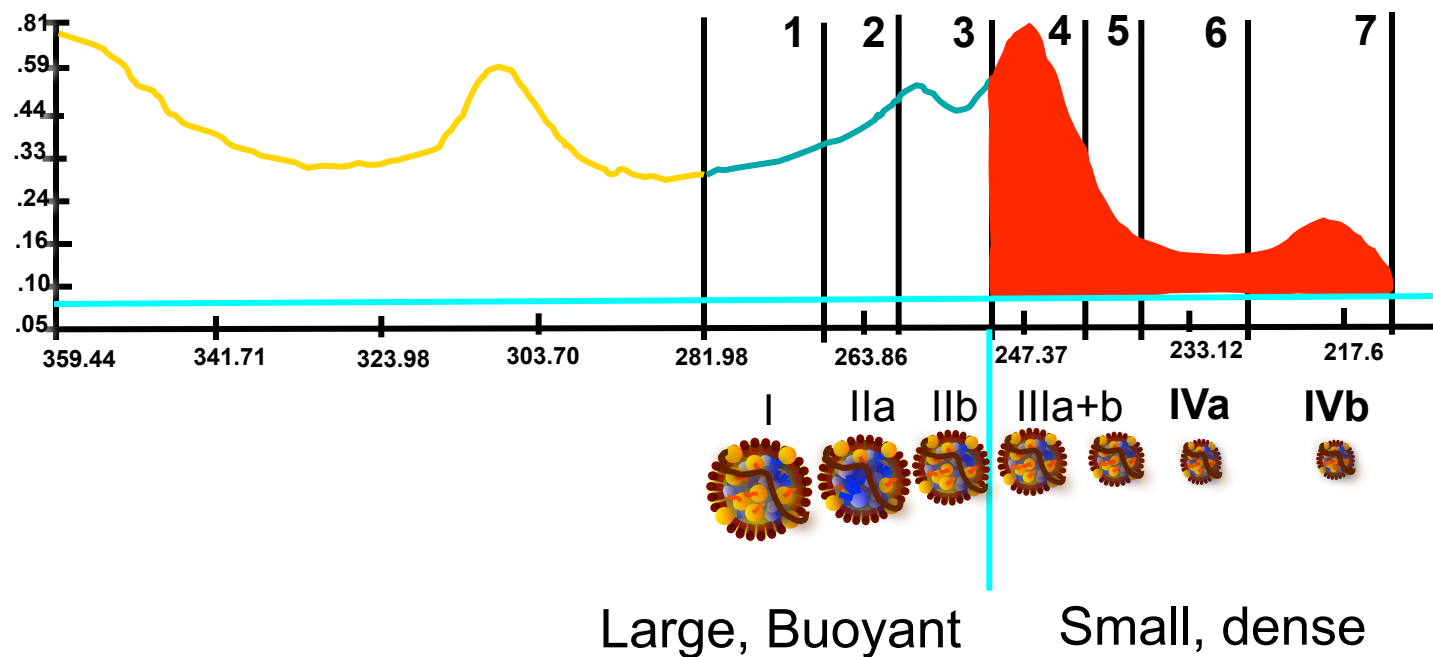
Borderline
High

High

Very High

LDL Sizing by 3 Segmented Non-Linear Gradient Gel Electrophoresis

LDL-S₃GGE™



Segmented LDL Subclass Determination

Using the NMR Lipoprofile

Small LDL-P (Small LDL Particle Number)

Under 600

Low

600-850

Moderate

850-1200

Borderline
High

> 1200

Very High

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 IDL-P is < 850 nmol/L (50th percentile)

Under 600

Low

600-850

Moderate

850-1200

Borderline
High

> 1200

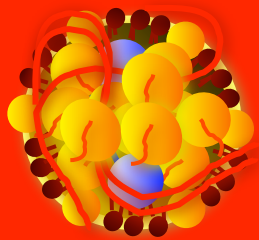
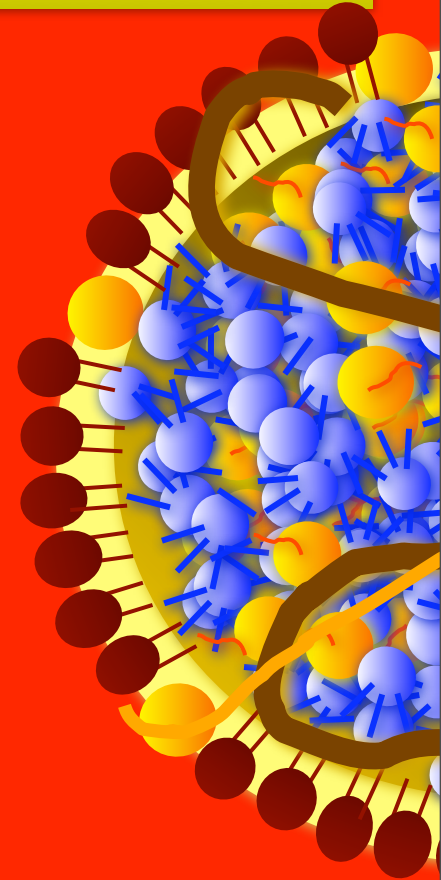
Very High

LDL & HDL Particles in Patients with Elevated TG

LDL Particle



VLDL Particle



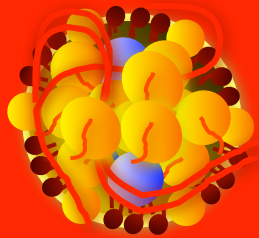
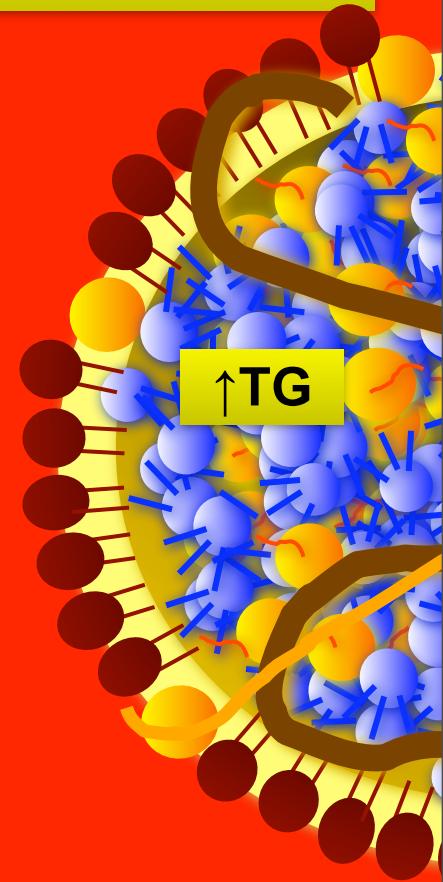
Mature HDL

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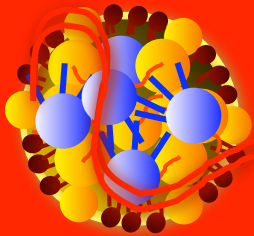


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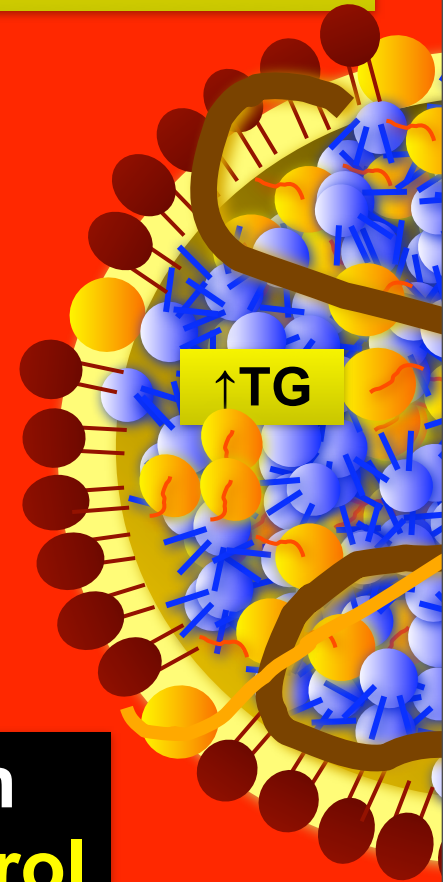
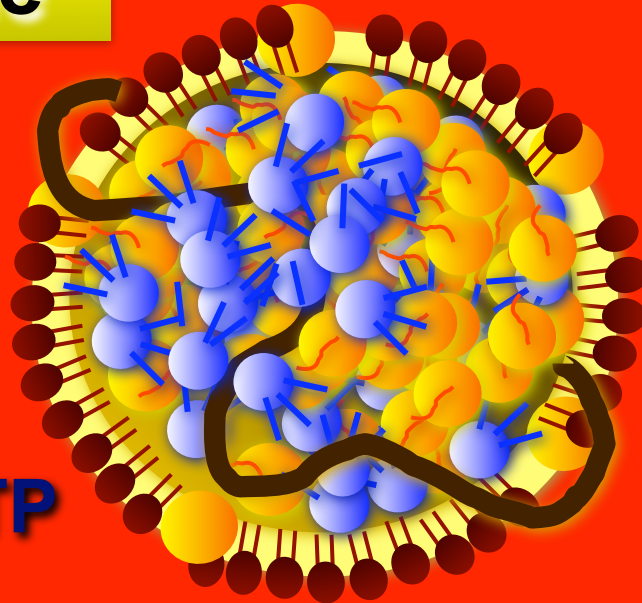
VLDL Particle



Mature HDL

CETP

**Cholesteryl Ester
Transfer Protein**



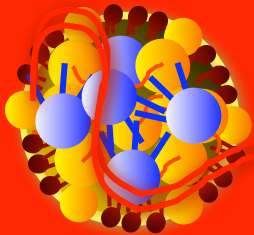
The LDL & HDL particle composition shifts with **more TG and **less cholesterol****

LDL & HDL Particles in Patients with Elevated TG

LDL Particle

VLDL Particle

**LDL-C & HDL-C
are reduced**



Mature HDL

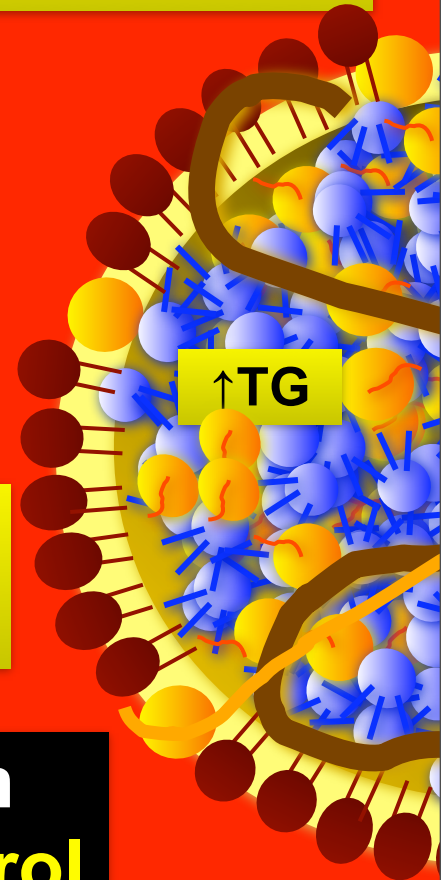
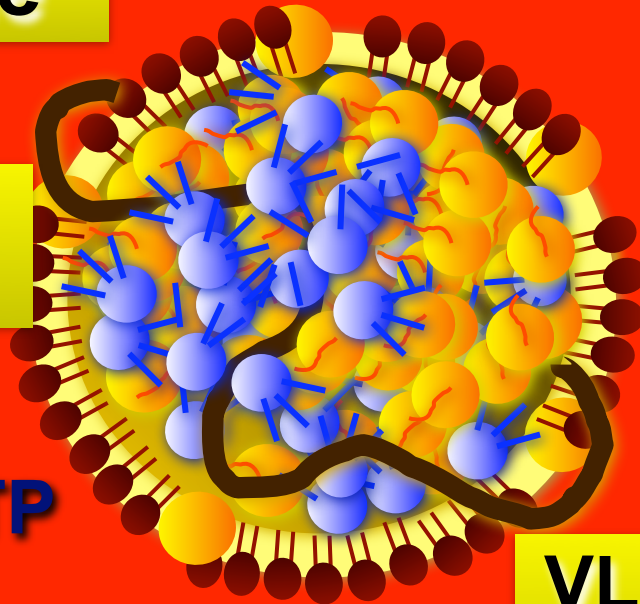
CETP

**Cholesteryl Ester
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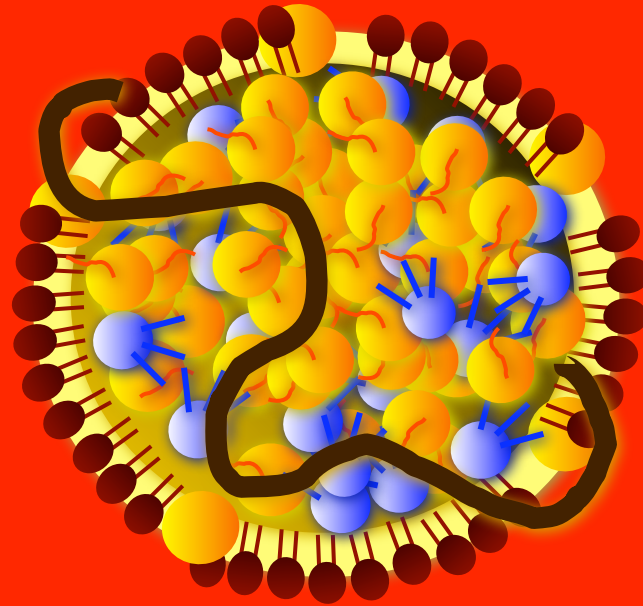
**VLDL-C is
increased**

↑TG

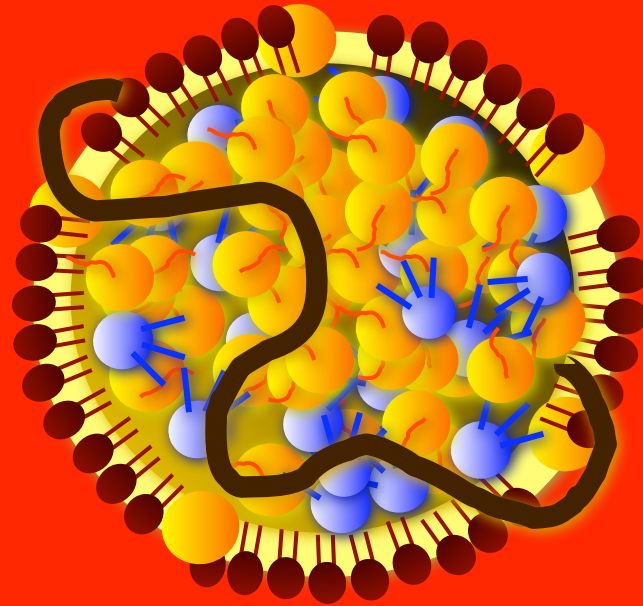
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Fate of TG-rich LDL Particles



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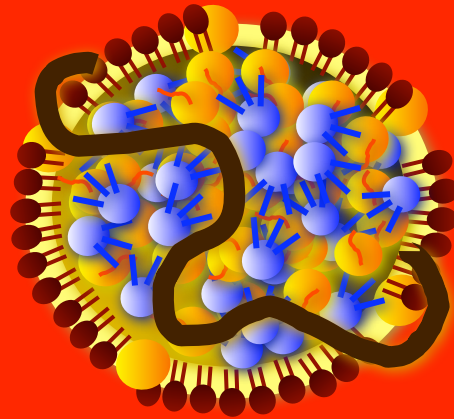


Hepatic Lipase
Has both TG-lipase and
phospholipase activity

Hepatic Lipase causes further lipolysis
(**hydrolysis of TG & phospholipids**) which
reduces the size of the LDL particle

Fate of TG-rich LDL Particles

It will take more
(up to 70%) LDL
particles to carry a
given level of
cholesterol



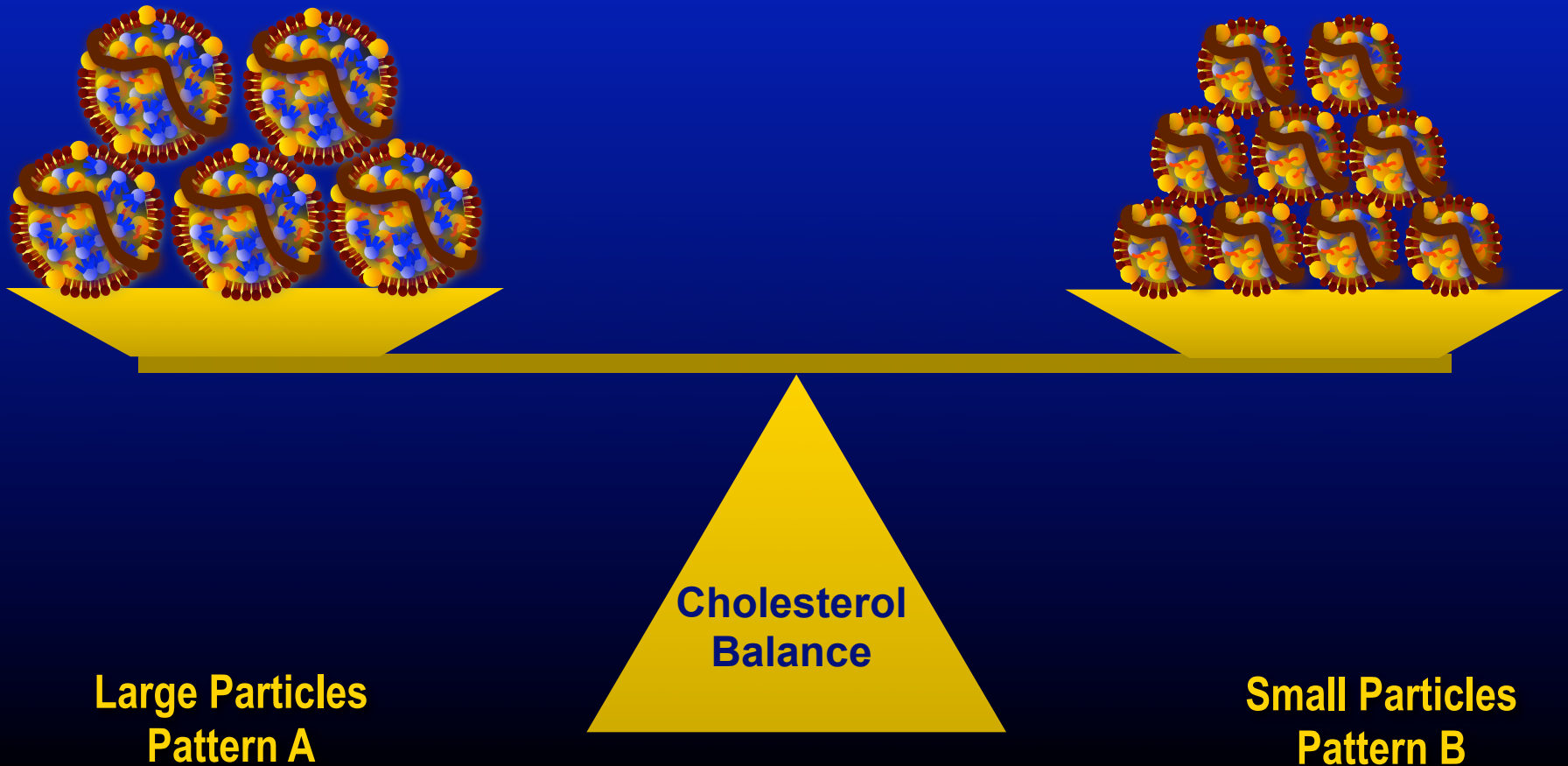
Hepatic Lipase
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↑ LDL-P

**LDL particle
size is
reduced**

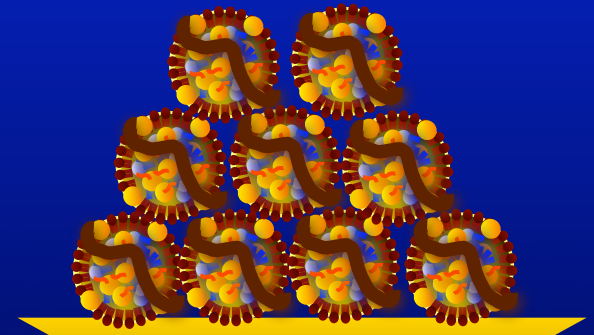
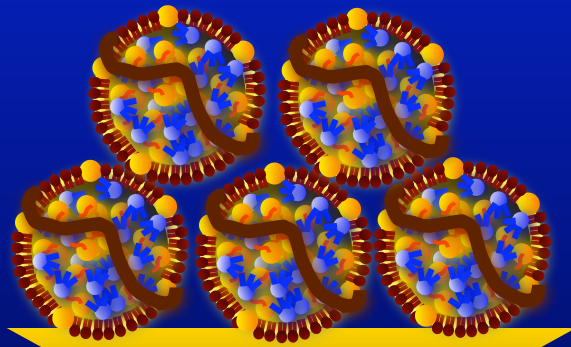
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Two Patients with the same LDL-C Who is at risk?



Two Patients with the same LDL-C Who is at risk?

The volume of a sphere is a third power of the radius



Cholesterol
Balance

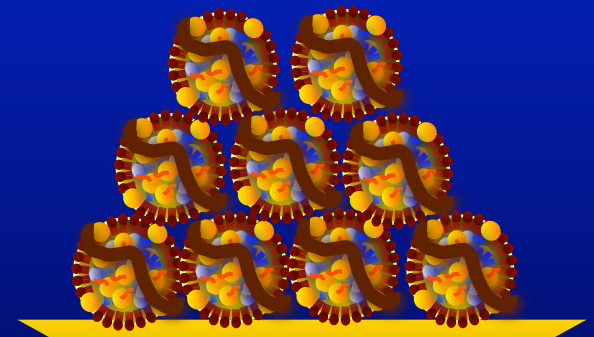
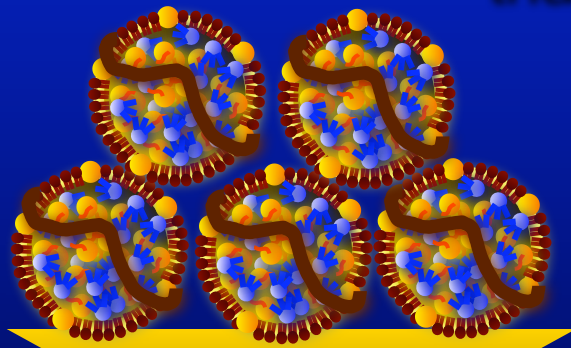
Large Particles
Pattern A

Small Particles
Pattern B

Two Patients with the same LDL-C Who is at risk?

At the same level of LDL cholesterol, people with small LDLs can have **up to 70%** more particles than people with large LDLs

The volume of a sphere is a third power of the radius



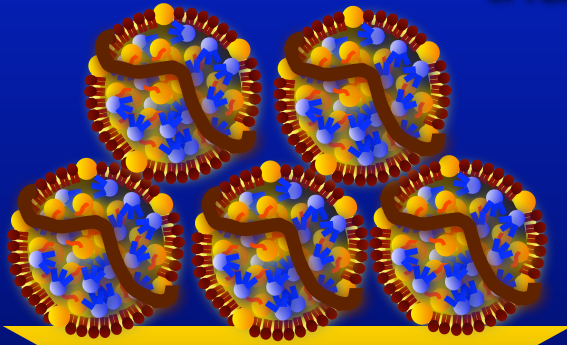
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Balance

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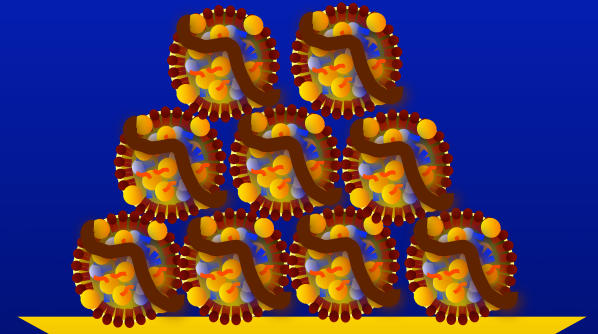
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Normal apoB & LDL
particle concentration
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Cholesterol
Balance

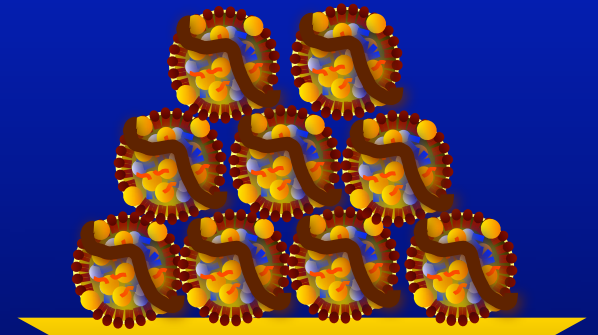
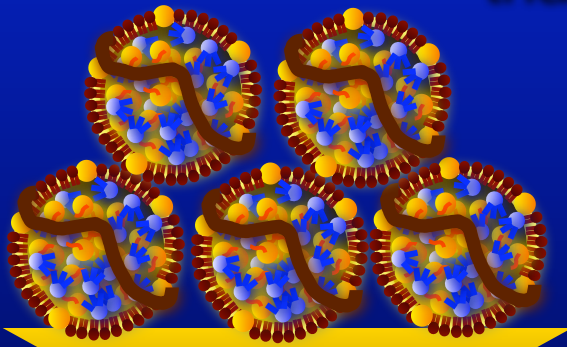
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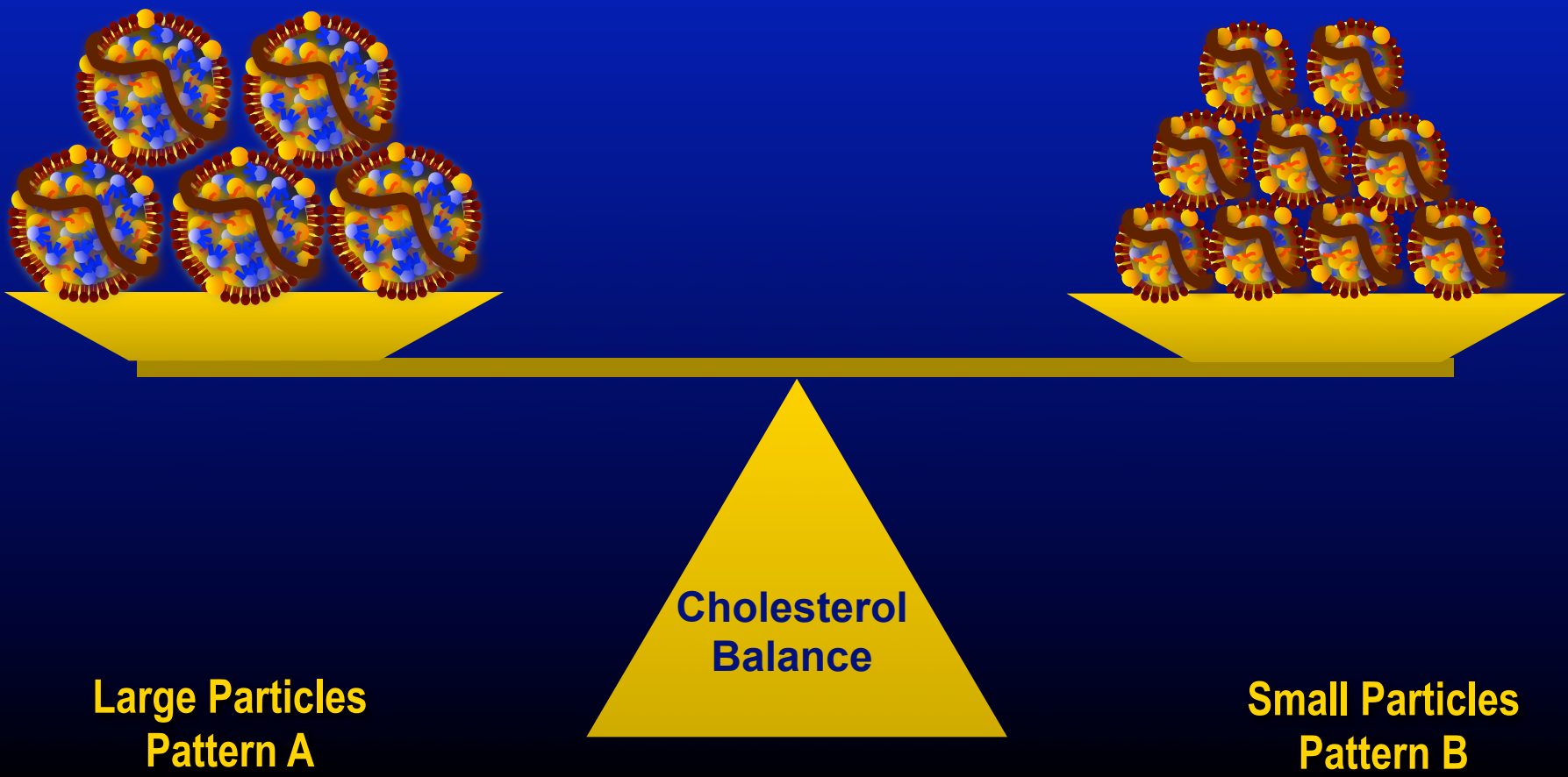
Increased apoB & LDL
particle concentration
(LDL-P)

Cholesterol
Balance

Large Particles
Pattern A

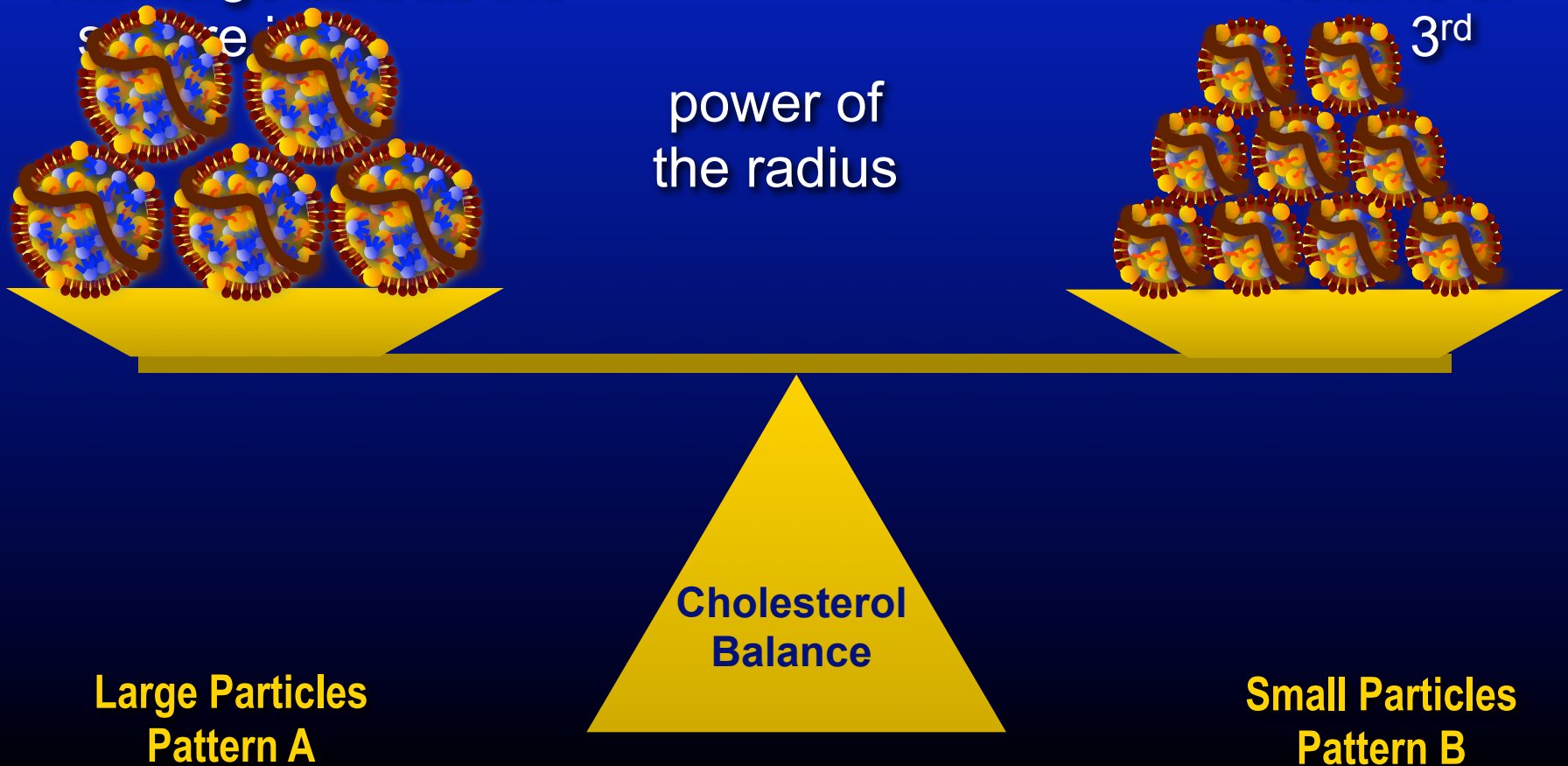
Small Particles
Pattern B

Two Patients with the same LDL-C Who is at risk?



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At the same level of LDL cholesterol, people with small, dense LDL can have **up to 70%** more particles than people with large LDL as the volume of



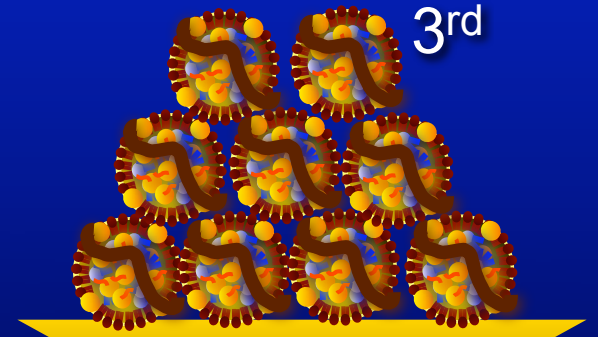
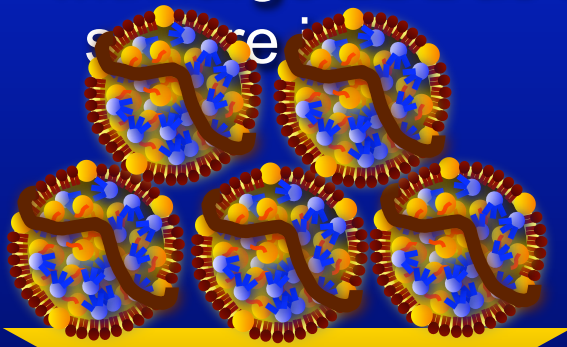
Two Patients with the same LDL-C Who is at risk?

At the same level of LDL cholesterol, people with small, dense LDL can have **up to 70%** more particles than people with large LDL as the

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3rd

power of
the radius



Normal apoB & LDL
particle concentration
(LDL-P)

Increased apoB & LDL
particle concentration
(LDL-P)

Cholesterol
Balance

Large Particles
Pattern A

Small Particles
Pattern B

Triglyceride Effects on

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1) Elevated TG are often associated with atherogenic chylomicron and VLDL remnants

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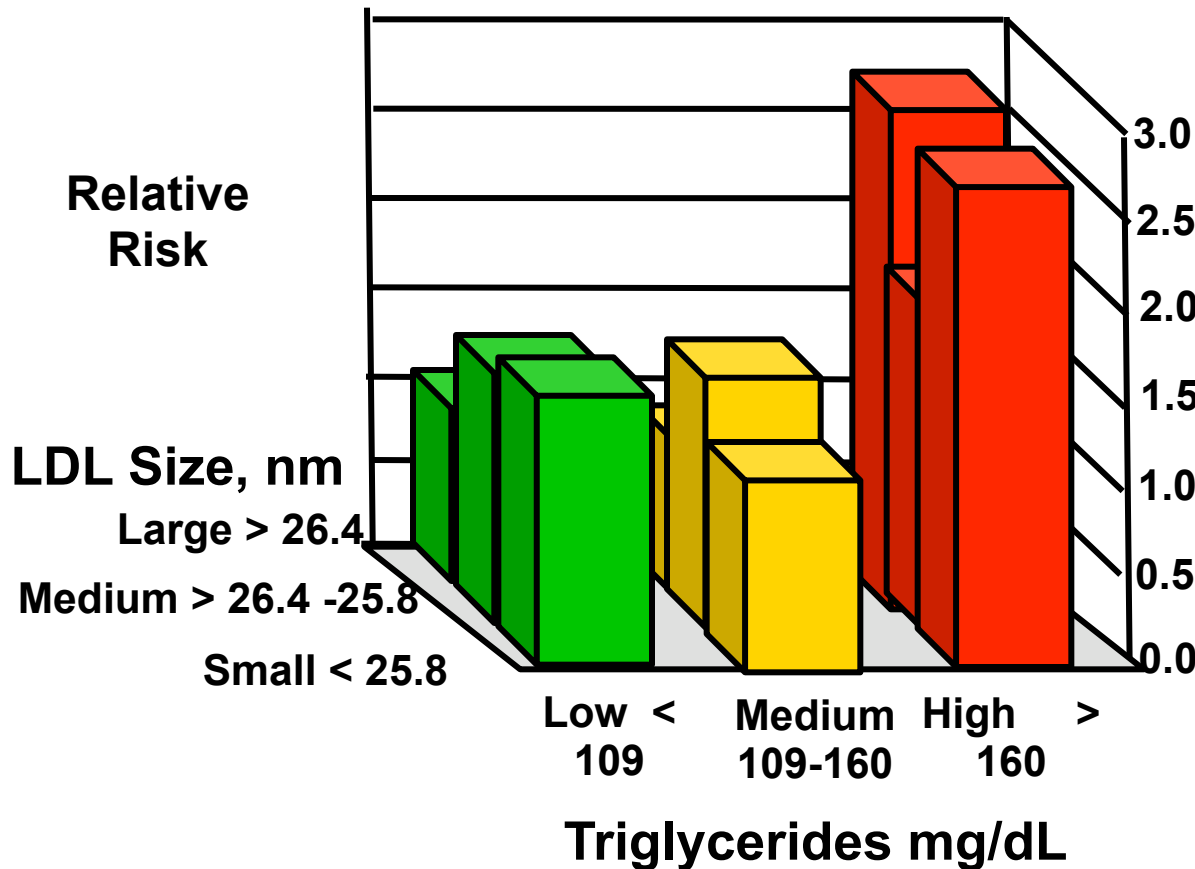
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- 4) Elevated hepatic TG concentrations result reduction of HDL particles overburdened with reverse cholesterol transport: **HDL-C drops**

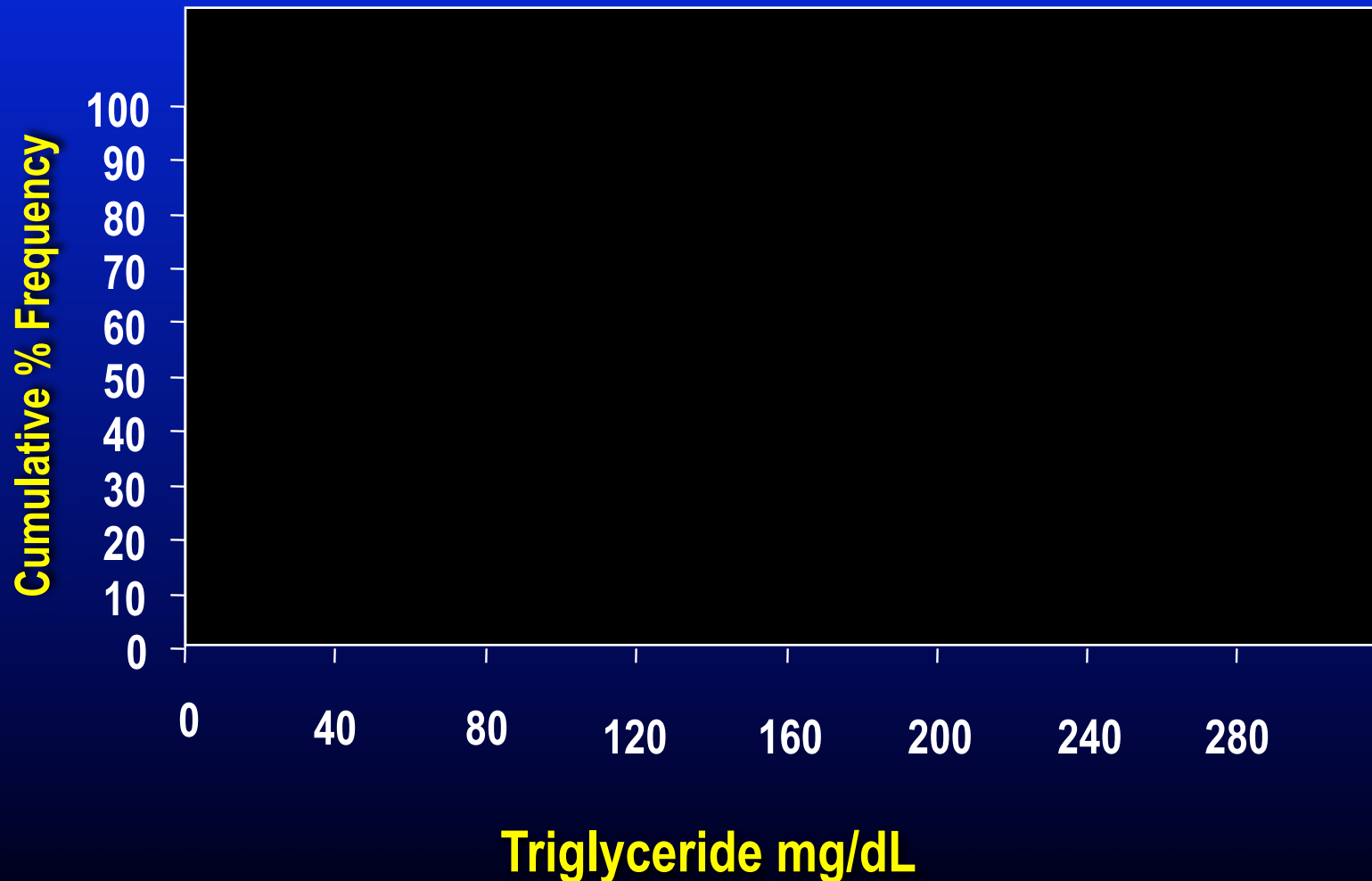
Physicians Health Study



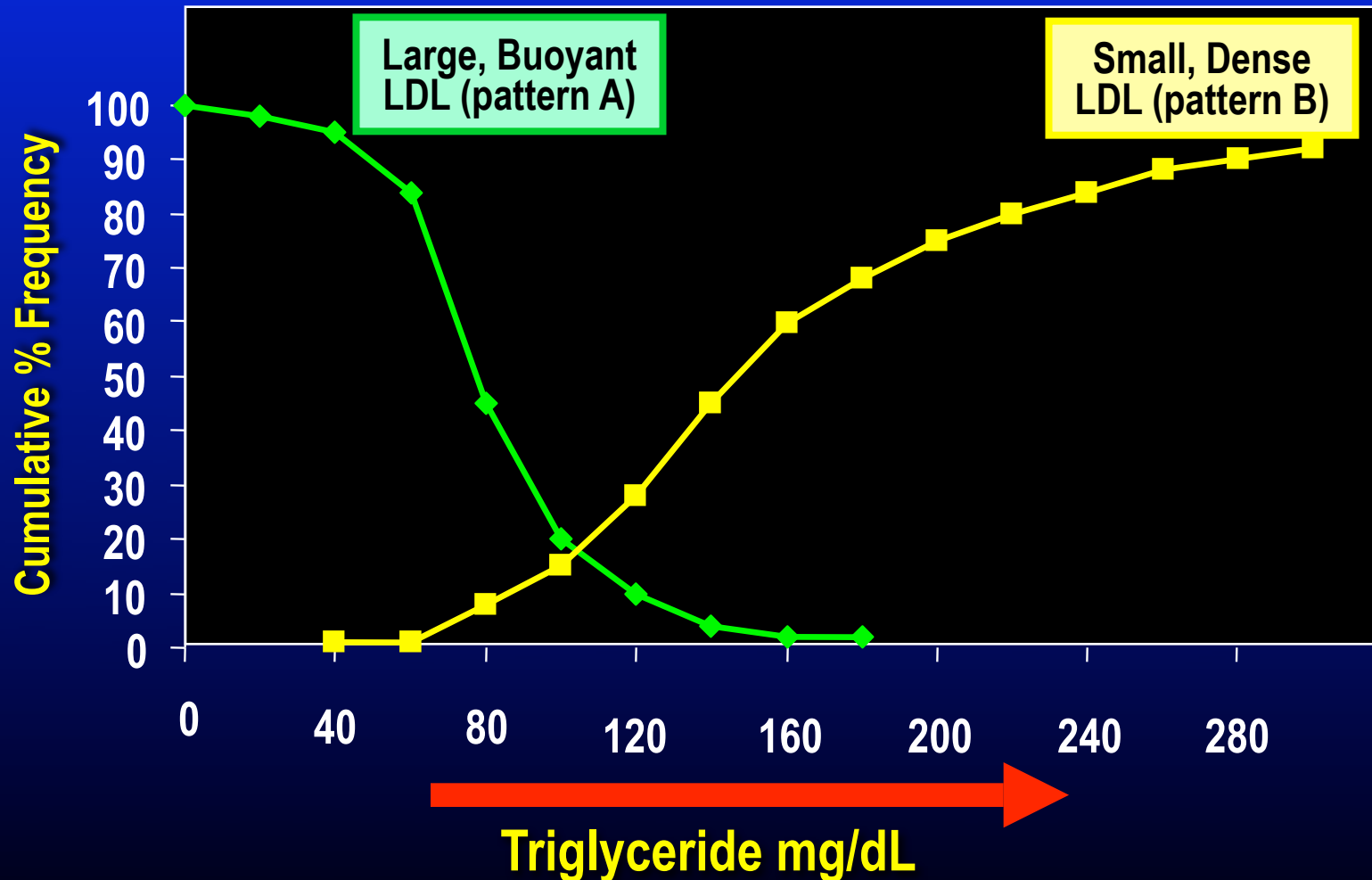
This figure demonstrates that the association between small LDL size and MI arises only from the association between small LDL size and high triglyceride concentration.

High triglyceride concentration is independently related to MI regardless of LDL size.

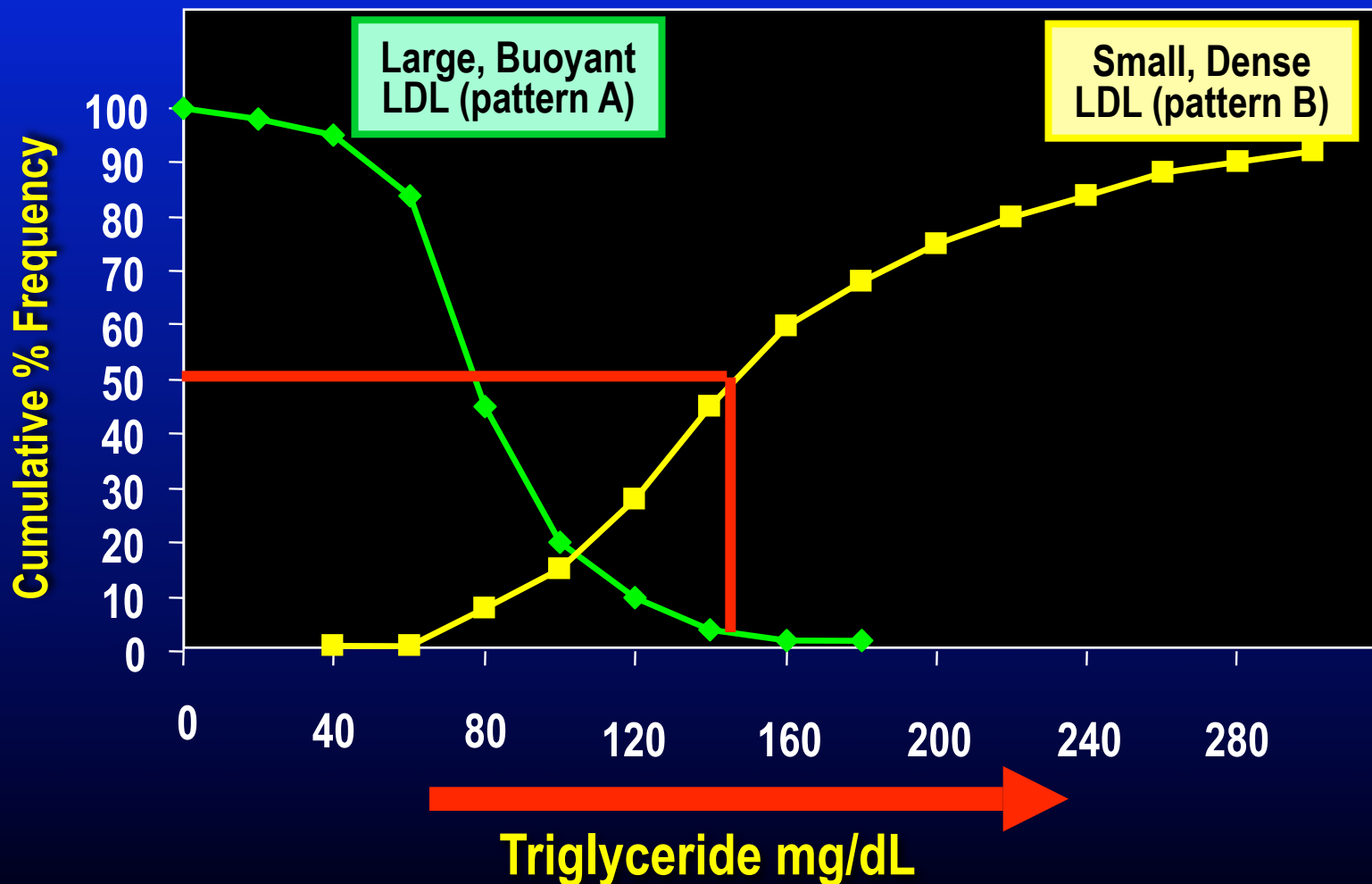
Relationship of Triglycerides and LDL Particle Size



Relationship of Triglycerides and LDL Particle Size



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LDL Particle Composition Heterogeneity

LDL Particle Composition Heterogeneity

- ★ LDL were isolated from 118 healthy men and women by preparative ultracentrifugation and detailed lipid compositional analyses as well as LDL size measurement by NMR were conducted.

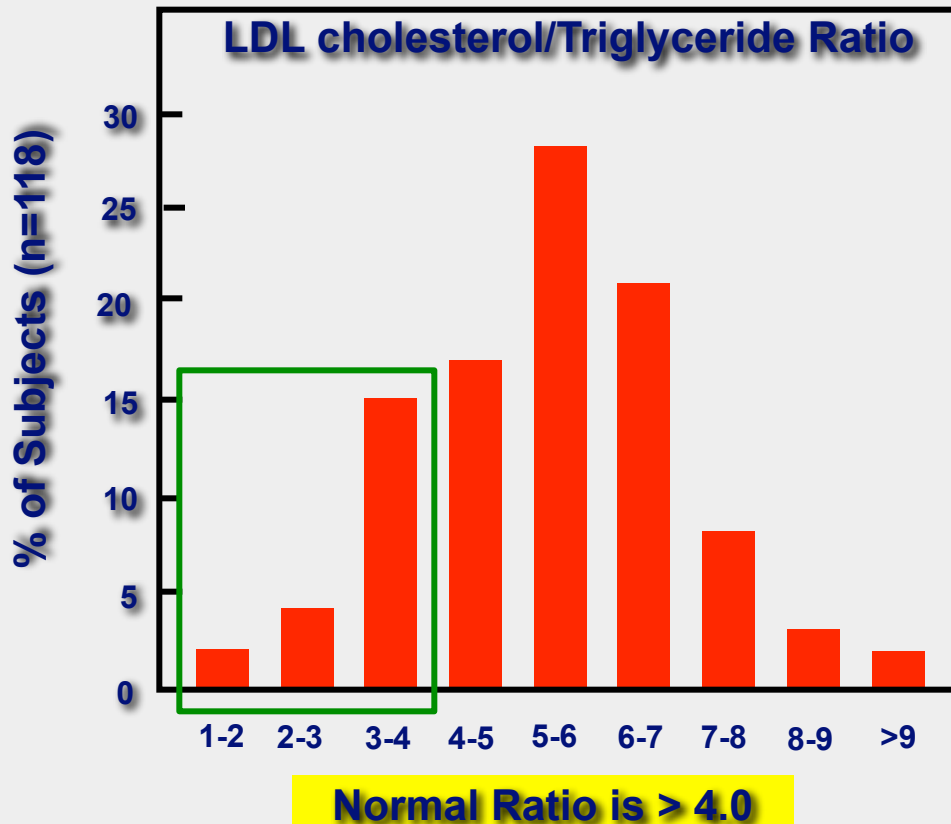
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LDL Particle Composition Heterogeneity

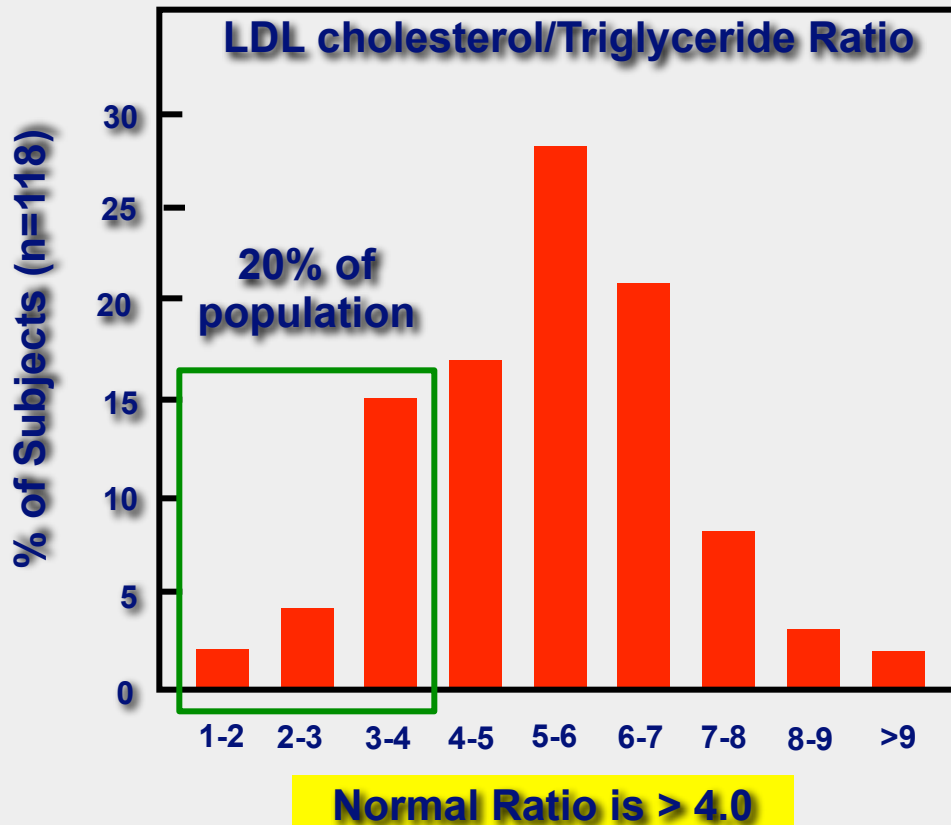
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- ★ Mean (SD) plasma triglyceride levels were 135 (89) mg/dL, representative of levels found in the general population. A total of 11 subjects (9%) had values 250 mg/dL, and only 2 had levels 400 mg/dL.
- ★ The measured ratios of cholesterol/triglyceride in the LDL of these subjects ranged from 1.8 to 11.5. The majority (65%) of the study population had large LDL particles of “normal” composition (cholesterol/triglyceride ratio > 4).
 - However, a surprisingly large percentage of subjects (21%) had LDL particles that were compositionally cholesterol depleted (cholesterol/triglyceride ratio < 4) compared with normal.

LDL Particle Composition Heterogeneity



Distribution of the measured ratios of cholesterol/triglyceride in LDL fraction (d=1.006-1.063 kg/L) by ultracentrifugation from 118 healthy subjects

LDL Particle Composition Heterogeneity



Distribution of the measured ratios of cholesterol/triglyceride in LDL fraction ($d=1.006-1.063$ kg/L) by ultracentrifugation from 118 healthy subjects

Even the most accurate LDL-cholesterol measurement will underestimate by about 10 to 25% the actual amounts of LDL these individuals have in their bloodstream, compared with those with LDL particles containing a normal amount of cholesterol.

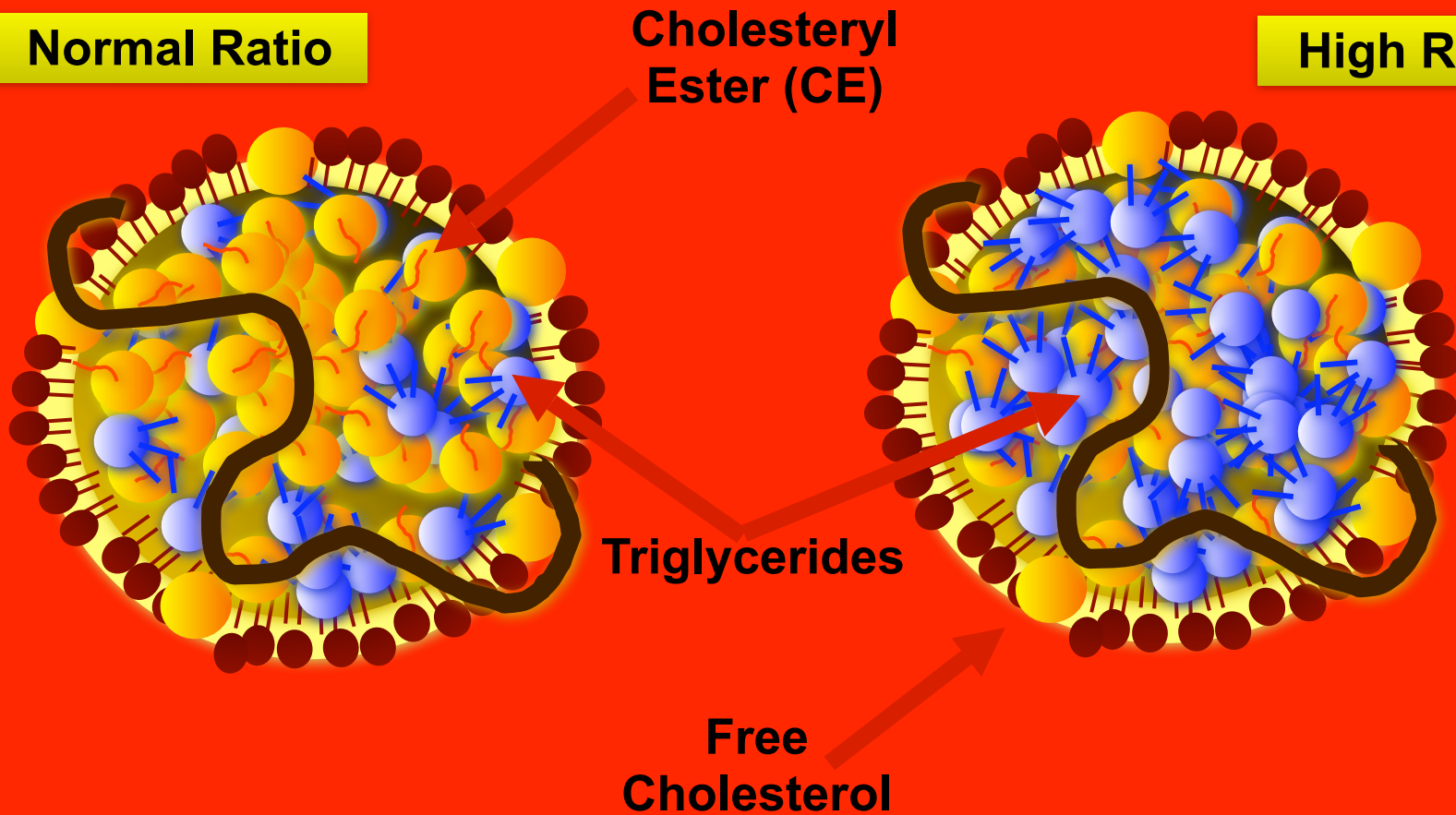
Or put another way, measured LDL cholesterol values, even for people with LDL particles of the same size, can easily vary by 10 to 40 mg/dL without there being any difference in LDL particle concentration

LDL Particle Composition

LDL Particle TG/CE composition differences

Normal Ratio

High Ratio

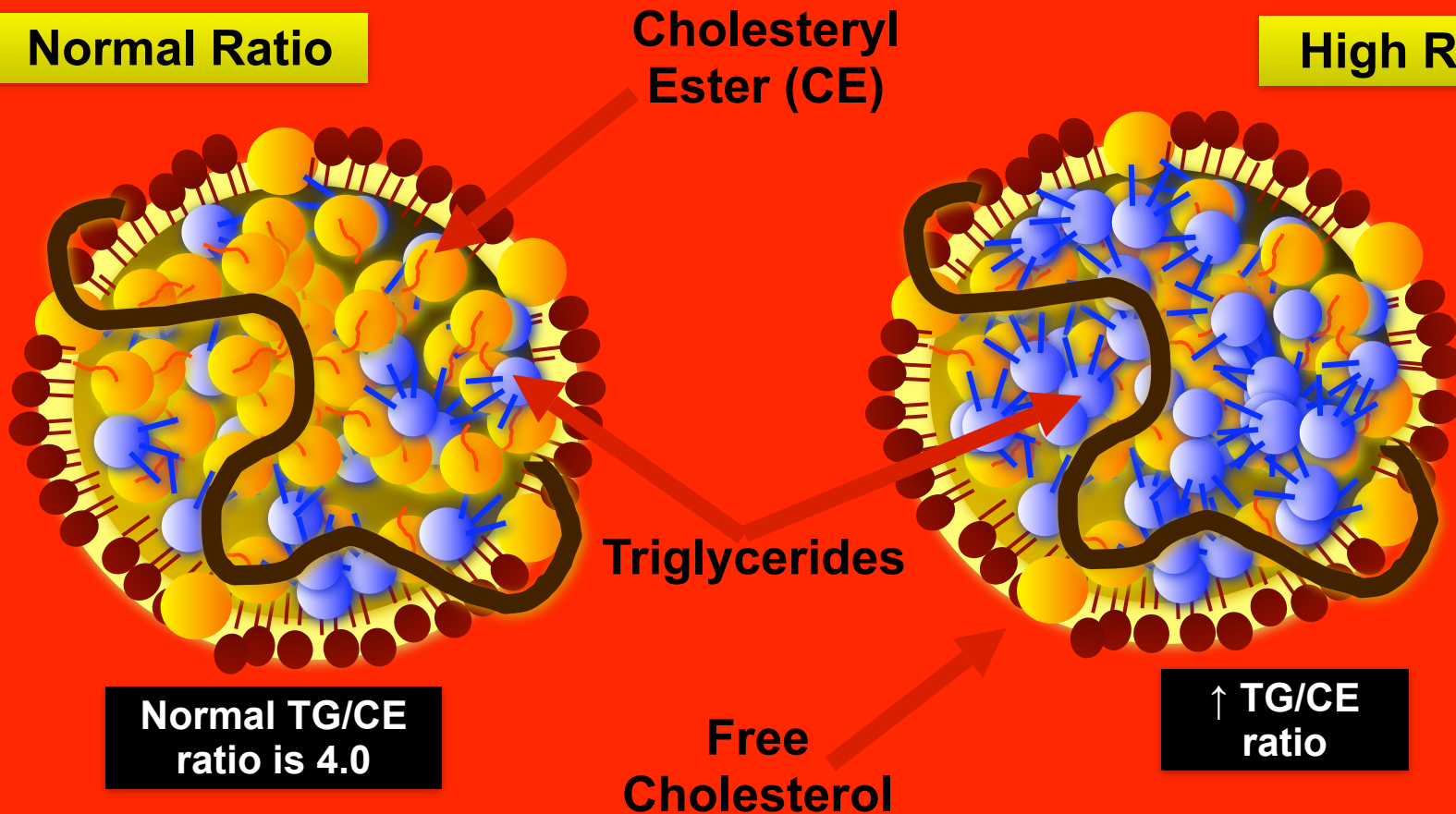


LDL Particle Composition

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

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

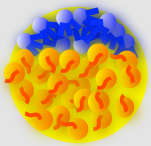
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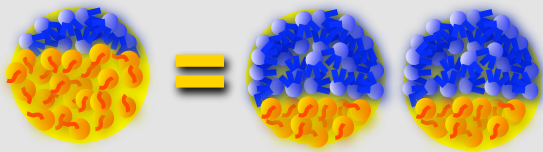
LDL-C = 100 mg/dL



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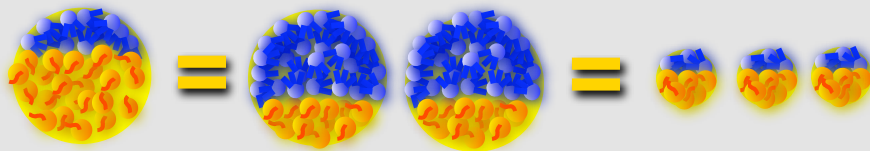
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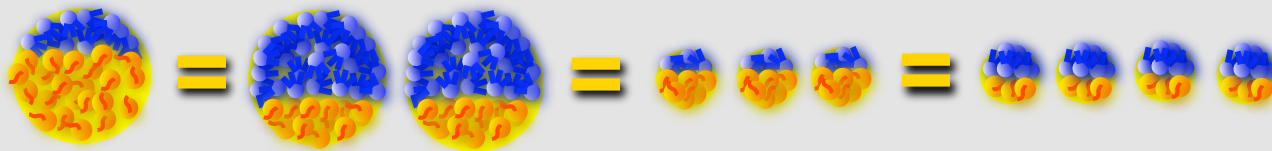
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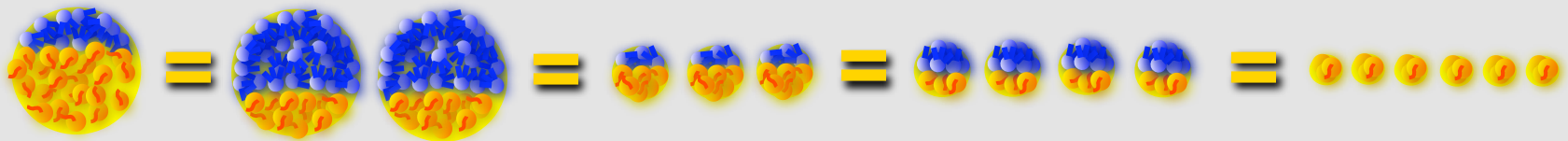
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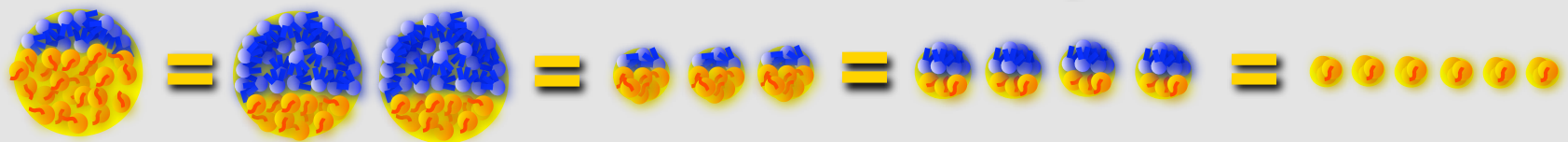
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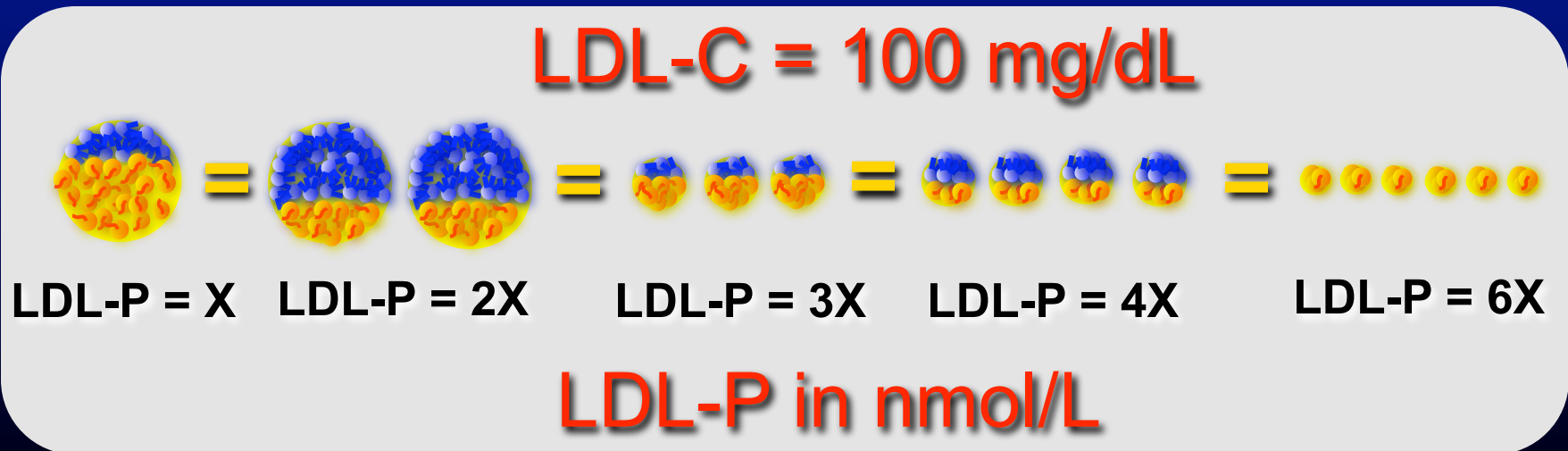
LDL-C = 100 mg/dL



LDL-P in nmol/L

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

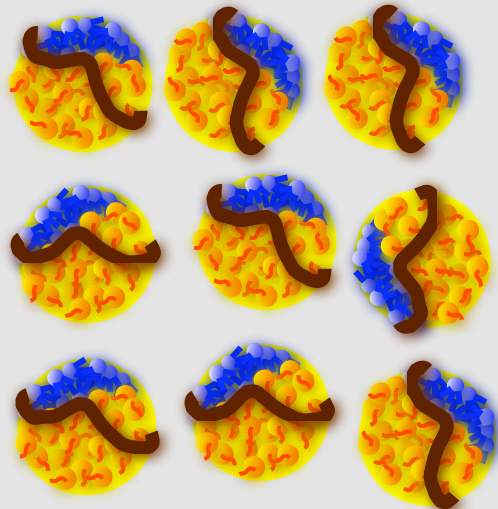
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LDL-C Often Fails to Reflect the Number of LDL Particles (LDL-P)

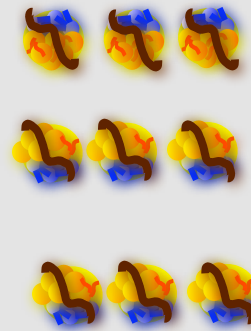
LDL-P in nmol/L

LDL-P = X



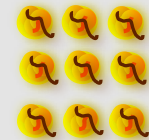
Large

LDL-P = X



Intermediate

LDL-P = X

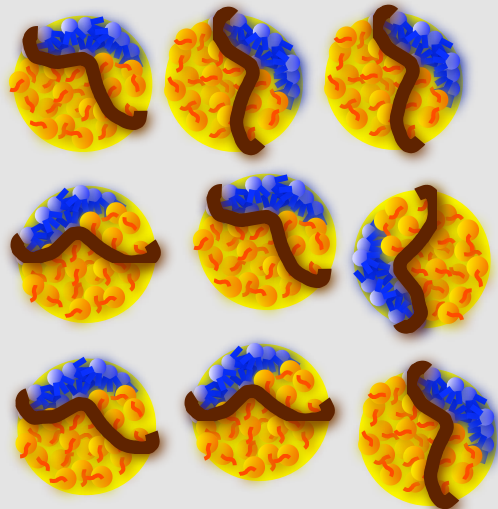


Small

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

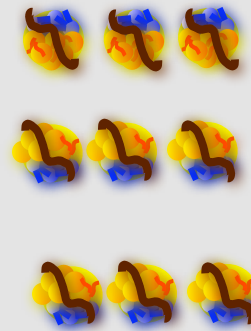
LDL-P in nmol/L

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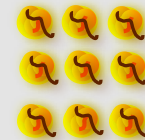
Large

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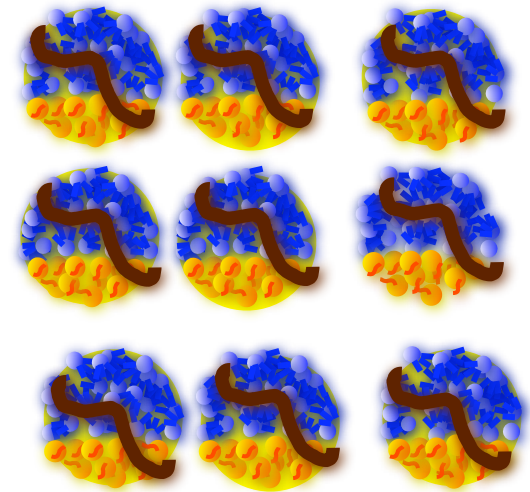
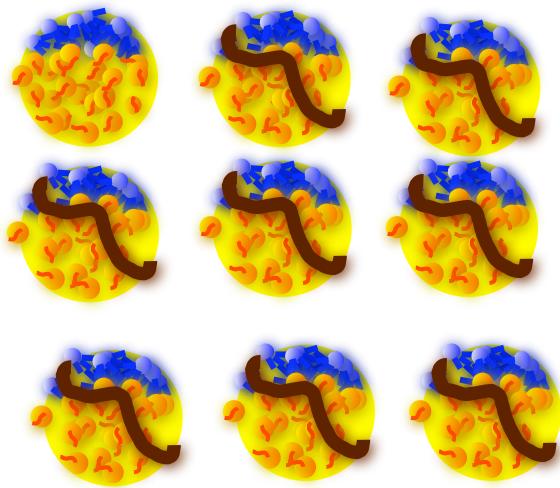


Small

LDL-C (mg/dL) >>> LDL-C >> LDL-C

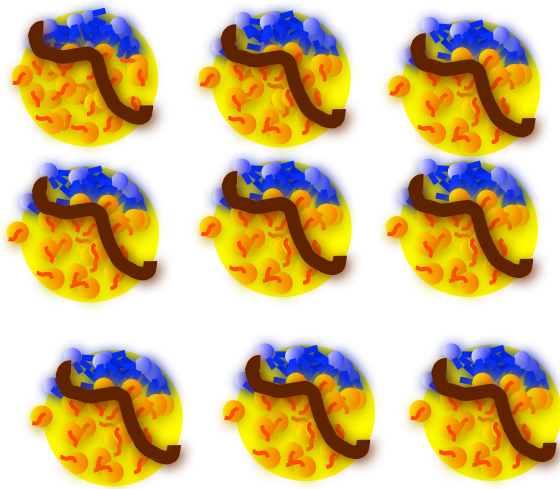
The Influence of TG Composition on LDL-P and LDL-C

LDL-P is Identical in Both Patients

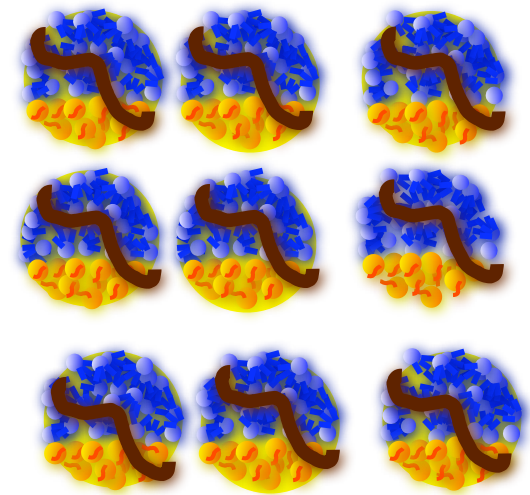


The Influence of TG Composition on LDL-P and LDL-C

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LDL-C is X



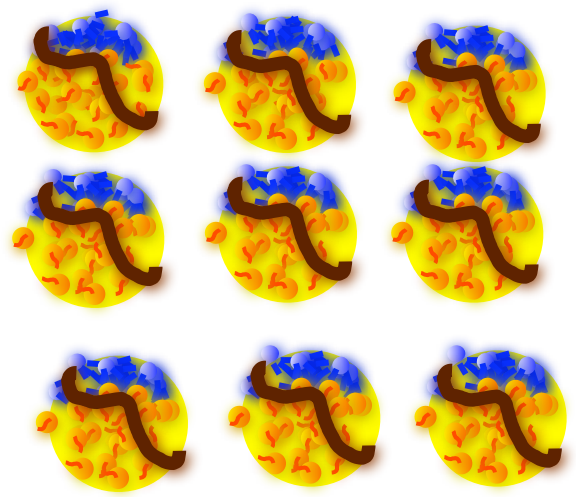
LDL-C is $< X$

TG levels high

Cholesterol Compositional Variability

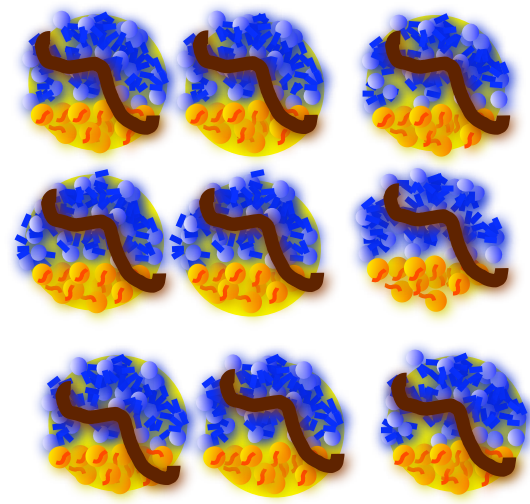
LDL-P & Size is Identical in All 3 Patients

Normal Composition



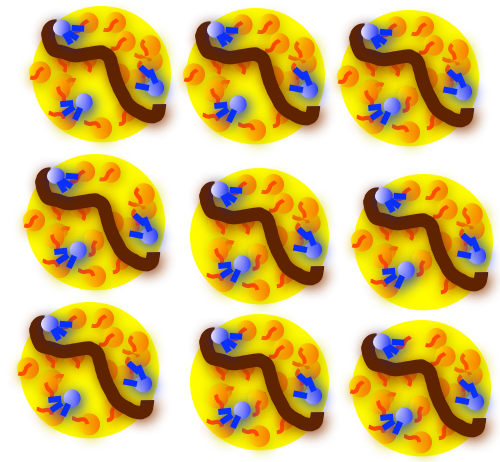
LDL-C is more

TG-rich, CE-poor



LDL-C is less

CE-poor



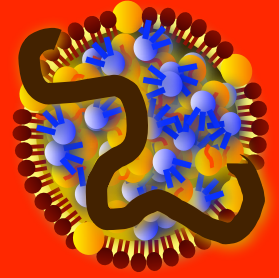
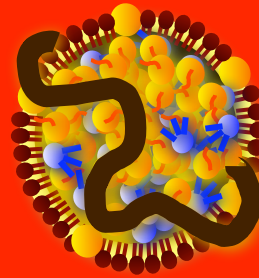
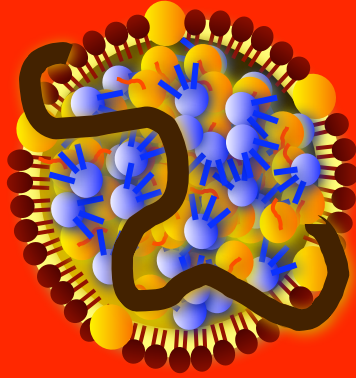
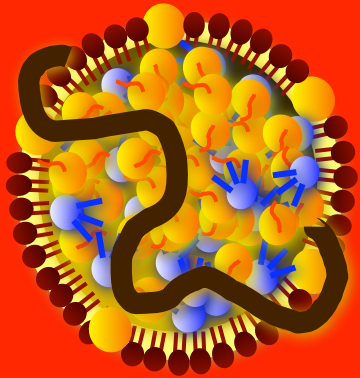
LDL-C is low

CE = cholesteryl ester

TG levels higher

LDL Particles & Composition

Normal core
lipid content



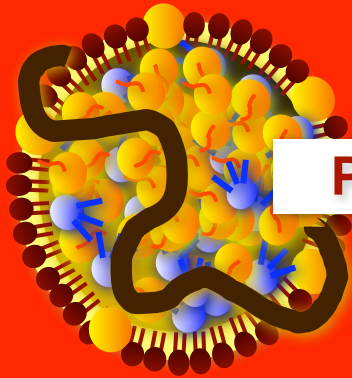
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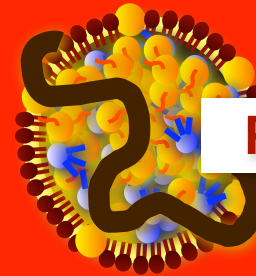
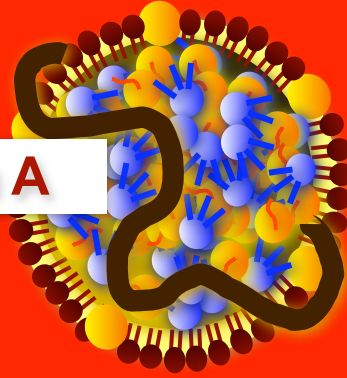
Cholesterol depleted,
TG enriched core

Normal core
lipid content

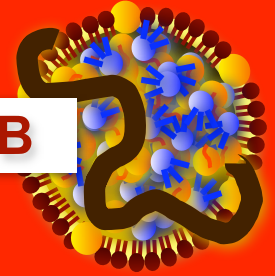
Cholesterol depleted,
TG enriched core



Pattern A



Pattern B



- ◆ LDL particles differ in diameter by about 12% or 3 nm
- ◆ The volume differences of the core are substantial because they scale according to the third power of the radius

LDL Particles & Composition

Normal core
lipid content

Cholesterol depleted,
TG enriched core

Normal core
lipid content

Cholesterol depleted,
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 - For LDL particles differing by 3 nm, there is 40% less cholesterol in the smaller particle

LDL Particles & Composition

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lipid content

Cholesterol depleted,
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Normal core
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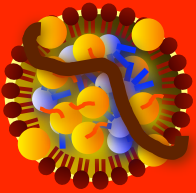
Cholesterol depleted,
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 - For LDL particles differing by 3 nm, there is 40% less cholesterol in the smaller particle
 - Patients with small particles will require almost 70% more particles to carry the same amount of LDL-C

Effects of Compositional Abnormalities in LDL Particle Populations

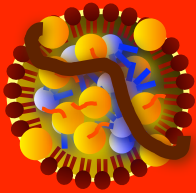
Large LDL



**Normal core
lipid content**

Effects of Compositional Abnormalities in LDL Particle Populations

Large LDL

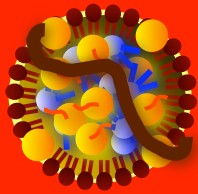


**Normal core
lipid content**

LDL-C =
~150 mg/dl

Effects of Compositional Abnormalities in LDL Particle Populations

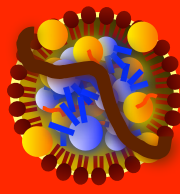
Large LDL



Normal core lipid content

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Large LDL

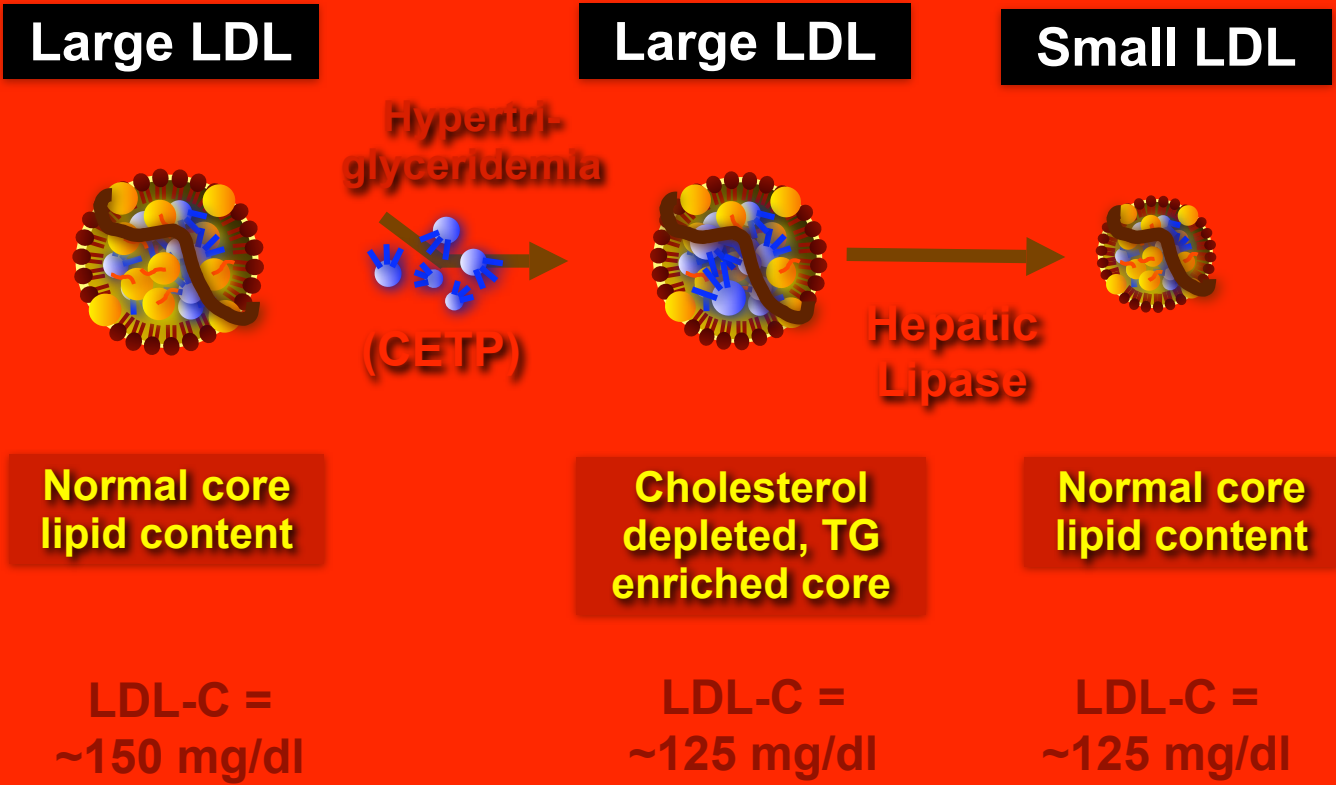


Cholesterol depleted, TG enriched core

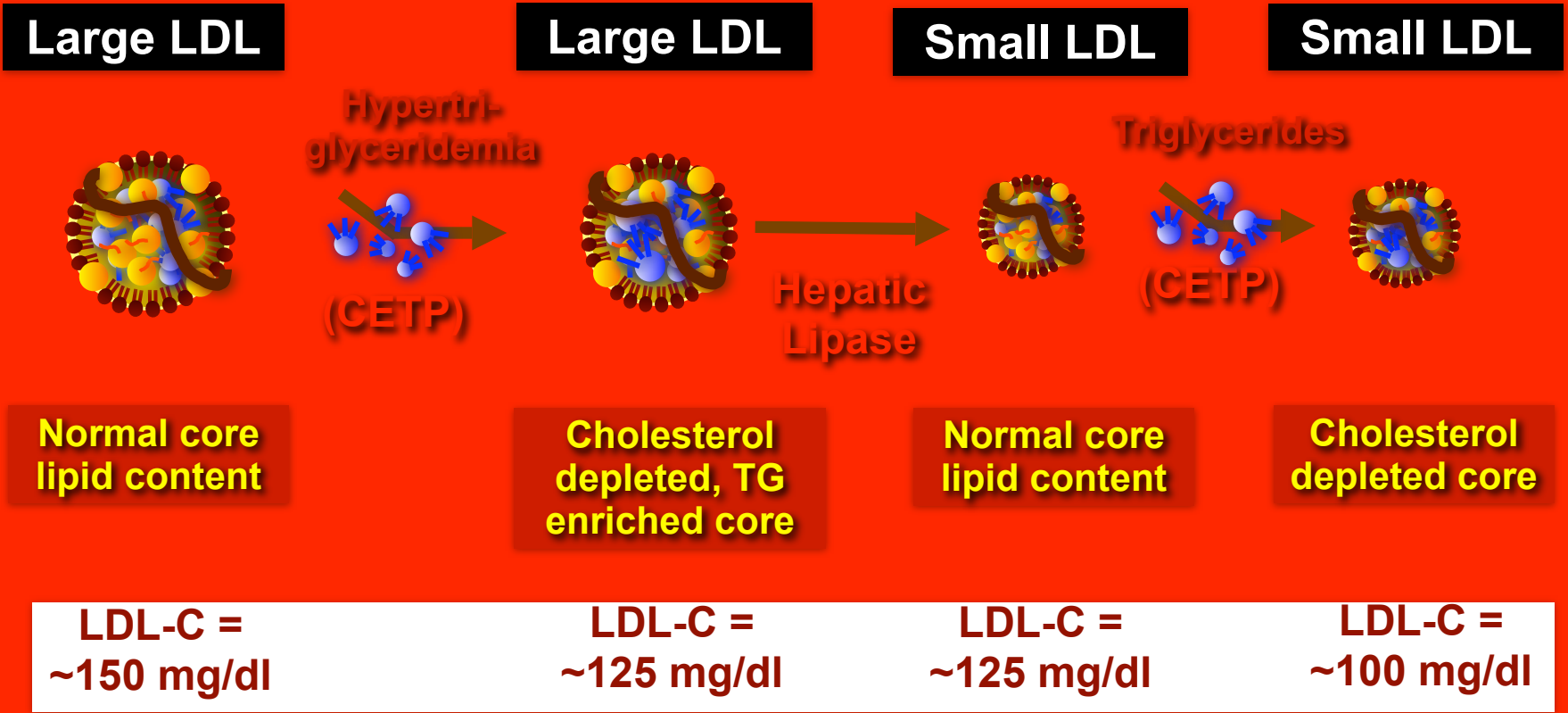
LDL-C =
~125 mg/dl

**Hypertri-
glyceridemia**
A diagram showing a green arrow pointing from left to right, representing the action of CETP. On the left, a blue Y-shaped molecule (CETP) is shown interacting with the surface of the normal LDL particle. On the right, the same CETP molecule is shown interacting with the surface of the modified LDL particle, facilitating the exchange of lipids between the two particles.
(CETP)

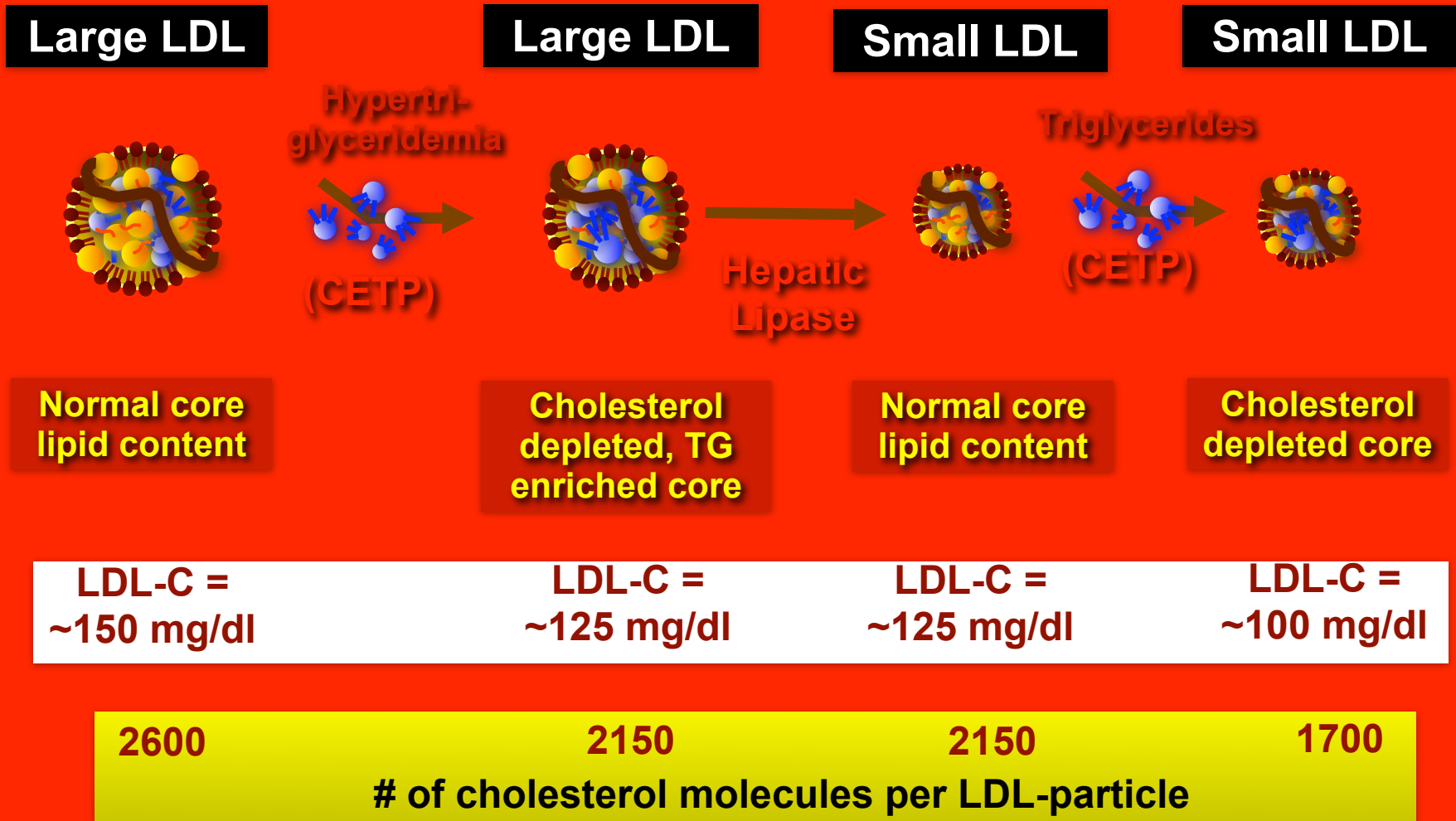
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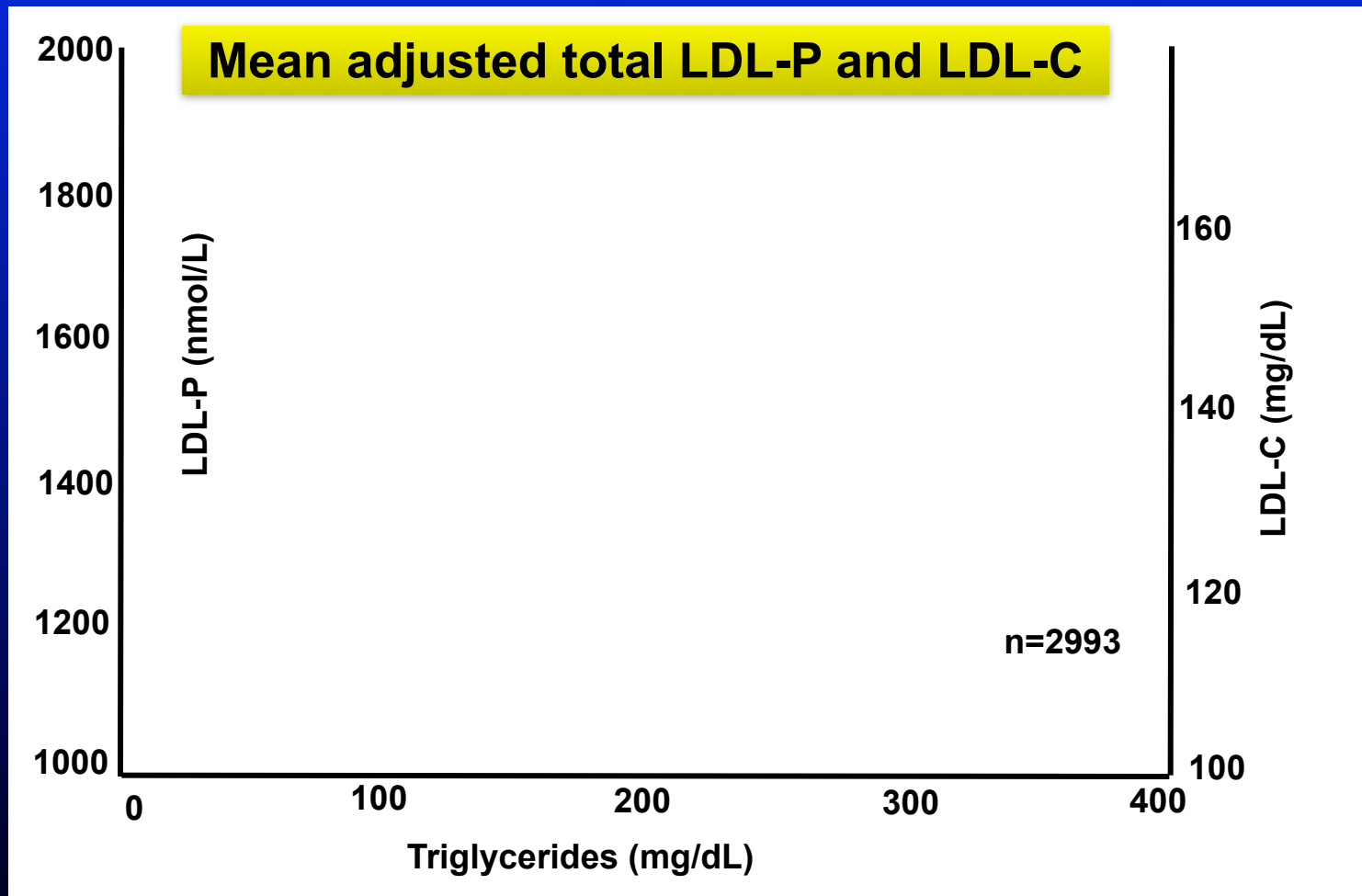
Effects of Compositional Abnormalities in LDL Particle Populations



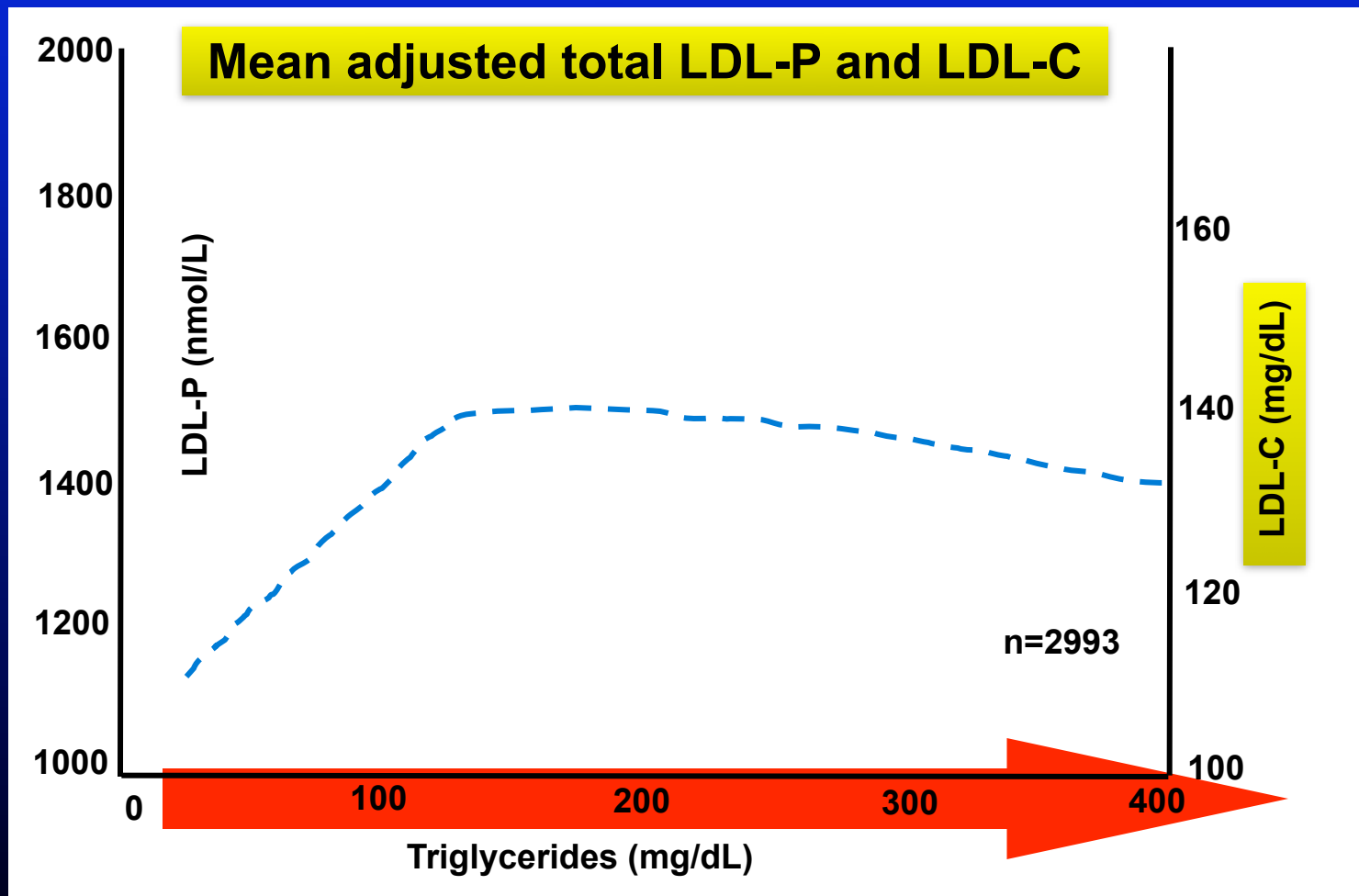
Effects of Compositional Abnormalities in LDL Particle Populations



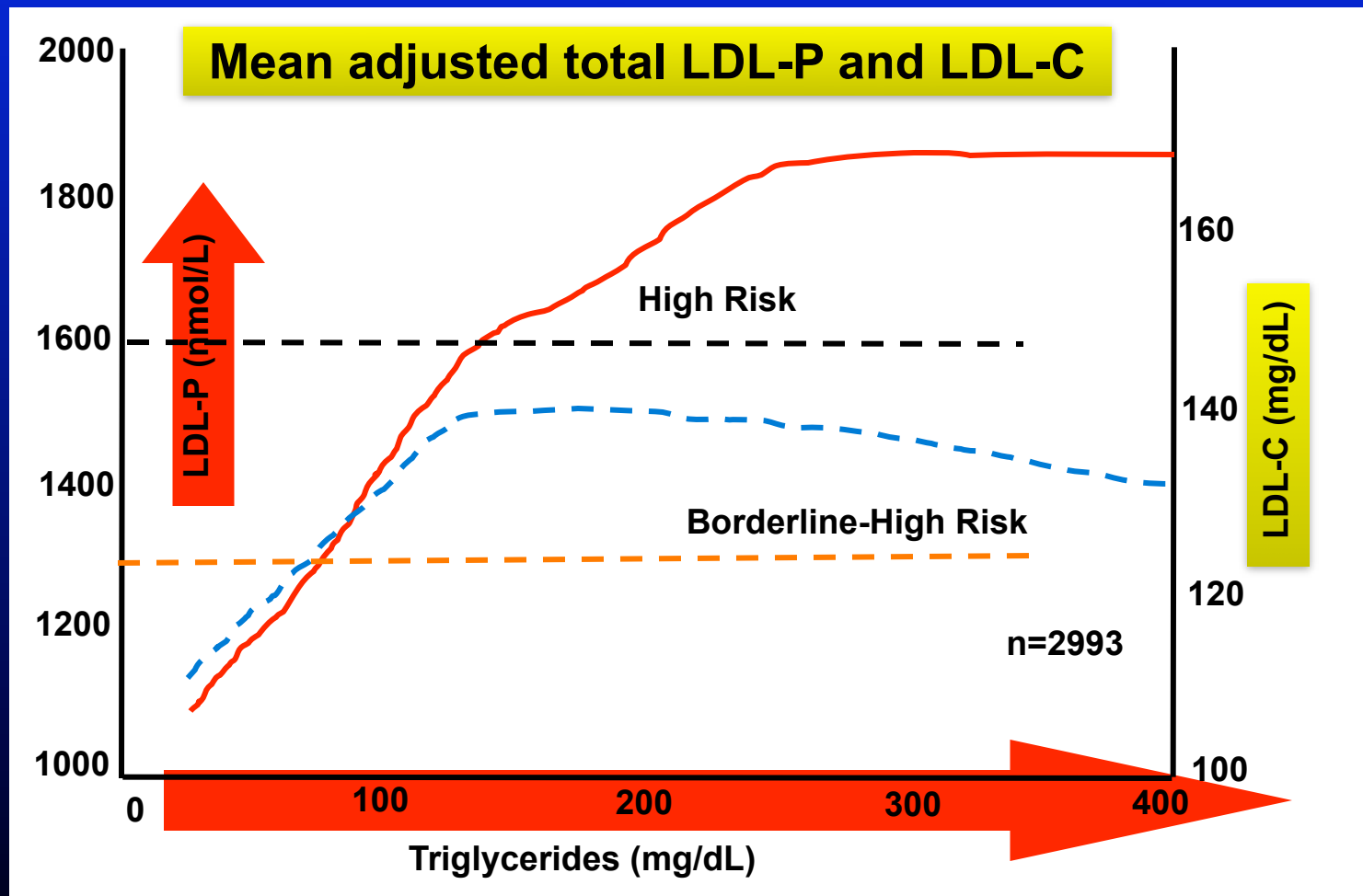
Framingham Offspring Study LDL-P and Metabolic Syndrome



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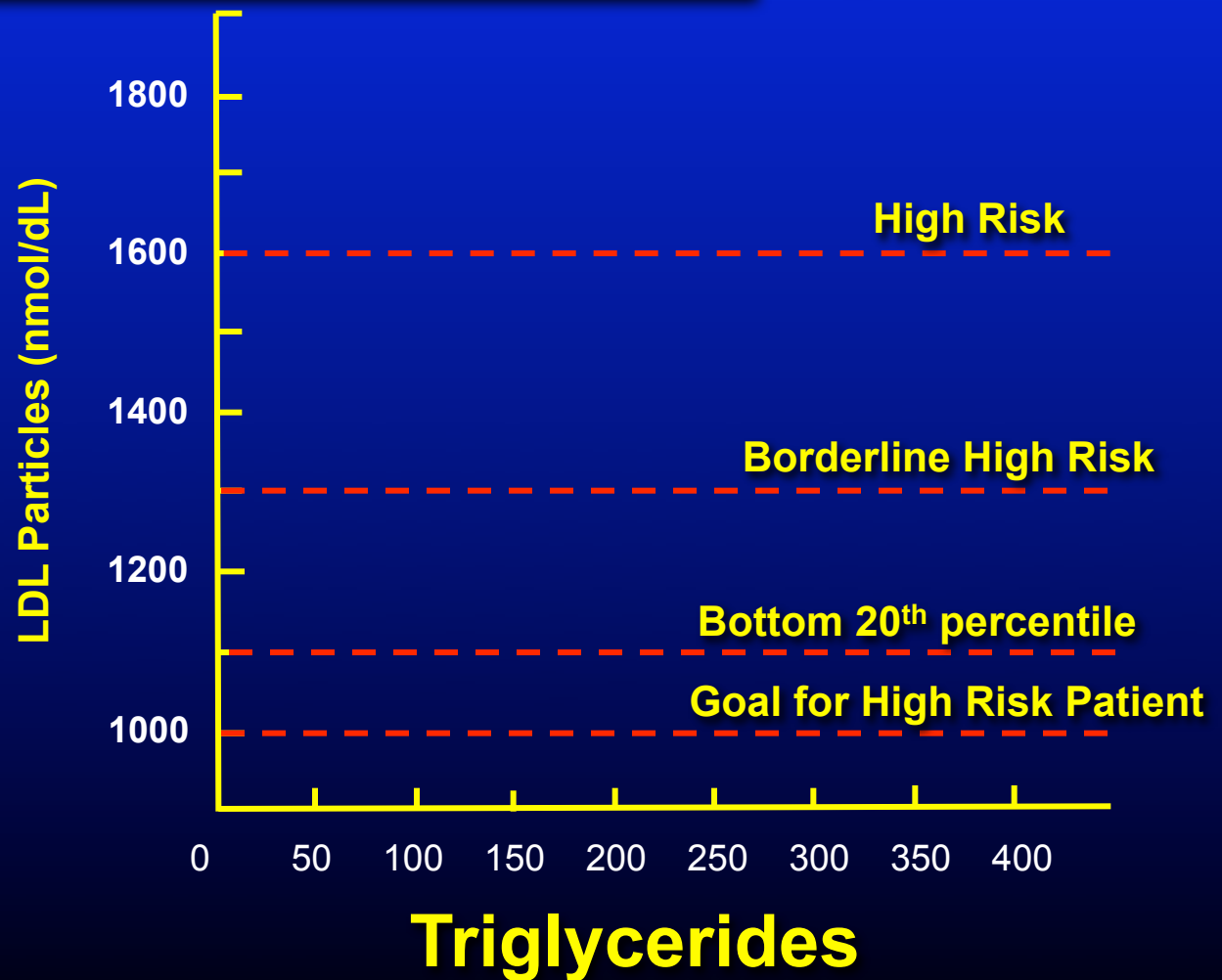


Framingham Offspring Study LDL-P and Metabolic Syndrome



Framingham Offspring Study

LDL-P (particle #) and TG

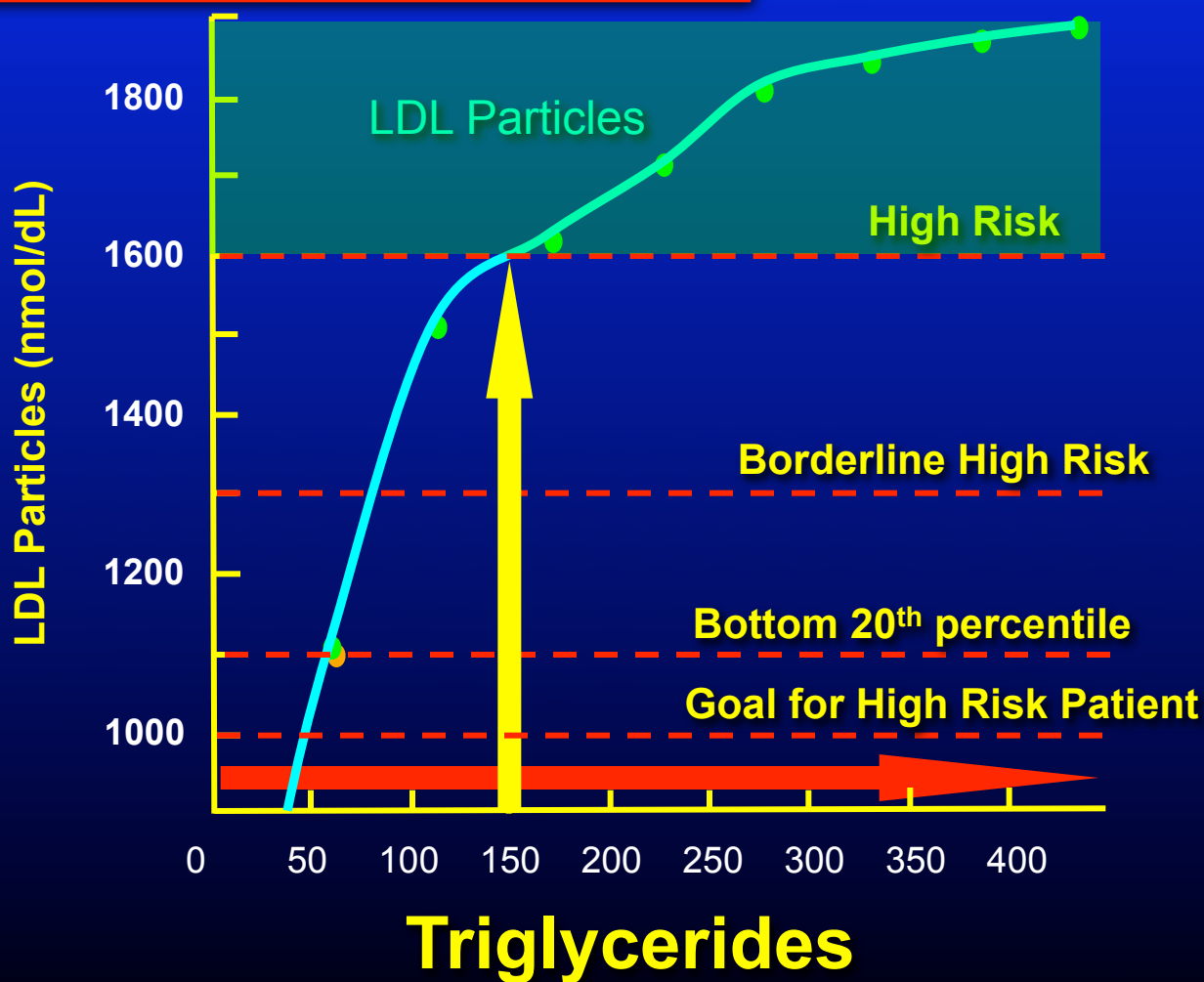


(n = 3,437)

Framingham Offspring Study

LDL-P (particle #) and TG

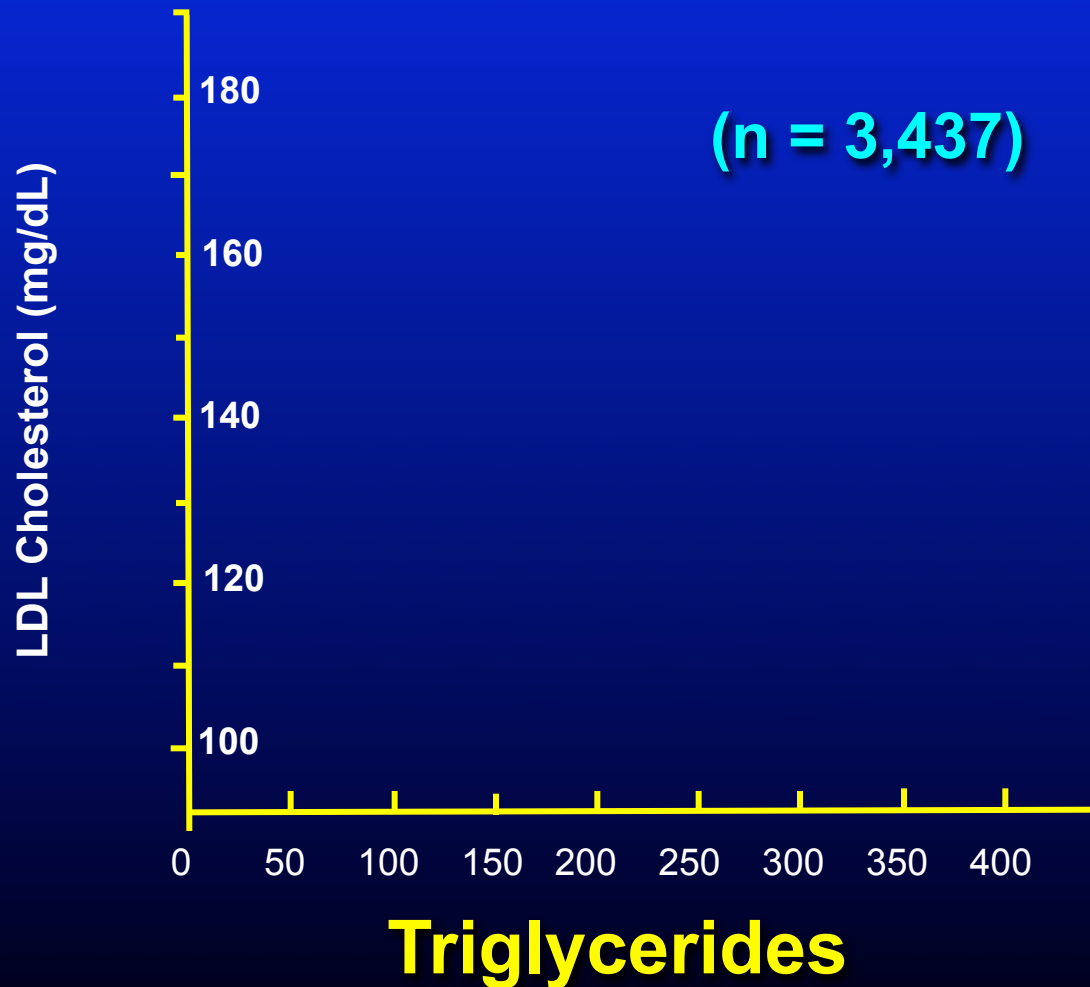
As **TG** levels rise so does LDL particle concentration



(n = 3,437)

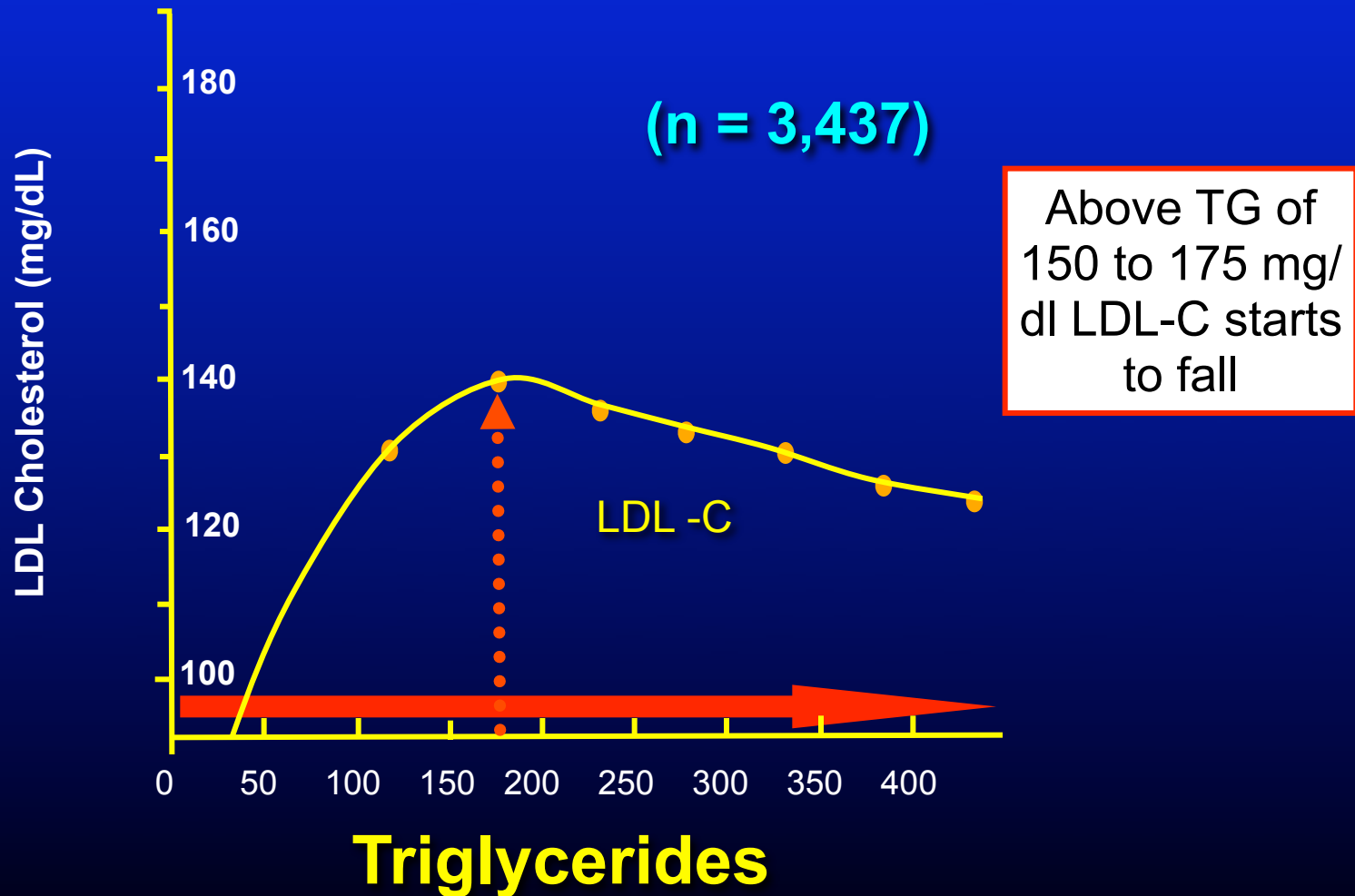
Framingham Offspring Study

TG and LDL-C



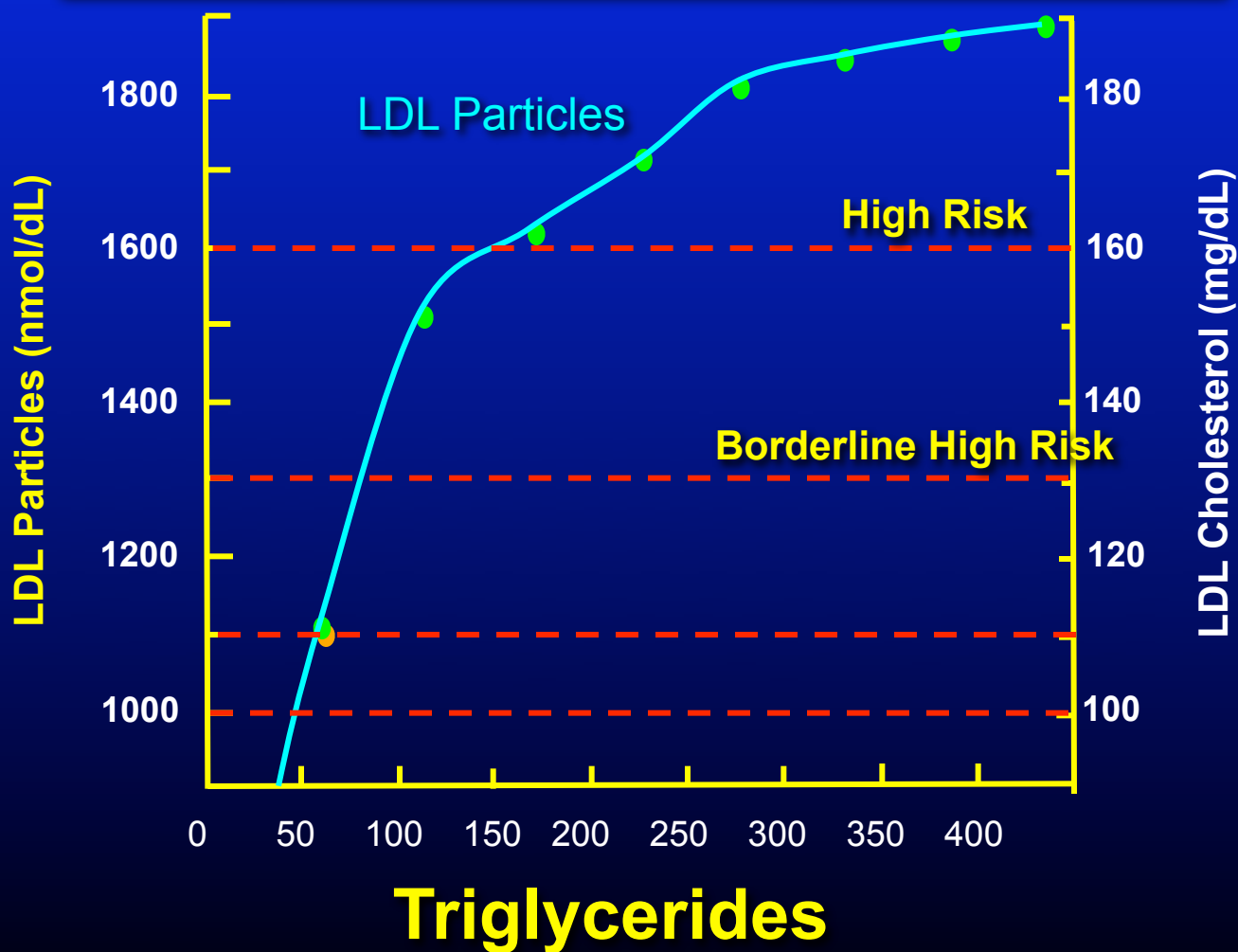
Framingham Offspring Study

TG and LDL-C



Framingham Offspring Study

TG, LDL particle # and LDL-C

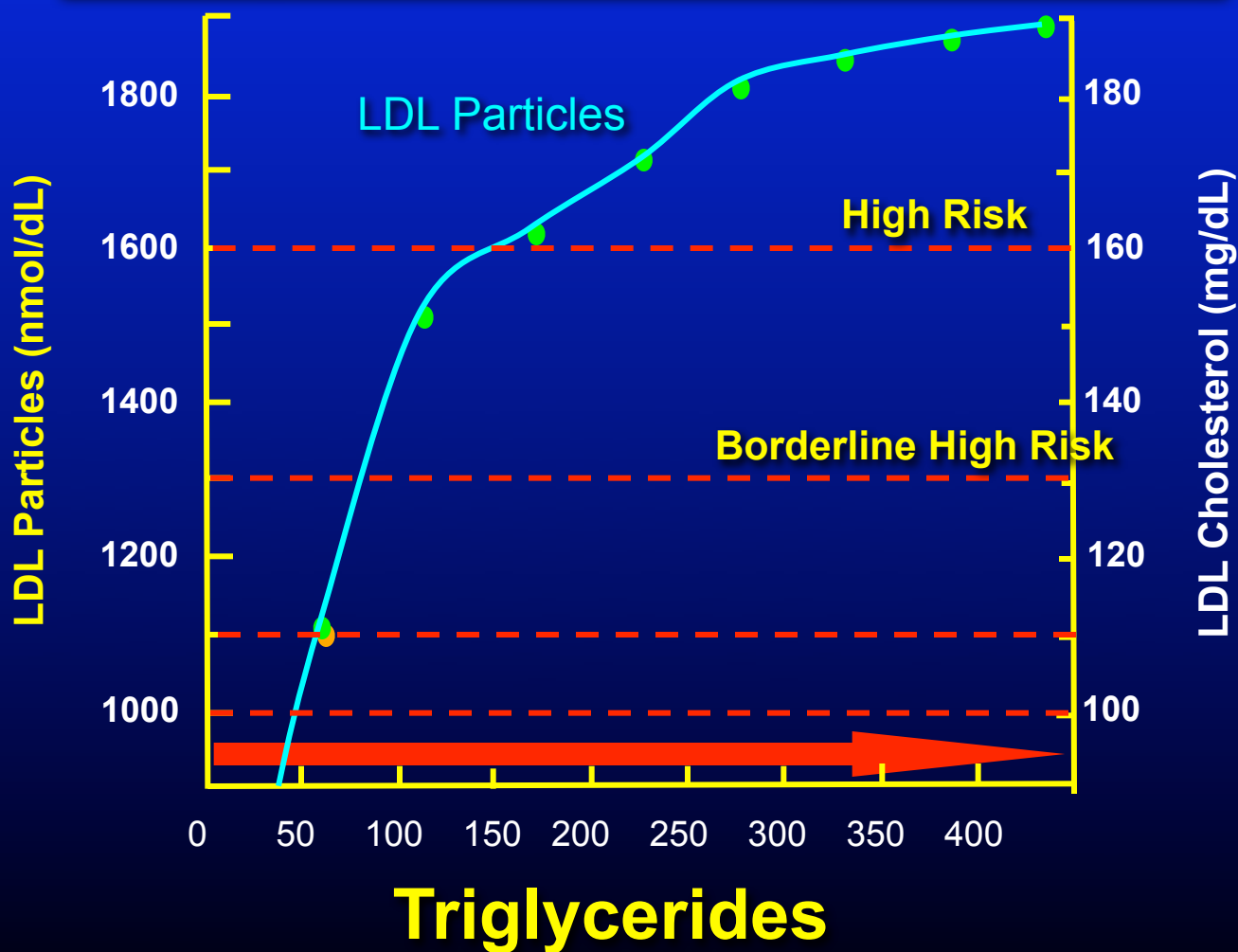


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Framingham Offspring Study

TG, LDL particle # and LDL-C

As TG rises so does LDL particle concentration



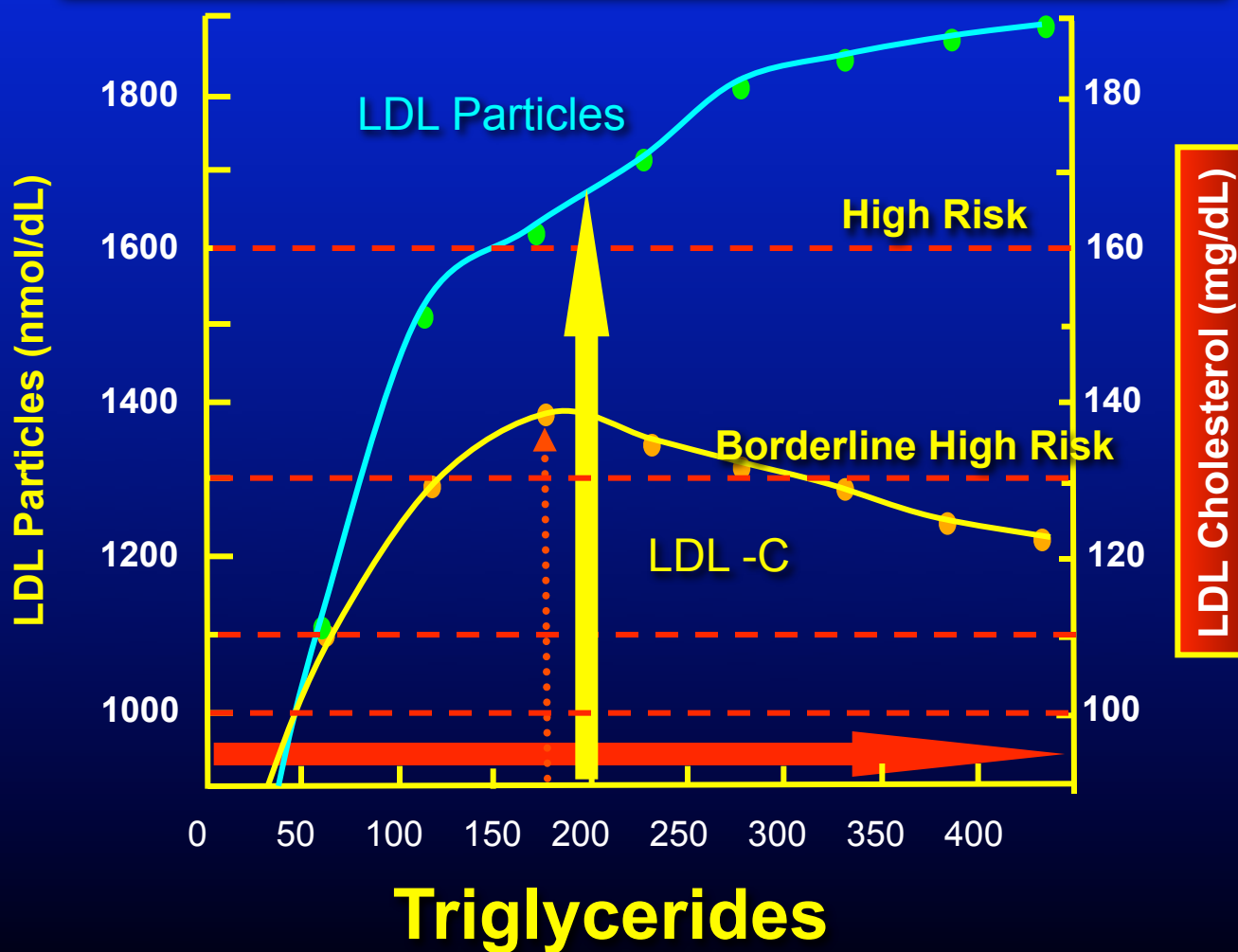
(n = 3,437)

Framingham Offspring Study

TG, LDL particle # and LDL-C

As TG rises so does LDL particle concentration

Above TG of 150 to 175 mg/dl LDL-C starts to fall



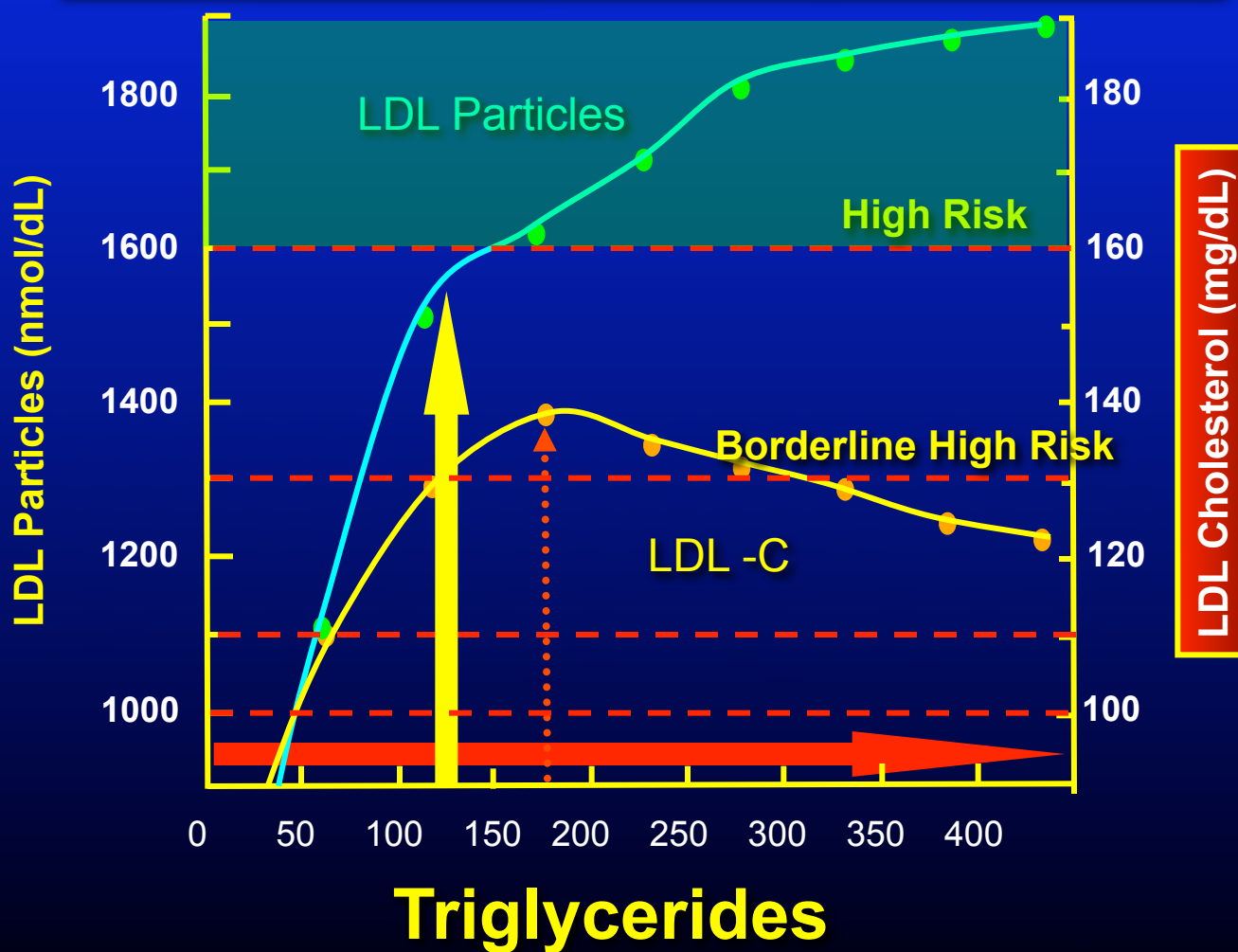
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Framingham Offspring Study

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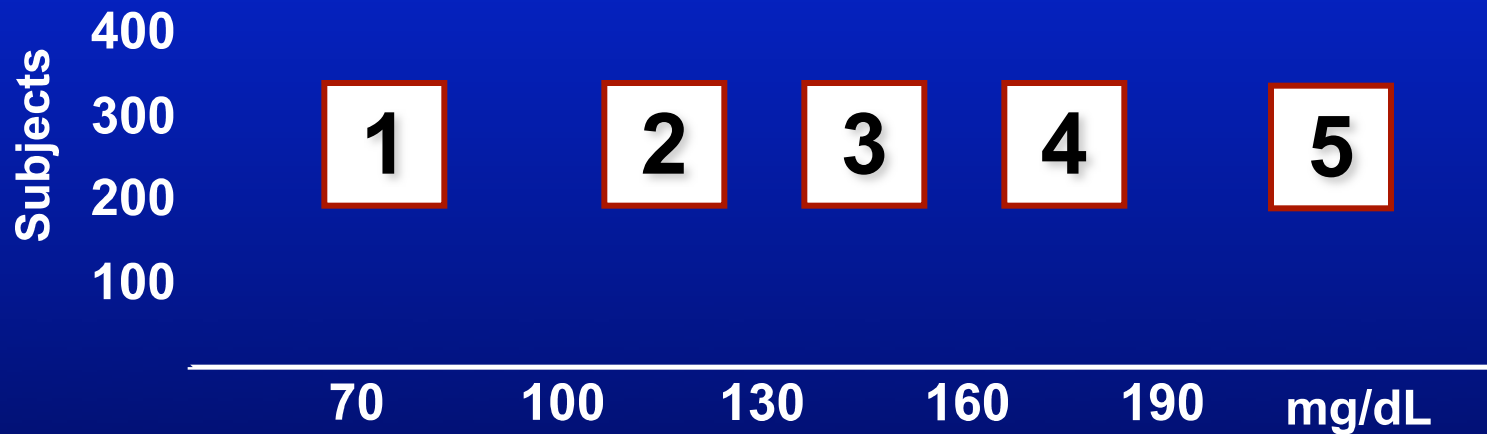
As TG rises so does LDL particle concentration

Above TG of 150 to 175 mg/dl LDL-C starts to fall

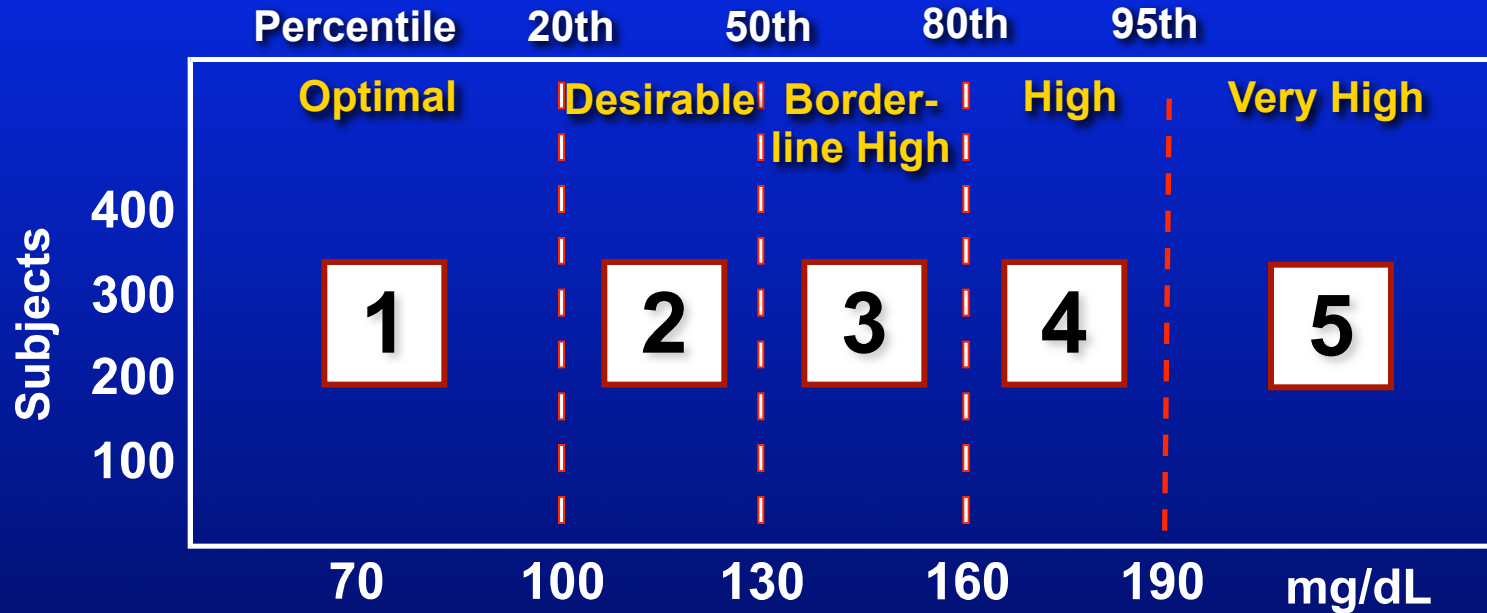


(n = 3,437)

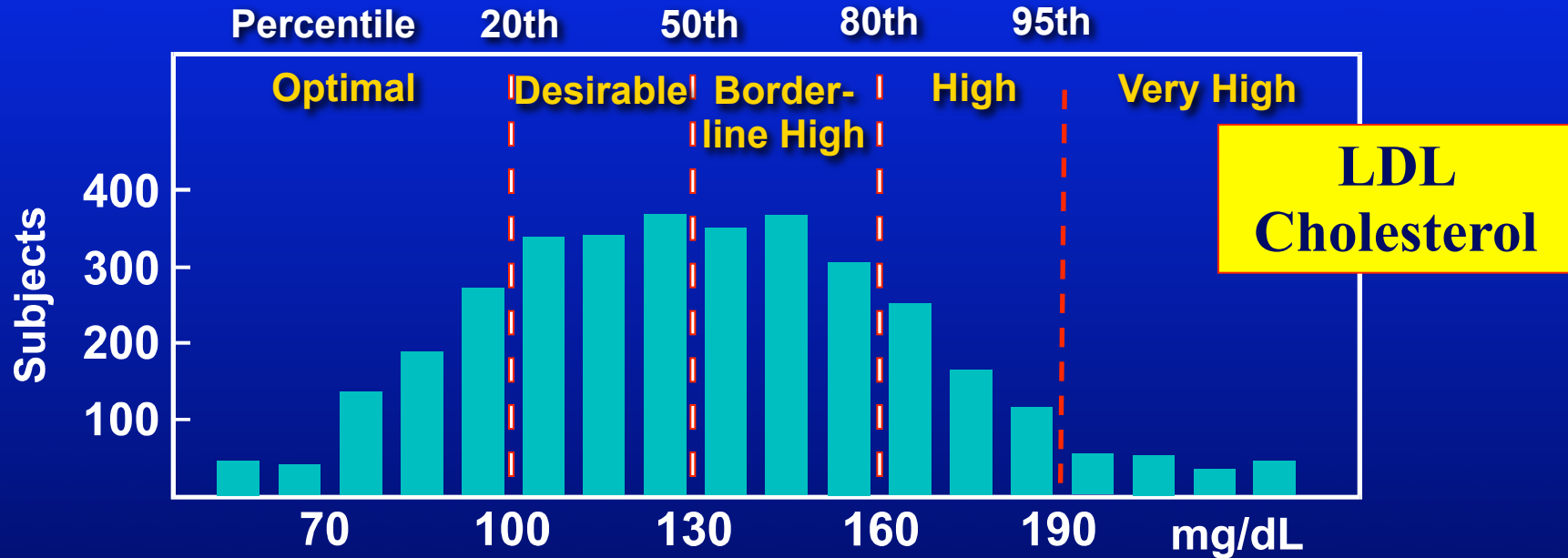
LDL Cholesterol and Particle Distribution Framingham Offspring Study (n = 3437)



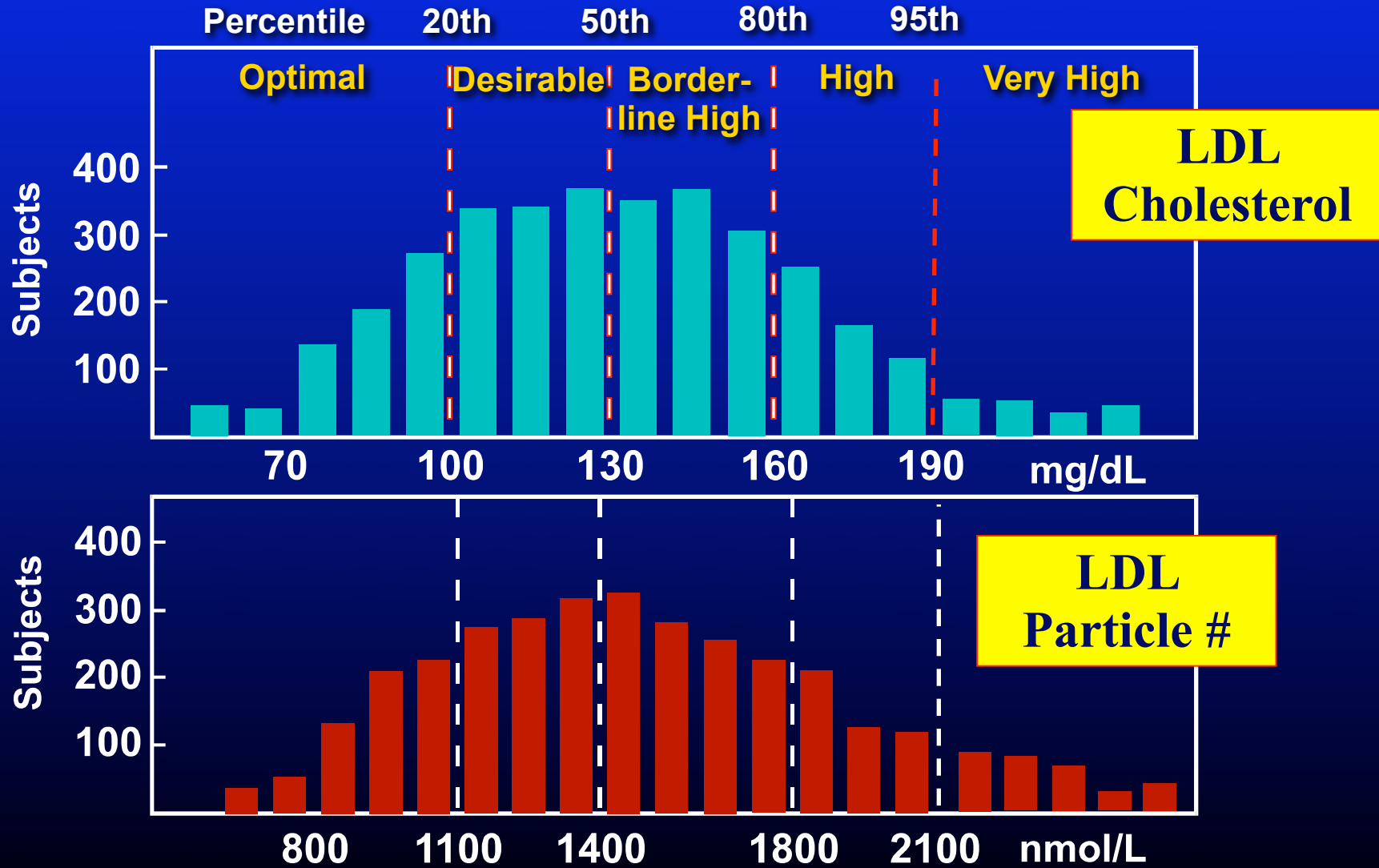
LDL Cholesterol and Particle Distribution Framingham Offspring Study (n = 3437)



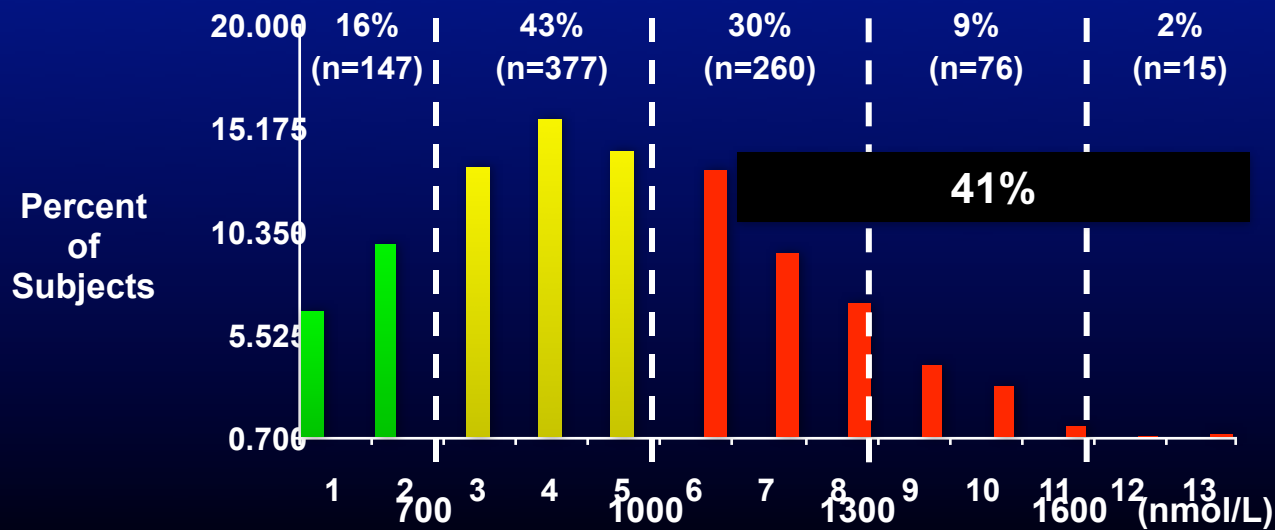
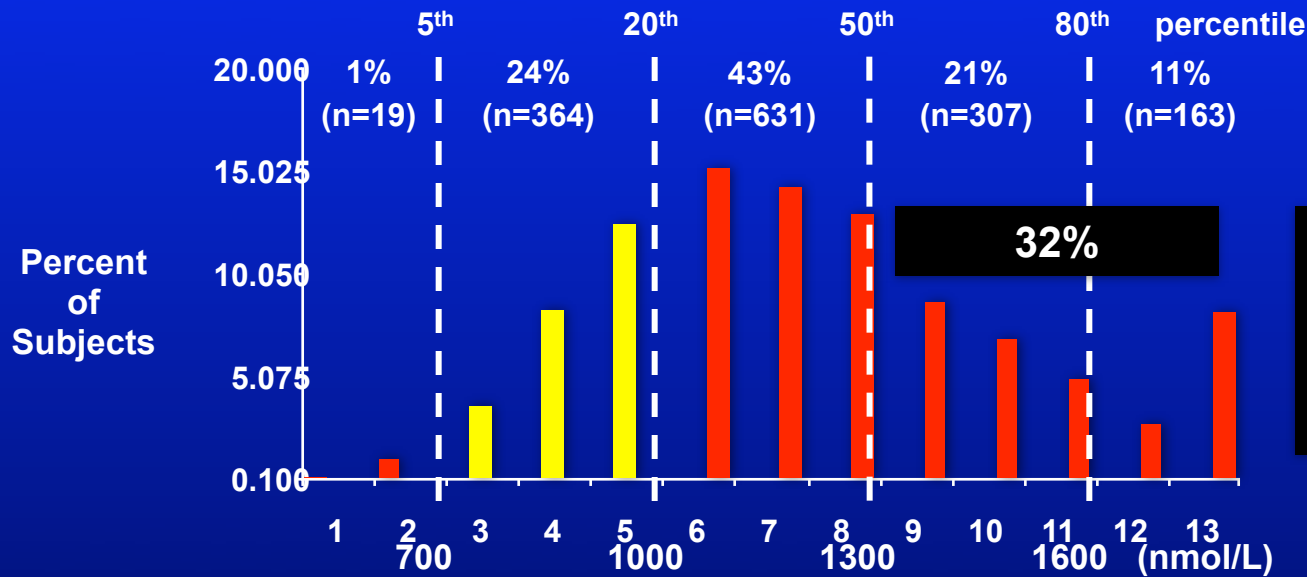
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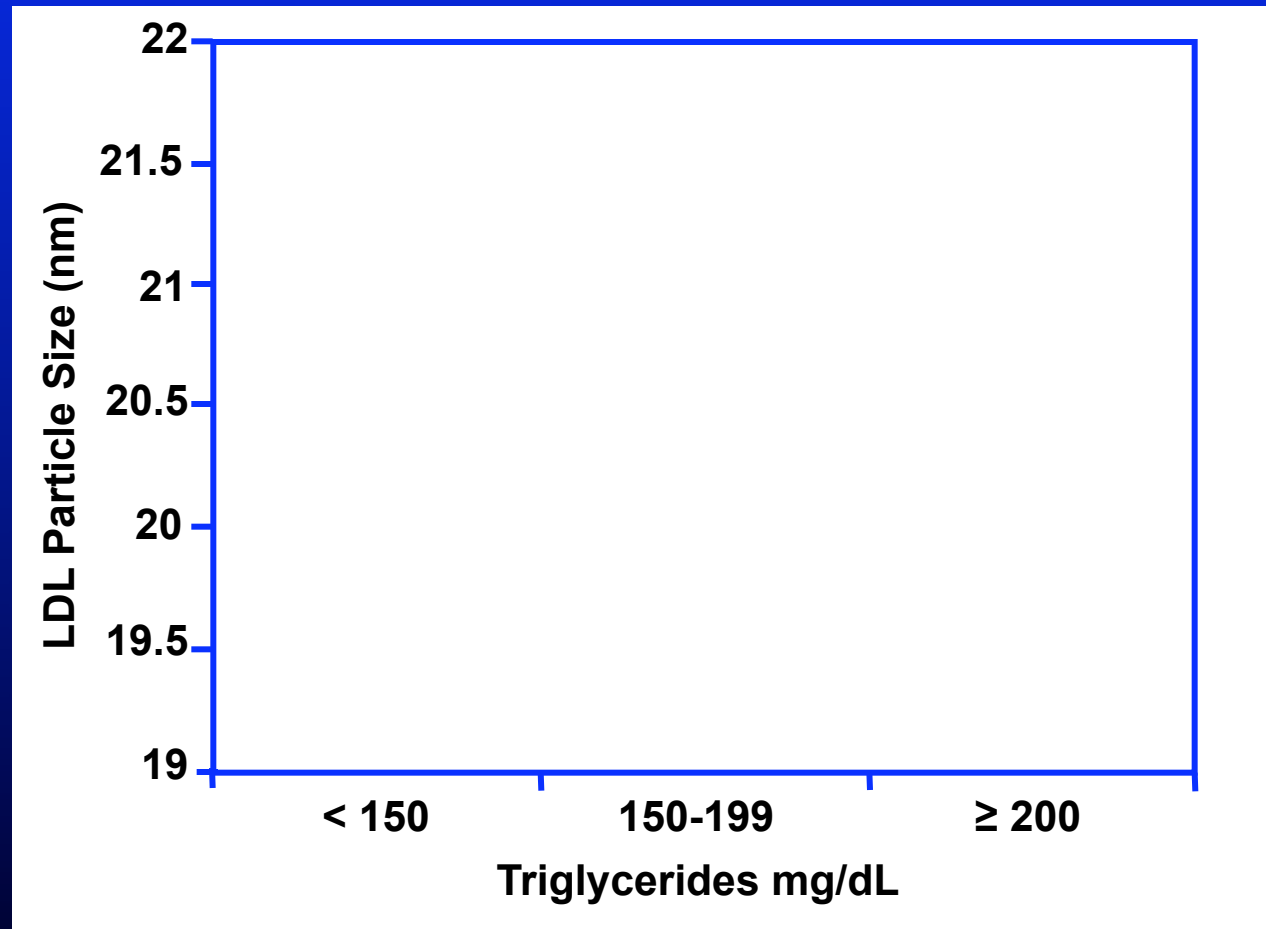
LDL Cholesterol and Particle Distribution Framingham Offspring Study (n = 3437)



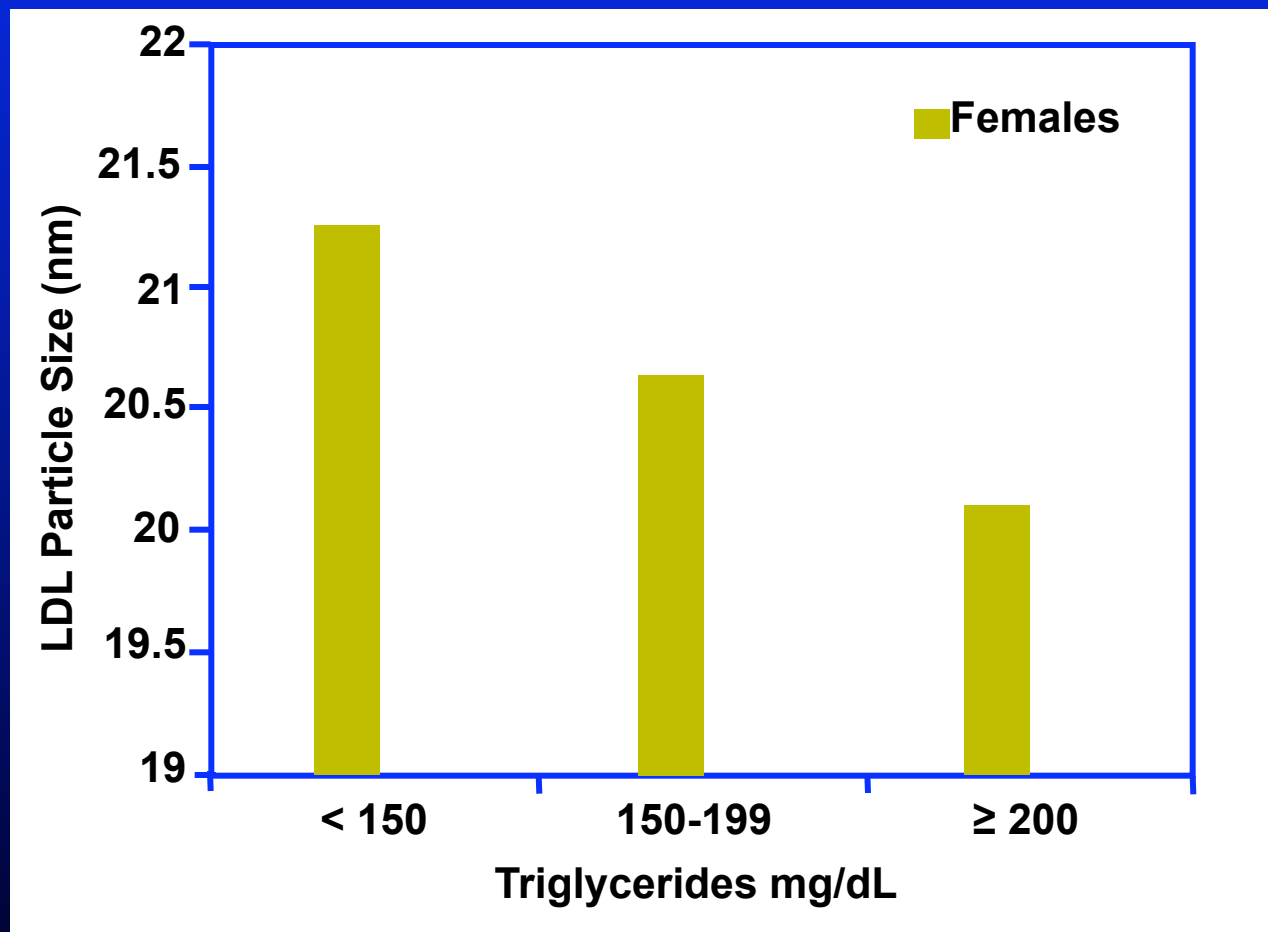
LDL Particle Number Distribution in T2DM Subjects with Normal, at Goal LDL-C



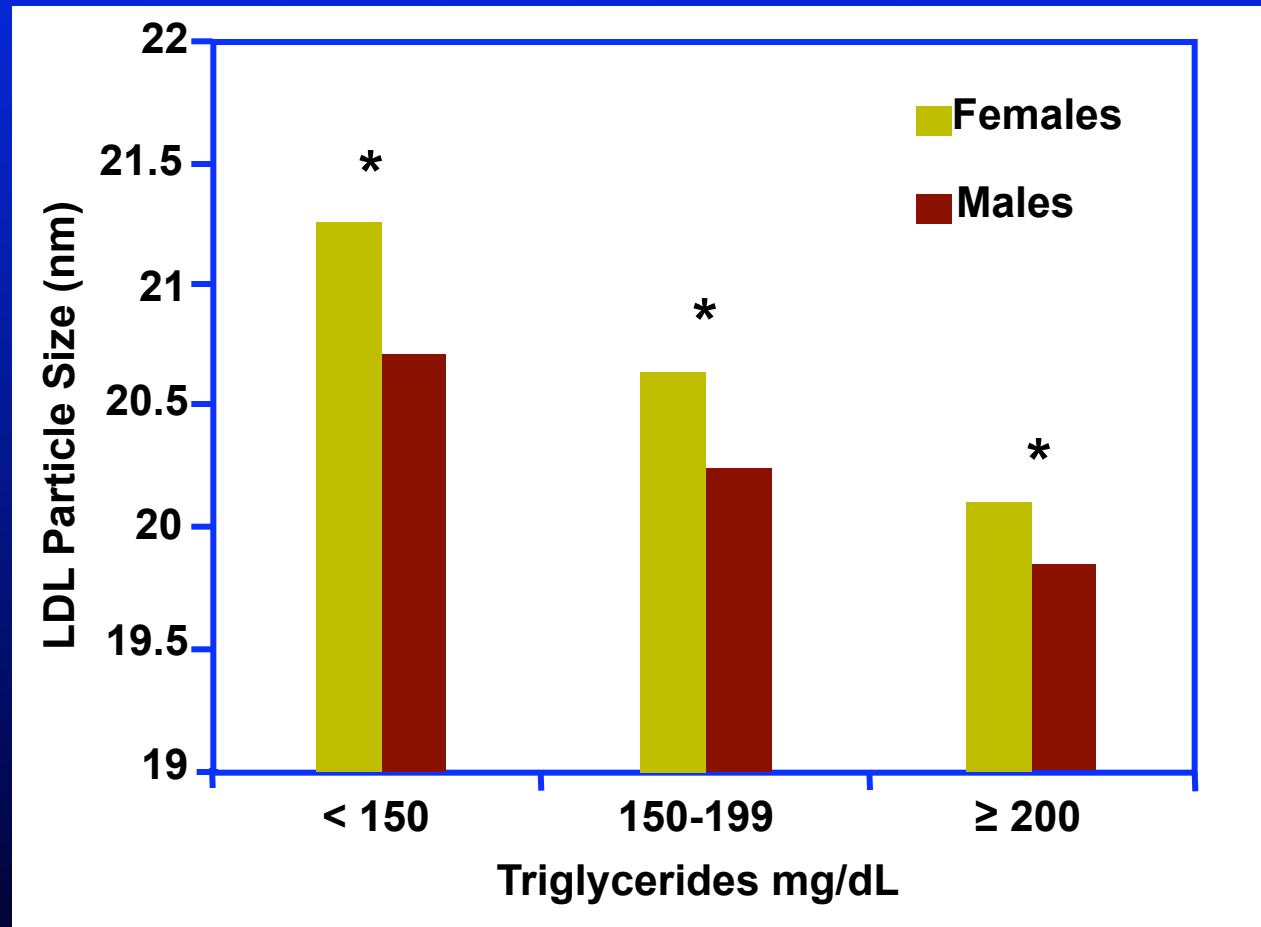
Relationship of Small LDL to Triglycerides



Relationship of Small LDL to Triglycerides

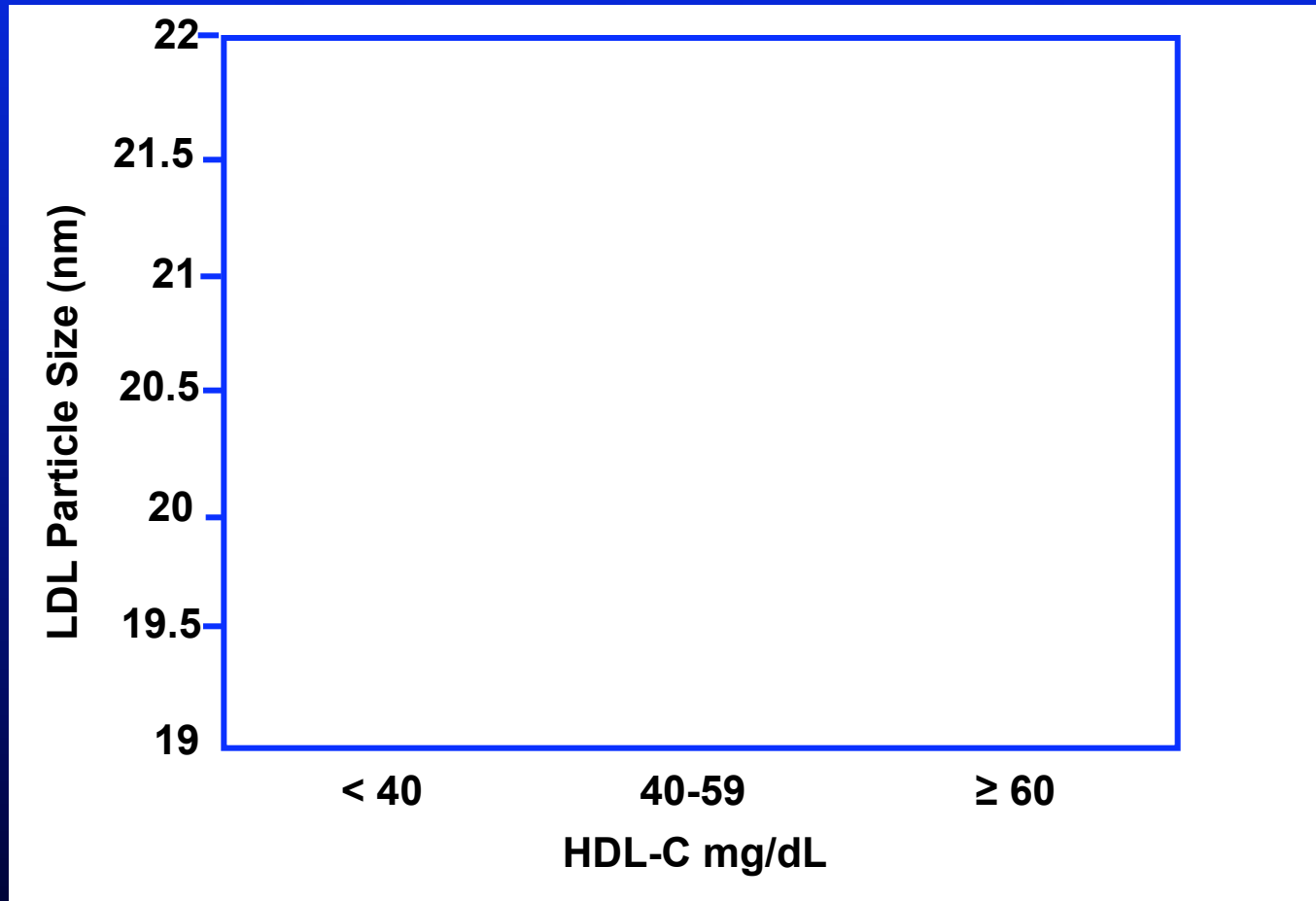


Relationship of Small LDL to Triglycerides

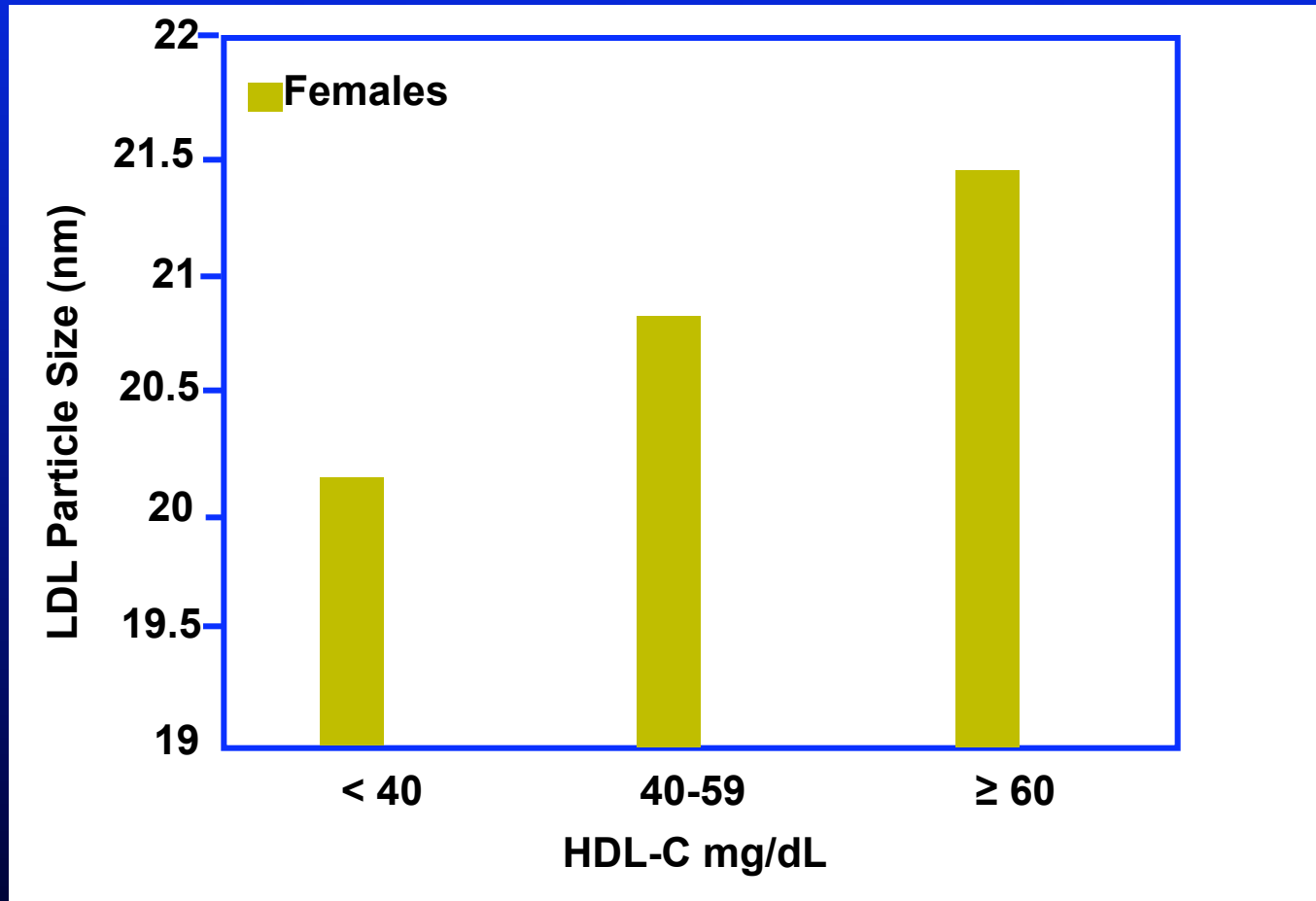


Mean LDL particle size was significantly smaller (*p < 0.05) in men compared with women for any given TG category

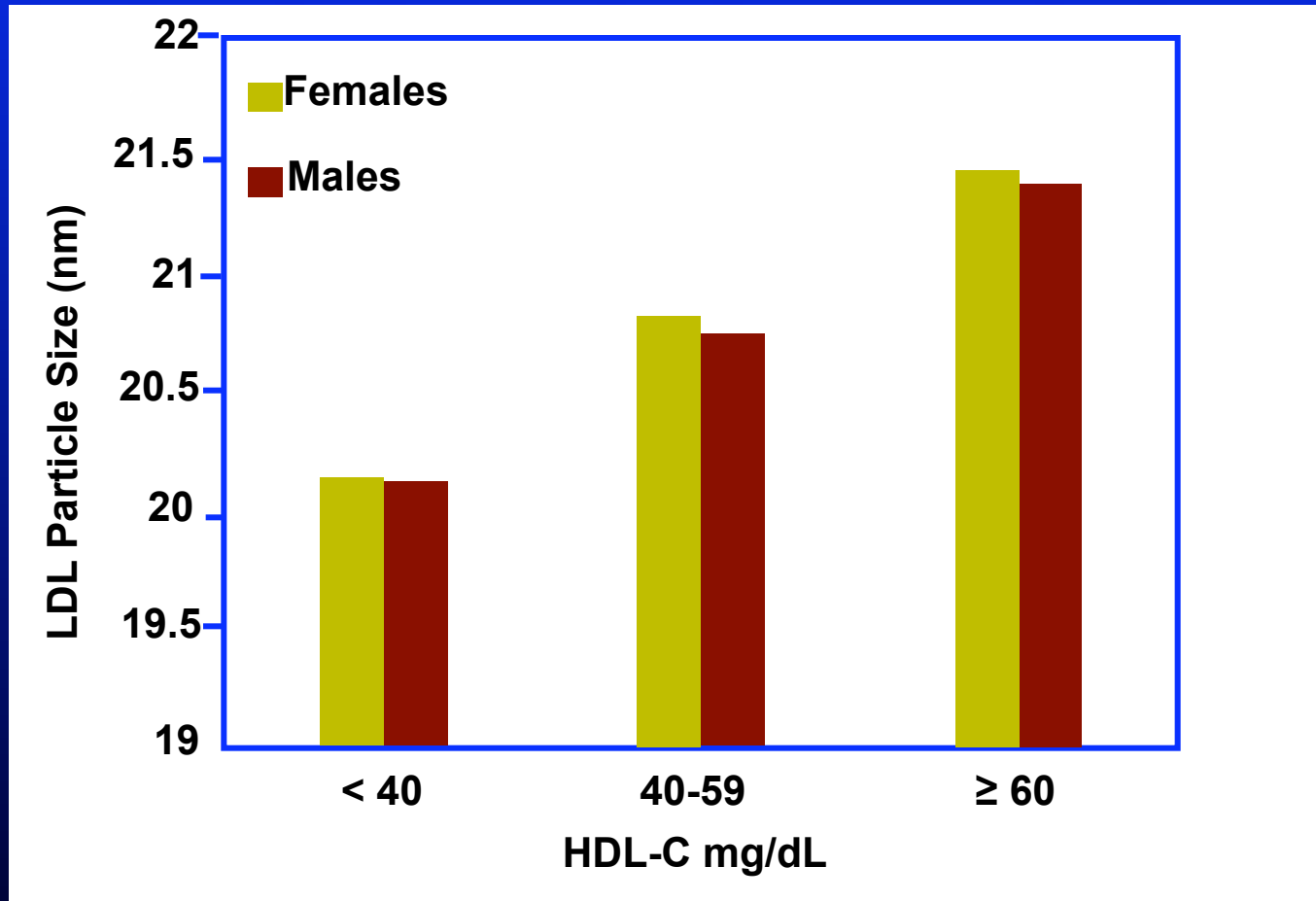
Relationship of Small LDL to HDL-C



Relationship of Small LDL to HDL-C

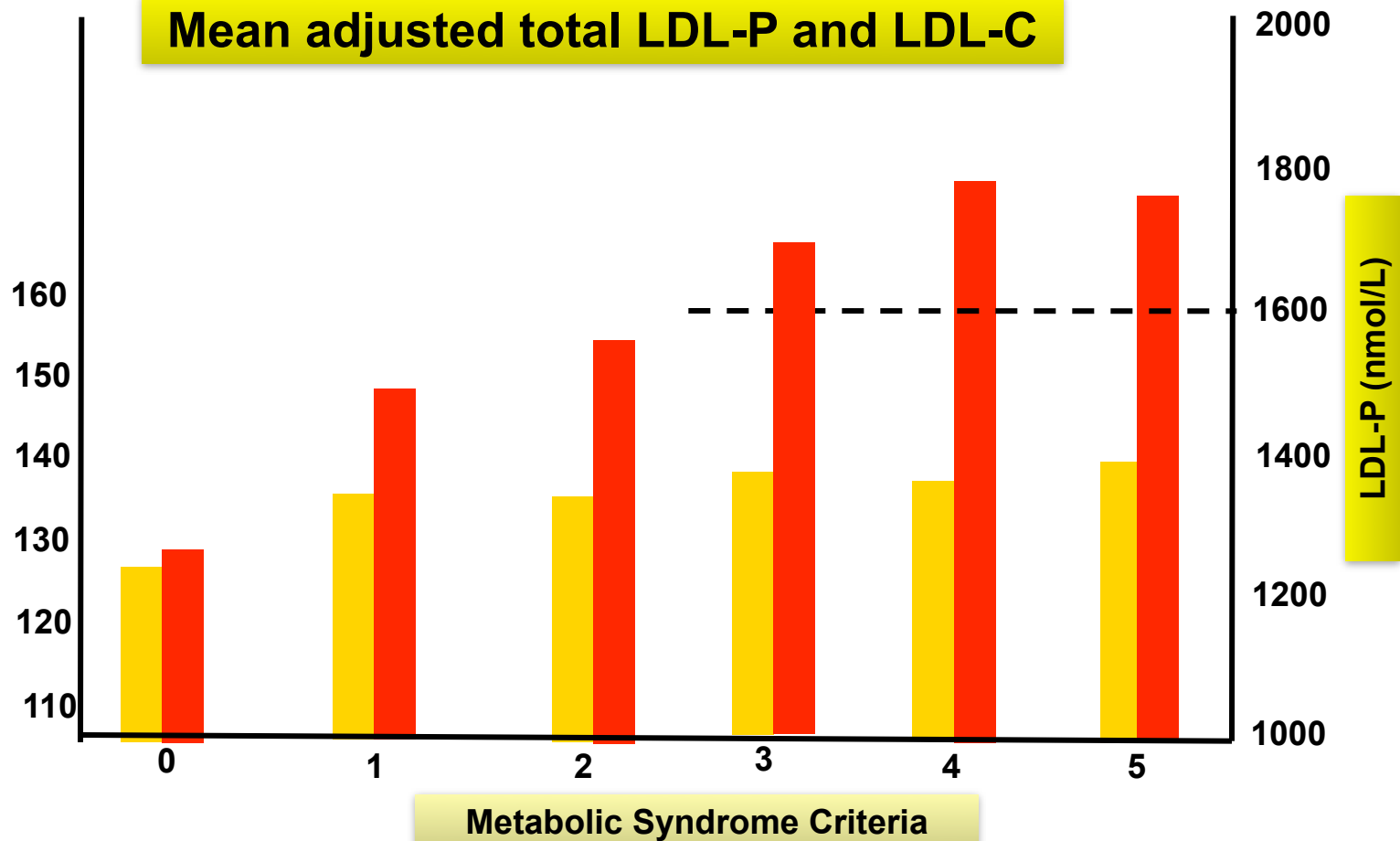


Relationship of Small LDL to HDL-C

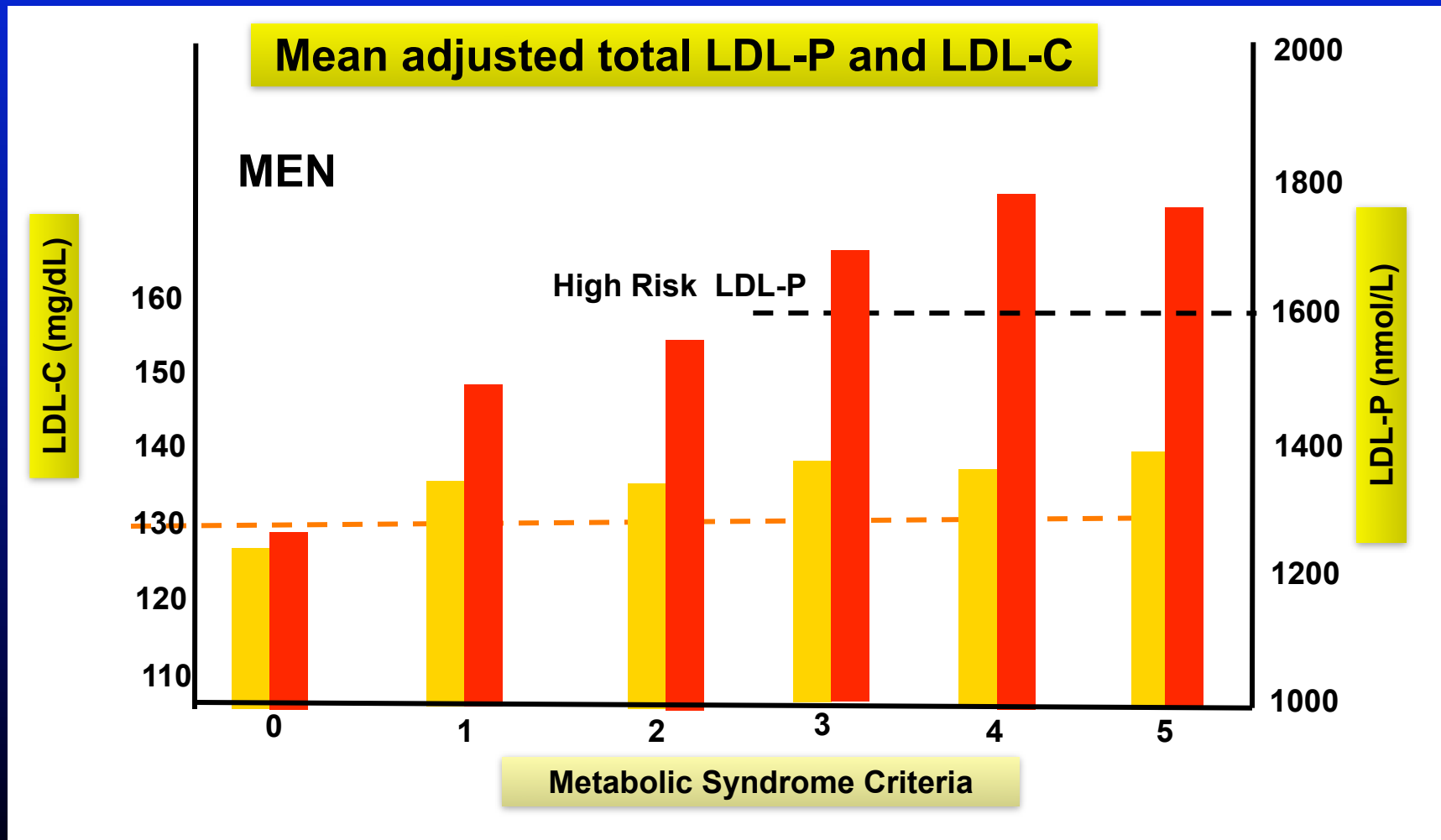


Mean LDL particle size was smaller (p = NS) in men compared with women for any given HDL-C category

Framingham Offspring Study LDL-P and Metabolic Syndrome



Framingham Offspring Study LDL-P and Metabolic Syndrome



ADA and ACC Consensus Statement on Lipoprotein Management

Particle Quantification

- ✦ apoB should be used to guide adjustments to therapy
- ✦ LDL-P as measured by NMR appears equally informative as apoB
- ✦ The panel recommends that the apoB goal be reached

ADA and ACC Consensus Statement on Lipoprotein Management

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ADA and ACC Consensus Statement on Lipoprotein Management

TREATMENT GOALS

High-risk patients,

- 1) no diabetes or known clinical CVD but 2 or more additional major CVD risk factors or
- 2) Diabetes but no other CVD risk factors

Highest-risk patients,

- 1) known CVD or
- 2) Diabetes plus one or more additional CVD risk factor

LDL-C (mg/dL) Non-HDL-C (mg/dL) ApoB (mg/dL)

< 70

< 100

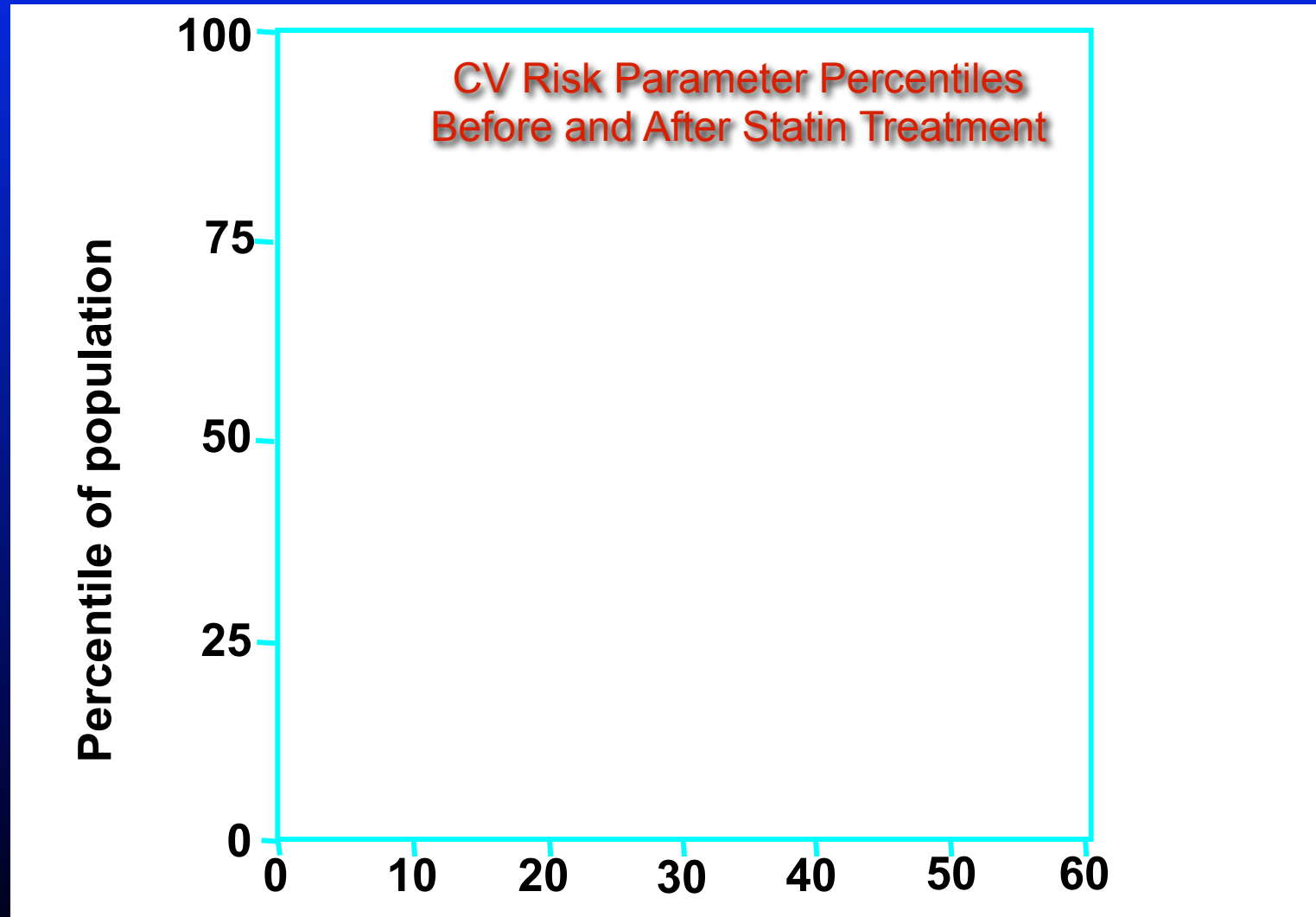
< 80

< 100

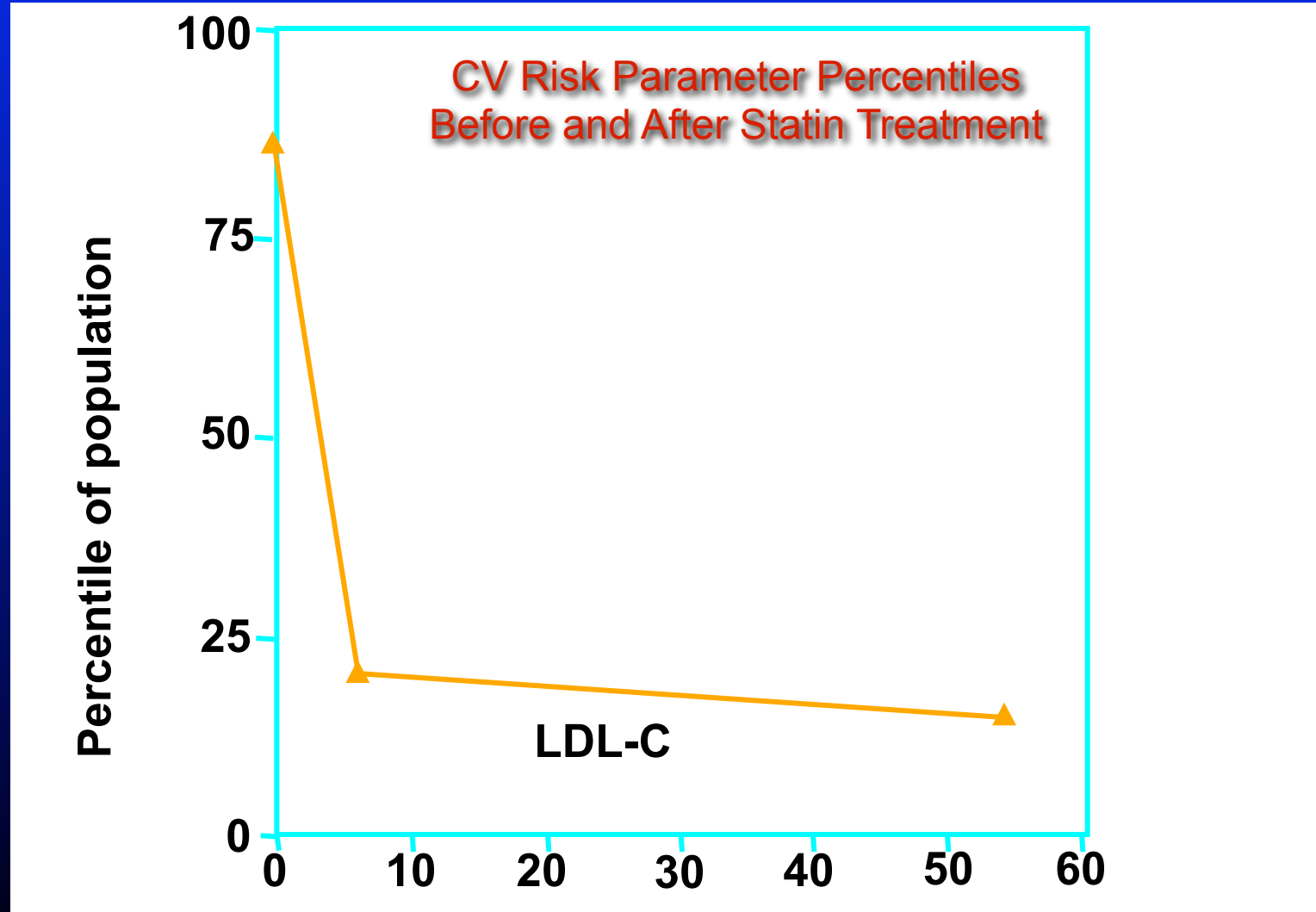
< 130

< 90

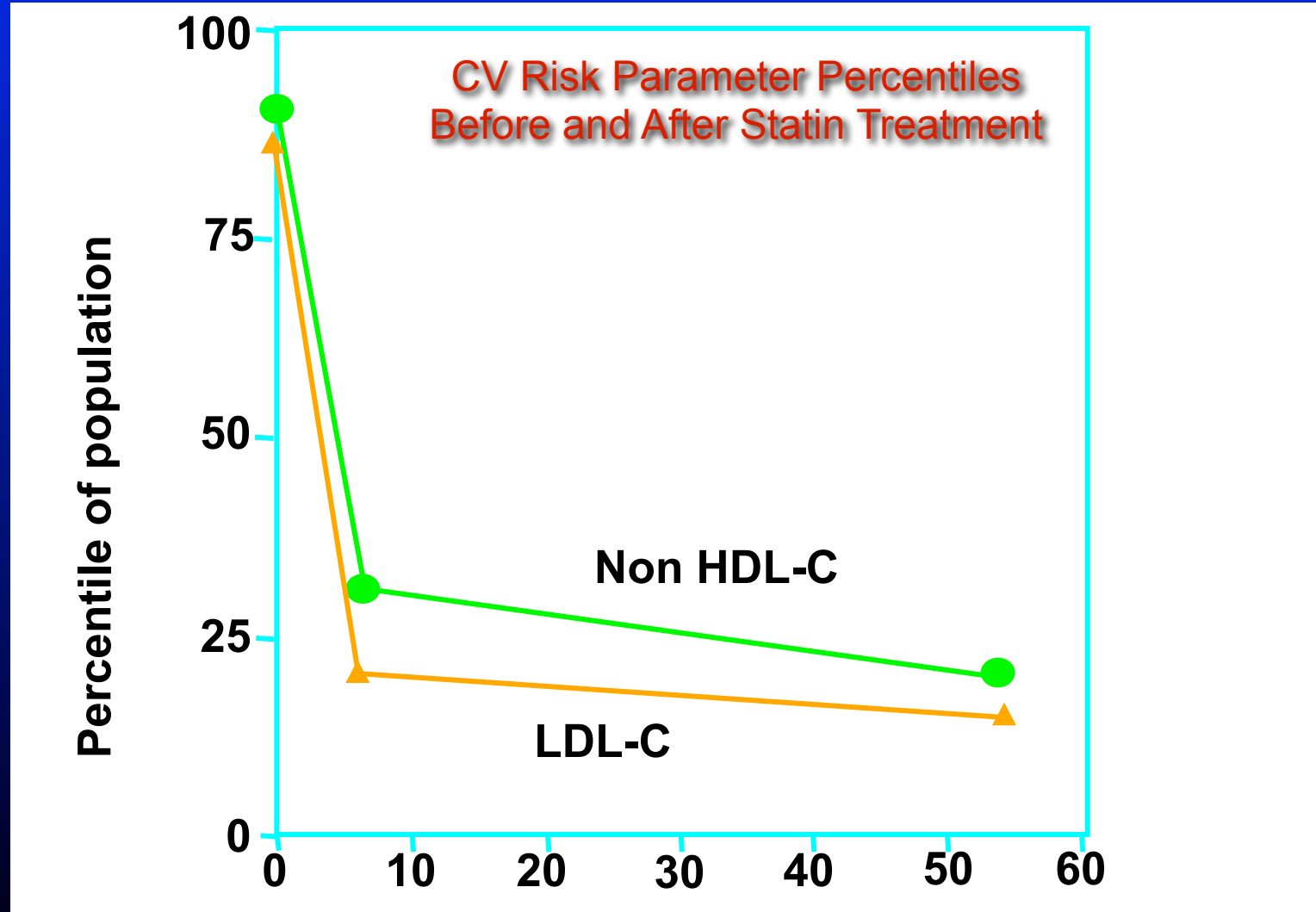
Atorvastatin Comparative Cholesterol Efficacy and Safety Study (ACCESS)



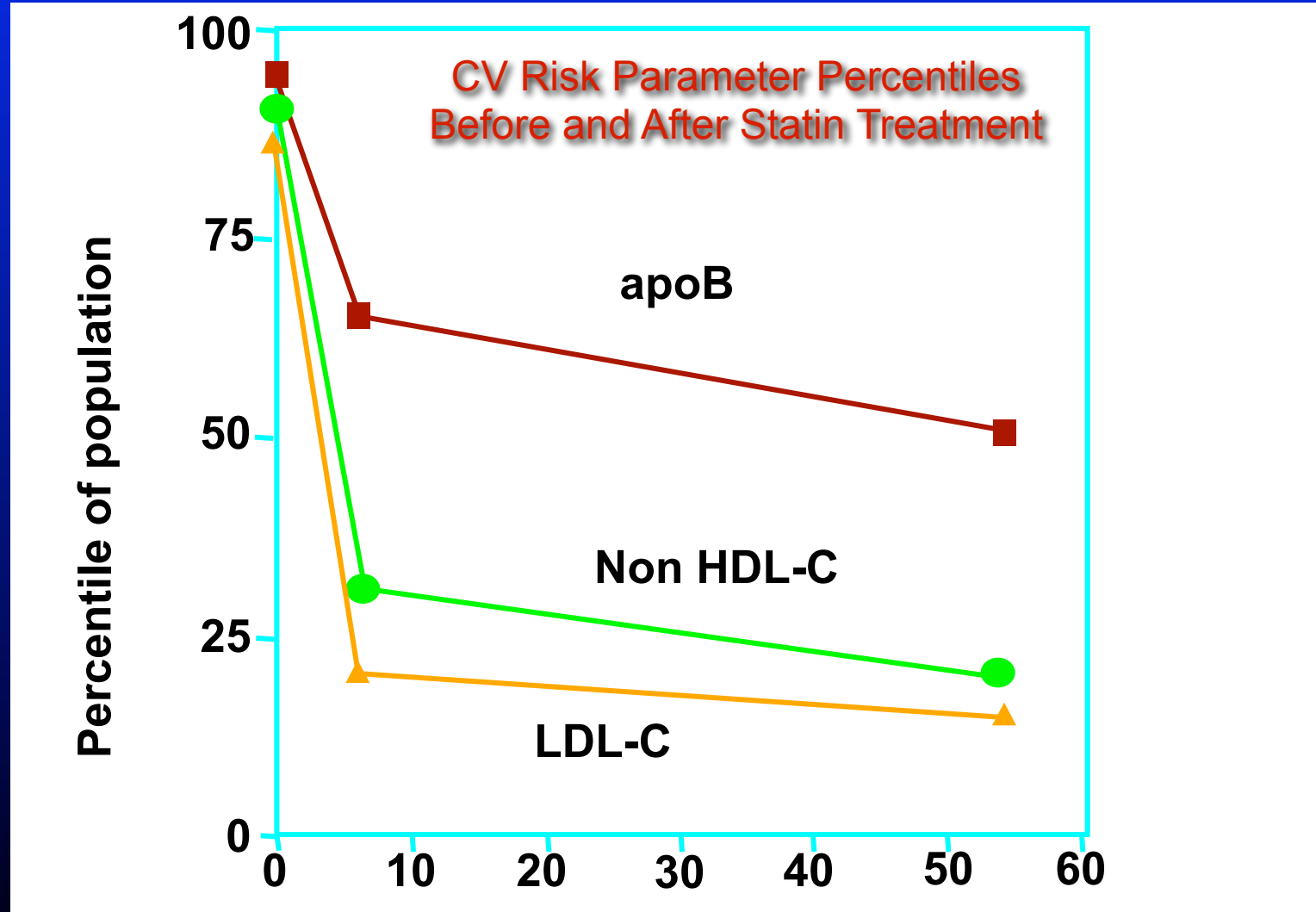
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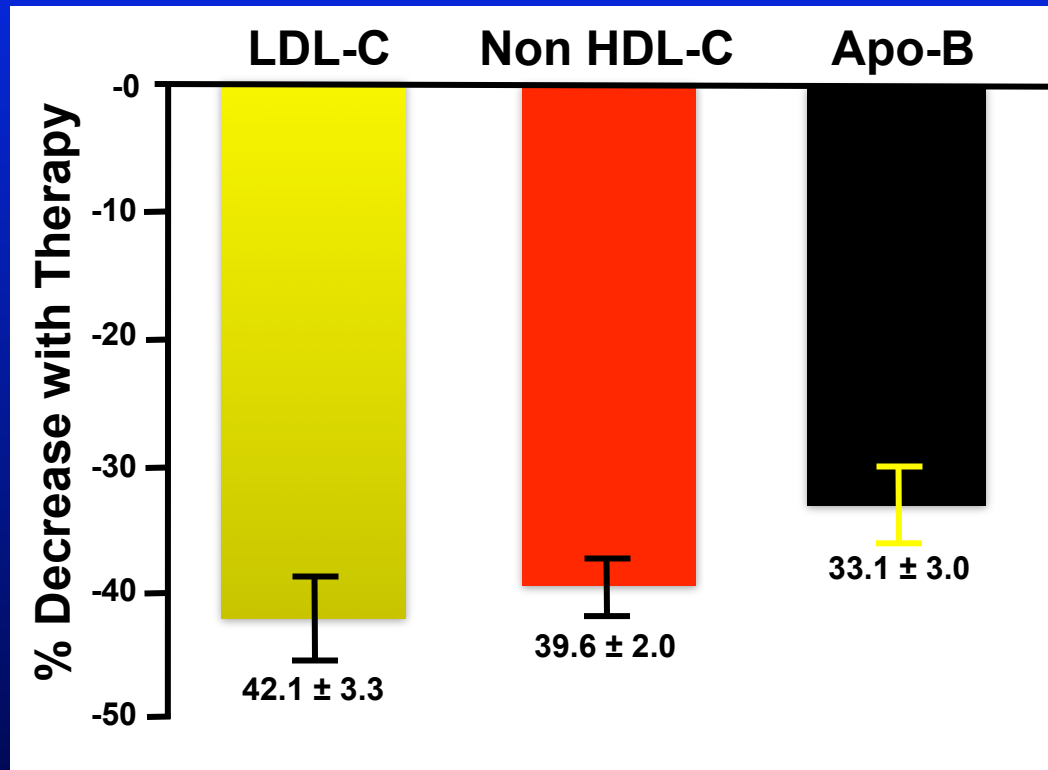


Atorvastatin Comparative Cholesterol Efficacy and Safety Study (ACCESS)



On Therapy LDL-C vs Non HDL-C vs ApoB

N = 17,035



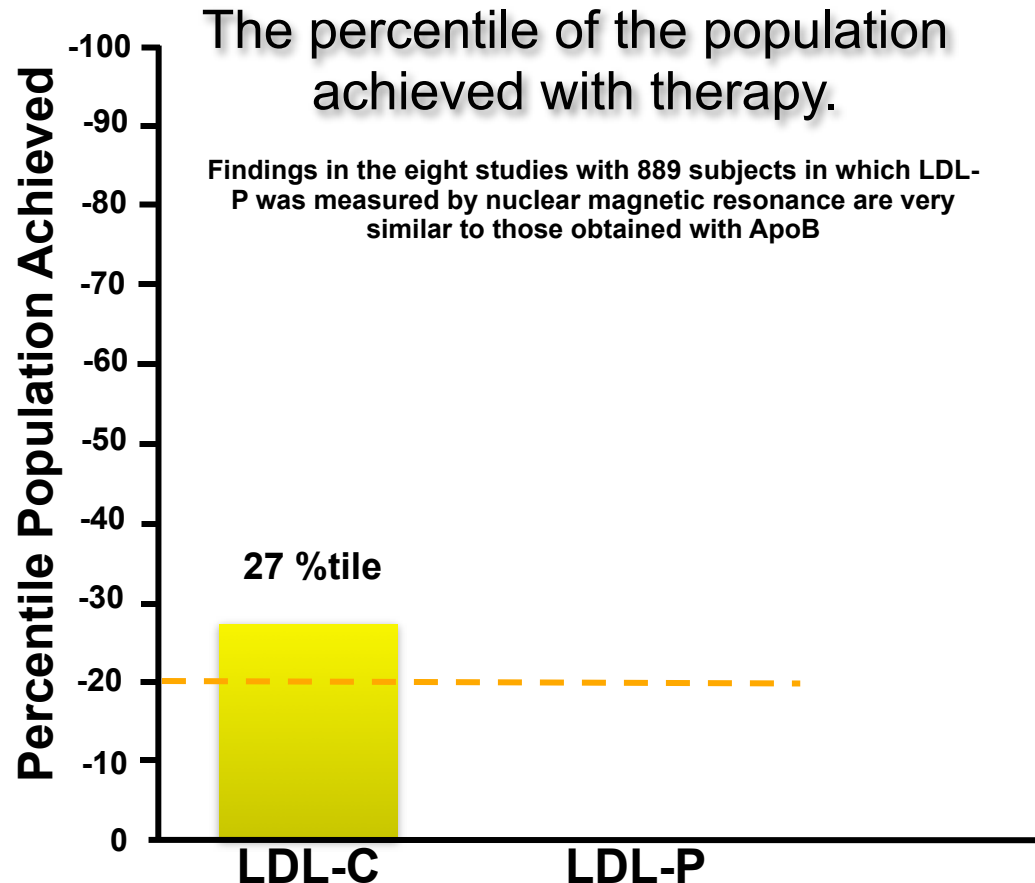
Average achieved LDL-C percentile was the 27th %tile. In contrast, average on-treatment LDL-P only was reduced to the 51st percentile (P 0.007). Thus, the reduction in LDL-P was significantly less than LDL-C.

The decrease in non-HDL-C was significantly less (P 0.001) than the decrease in LDL-C, whereas the decrease in ApoB was significantly less than the decrease in either LDL-C or non-HDL-C (P 0.001).

Findings in the eight studies with 889 subjects in which LDL-P was measured by nuclear magnetic resonance are very similar to those obtained with ApoB, and are equally consistent.

Average percent decreases in LDL-C and LDL-P were 35.9 ± 3.5% and 30.6 ± 2.8%, respectively.

On Therapy LDL-C vs LDL-P

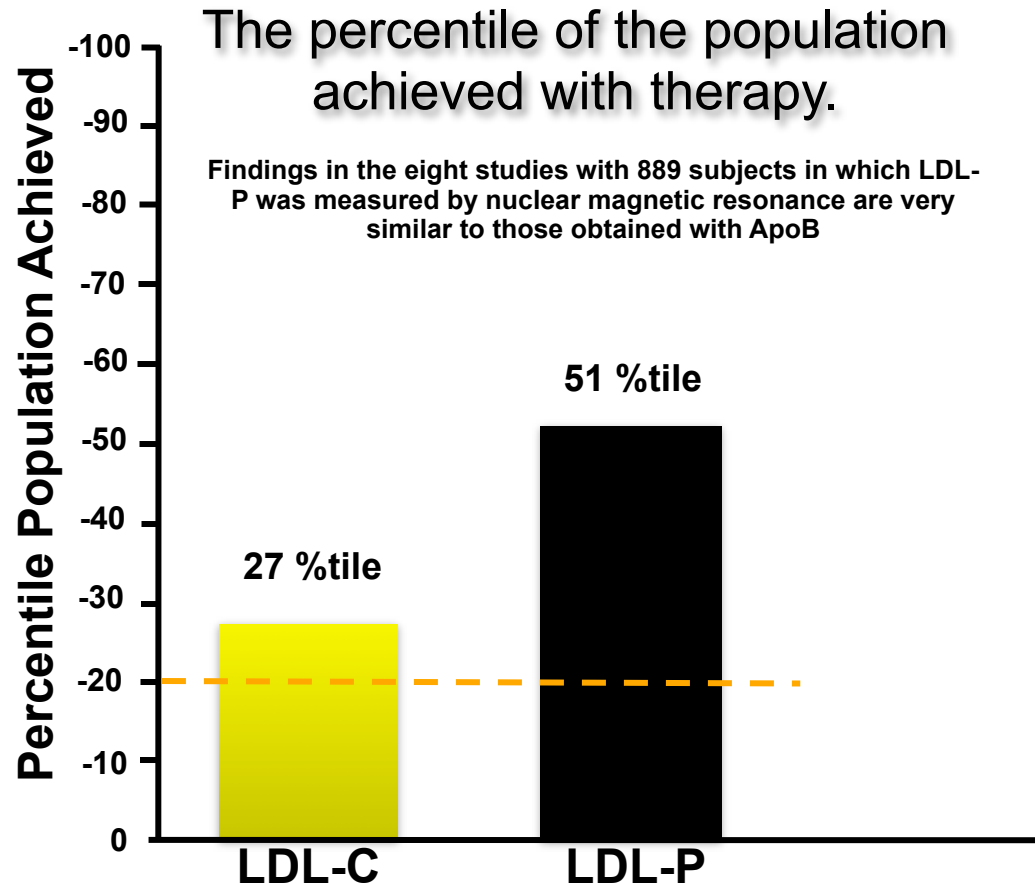


Very similar results were obtained in eight studies of LDL lowering in 889 subjects in which the responses of **LDL-C** and LDL particle number (**LDL-P**) assessed by nuclear magnetic resonance spectroscopy were compared.

LDL-C was reduced to the 27th percentile of the population, whereas LDL-P was only reduced to the 51st percentile of the population ($P < 0.007$).

Thus, the reduction in LDL-P was significantly less than LDL-C.

On Therapy LDL-C vs LDL-P



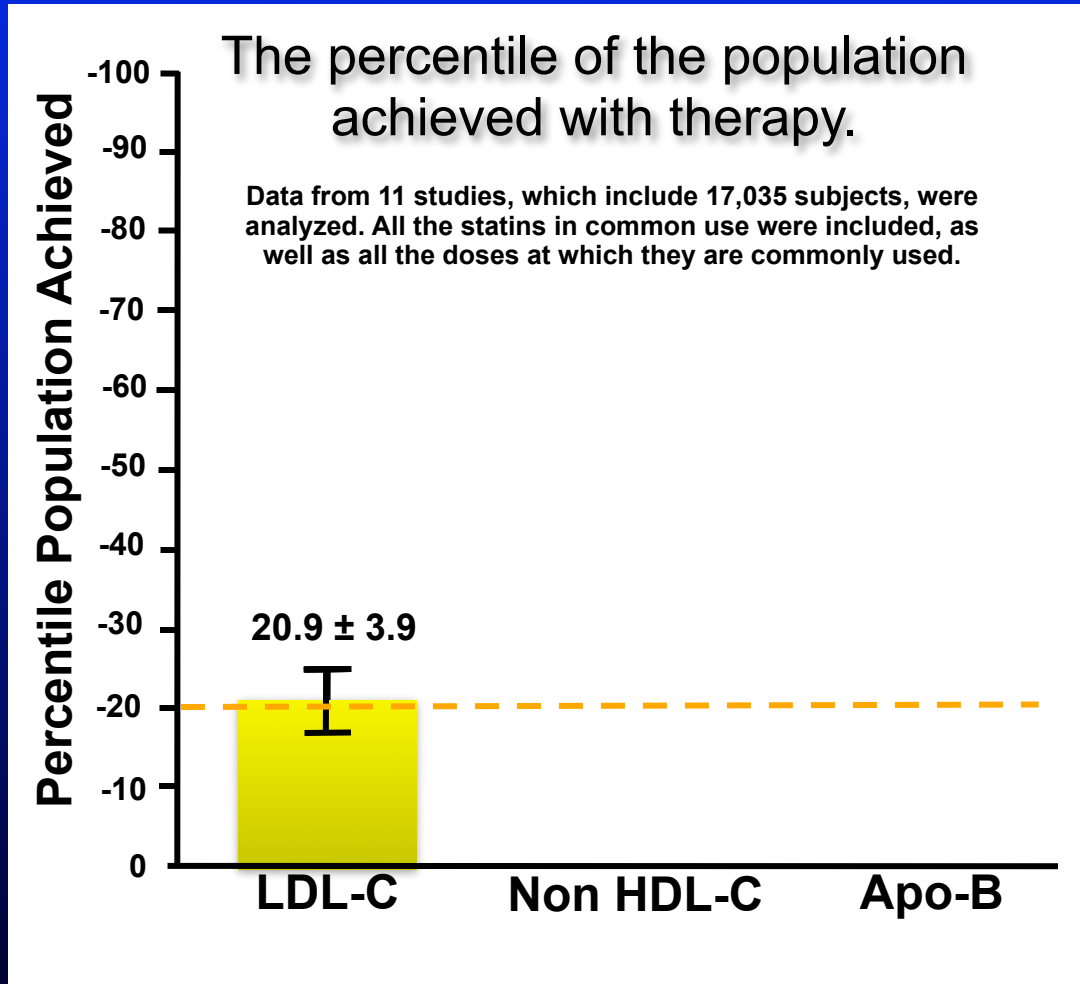
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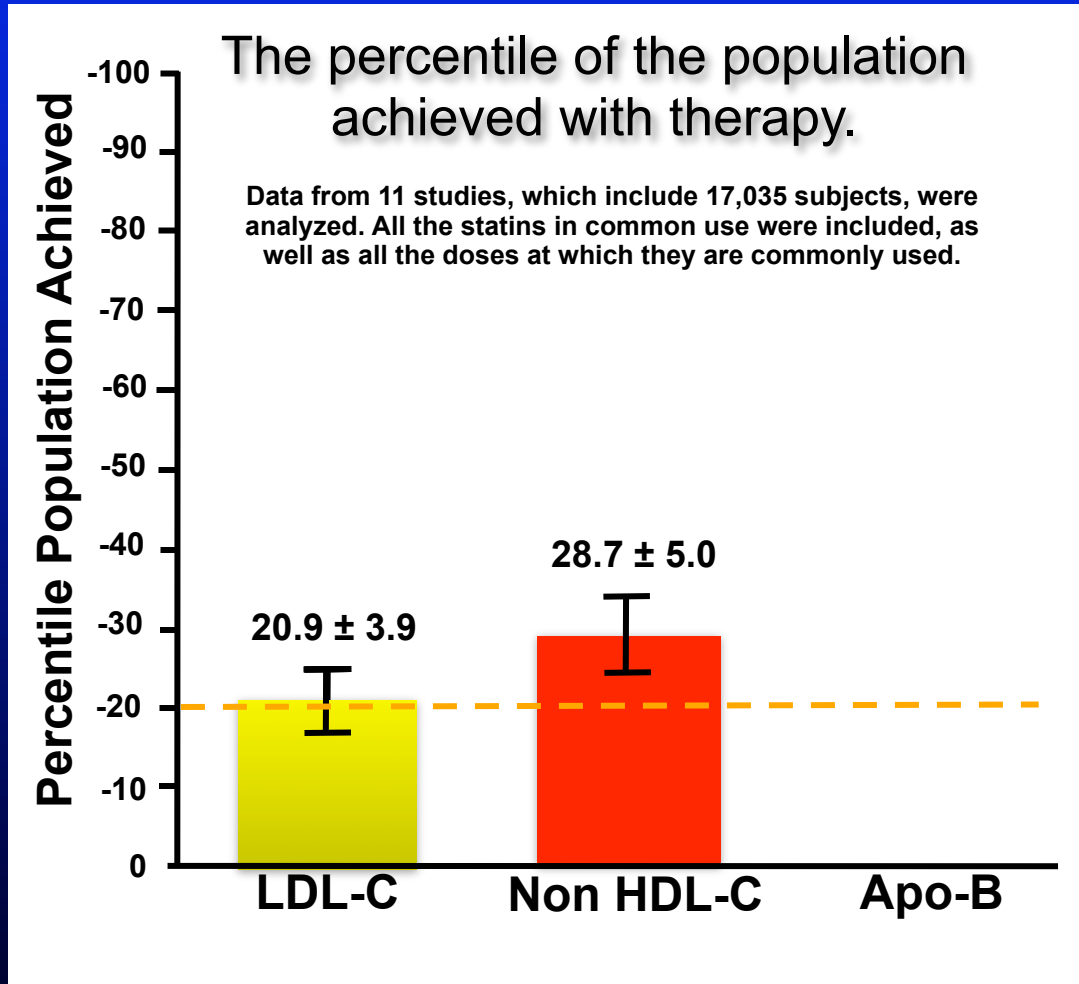
Thus, the reduction in LDL-P was significantly less than LDL-C.

On Therapy LDL-C vs Non HDL-C vs ApoB

LDL-C, on average, was reduced to a level equal to the 22nd percentile of the reference population.



On Therapy LDL-C vs Non HDL-C vs ApoB

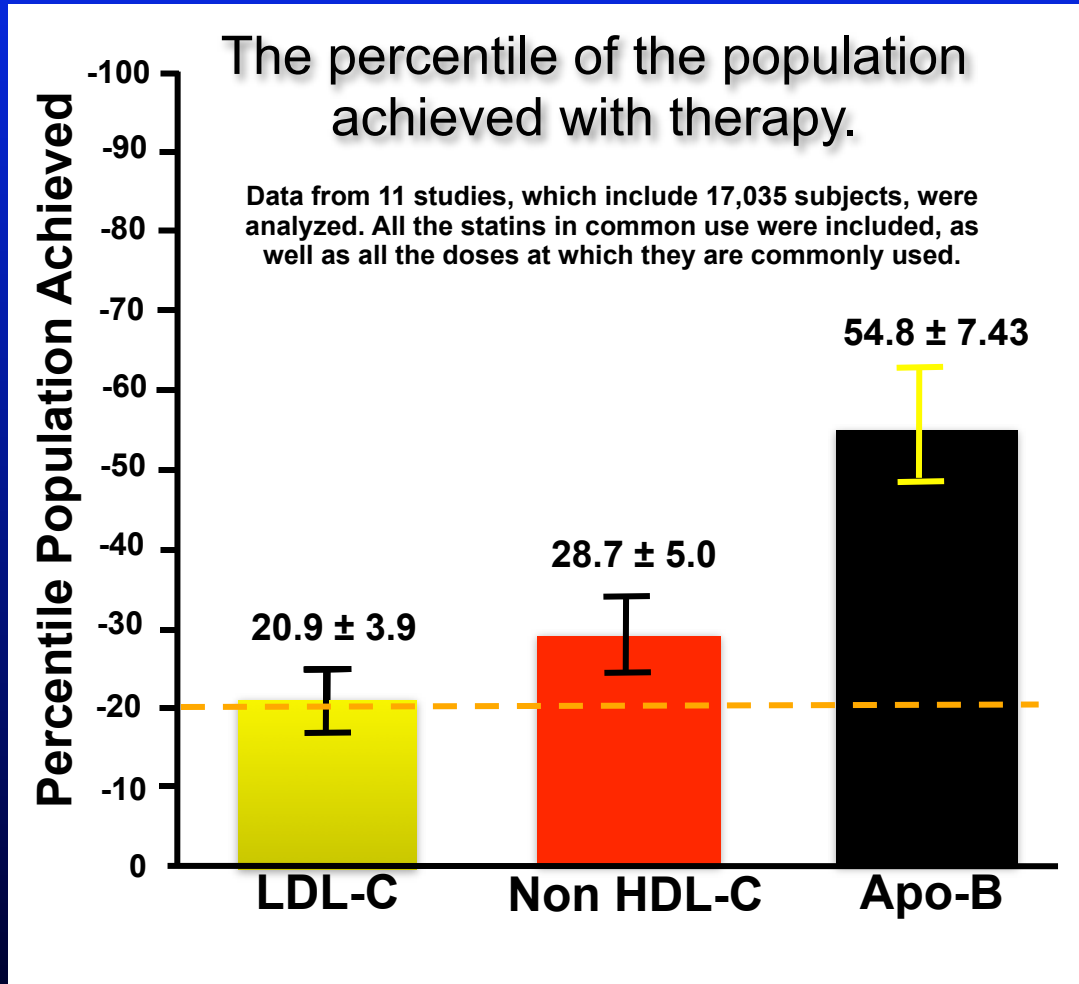


LDL-C, on average, was reduced to a level equal to the 22nd percentile of the reference population.

The corresponding average concentration achieved for non HDL-C was the 29th percentile value, which was a significantly lesser change than achieved with LDL-C (P 0.001).

Both differ substantially with the findings obtained for ApoB.

On Therapy LDL-C vs Non HDL-C vs ApoB



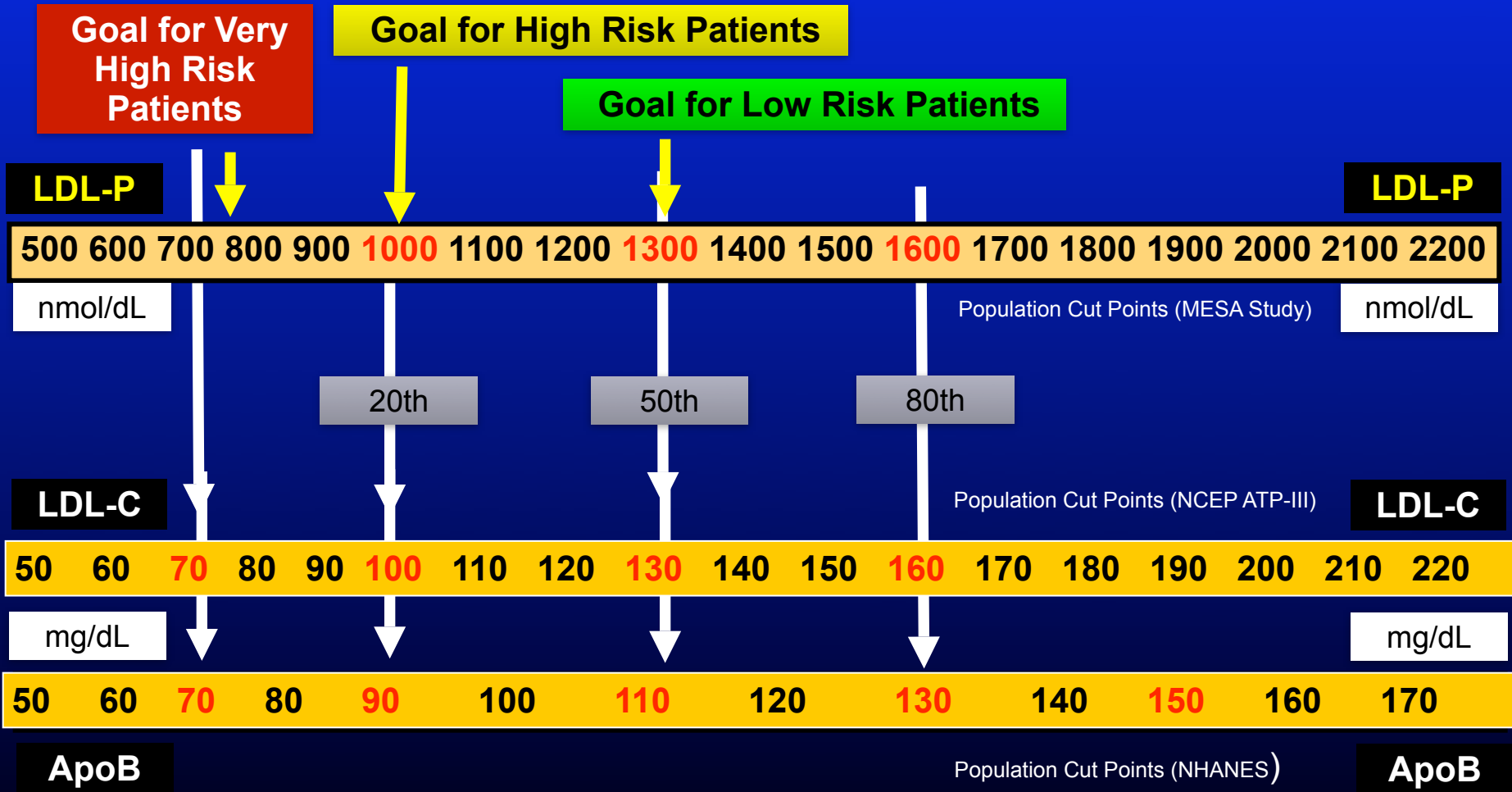
LDL-C, on average, was reduced to a level equal to the 22nd percentile of the reference population.

The corresponding average concentration achieved for non HDL-C was the 29th percentile value, which was a significantly lesser change than achieved with LDL-C (P 0.001).

Both differ substantially with the findings obtained for ApoB.

ApoB was only decreased to the 55th percentile of the population, a drop that is significantly less than achieved with LDL-C or non HDL-C (P 0.001 in both comparisons).

Population Percentile Cut Points & Goals for LDL-P, LDL-C and Apolipoprotein B



Evidence Supporting LDL-P over ApoB: Prospective Epidemiologic Studies & Clinical Trials

- ▶ Five studies have included measures of plasma apo B (highly correlated with LDL apo B) and NMR LDL-P, allowing comparison of the strengths of their disease associations.
- ▶ In all five studies, apo B was related less strongly to CVD than to LDL-P:

VA-HIT¹

Veteran's Administration HDL Intervention Trial

WHS²

Women's Health Study

FOS³

Framingham Offspring Study

JHS⁴

Johns Hopkins Sibling Study

VTE Study⁵

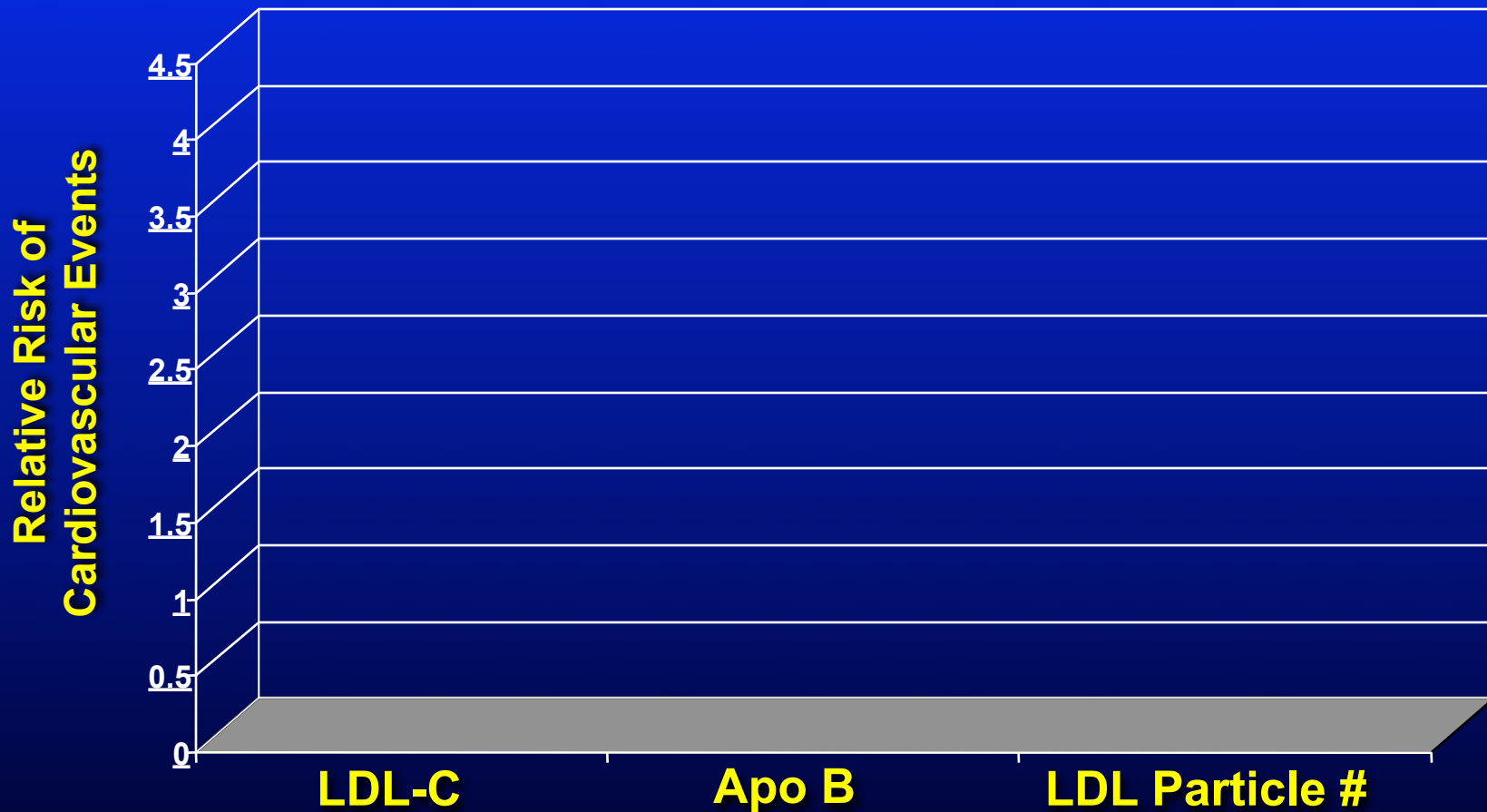
Venous Thrombosis Study in Men

Jeyarajah EJ et al. Clin Lab Med 26 (2006) 847–870

1 Circulation 2006;113:1556–63. 2 Circulation 2002;106:1930–7 3 J Clin Lipidol 2007;1:583-502 4 JACC 2002;39:274A 5 Circulation 2005;112:893–9

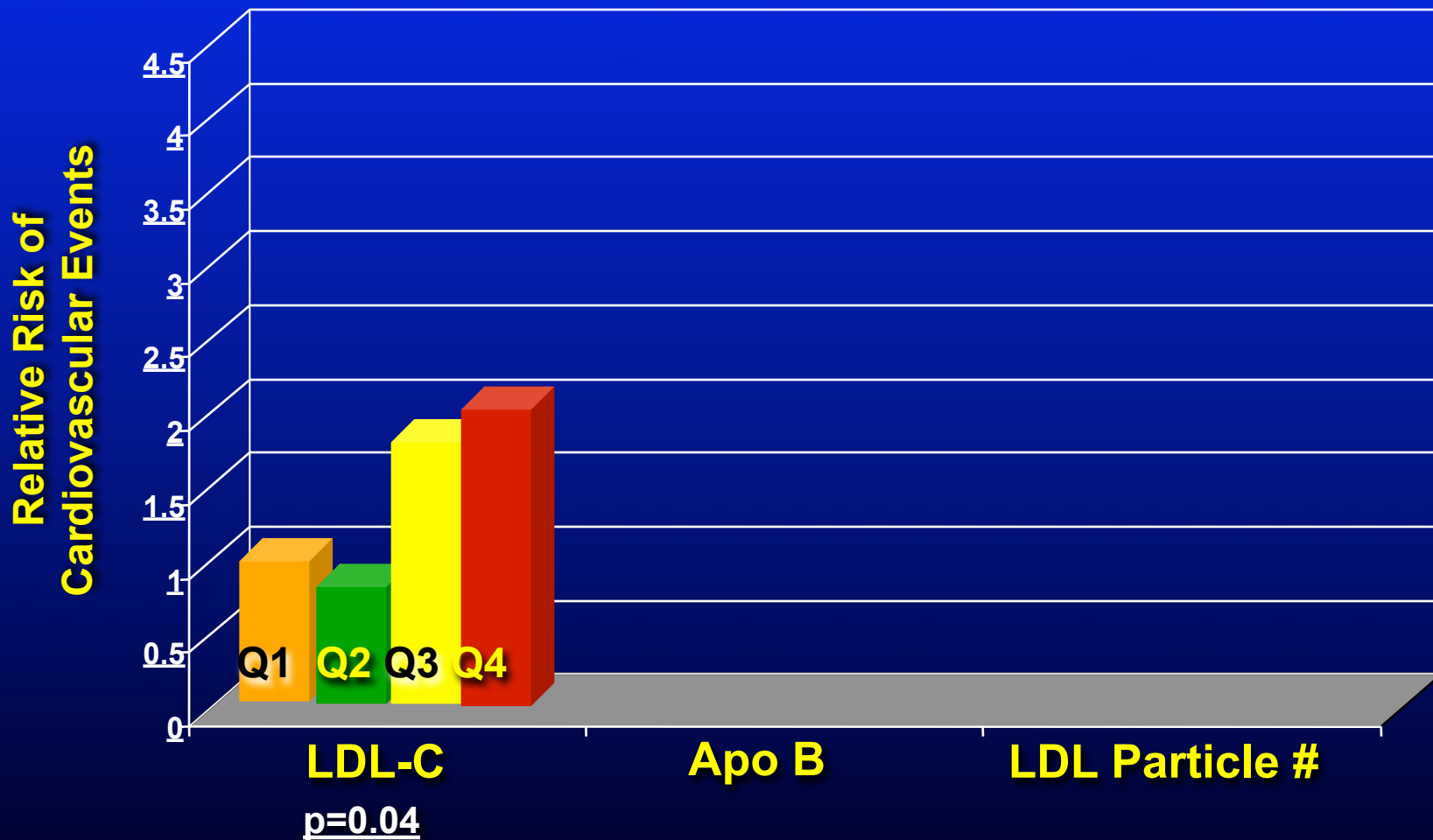
Women's Health Study: of CV Events by Quartile of Plasma Level

RR



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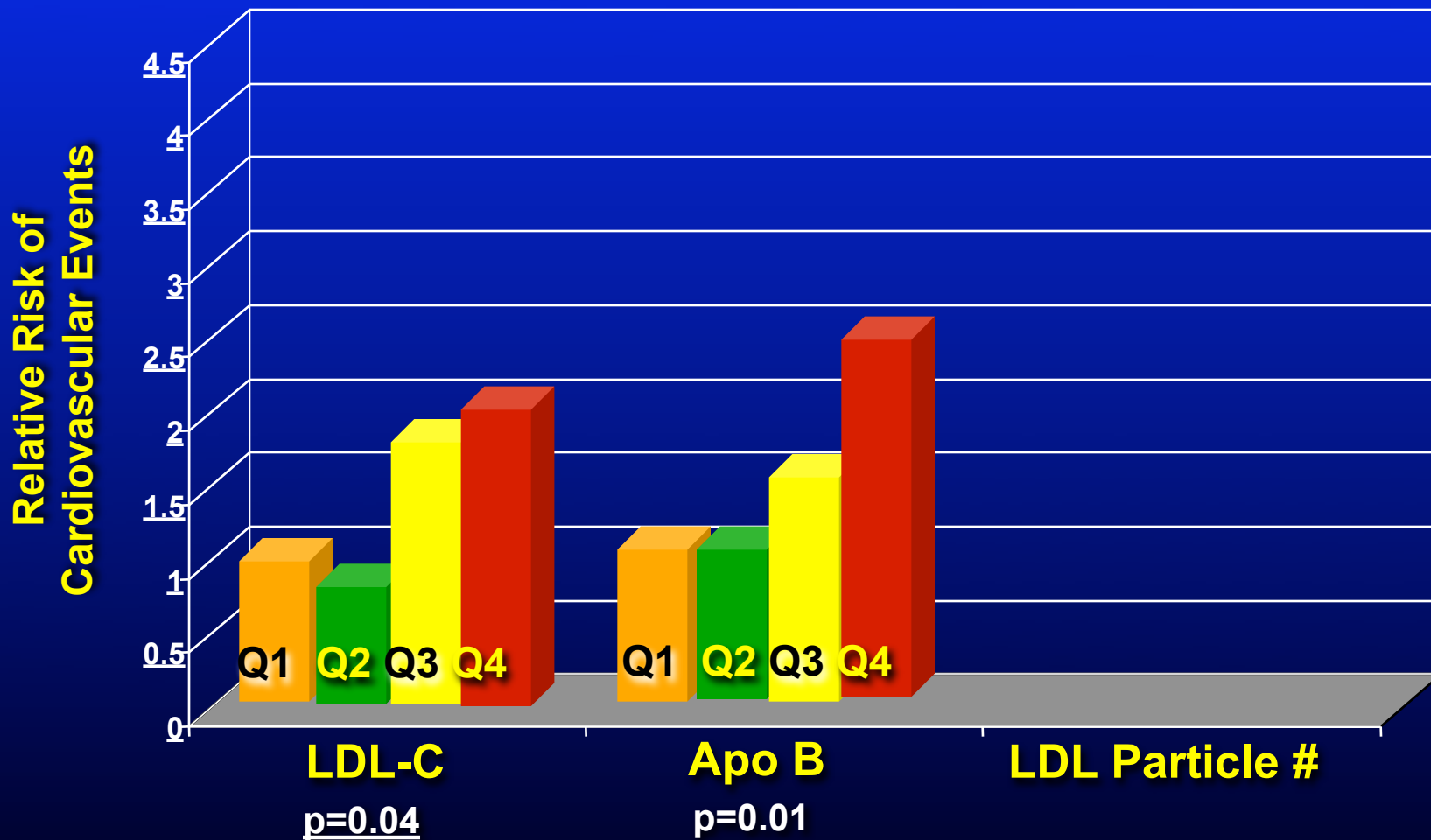


p values compare highest vs lowest quartiles

Blake GJ, et al. *Circ* 2002;106:1930-1937

Women's Health Study: of CV Events by Quartile of Plasma Level

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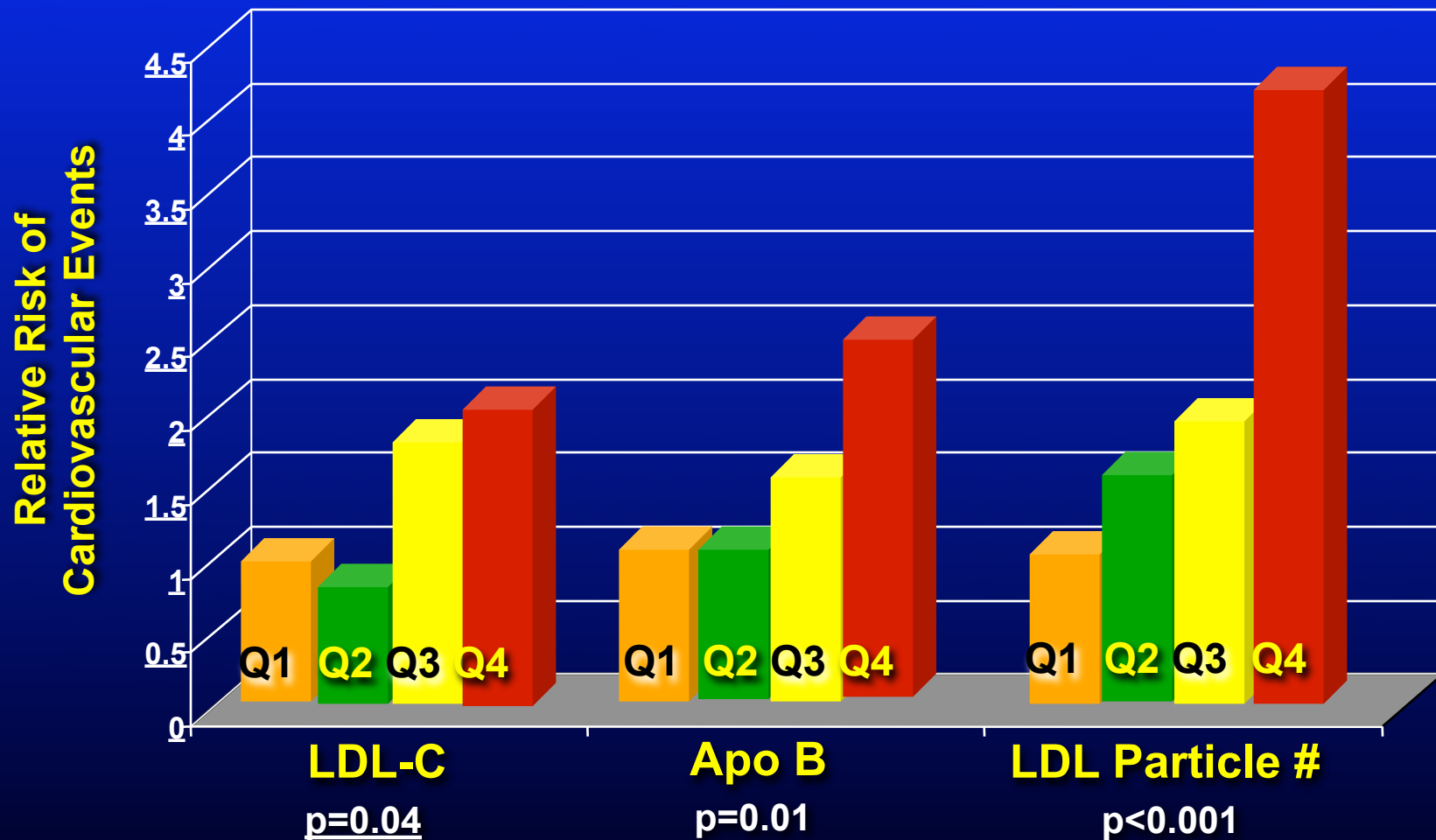


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