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Certified Cardiometabolic Health Professional (CCHP)

An Overview of Lipoproteins & Their Functions

Alan Chait MD

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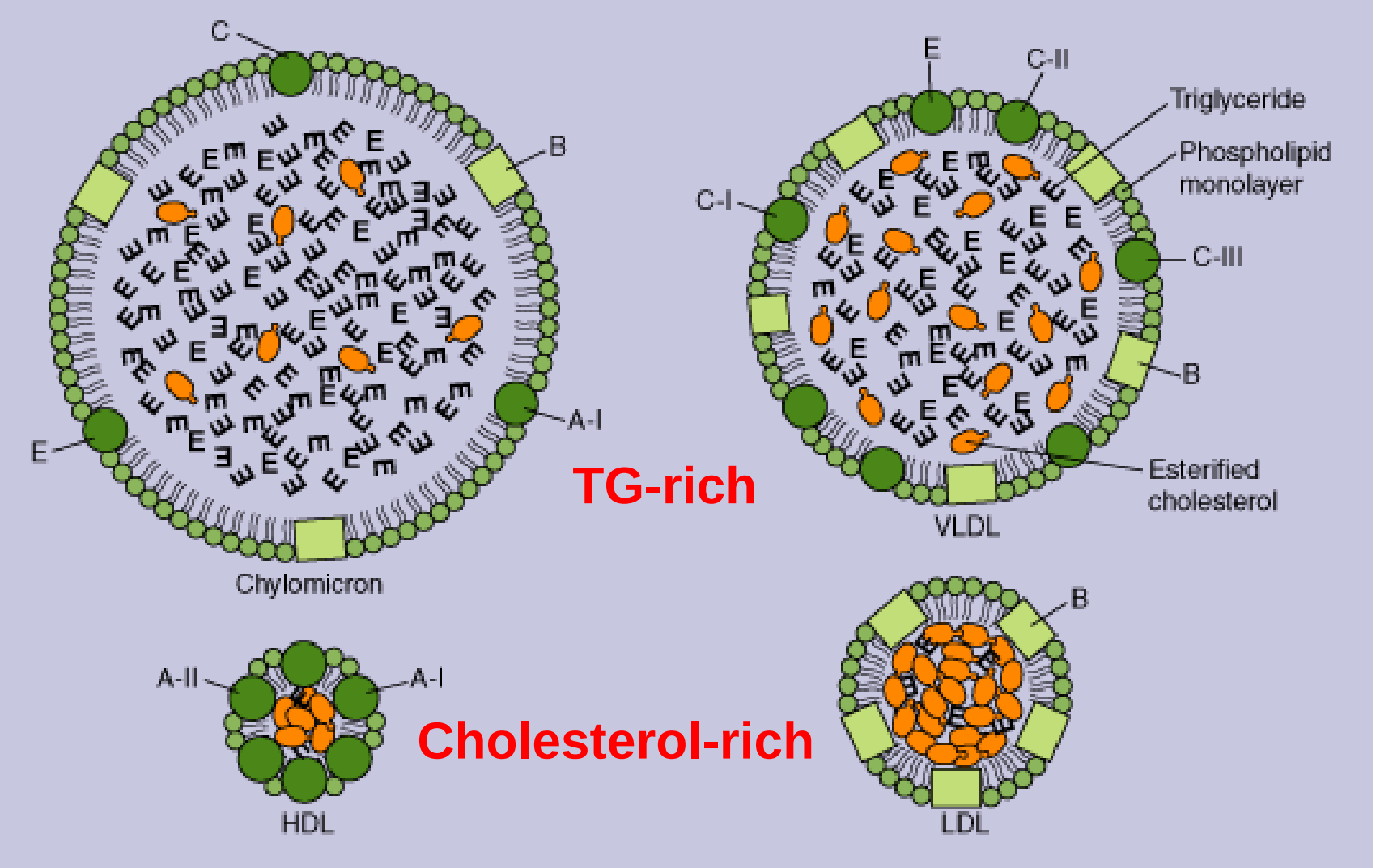
Duality of Interests

- Consultant/Advisory board
  - Pfizer
- Data safety monitoring board
  - LIB therapeutics
- Stock
  - Theripion

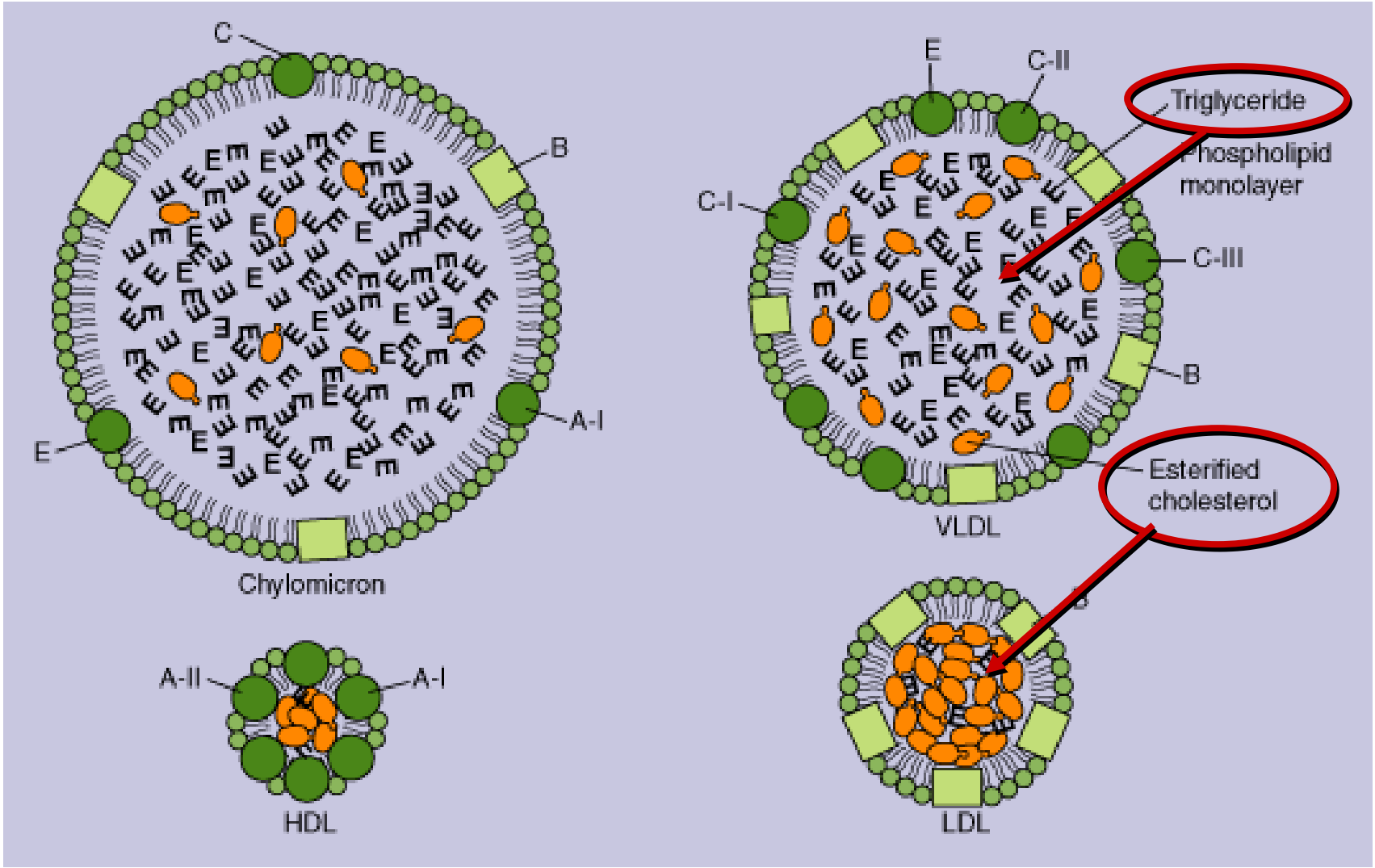
Overview

- Lipoprotein classes and their structure
- Lipoprotein physiology
  - Triglyceride-rich lipoproteins
  - Low density lipoproteins (LDL)
    - Chylomicrons and very low-density lipoproteins (VLDL)
  - High density lipoproteins (HDL)
- Functions of lipoproteins
- Measurement of plasma lipoproteins

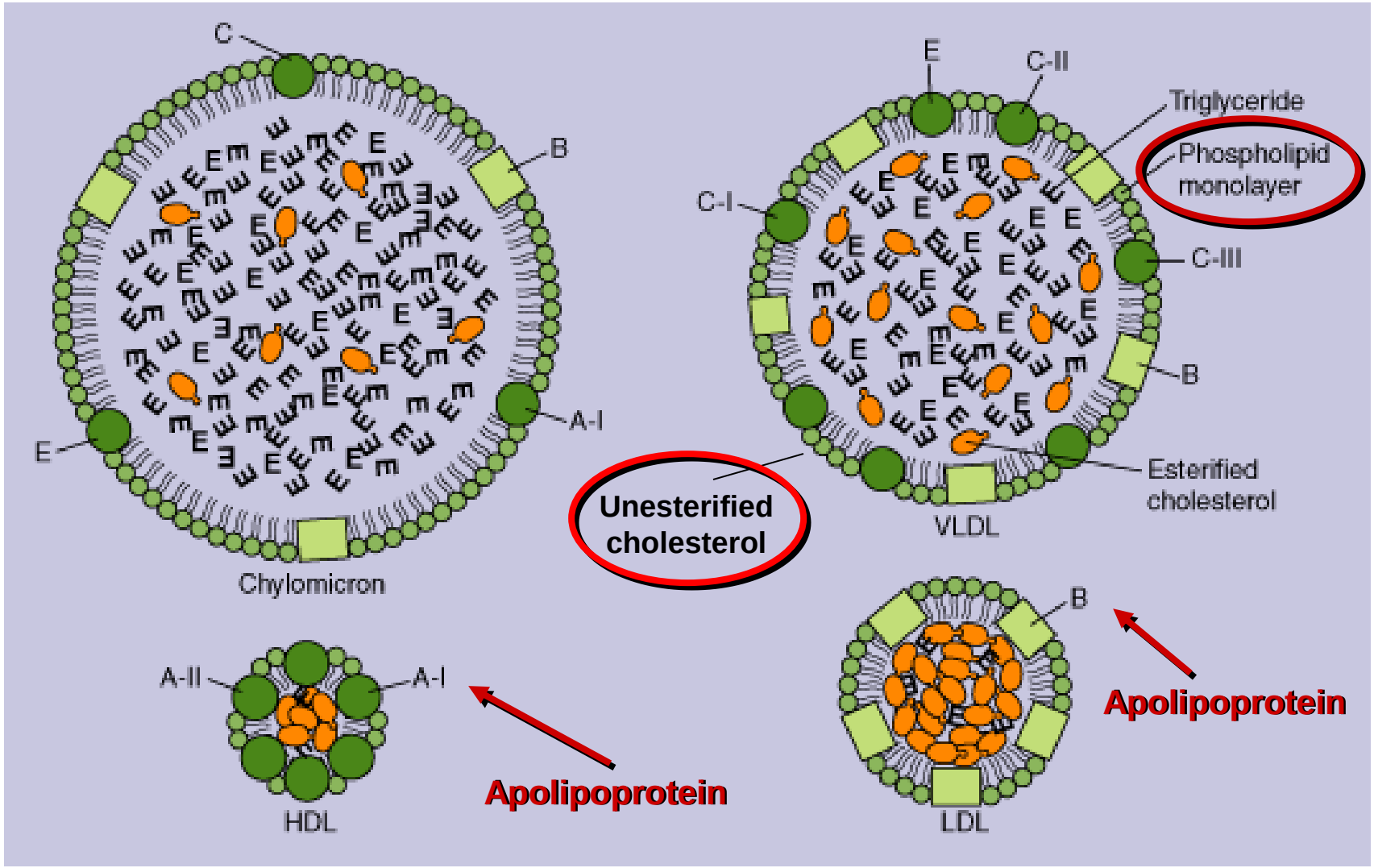
Lipoprotein Structure



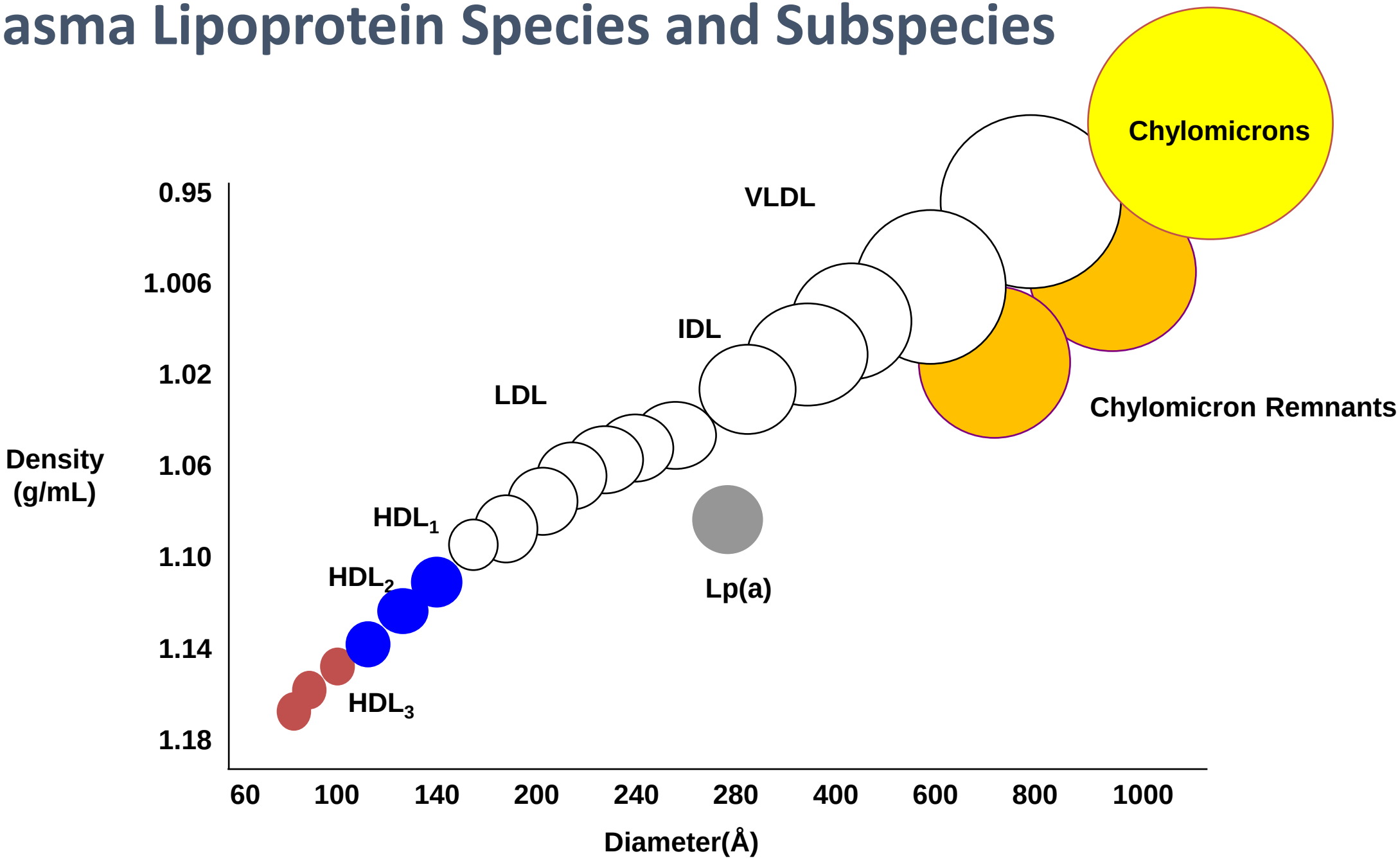
Lipoprotein Structure – Core Lipids



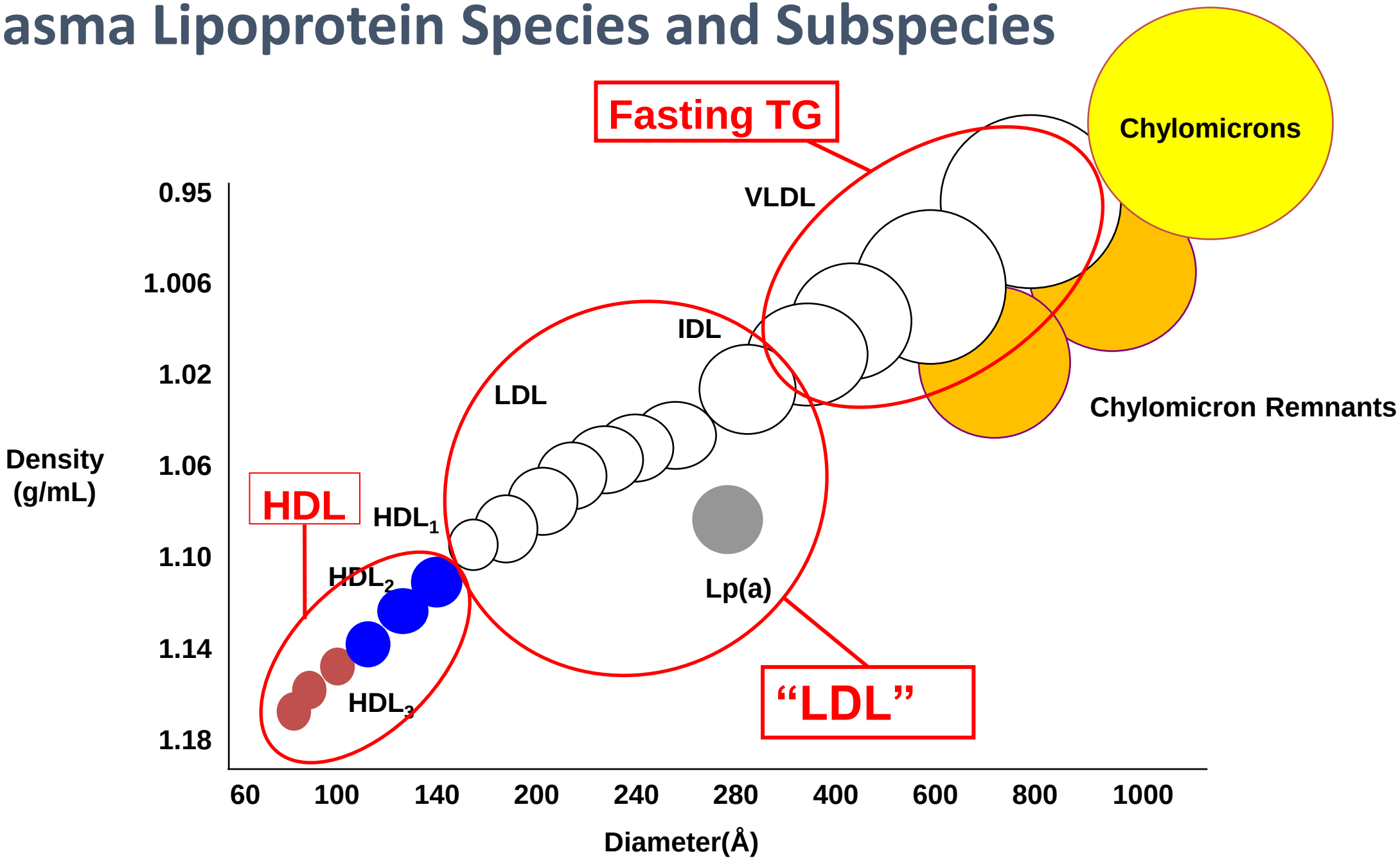
Lipoprotein Structure – Surface Layer



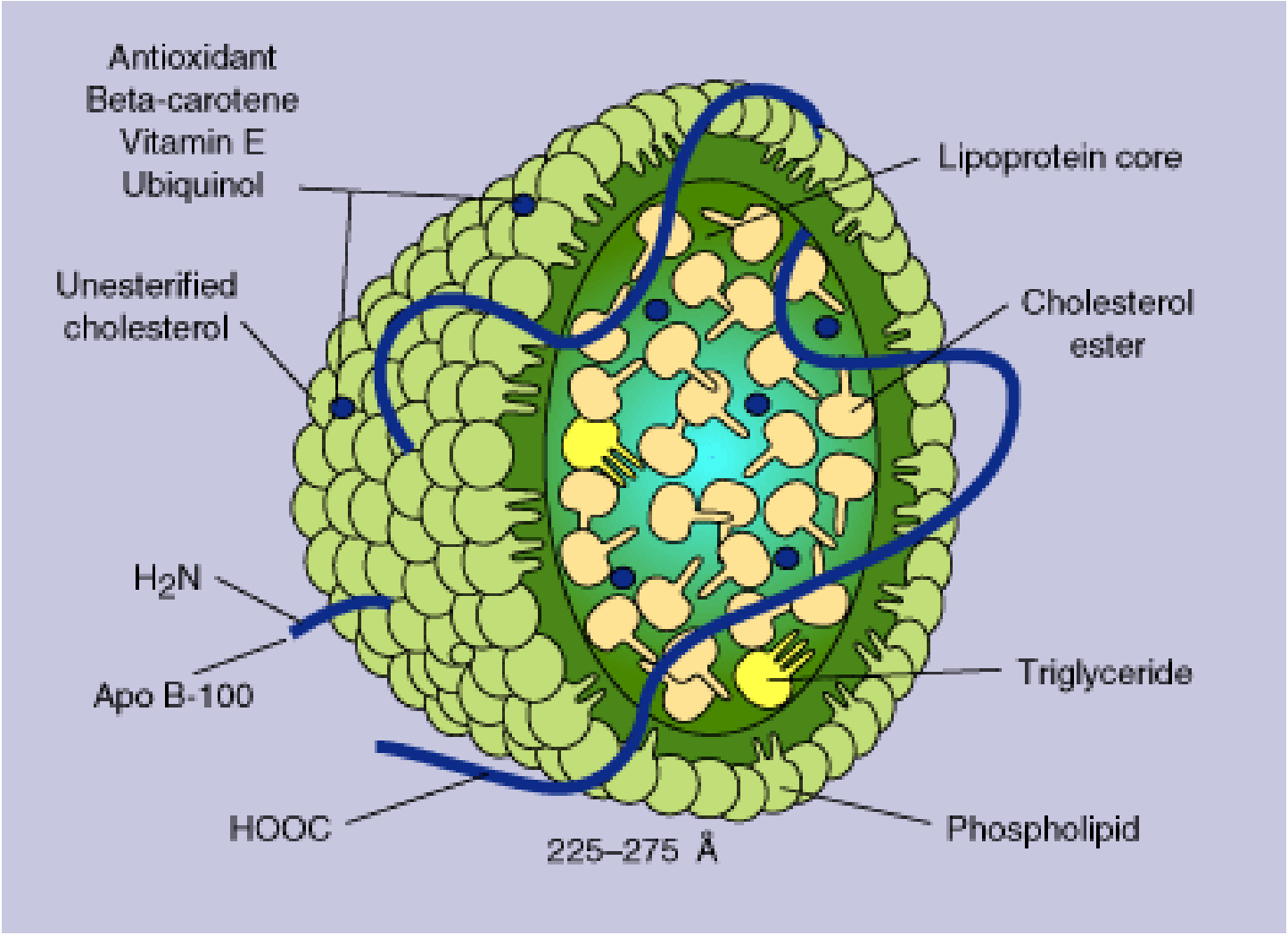
Plasma Lipoprotein Species and Subspecies



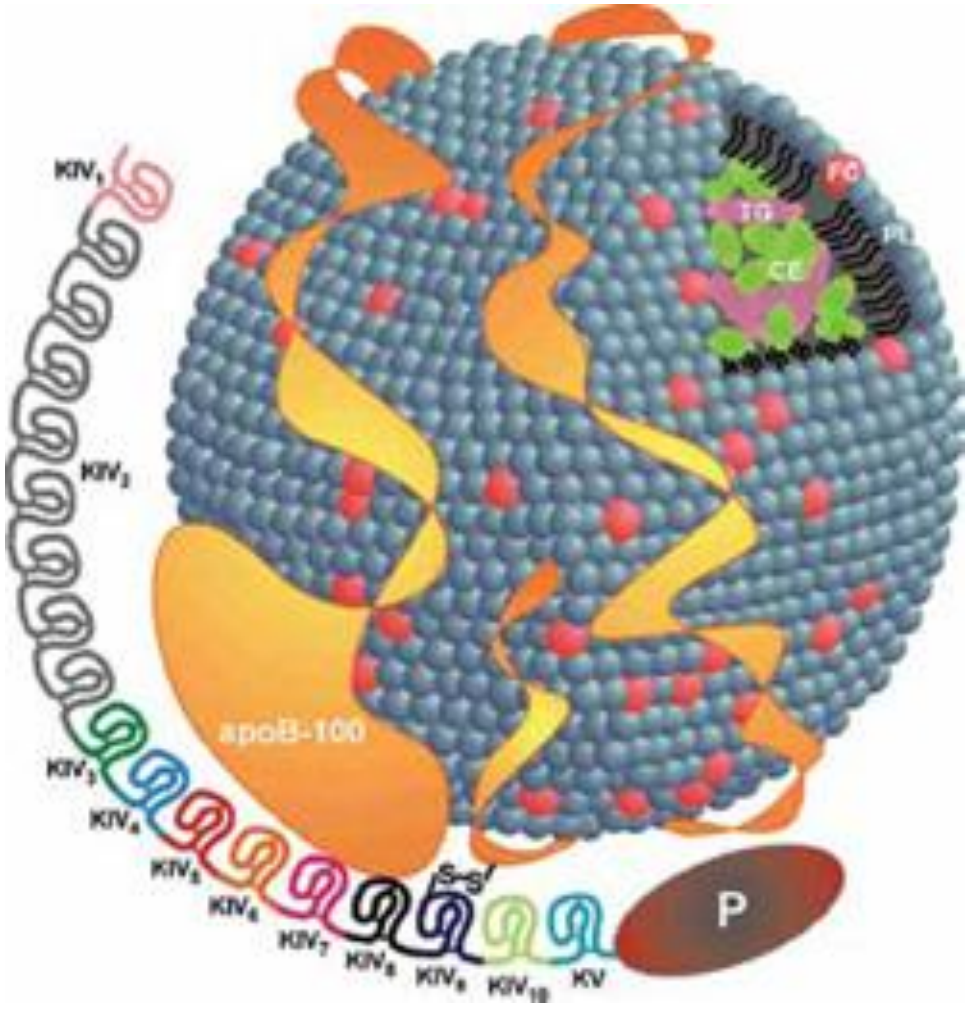
Plasma Lipoprotein Species and Subspecies



Topographical Structure of LDL



Lipoprotein (a)



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TG-rich Lipoproteins

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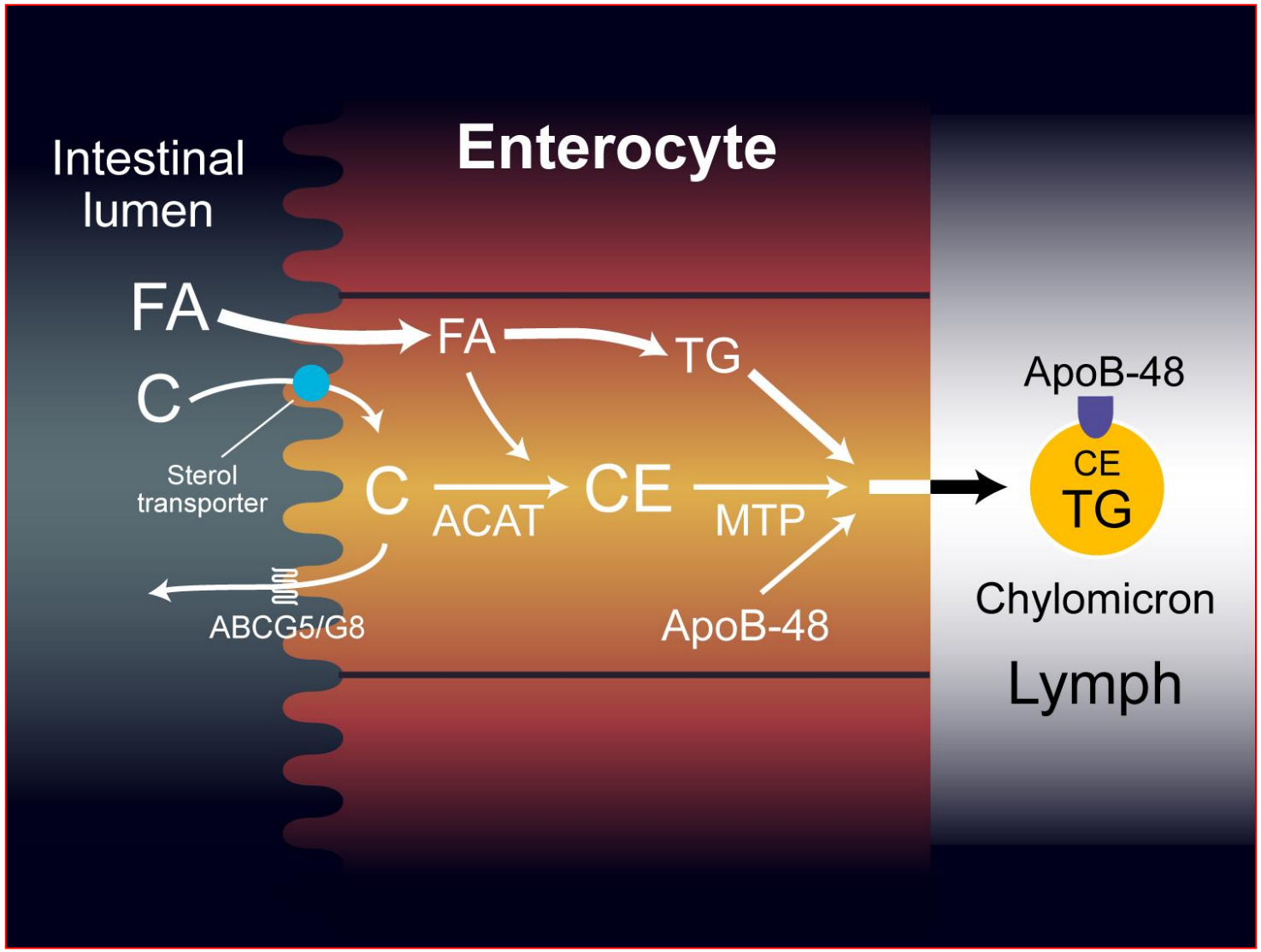
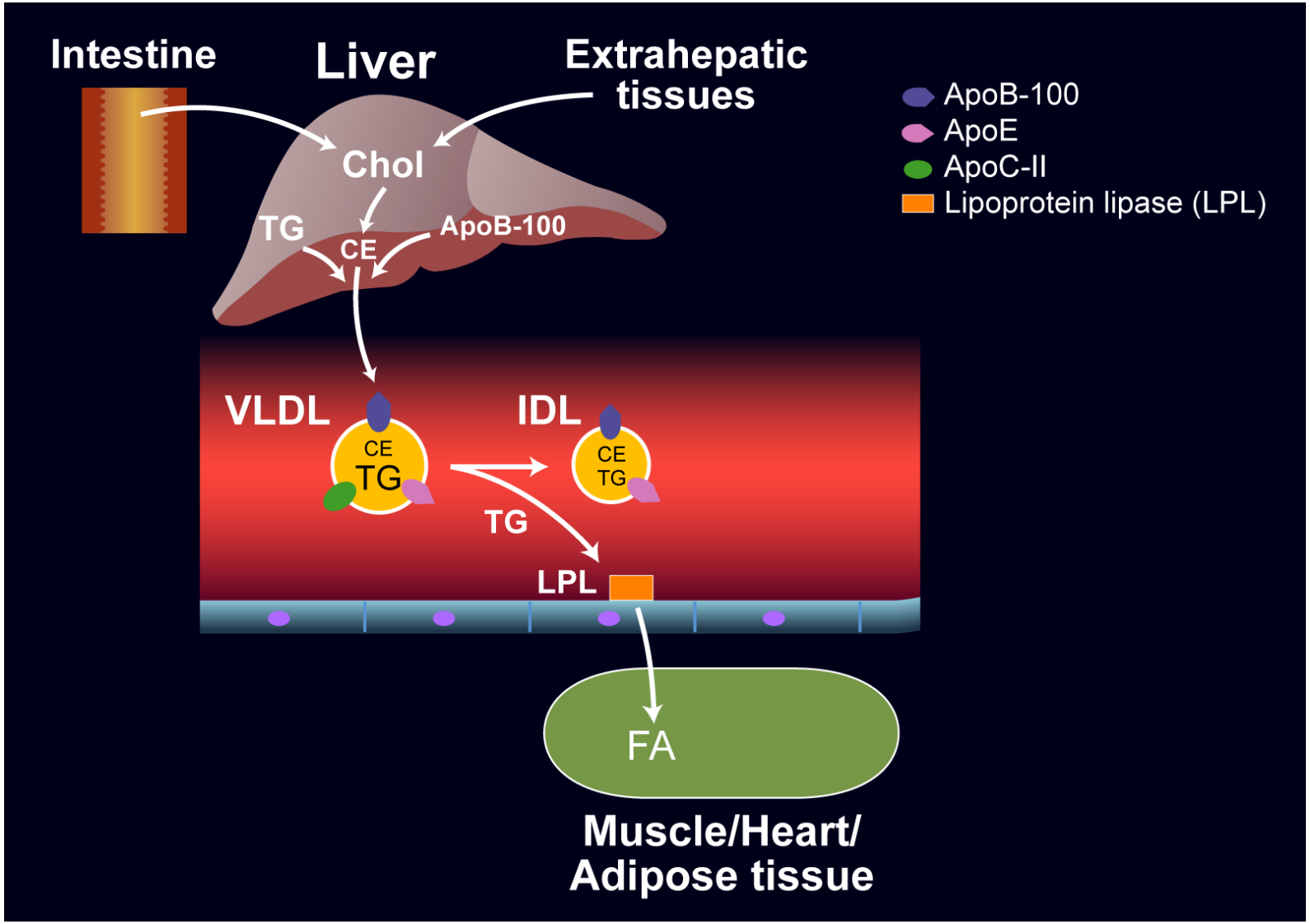
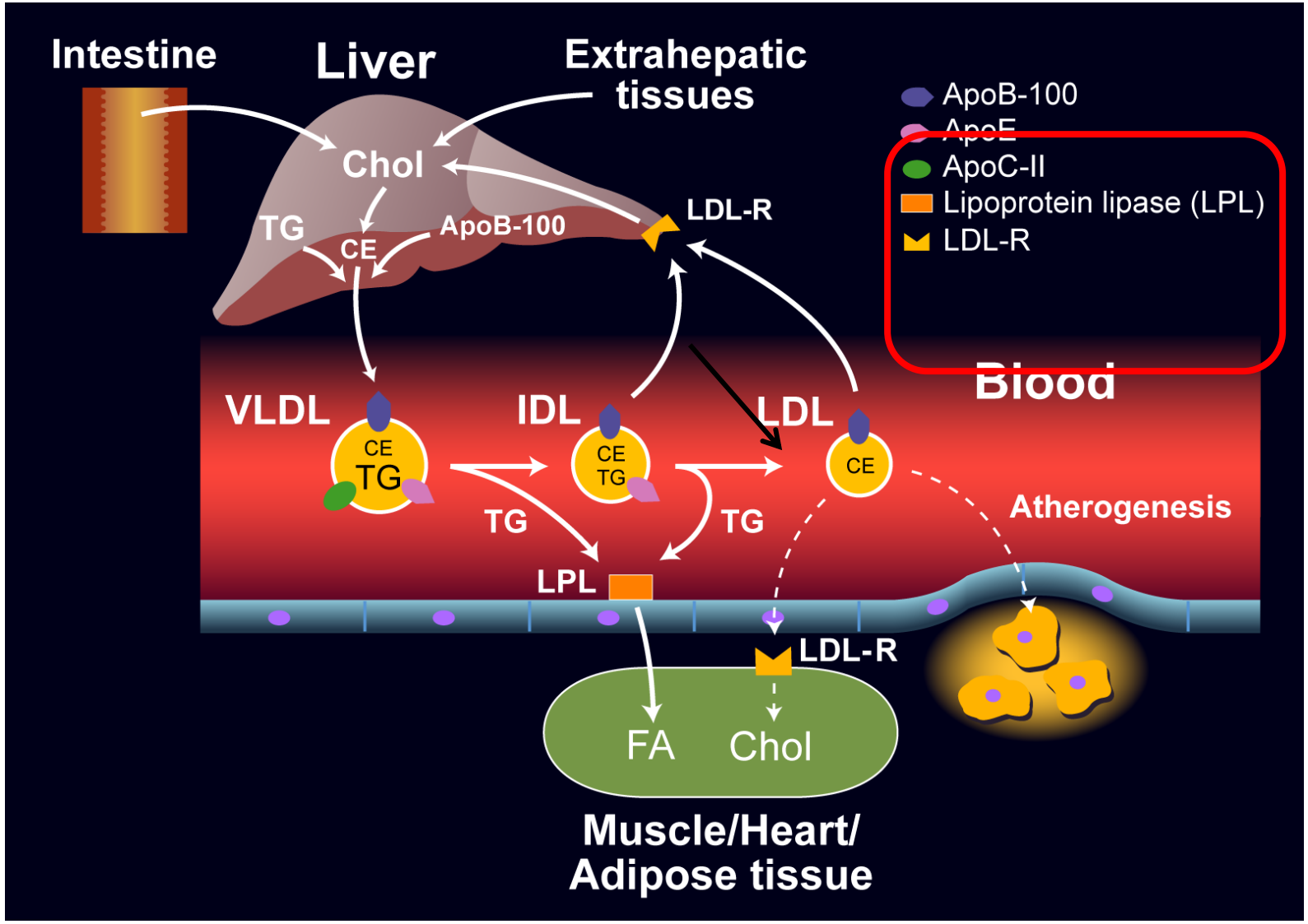
Exogenous Pathway: Chylomicron Formation



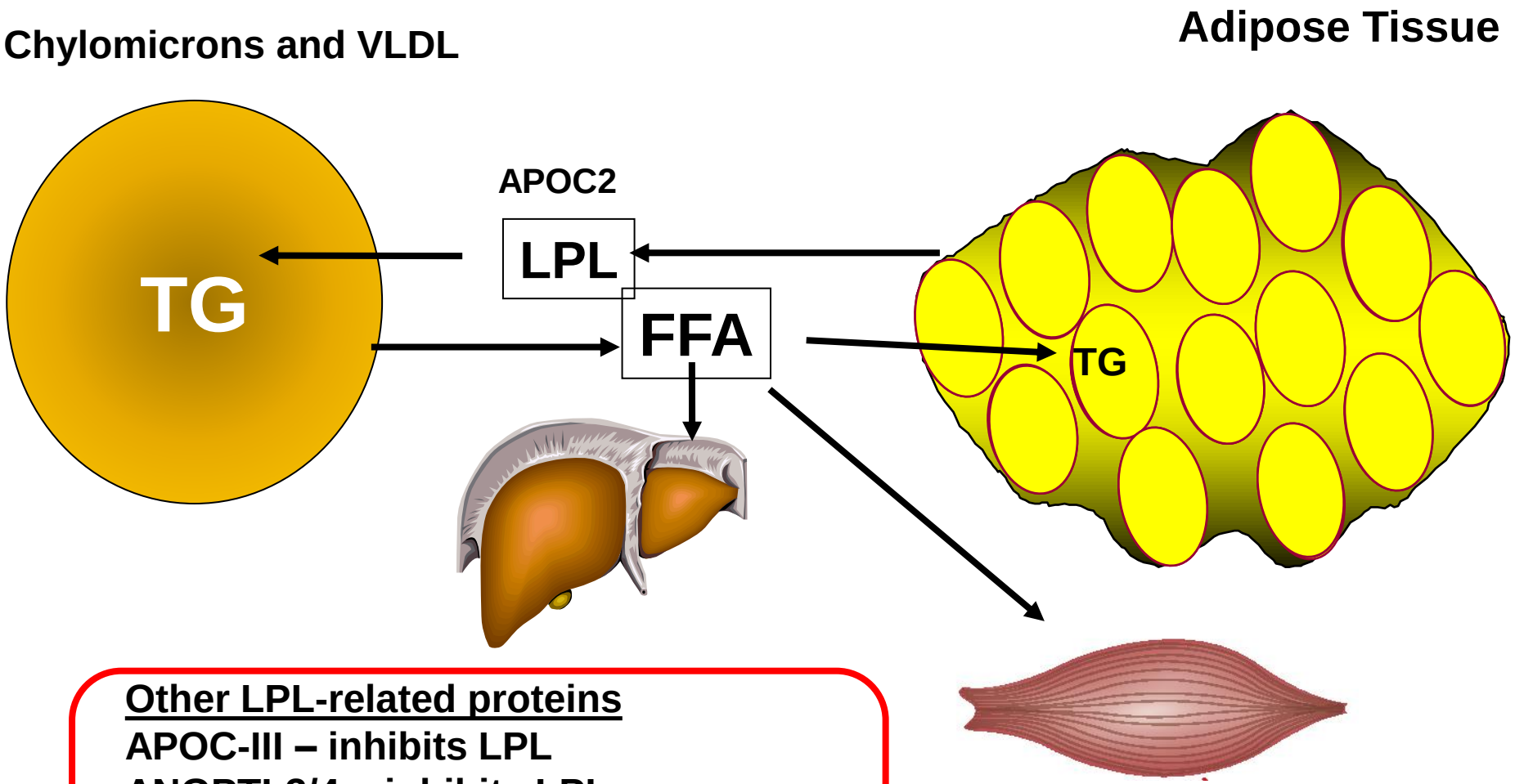
Endogenous Pathway of TG Transport



Endogenous Pathway of TG Transport



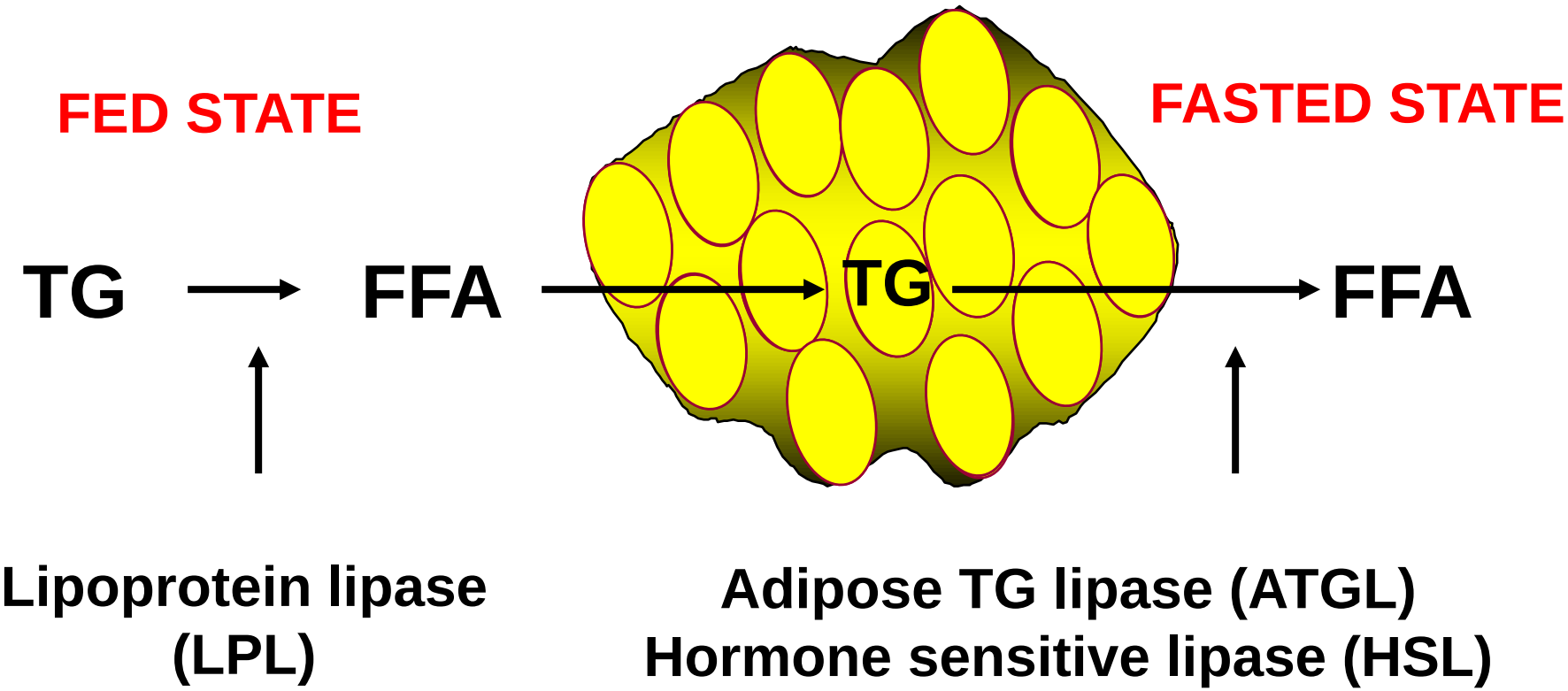
LPL-mediated TG Hydrolysis



Other LPL-related proteins

APOC-III – inhibits LPL
ANGPTL3/4 – inhibits LPL
GPI-HBP1 – tethers LPL to ECs
LMF1 - maturation and transport of LPL through the secretory pathway

Dynamic Uptake and Mobilization of FFA from Adipose Tissue



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LDL

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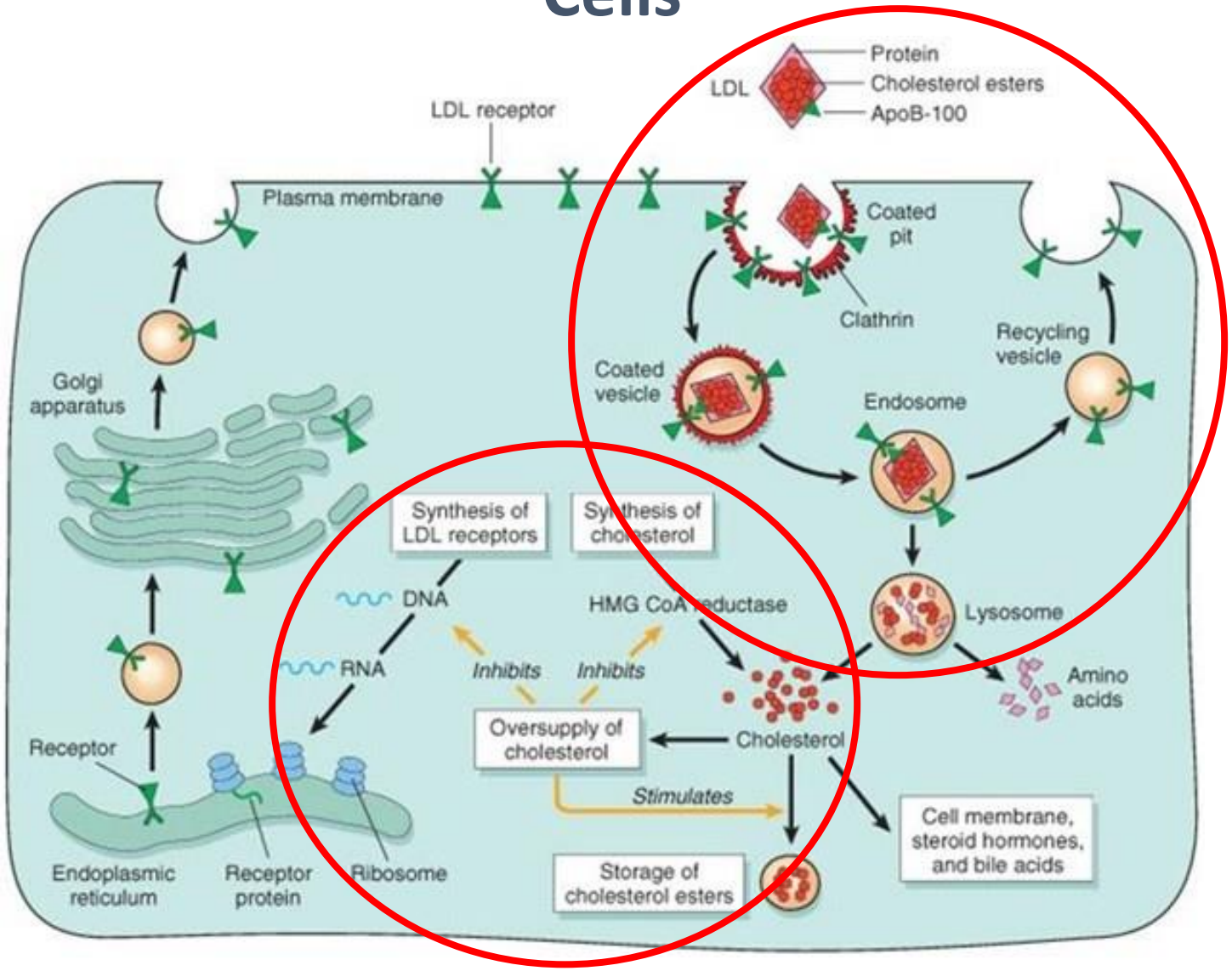
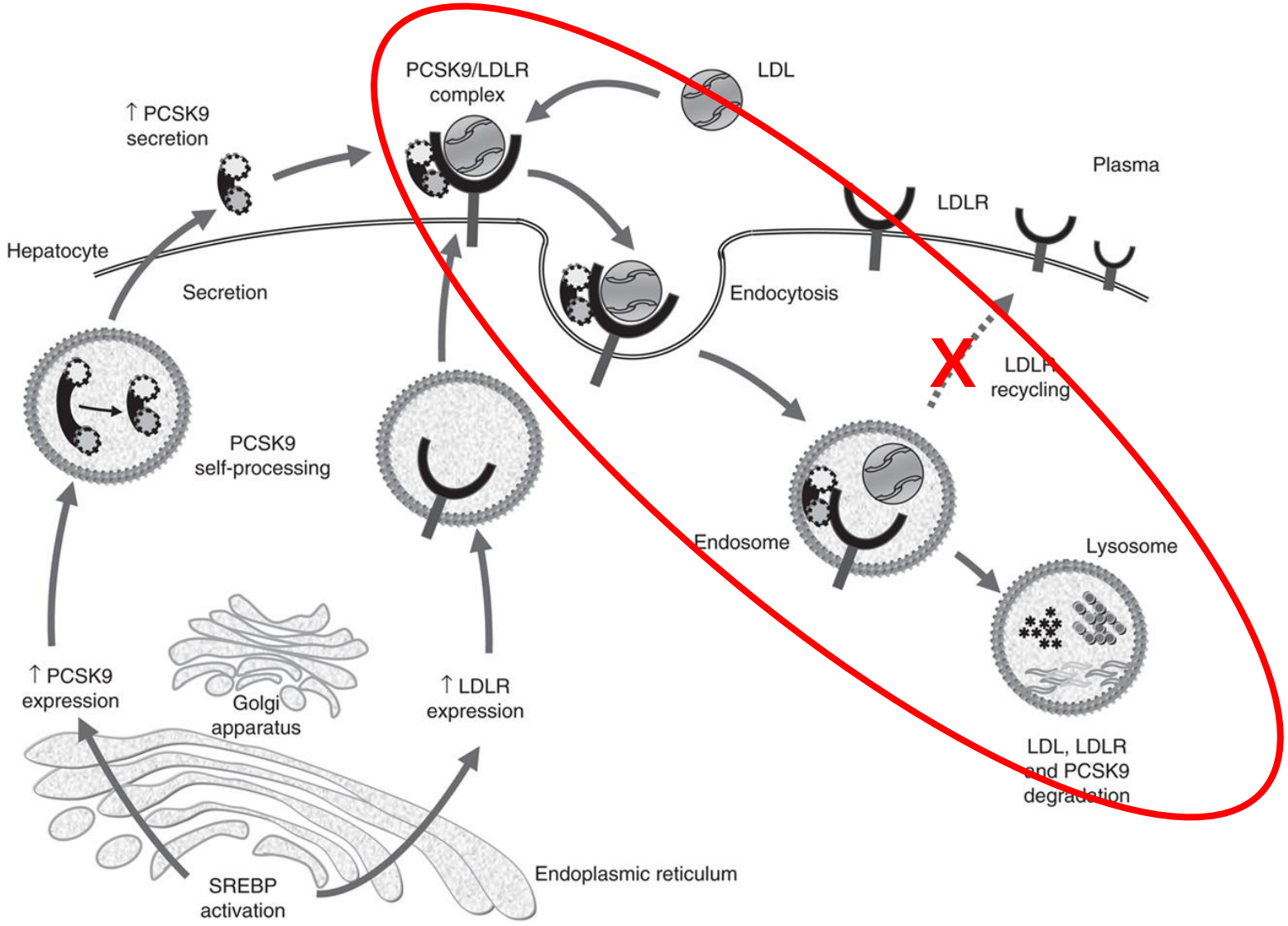
LDL Receptor-Mediated Endocytic Pathway of Cholesterol Delivery to Cells



Role of Proprotein Convertase Subtilisin/kexin Type 9 (PCSK9) in LDL Receptor Recycling



Farnier er al, Am J. Cardiovasc Drug 2011

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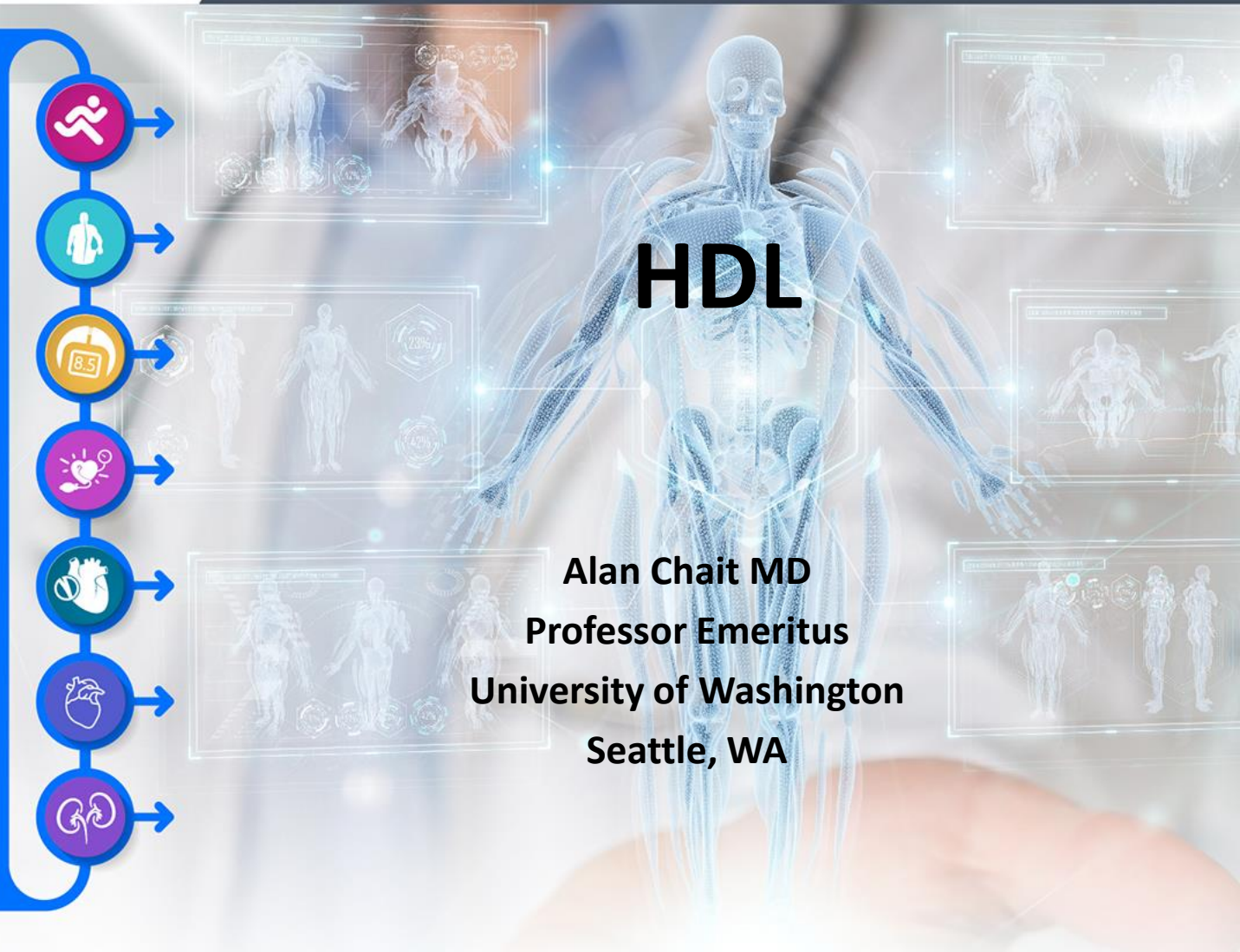

HDL

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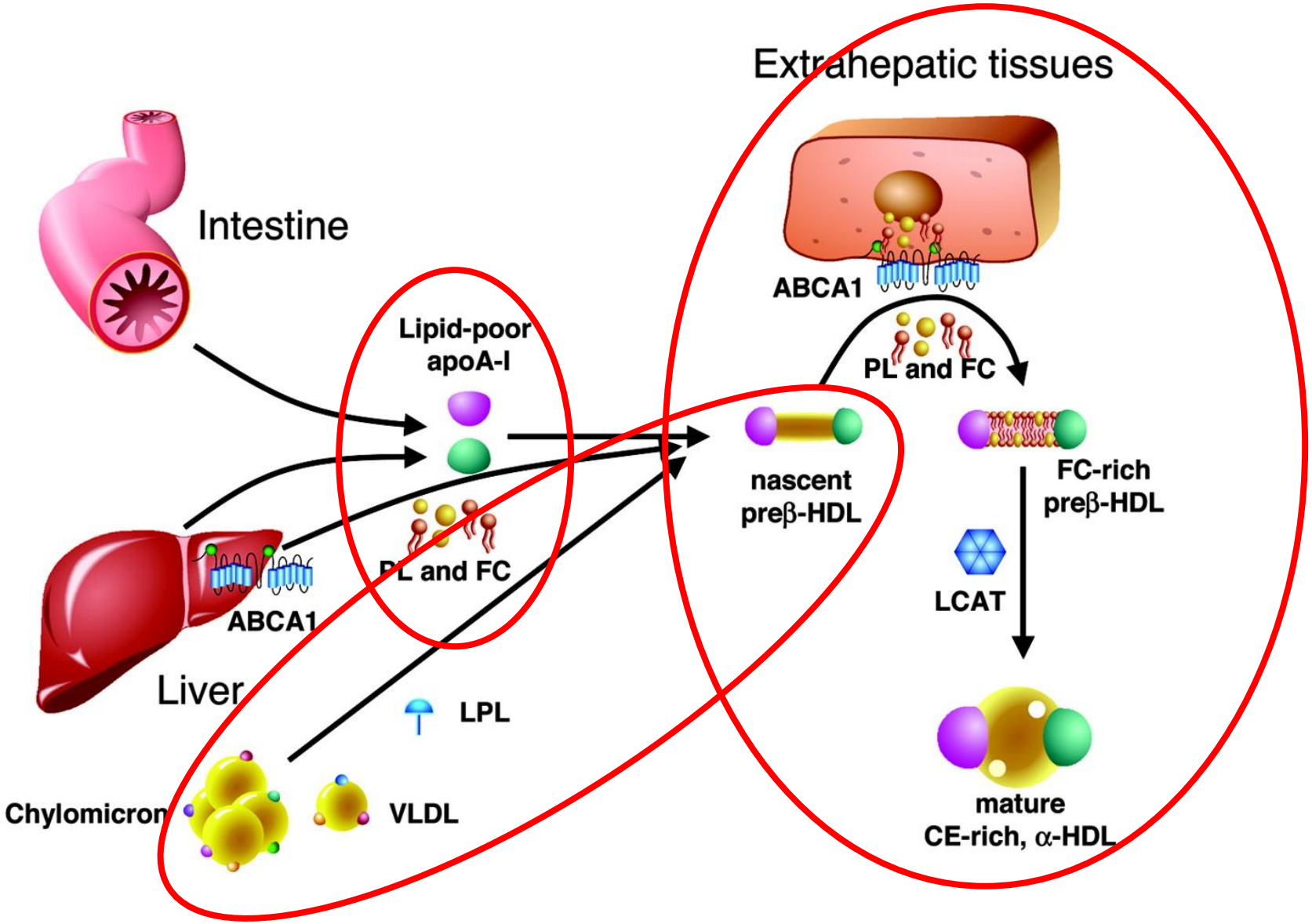
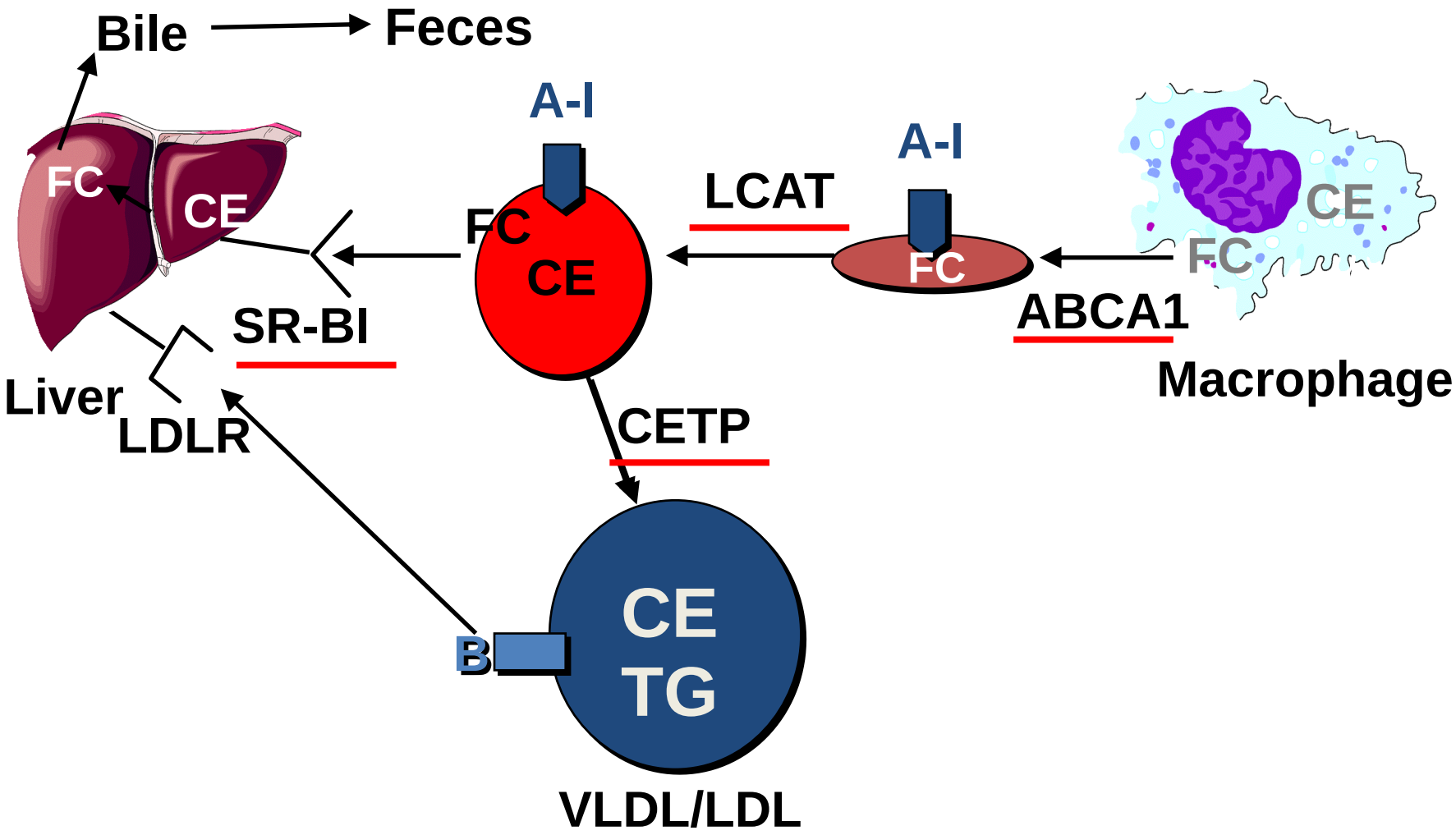
Genesis of HDL

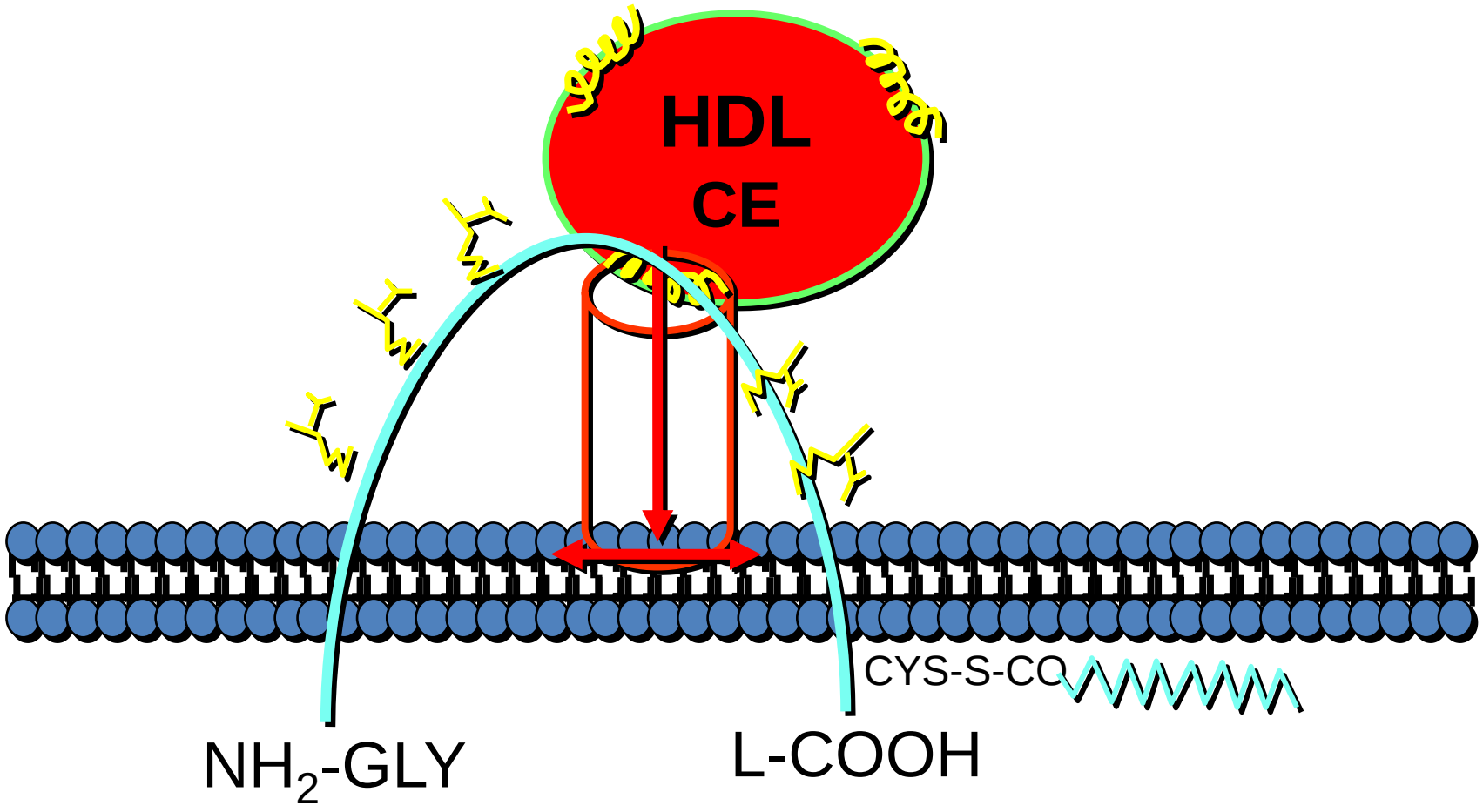


Lewis and Rader, Circulation Research. 2005;96:1221-1232

Reverse Cholesterol Transport

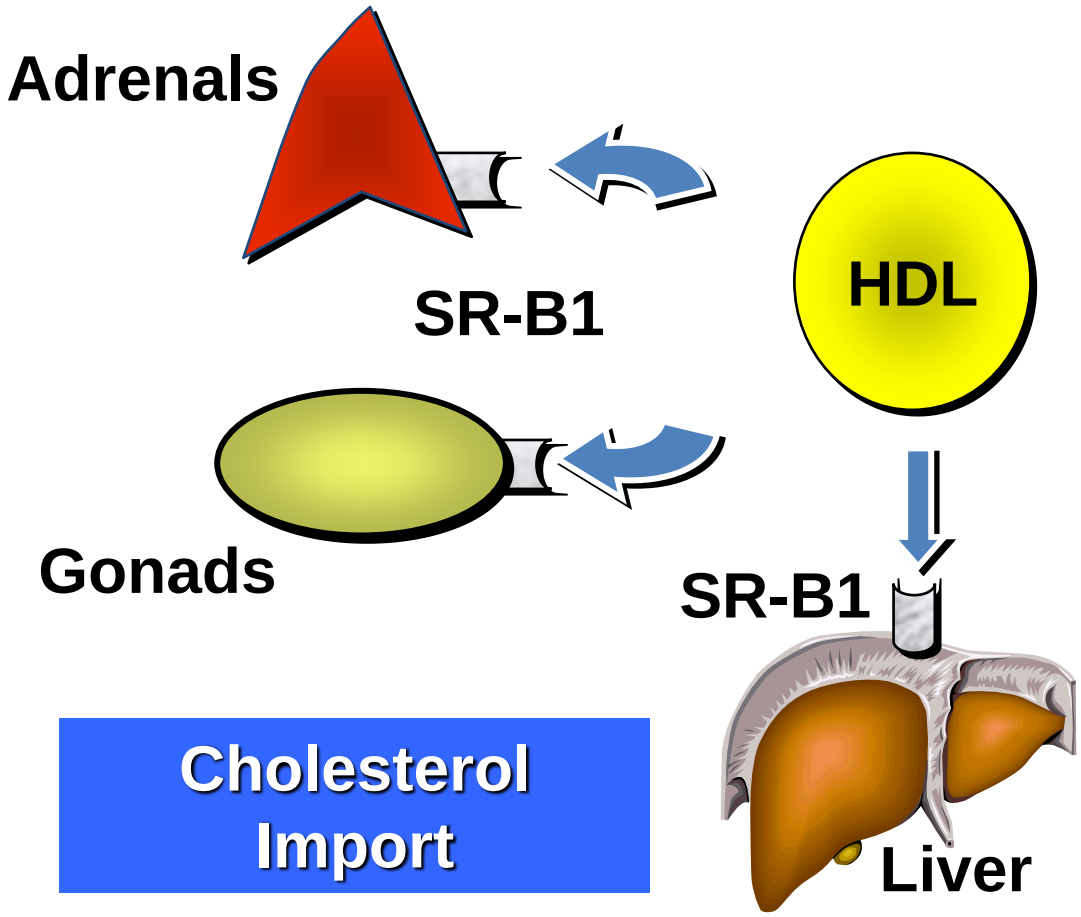


SR-B1–Mediates Selective Uptake of HDL Cholesterol Ester



Acton S et al. Science 1994;271:518-521; Williams DL et al. Curr Opin Lipidol 1999;10:329-339.

Role of SRB-1 in Cholesterol Transport by HDL



Libby et al. Biochim Biophys Acta 2000;1529:299-309.

Functions of Lipoproteins

- Transport of exogenous and endogenous triglycerides for energy purposes
- Delivery of cholesterol to tissues
  - Plasma membrane synthesis
  - Liver for bile salts
  - Adrenals for steroids
  - Gonads for gonadal hormones
- Removal of excess cholesterol from tissues
- Transport of fat-soluble vitamins

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Measurement of Plasma Lipids and Lipoproteins

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Initial Lab Evaluation

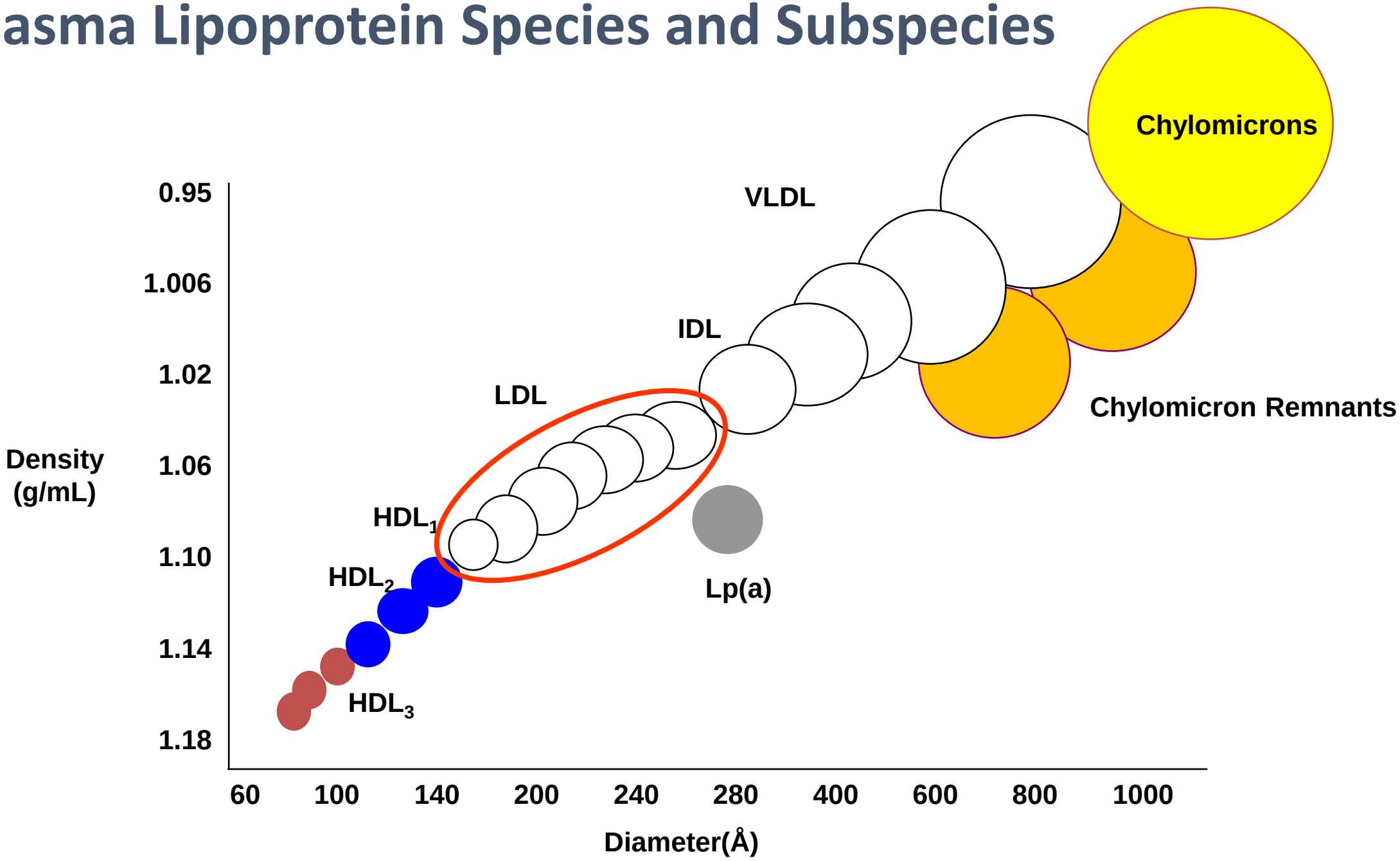
- Lipid panel (Chol, TG, LDL-C, HDL-C)
  - (LDL-C = TC minus HDL-C minus TG/5 for TG<400 mg/dL)
- Apo B
- Lp(a)
- BMP
- TFTs

Do Not Routinely Order

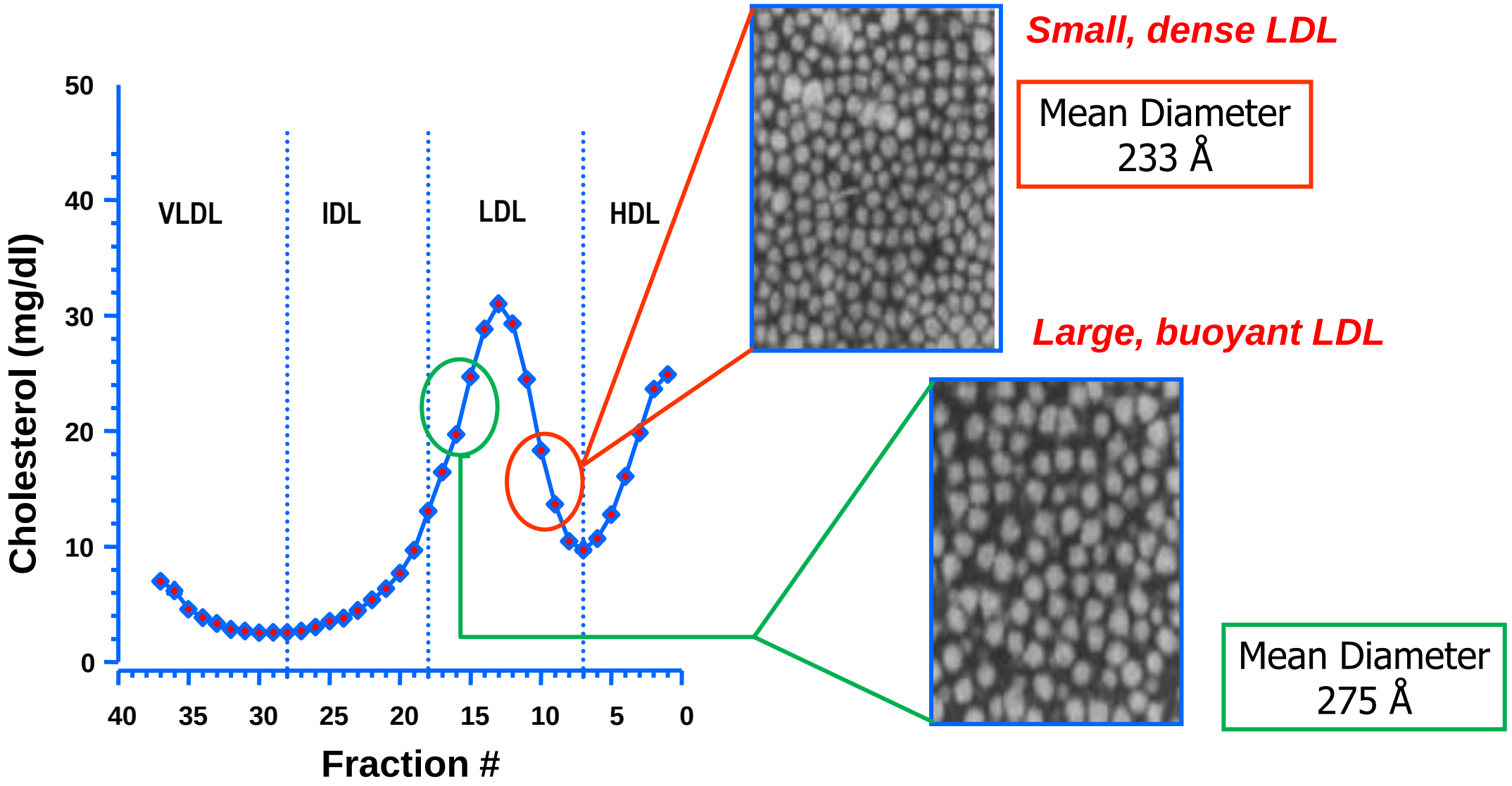
- ApoA-I
- Various tests for lipoprotein subclasses
- hsCRP
- Direct LDL

Use of Risk Prediction Tables like Framingham, ACC/AHA and UKPS Risk Engine can be misleading with complex patients

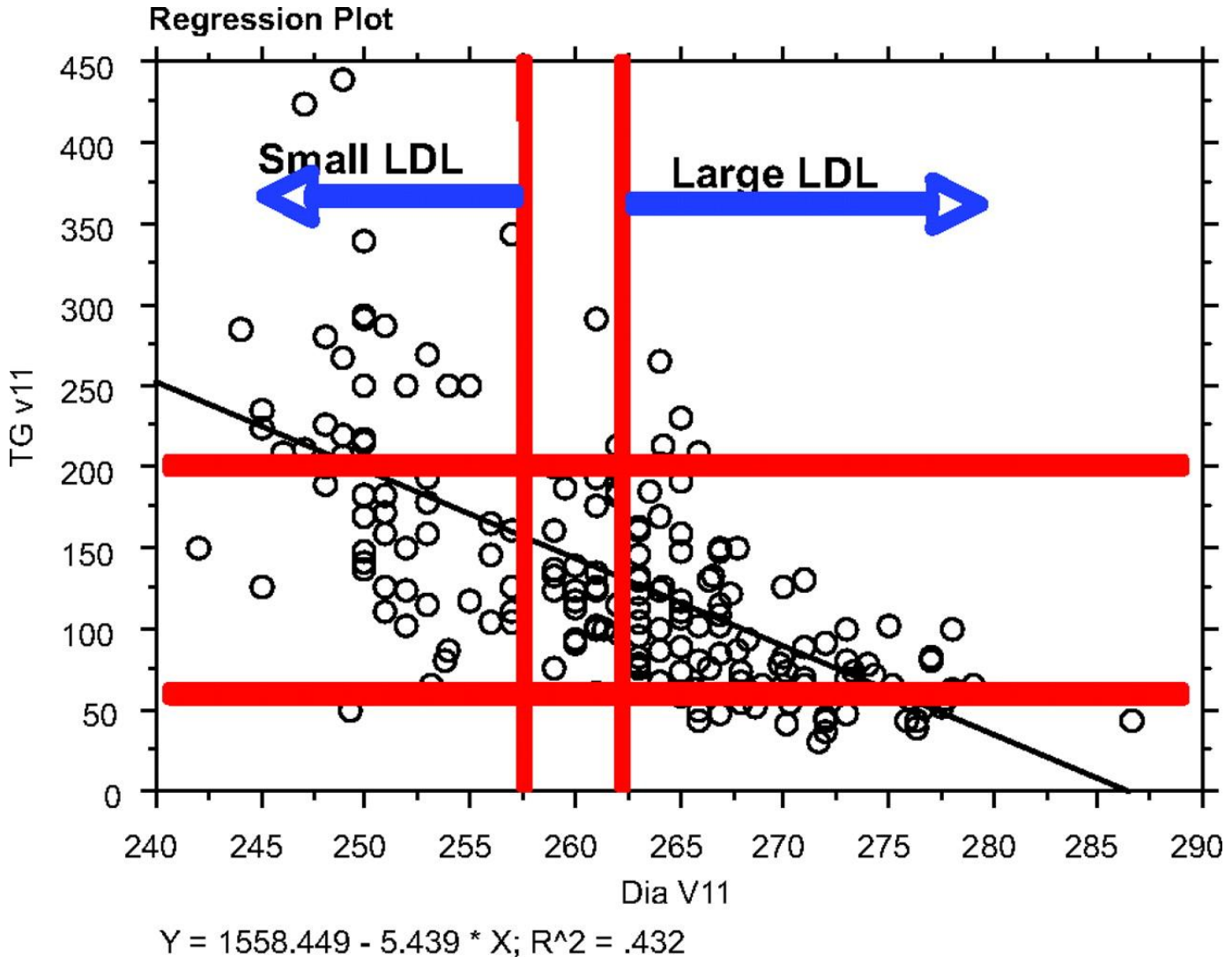
Plasma Lipoprotein Species and Subspecies



Lipoprotein Distribution by Density Gradient Ultracentrifugation



LDL Size and Density is Inversely Related to TG Concentration



Superko, Circulation. 2009;119:2383-95

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Dyslipidemia: Approach to Diagnosis, Pathophysiology & Association with ASCVD Risk

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Overview

- Approach to diagnosis
- Secondary forms of hyperlipidemia
- Pathophysiology
  - Single gene mutations leading to hypercholesterolemia
  - Single gene mutations leading to hypertriglyceridemia
  - Very severe hypertriglyceridemia
  - Remnant removal disease
  - Increased Lp(a)

Overview (continued)

- Mutations leading to hypolipidemia
- Classification of lipoprotein disorders
- Interaction of lipoproteins with the artery wall leading to atherosclerosis
- LDL and cardiovascular disease (CVD)
- Hypertriglyceridemia and CVD
- HDL and CVD

Pathophysiology and Approach to Diagnosis

- Rule out secondary causes of hypercholesterolemia and hypertriglyceridemia
- Take careful family history for potential genetic forms of dyslipidemia
- Look for physical findings that might give clues to the nature of the dyslipidemia such a tendon xanthomata, palmar xanthomata, eruptive xanthomata, features of partial lipodystrophy and corneal opacification

Secondary Causes of Hypercholesterolemia

Disorders

- Increased intake of saturated or trans fatty acids
- Hypothyroidism
- Obstructive liver disease
- Nephrotic syndrome
- Pregnancy
- Growth hormone deficiency
- Anorexia nervosa
- Monoclonal gammopathy
- Cushing’s syndrome
- Acute intermittent porphyria
- Hepatoma

Drugs

- Cyclosporine and tacrolimus
- Amiodarone
- Glucocorticoids
- Danazol
- Some progestins
- Protease inhibitors
- Anabolic steroids
- Androgen deprivation therapy
- Retinoids
- Thiazide and loop diuretics
- Thiazolidinediones

Adapted from Feingold, K. Endotext 2000

Secondary Causes that Can Interact with Genetic Forms of Hypertriglyceridemia

Conditions

- Undiagnosed or poorly controlled diabetes
- Hypothyroidism
- Pregnancy
- Chronic renal failure
- Nephrotic syndrome
- Weight regain after weight loss

Drugs

- Alcohol
- Beta-adrenergic blocking agents
- Diuretics (thiazide and loop)
- Oral estrogens, SERMS such as tamoxifen and raloxifine
- Glucocorticoids
- Atypical anti-psychotics such as olanzapine and mirtazapine
- Bile acid sequestrants
- Sirolimus, tacrolimus
- Cyclosporine
- RXR agonists such as cis-retinoic acid and bexarotene
- HIV protease inhibitors
- L-asparaginase
- Alpha-interferon
- Propofol
- Lipid emulsions

Adapted from Chait and Subramanian Endotext 2019

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Pathophysiology - Mutations

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Single Gene Mutations Leading to Hypercholesterolemia

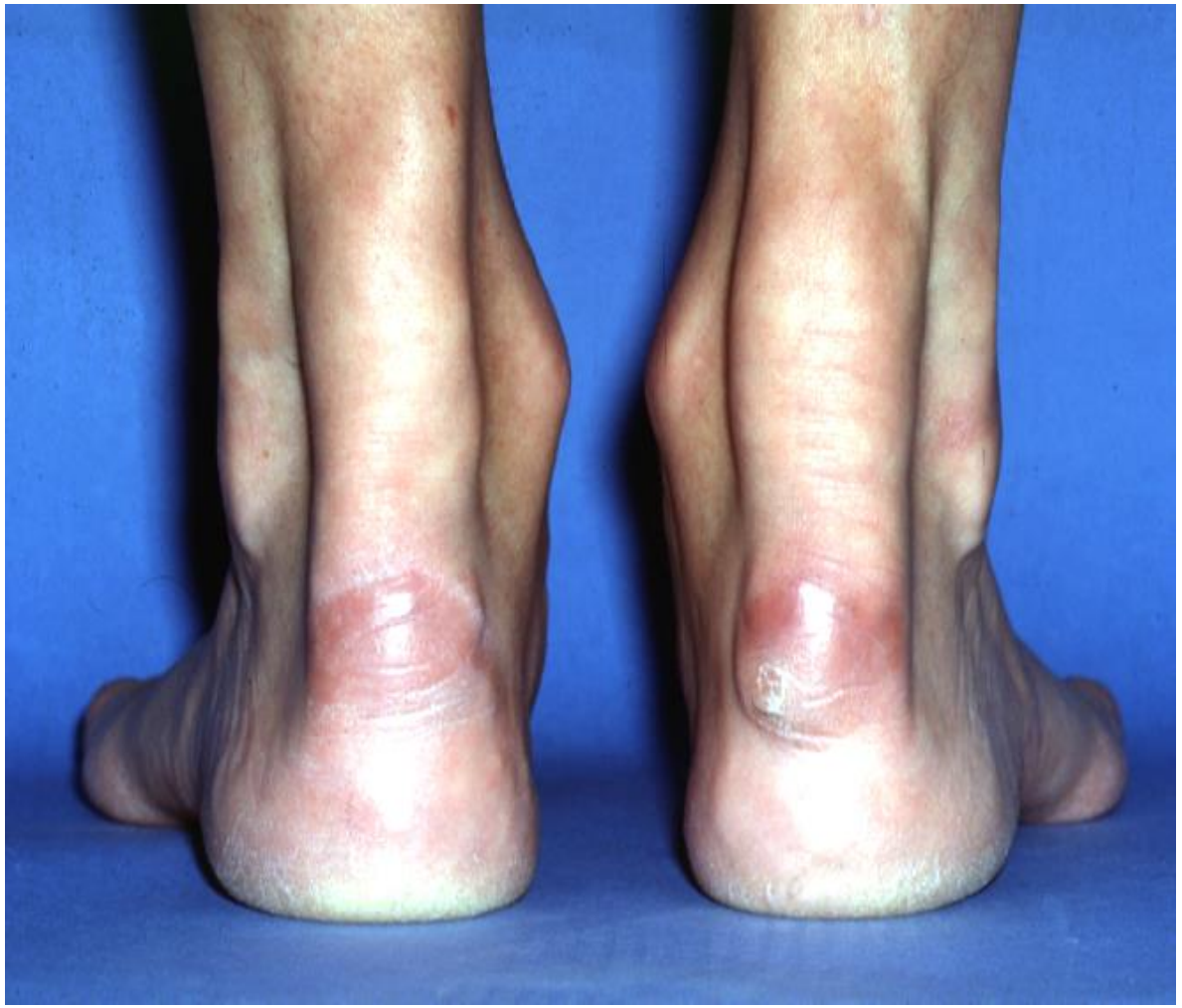
- LDL receptor
  - FH
- APOB100
  - Familial defective APOB
- PCSK9
  - Pseudo FH (gain of function mutation)
- APOE
  - Remnant removal disease
- ABCG5/8
  - Pseudo FH (β-sitosterolemia)

Familial Hypercholesterolemia (FH)

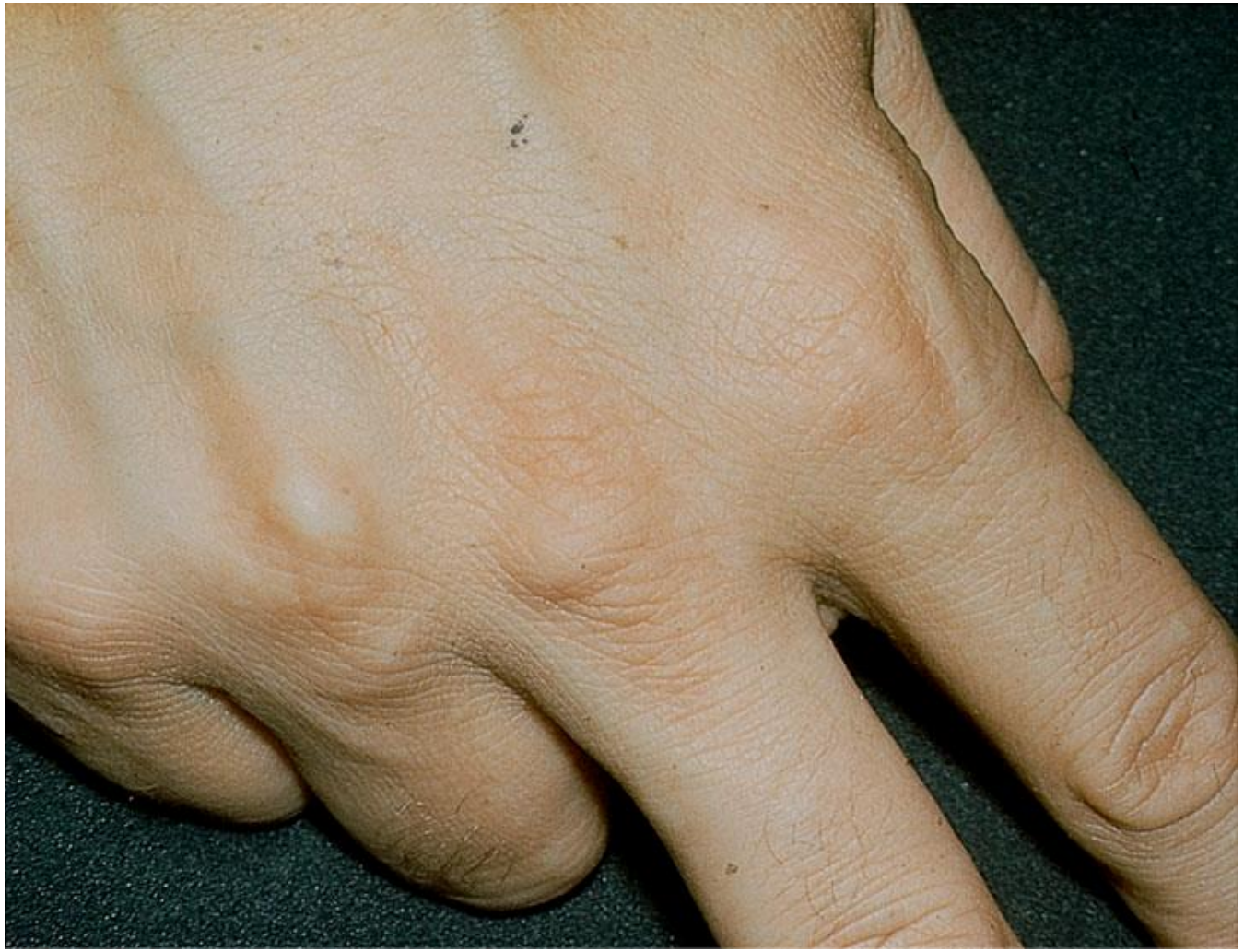
- Autosomal dominant disorder
- Mutation of LDL receptor, PCSK9 (gain-of-function) or APOB-100 (FDB)
- Frequency of LDL-R mutation ~1/250 (heterozygous)
- LDL usually >200 mg/dL, with normal TGs
- Corneal arcus (non-specific)
- Tendon xanthoma (specific)

Mutations in all 3 genes present as clinical "FH"

Tendon Xanthomas in a Patient with Familial Hypercholesterolemia

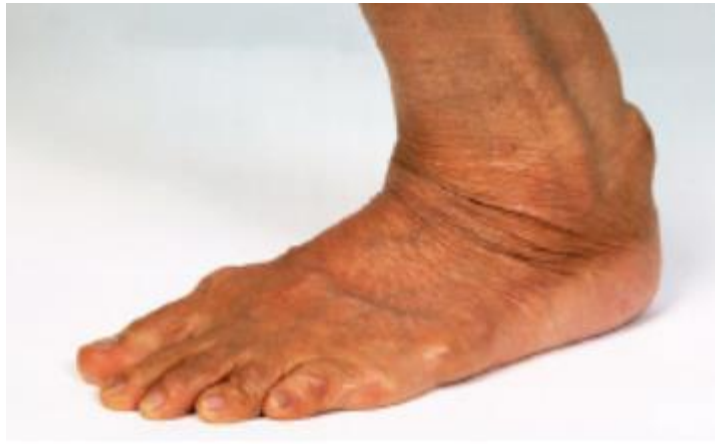


Tendon Xanthoma on Extensor Surface of Hand



Homozygous FH

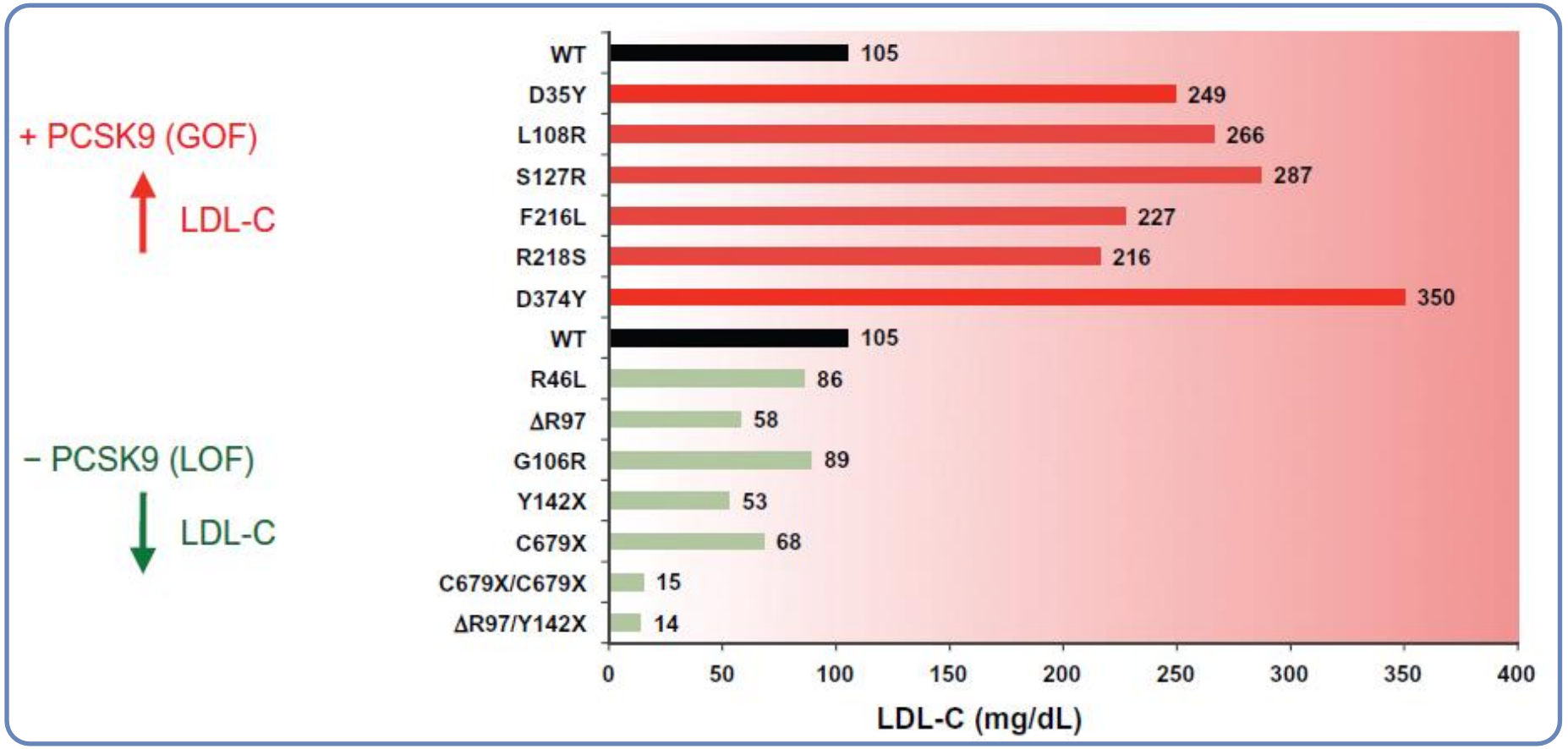
- Frequency ~1/160,000 to 1/1,000,000
- Both copies of LDL receptor are mutated
- Very high LDL-C levels (>500 mg/dL)
- Huge xanthomas
- CAD often occurs in teens
- Extremely difficult to treat



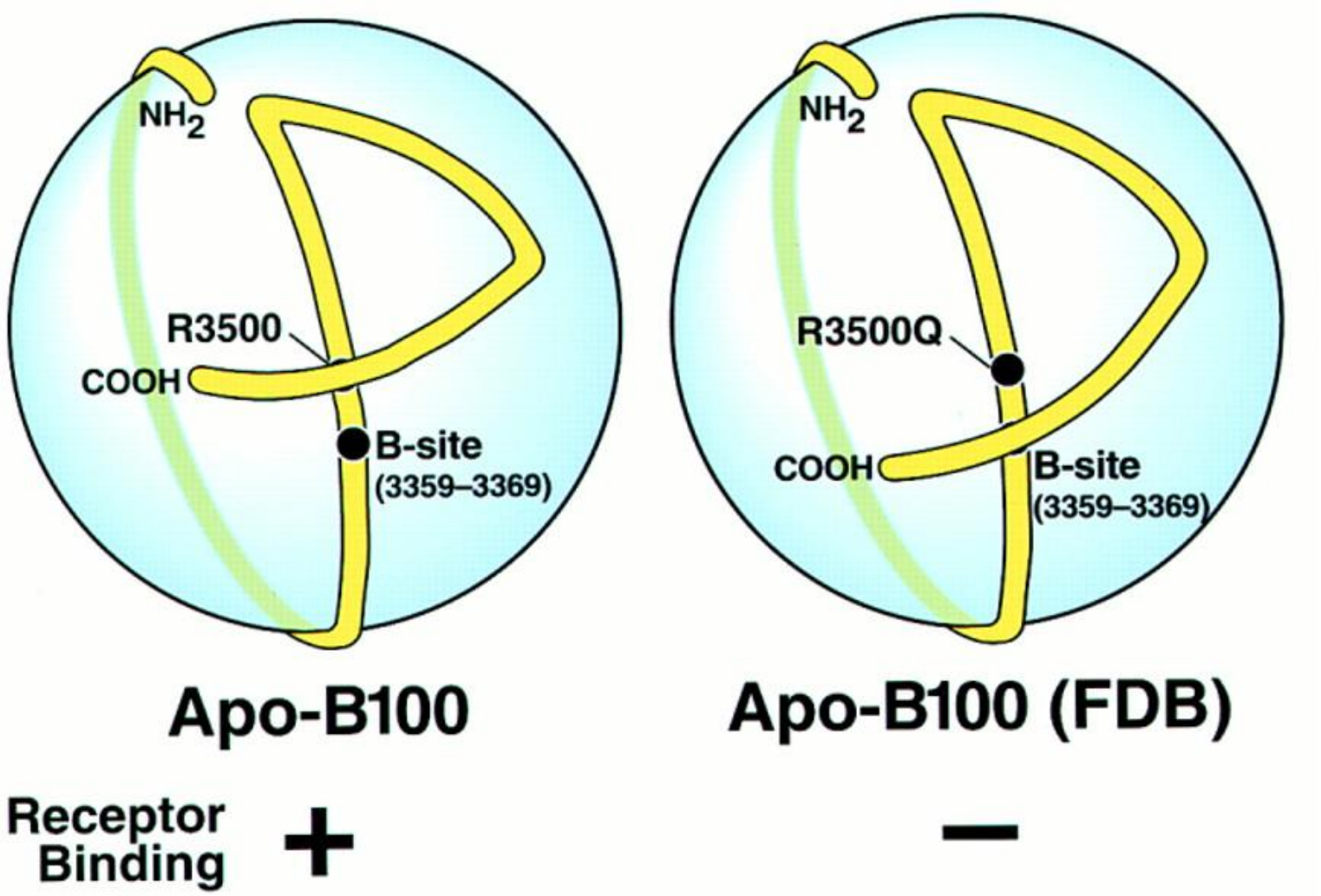
Proprotein Convertase subtilisin/kexin Type 9 (PCSK9)

- Circulating protease involved in degradation of LDL receptor protein
- Gain of function mutations in humans mimic autosomal dominant FH
- Loss of function mutations have reduced LDL levels and are protected against CAD
- Transgenic mice have hypercholesterolemia
- Knockout mice have hypocholesterolemia
- Good drug target

Effect of Human Mutations in PCSK9 on Plasma LDL-C



Absent LDL Receptor Binding in Familial Defective APOB (FDB)



Boren et al, J. Clin Invest 1998

Single Gene Mutations Leading to Hypertriglyceridemia

- LPL
  - Familial Chylomicronemia Syndrome (FCS)
- GPI-HDLBP1
  - FCS
- APOC2
  - FCS
- APOE
  - Remnant removal disease (Type III)
- Lamin A/C
  - Dunnigan partial lipodystrophy

Most genetic forms of HTG are not due to single gene mutations, but rather due to small effect common variants in multiple genes

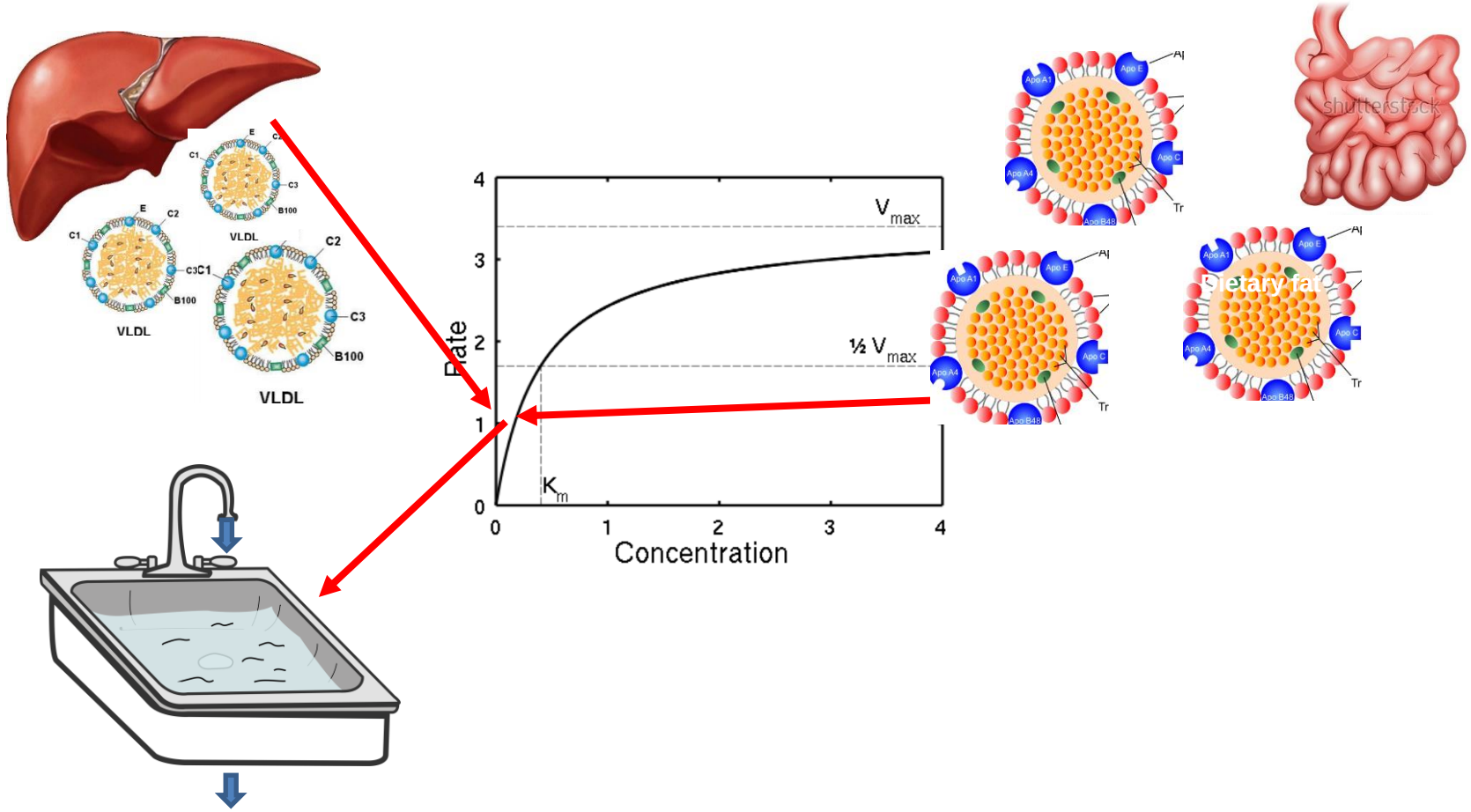
Very severe hypertriglyceridemia
(TG>1500-2000mg/dL)

- Occasionally caused by rare genetic mutations, e.g., LPL, APOC2 or GPI-HBP1 deficiency (~1%) – Familial Chylomicronemia Syndrome (FCS)
- Usually due to a combination of a 1º (common polygenic forms of HTG) and 2º cause (DM, EtOH, β-blocker, diuretic, protease inhibitors, atypical anti-psychotics) – Multifactorial Chylomicronemia Syndrome (MFCS)
- Sometimes associated with Familial Partial Lipodystrophy (FPLD)
- Can lead to features of Chylomicronemia Syndrome (pancreatitis, eruptive xanthomata, peripheral neuropathy and memory loss)

Chait and Eckel. Ann Int Med. 170:626-634, 2019

Situation 1: TG Removal Not Saturated

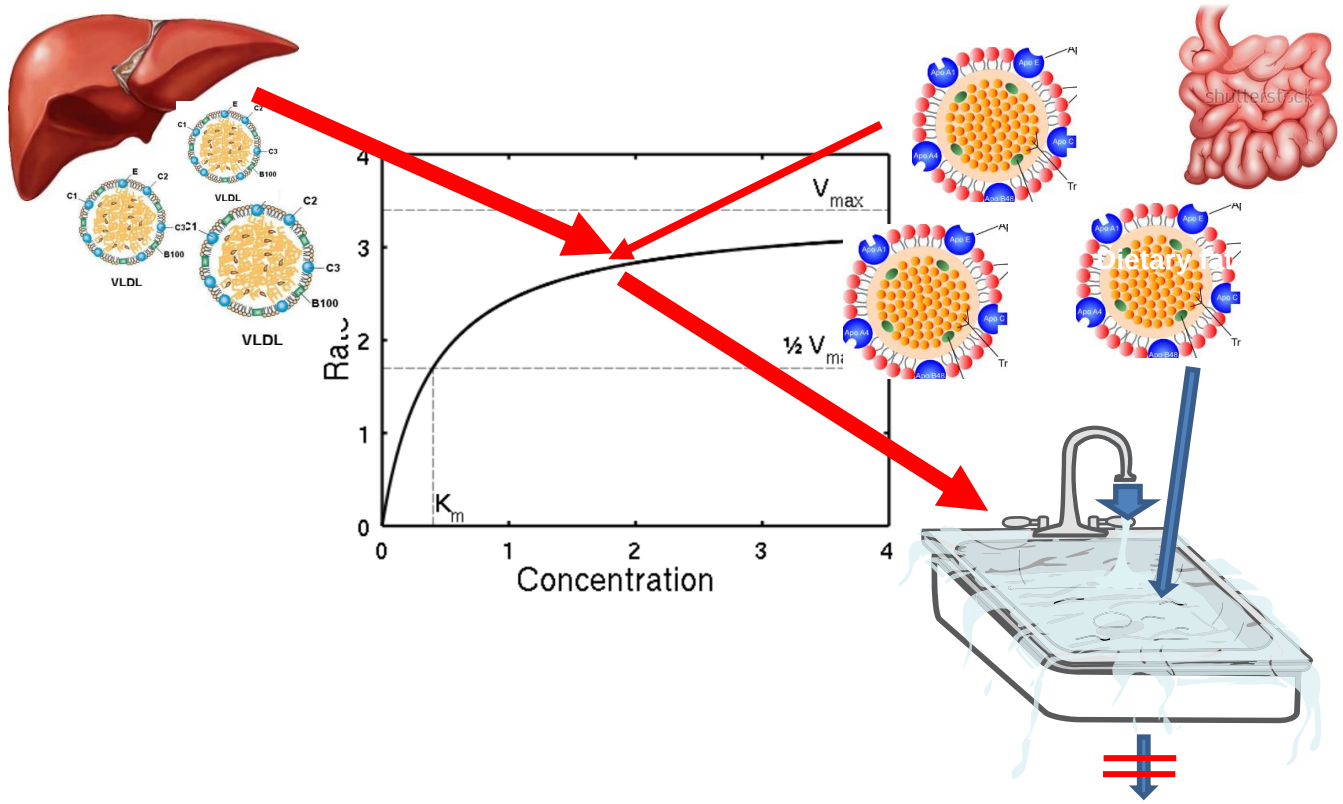
(Outflow = Inflow)



Chait and Eckel. Ann Int Med. 170:626-634, 2019

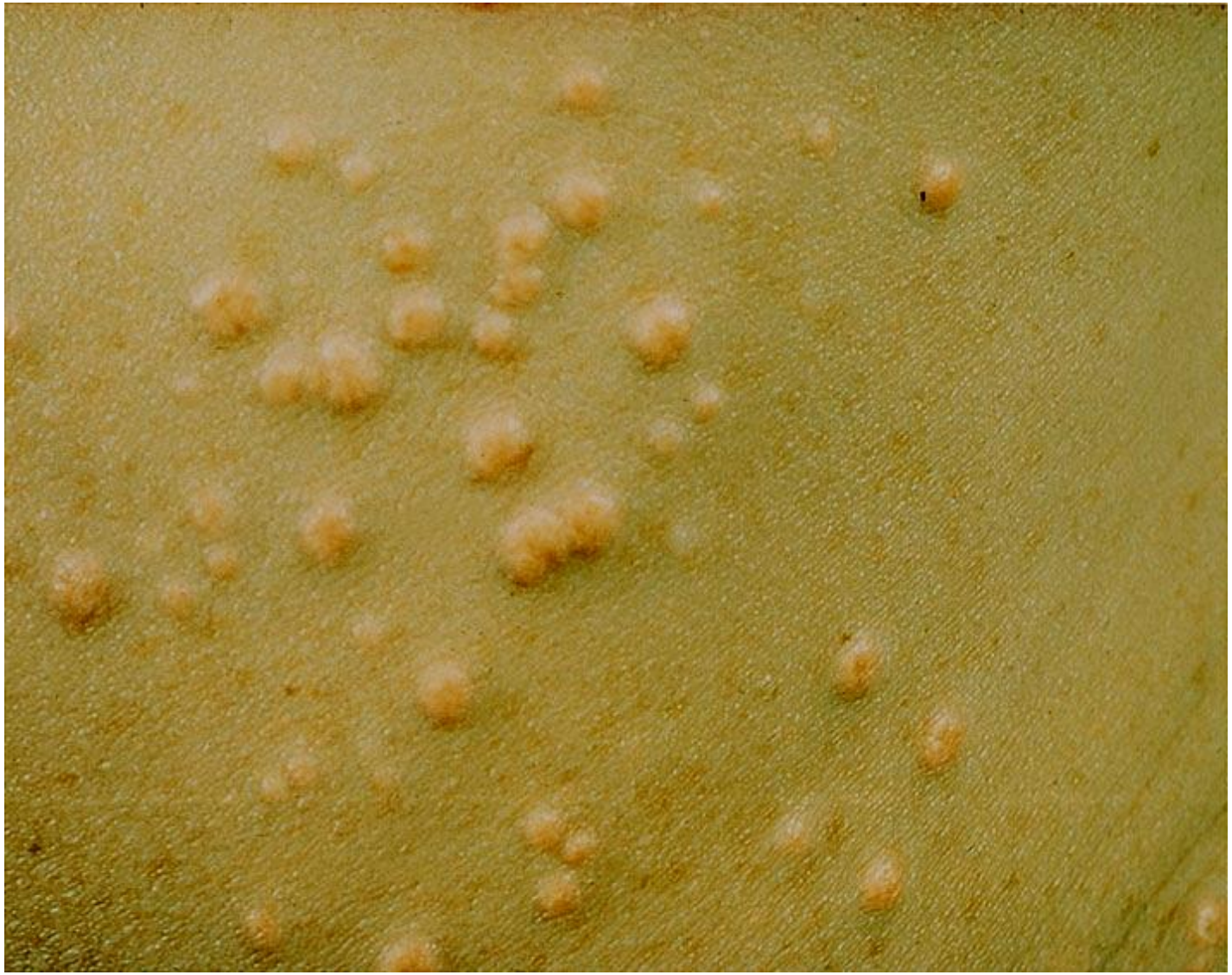
Situation 2: TG Removal Saturated

(Inflow > Outflow)



Chait and Eckel. Ann Int Med. 170:626-634, 2019

Eruptive Xanthomata



Combined Hyperlipidemia

- Familial combined hyperlipidemia
- Remnant removal disease
  (type III hyperlipoproteinemia)
- Secondary forms of hyperlipidemia

Familial Combined Hyperlipidemia

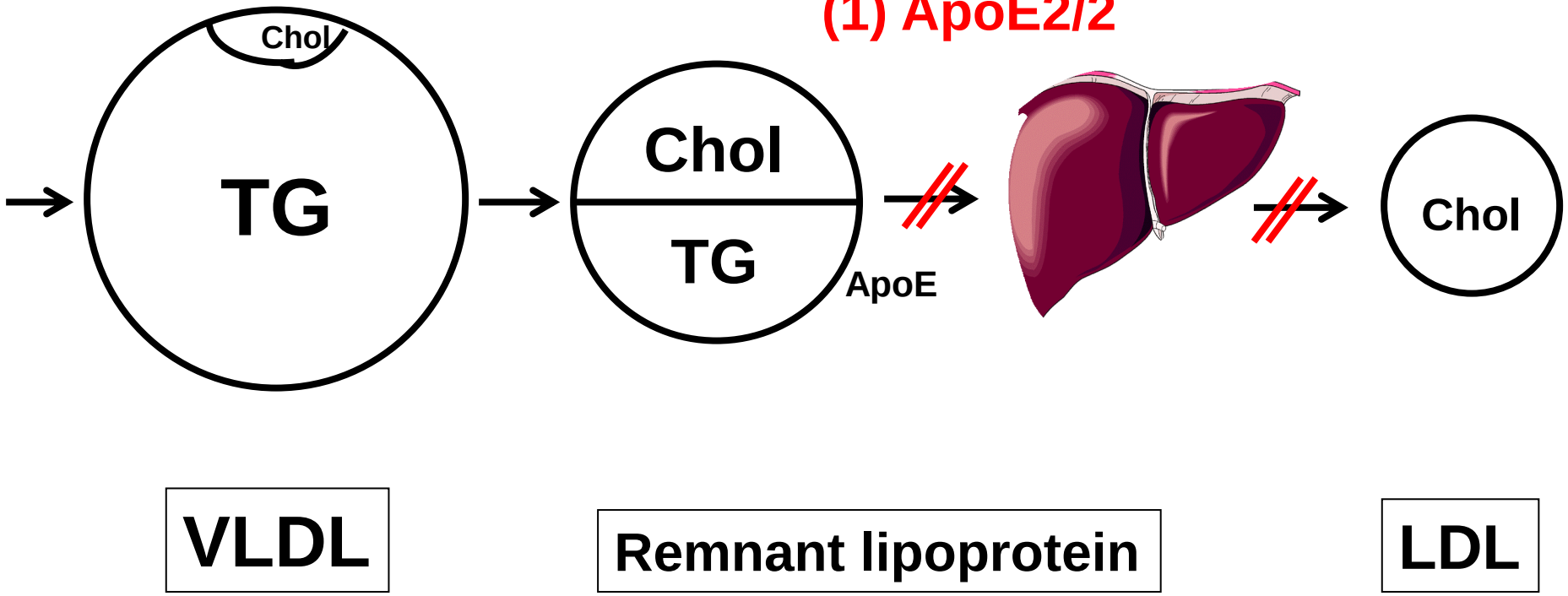
- Phenotype probably is the result of several different mutations, most of which are unknown
- Often only manifests in 20s and 30s
- Due to overproduction of APOB by the liver
- Characterized by presence of small, dense LDL
- Strong family history of premature CVD
- Often associated with features of the metabolic syndrome

Remnant Removal Disease

(type III hyperlipoproteinemia, dysbetalipoproteinemia)

(2) VLDL overproduction

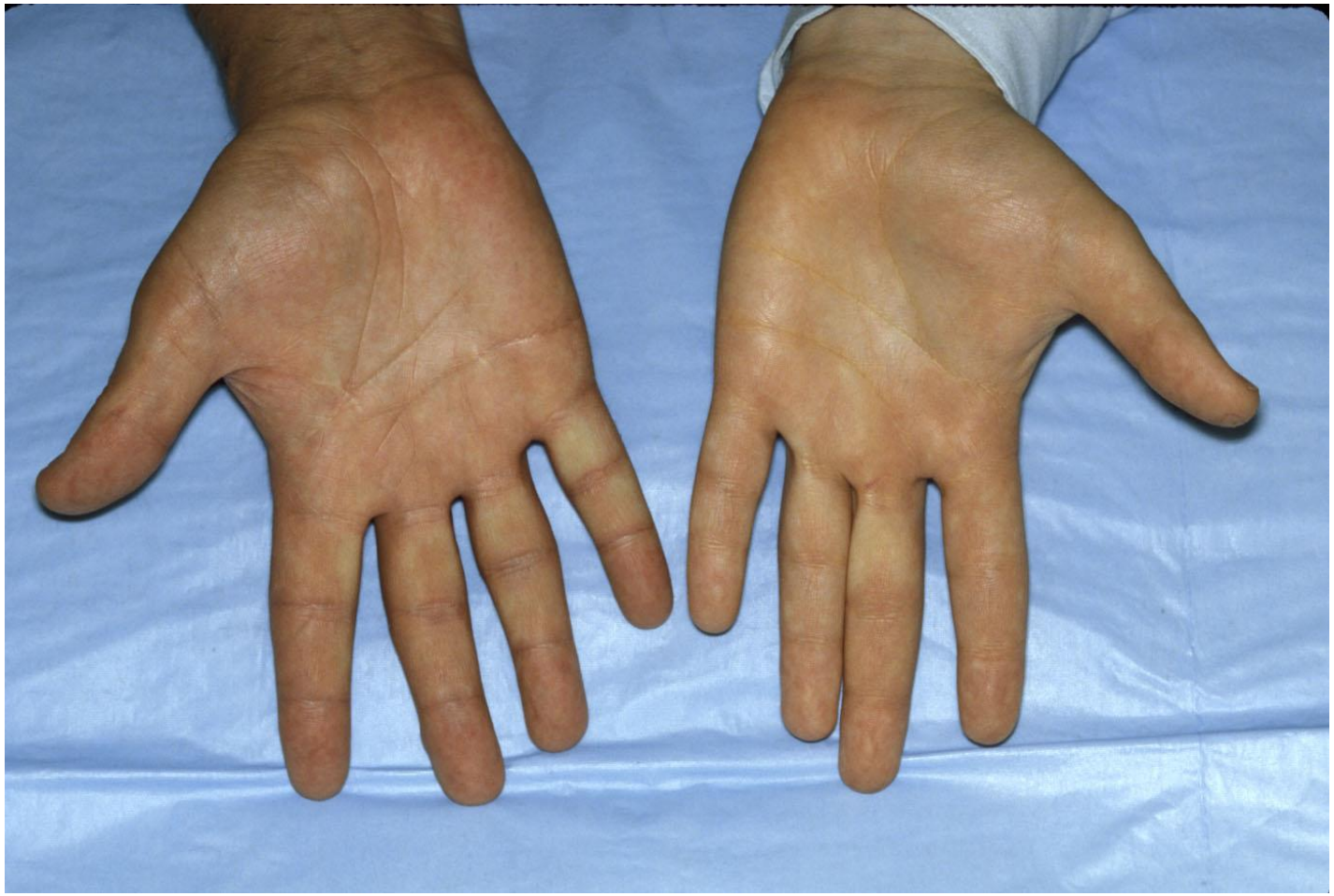
(1) ApoE2/2



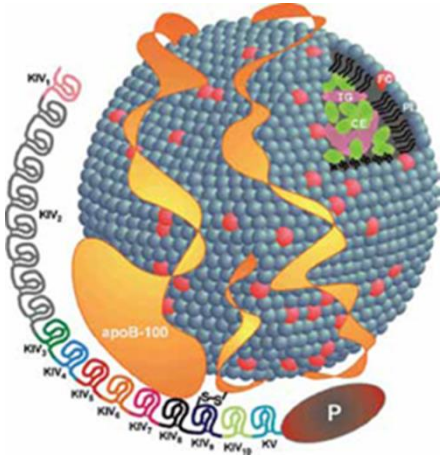
VLDL → **Remnant lipoprotein** → **LDL**

Chait A, Brunzell J, Albers J, Hazzard W. Type-III Hyperlipoproteinaemia ("remnant removal disease"). Insight into the pathogenetic mechanism Lancet: 8023:1176-8,1977

Palmar Xanthoma



Elevated Lp(a)



- Genetically determined
- Reported as ethnic-specific percentile in some clinics
- Often is sole identifiable cause of very early onset CVD
- Not dealt with in most guidelines

Nordesgaard et al, Eur Heart J. 2010 (23):2844-53.

Mutations Leading to Hypolipidemia

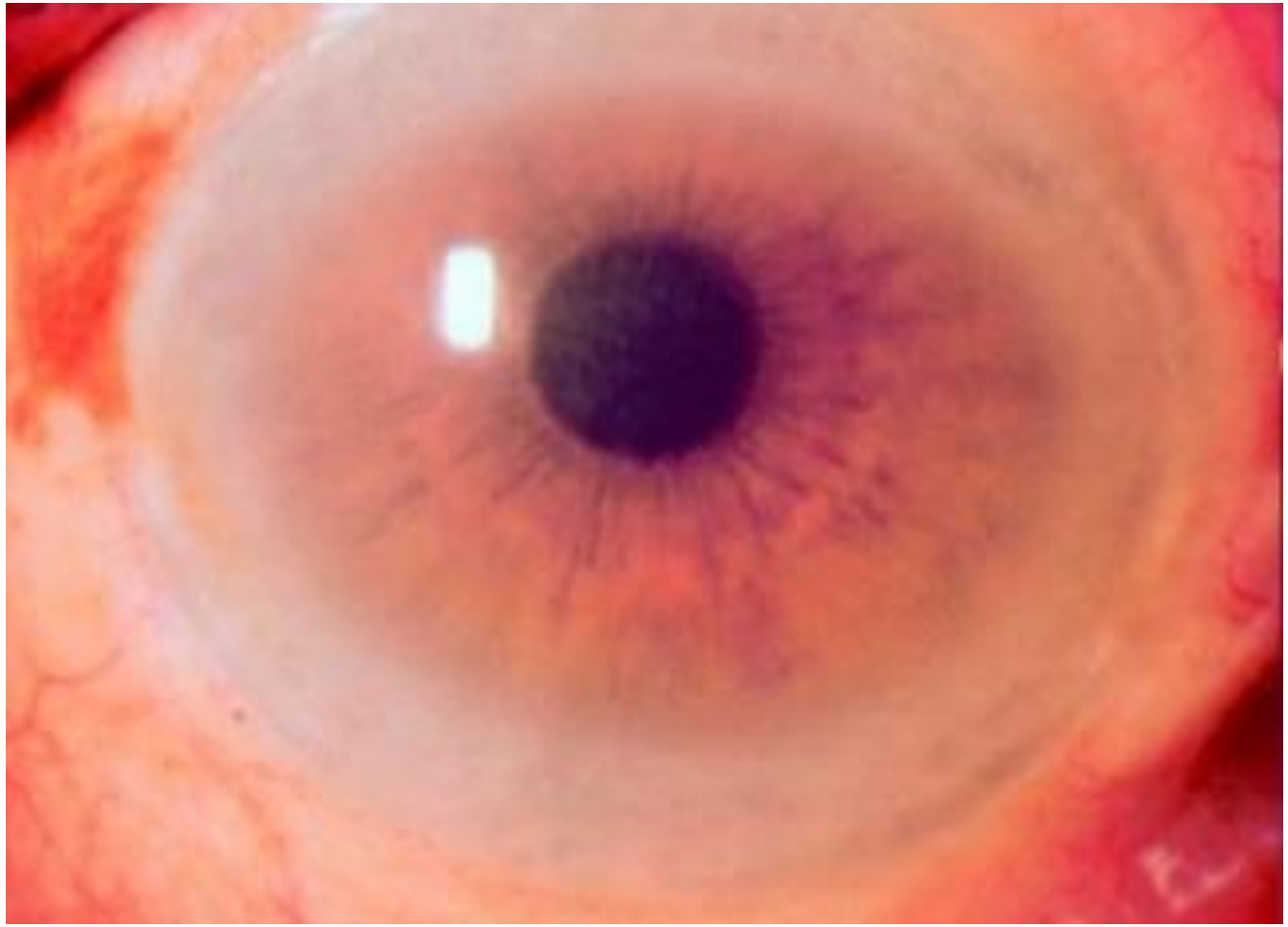
Mutated gene	Disorder
MTP	Abetalipoproteinemia
APOB	Hypobetalipoproteinemia
PCSK9	Hypobetalipoproteinemia
APOC3	Reduced TG levels
ABCA1	Tangier Disease
	Reduced HDL-C levels
APOA1	Reduced HDL-C levels
ANGPTL3	Familial Combined Hypolipidemia

Isolated Genetic Causes of Very Low HDL (<10mg/dL)

- Familial APOA1 deficiency
- LCAT deficiency
- Tangier disease (ABCA1 mutation)

Very rare

Corneal Opacity in LCAT Deficiency



Classification

- Fredricksen classification (Types I-V) from the 1960s was very useful at the time, but is descriptive, outdated and should no longer be used
- Hyperlipidemia/dyslipidemia can be divided into pure hypercholesterolemia, pure hypertriglyceridemia, combined hyperlipidemia, elevated Lp(a) and hypolipidemia
- Should stipulate whether primary or secondary and specify the genetic mutation where possible

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Interaction of Lipoproteins with the Artery Wall Leading to Atherosclerosis

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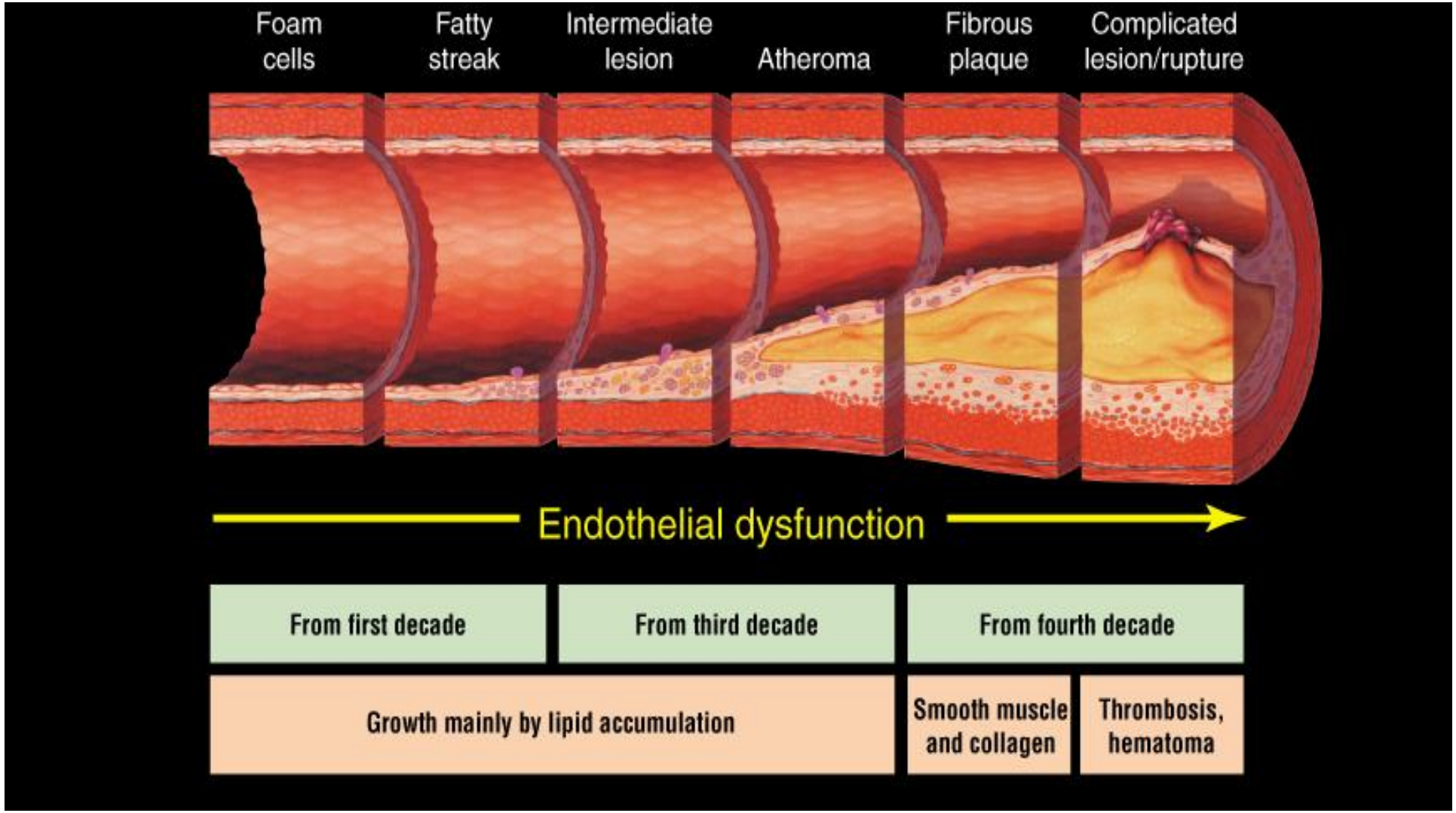
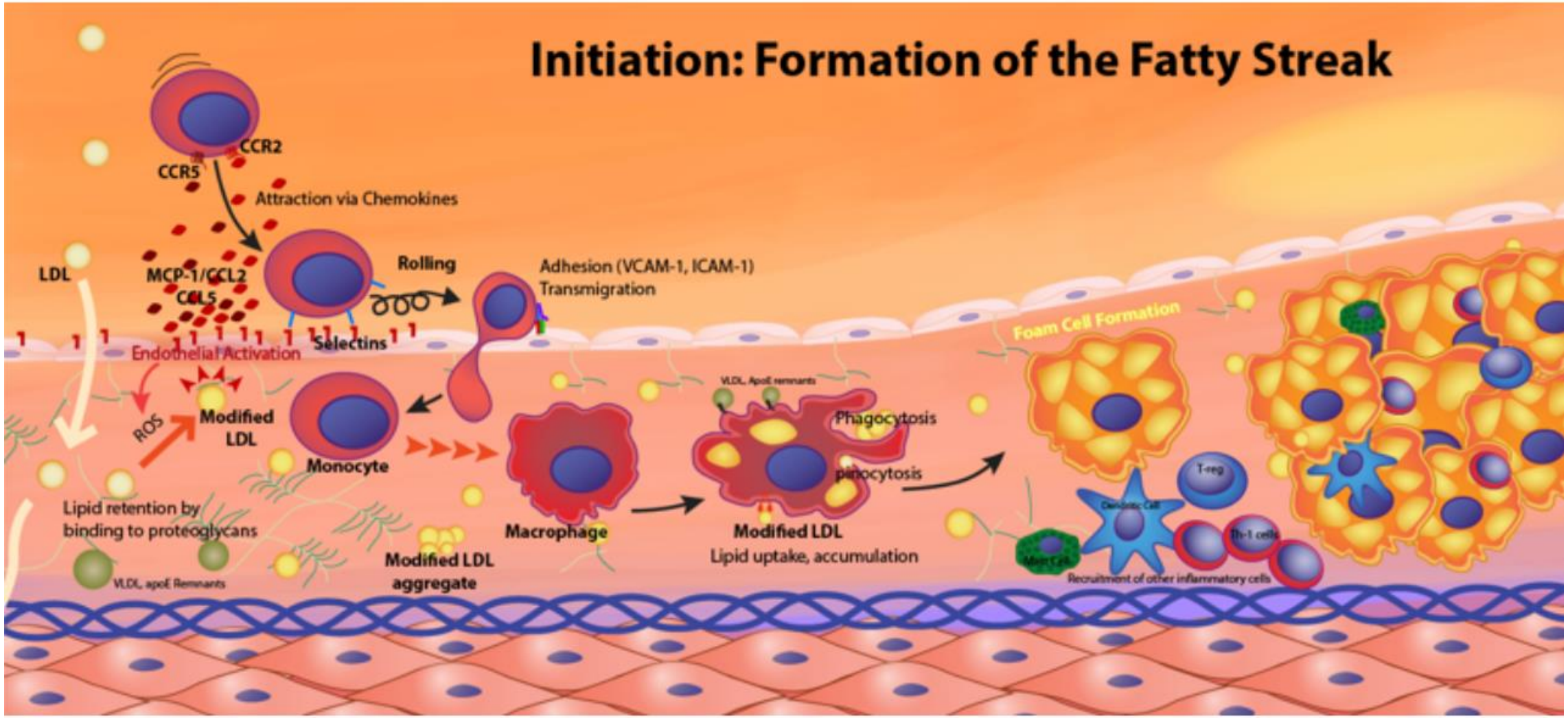
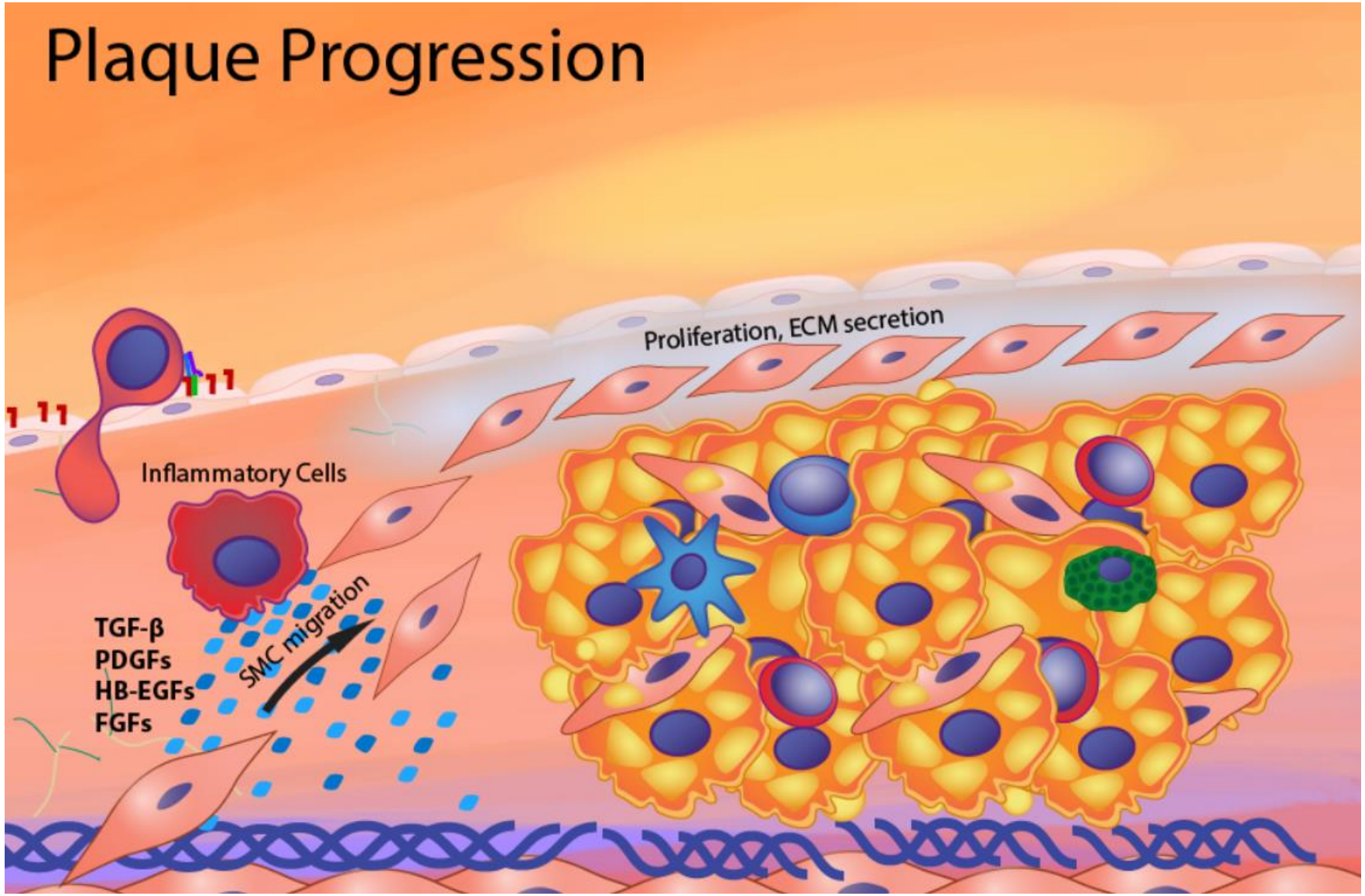
Atherosclerosis Timeline



Adapted from Pepine CJ. *Am J Cardiol.* 1998;82 (suppl 104).



Linton MF. In: Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000–.



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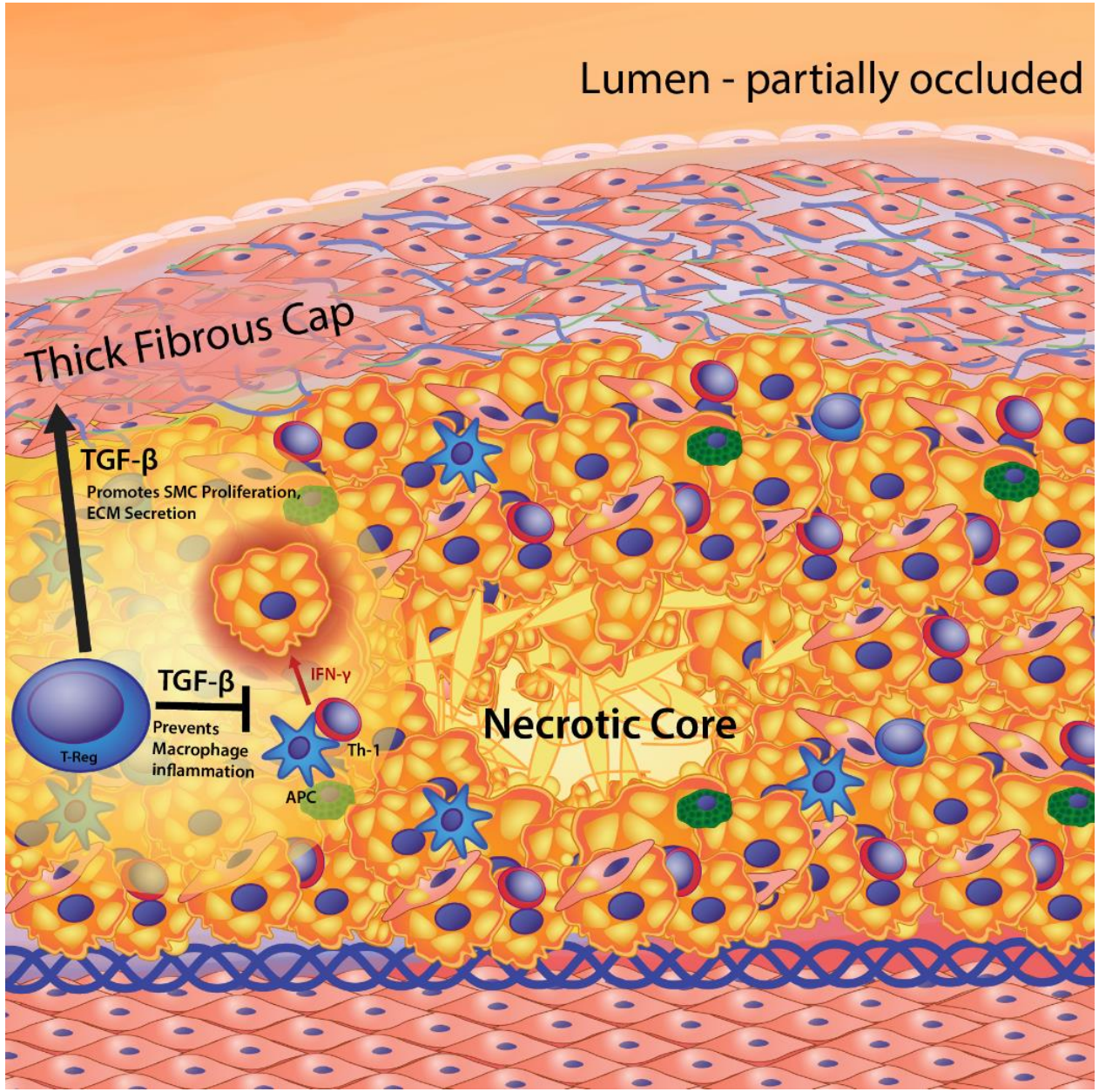

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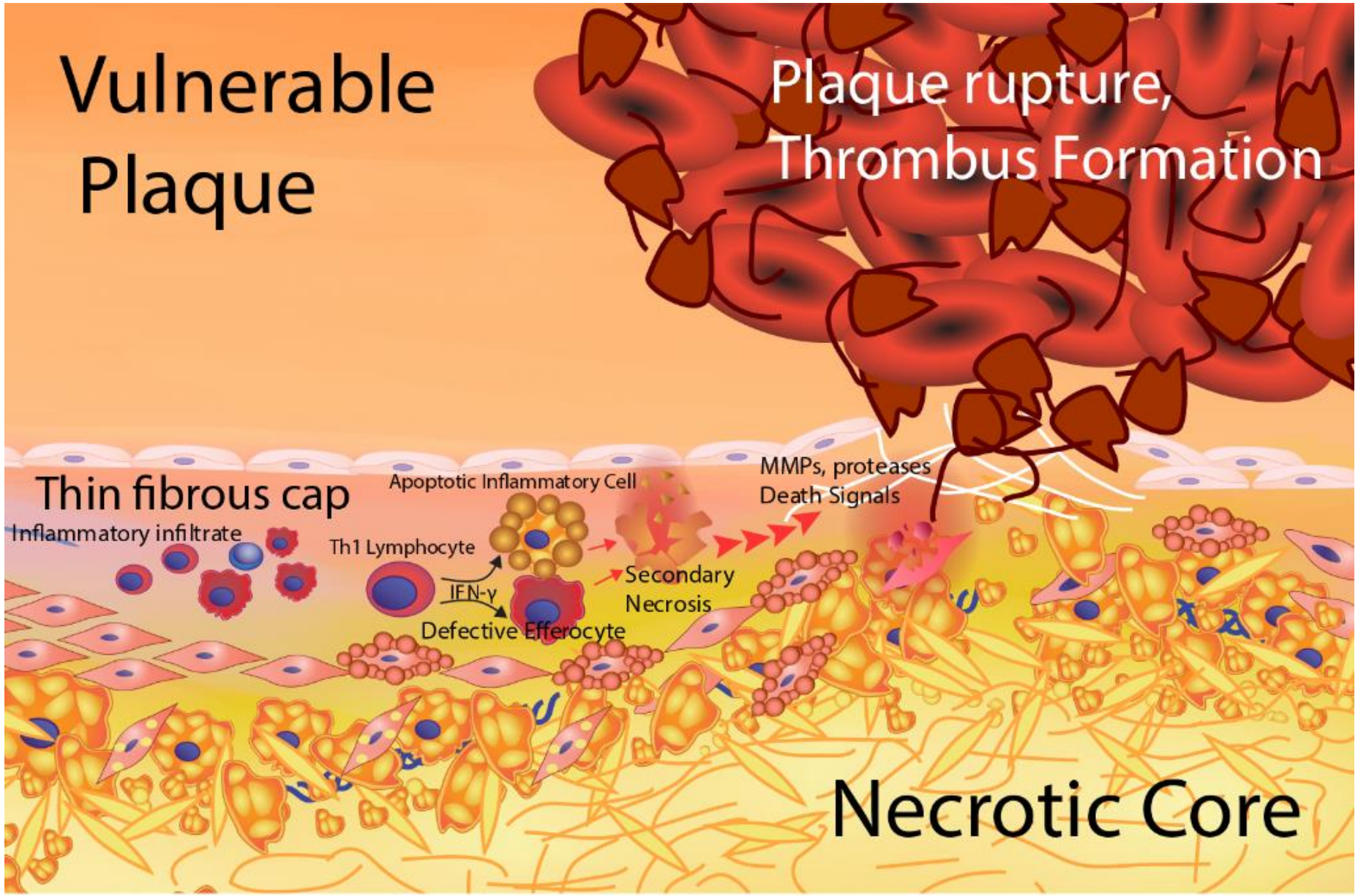
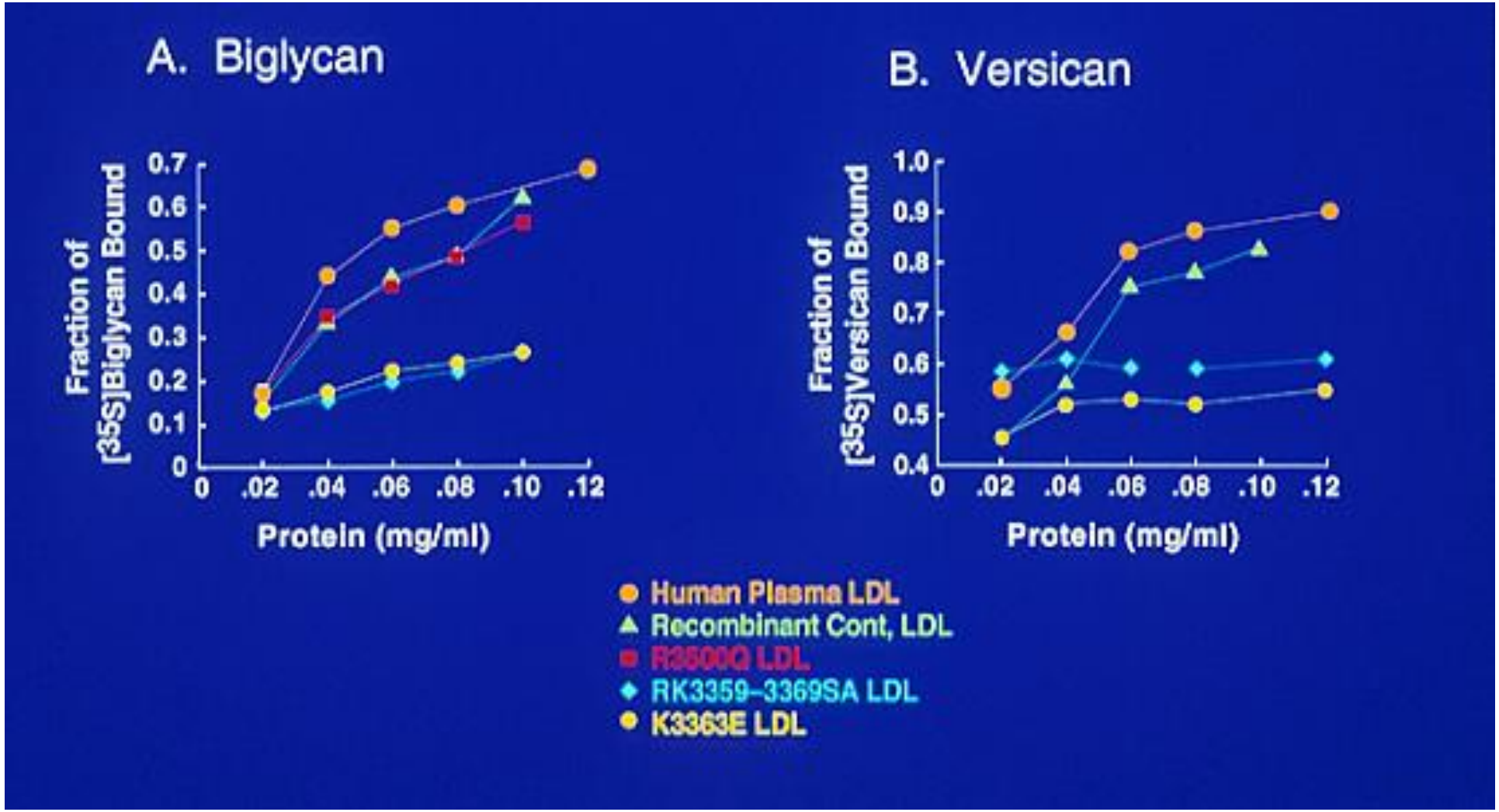


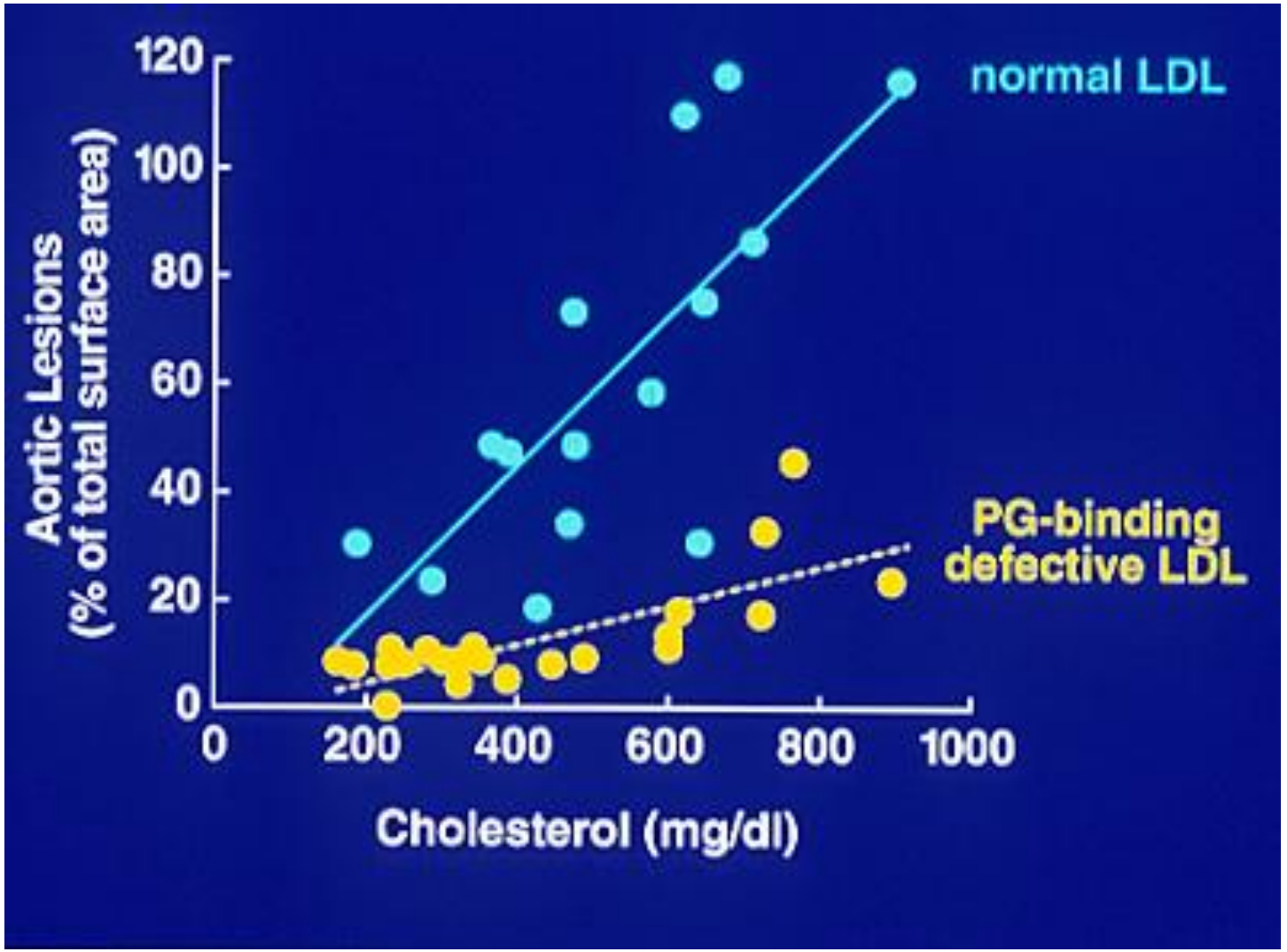
Linton MF. In: Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000–.

Effect of Site B Mutations on Proteoglycan Binding



Boren et al, JCI, 2000

Reduction in Atherosclerosis by B-site Mutation



Boren et al, Nature 2002

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LDL and CVD

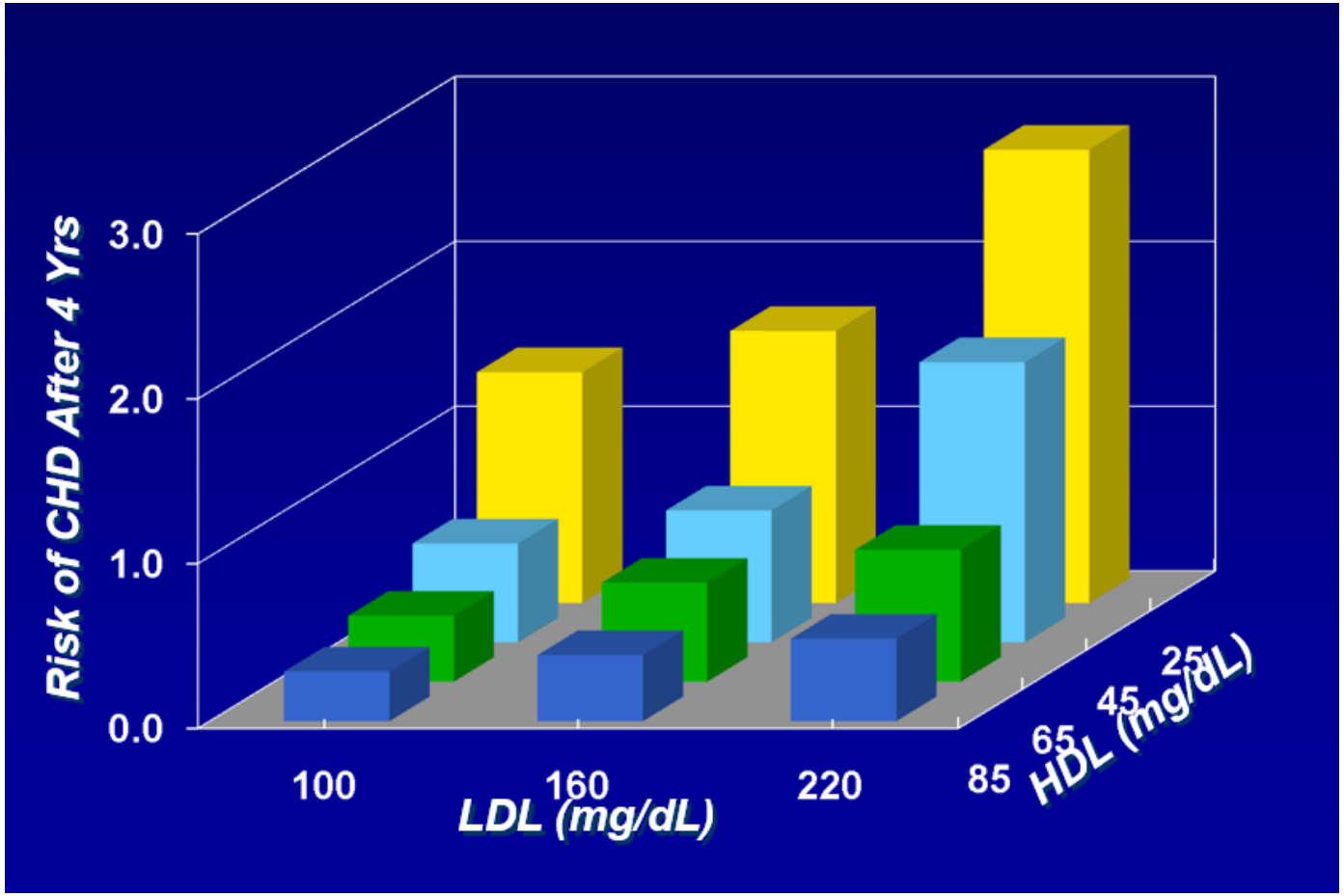
Alan Chait MD

Professor Emeritus

University of Washington

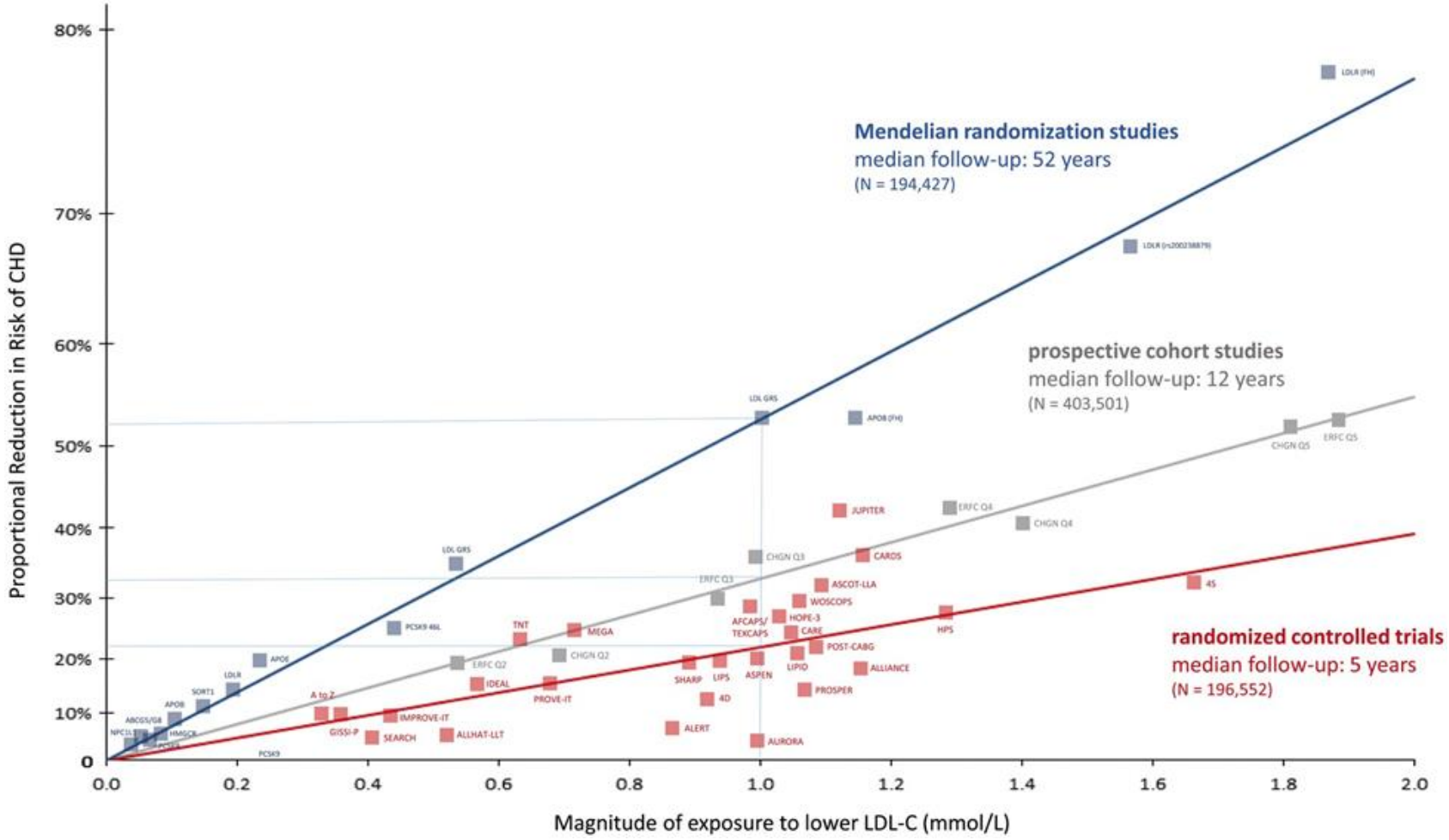
Seattle, WA

CHD Risk Associated with LDL and HDL



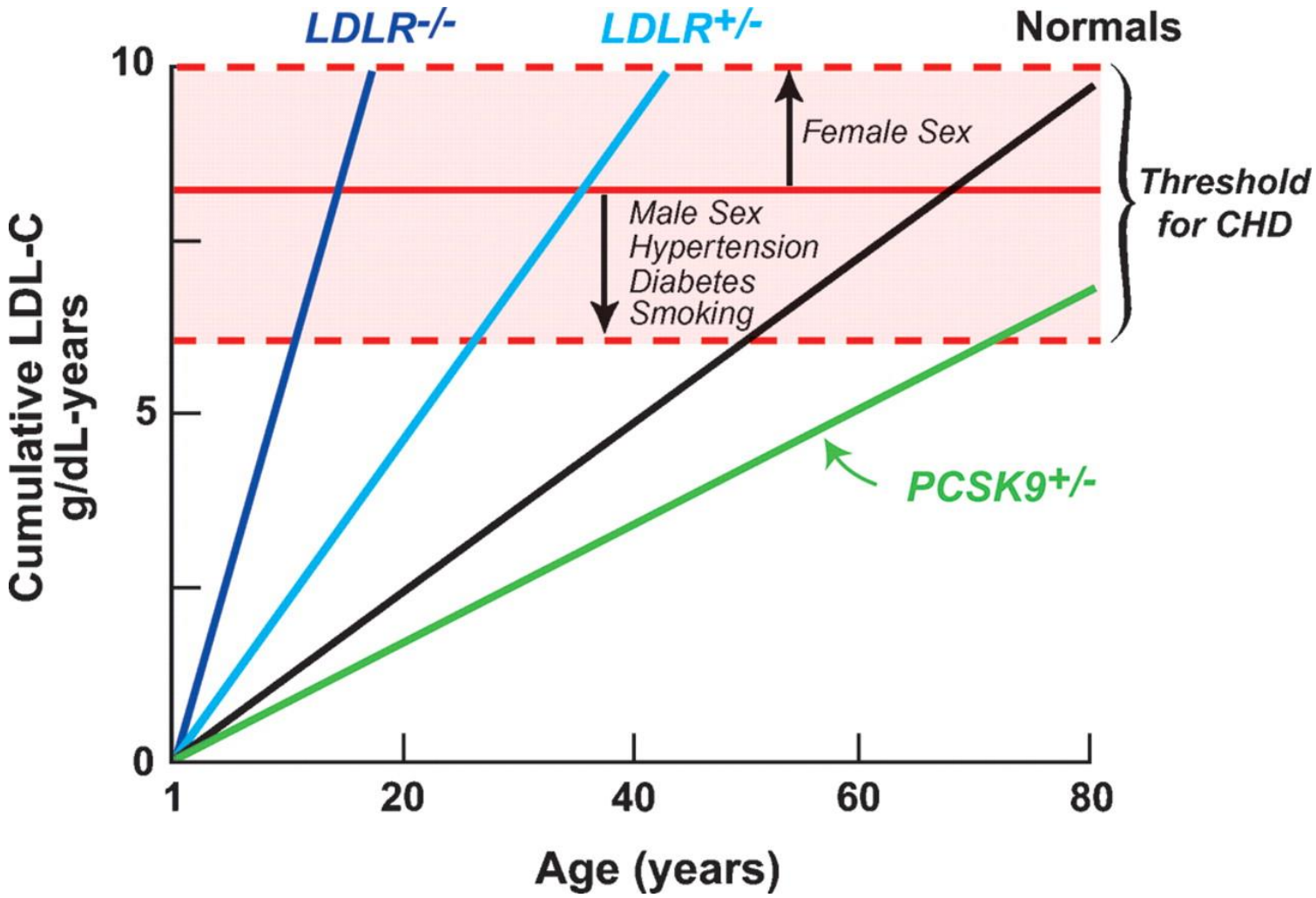
Gordon T et al. Am J Med 1977;62:707-714.

Association Between LDL-C and the Risk of CVD



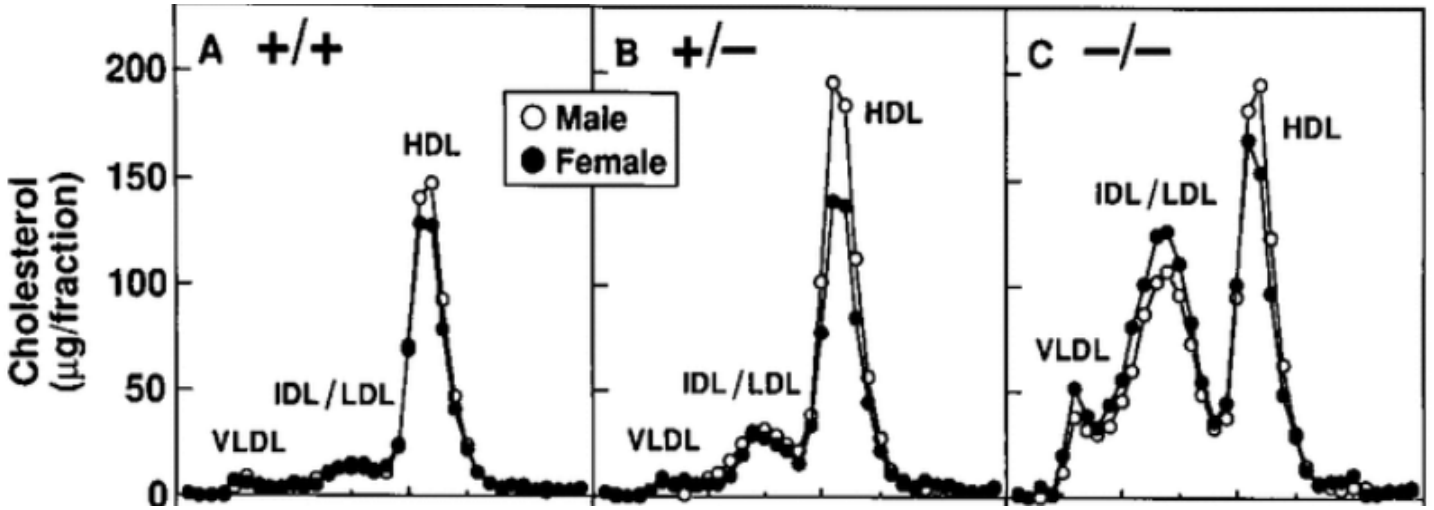
Ference et al, European Heart Journal (2017) 38, 2459–2472

Cumulative or Lifelong Risk

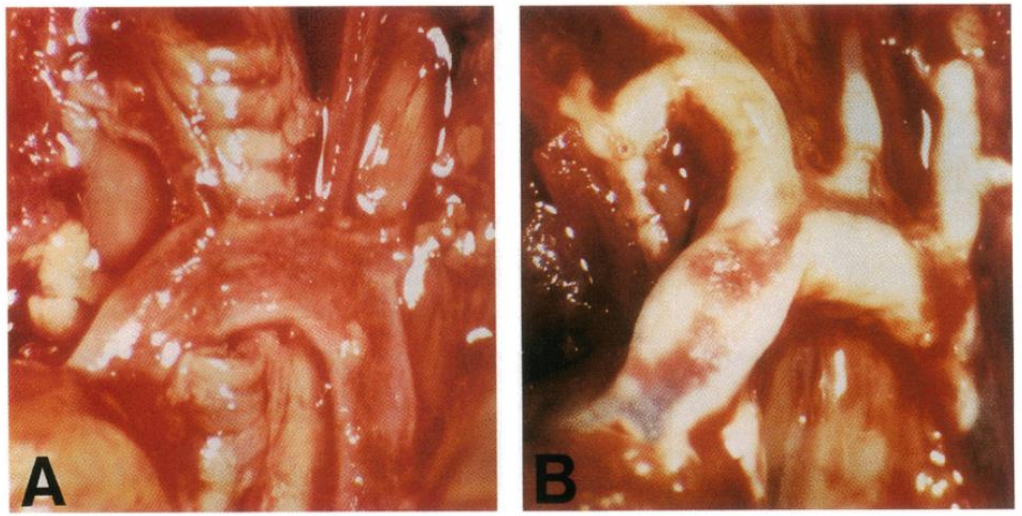


Horton et al, J. Lipid Res. 2009, 50:S172-7

Hypercholesterolemia & Atherosclerosis in LDLR-/- mice



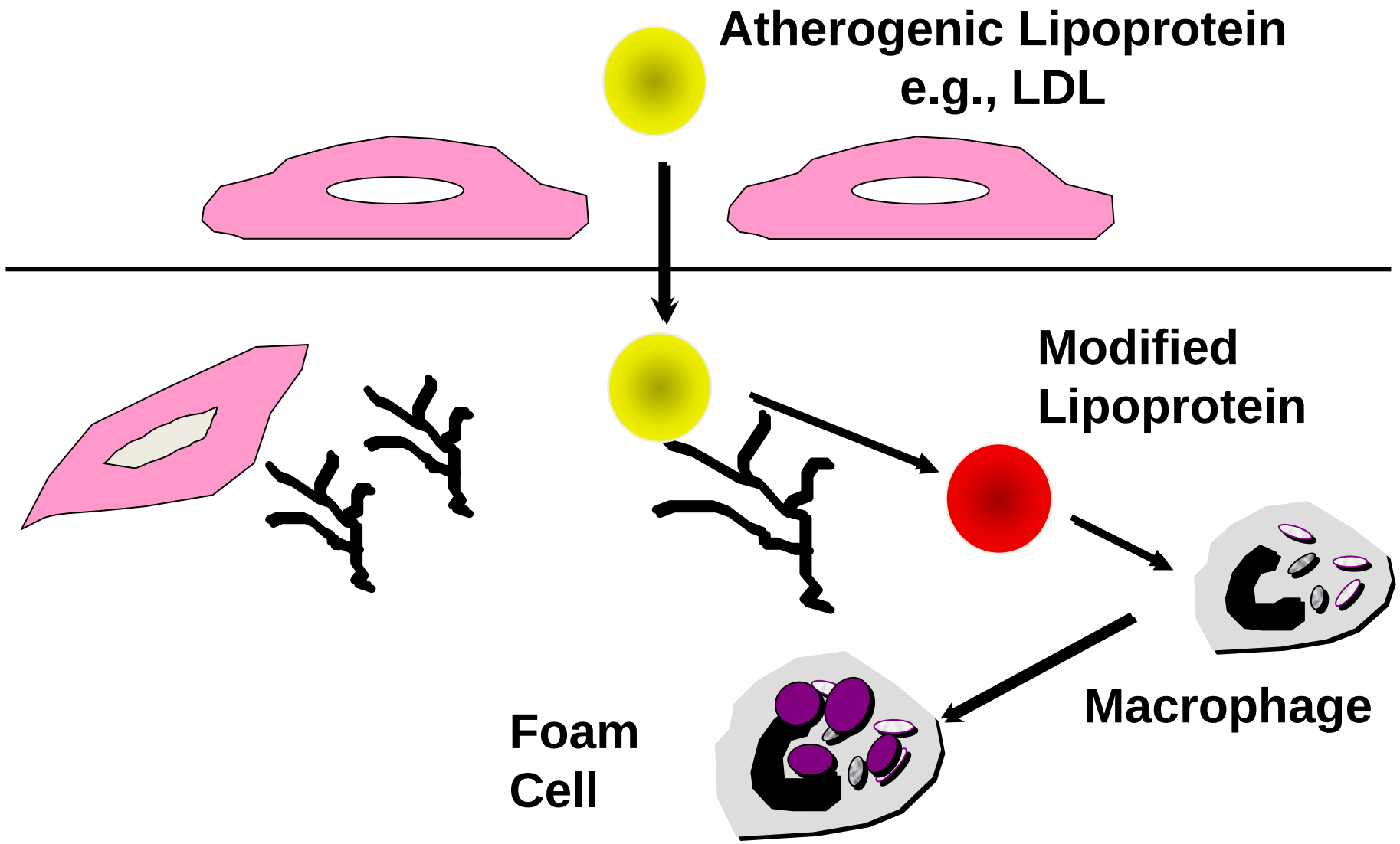
+/+



-/-

From Brown and Goldstein

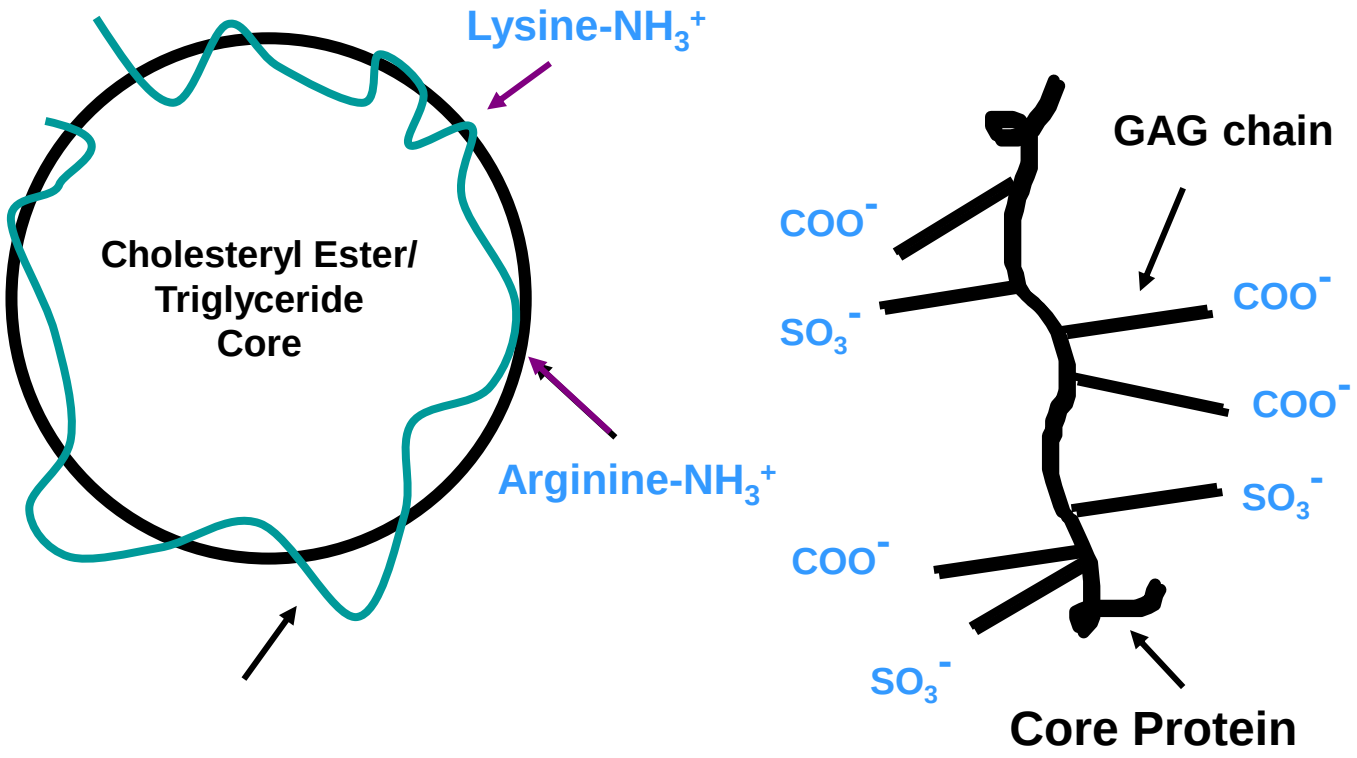
Lipoprotein Retention in Atherogenesis



Lipoprotein-Proteoglycan Interactions

Lipoprotein

Proteoglycan



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Hypertriglyceridemia and CVD

Alan Chait MD

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University of Washington

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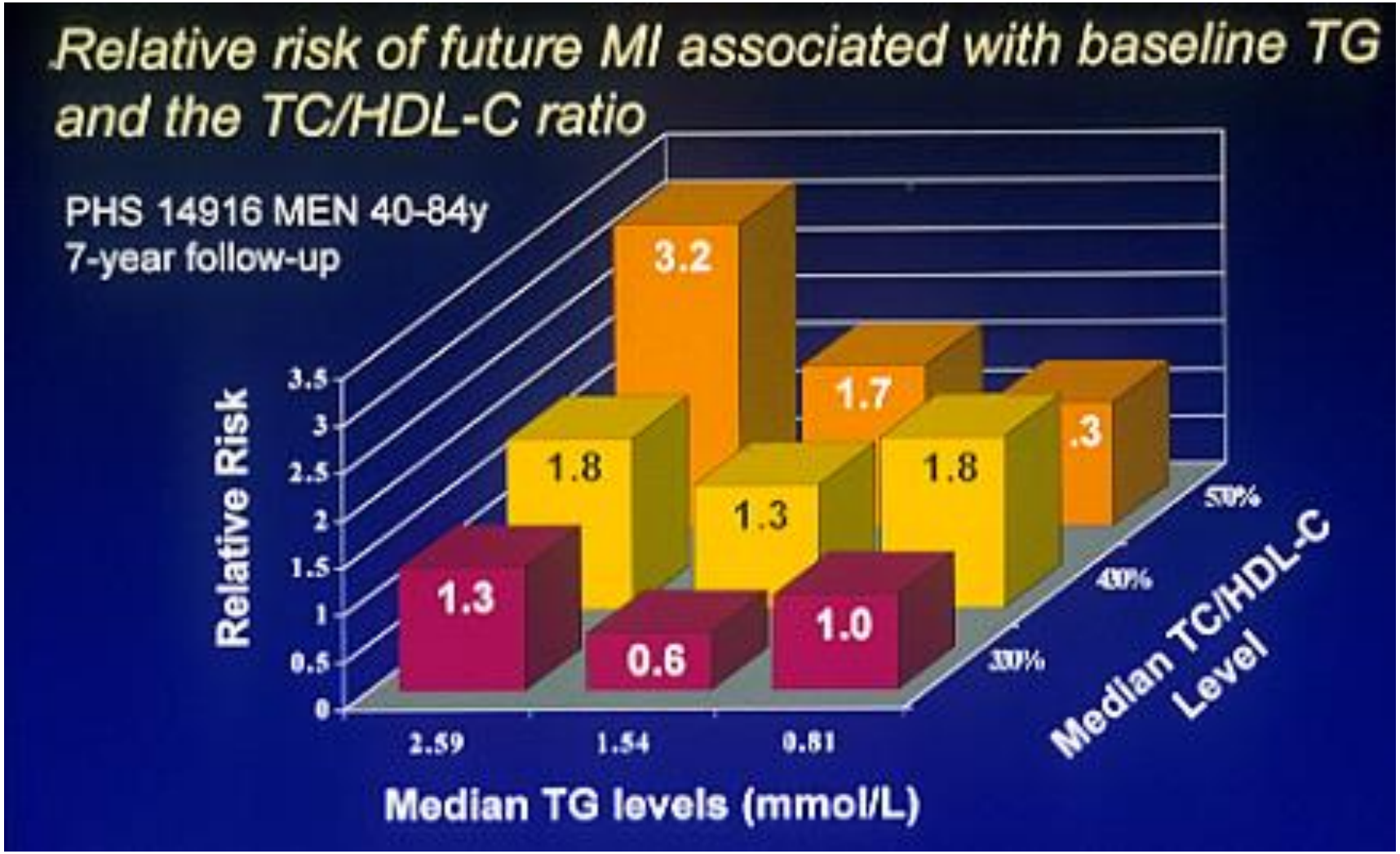
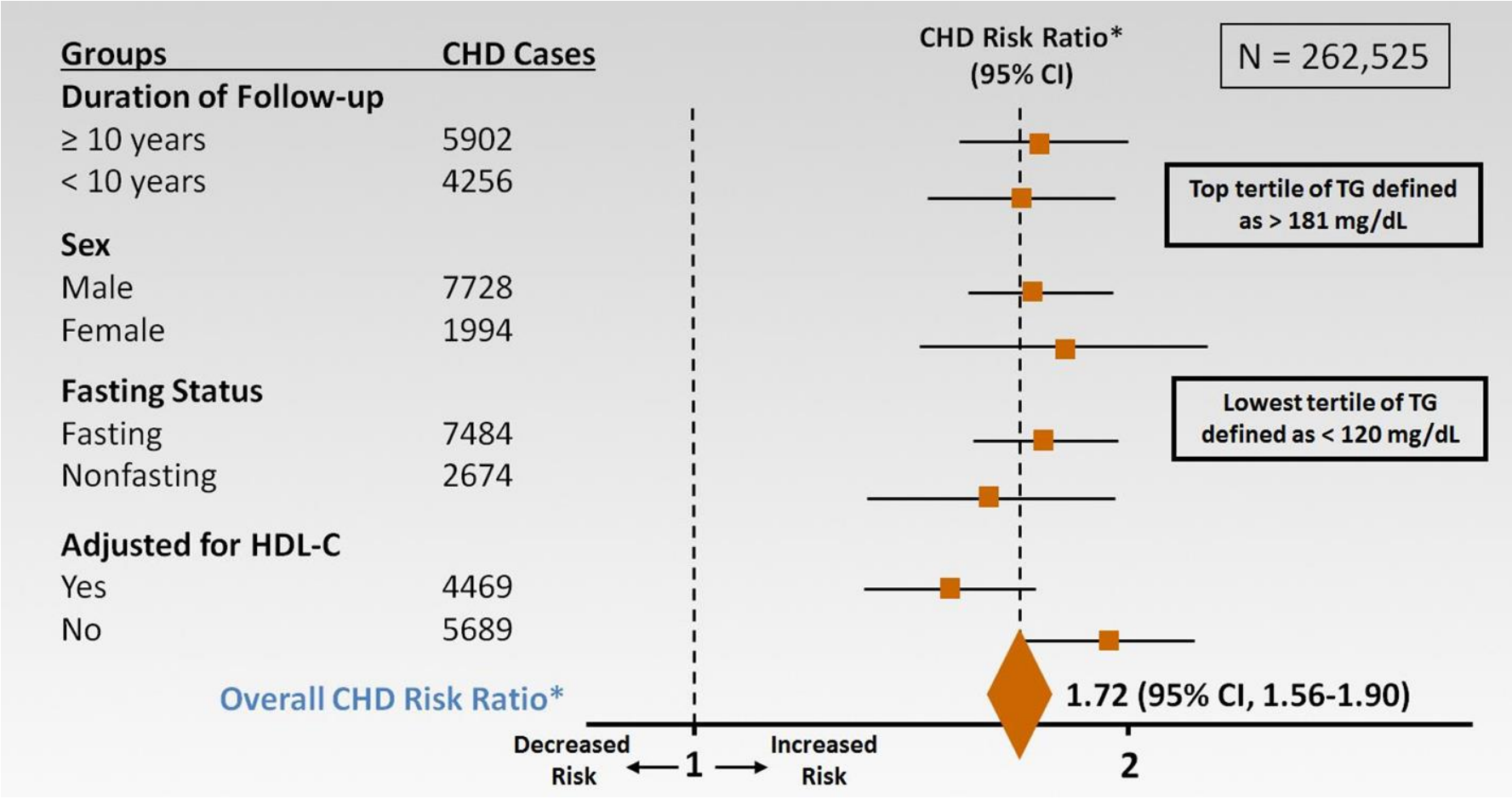
Hypertriglyceridemia and CVD



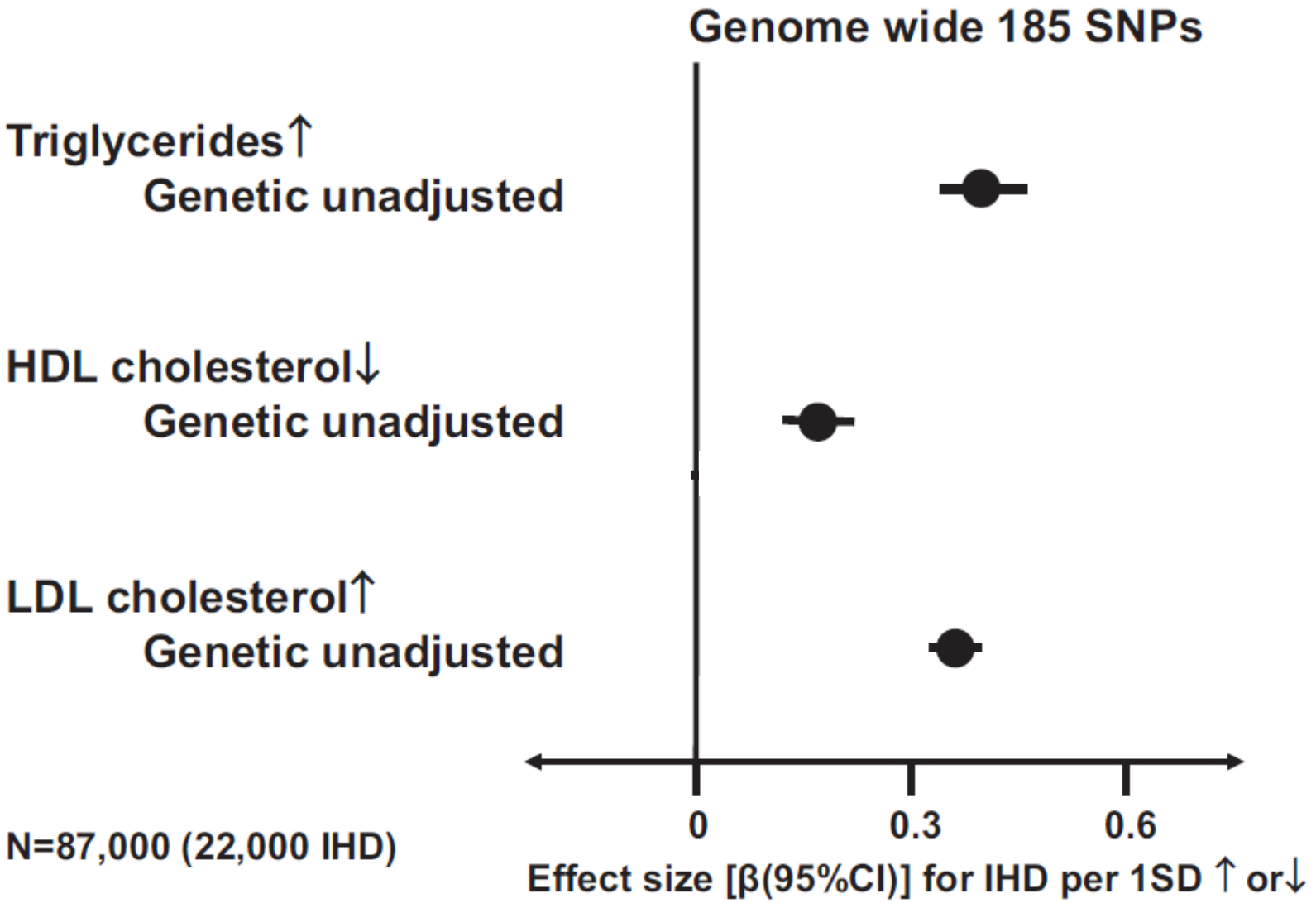
Stamfer, MJ et al. JAMA 276:882, 1996

Triglycerides and CVD risk: meta-analysis



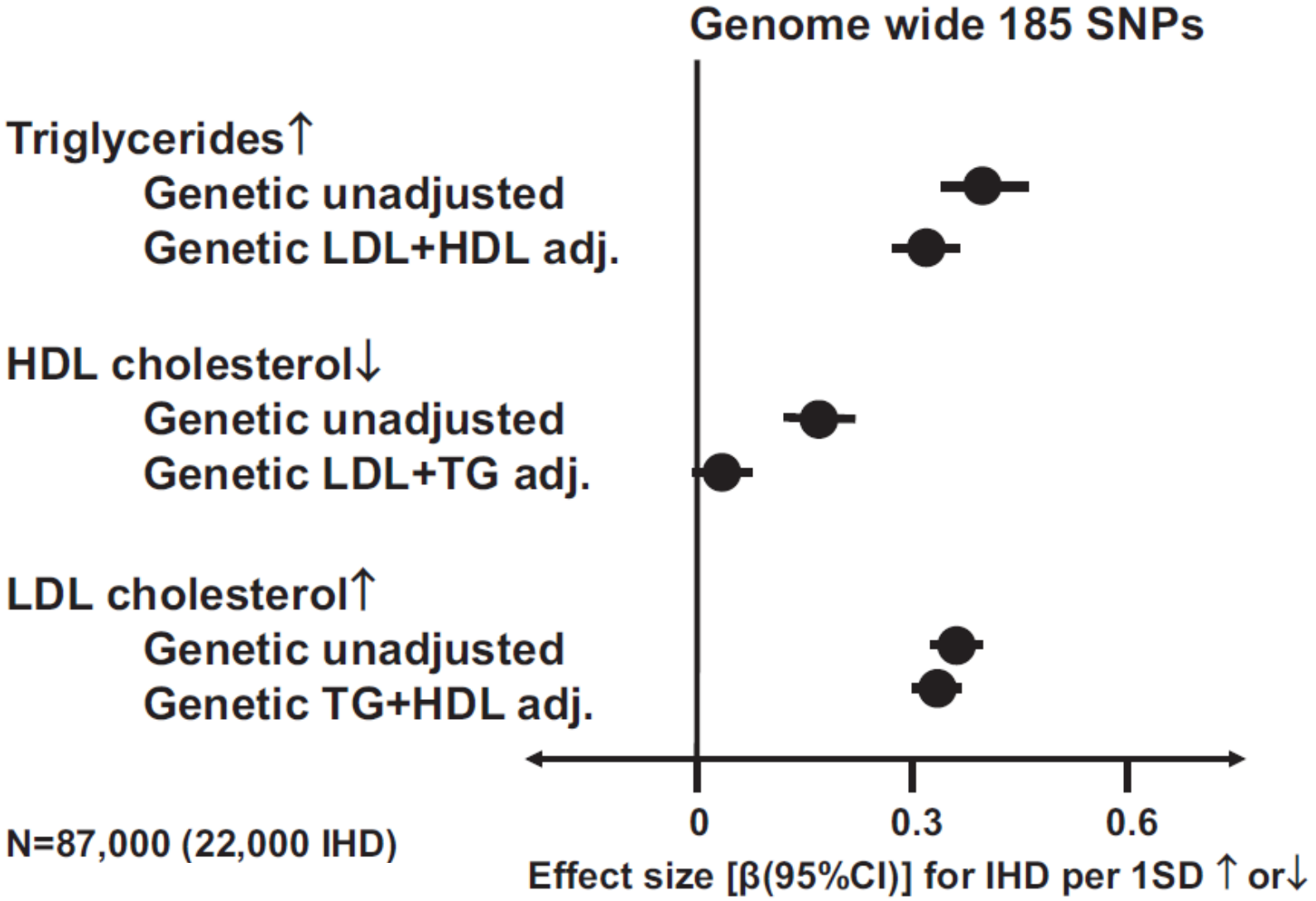
Sarwar et al, Lancet 2010;75(9726):1634-9.

Mendelian Randomization Study using 185 SNPs affecting Lipoproteins



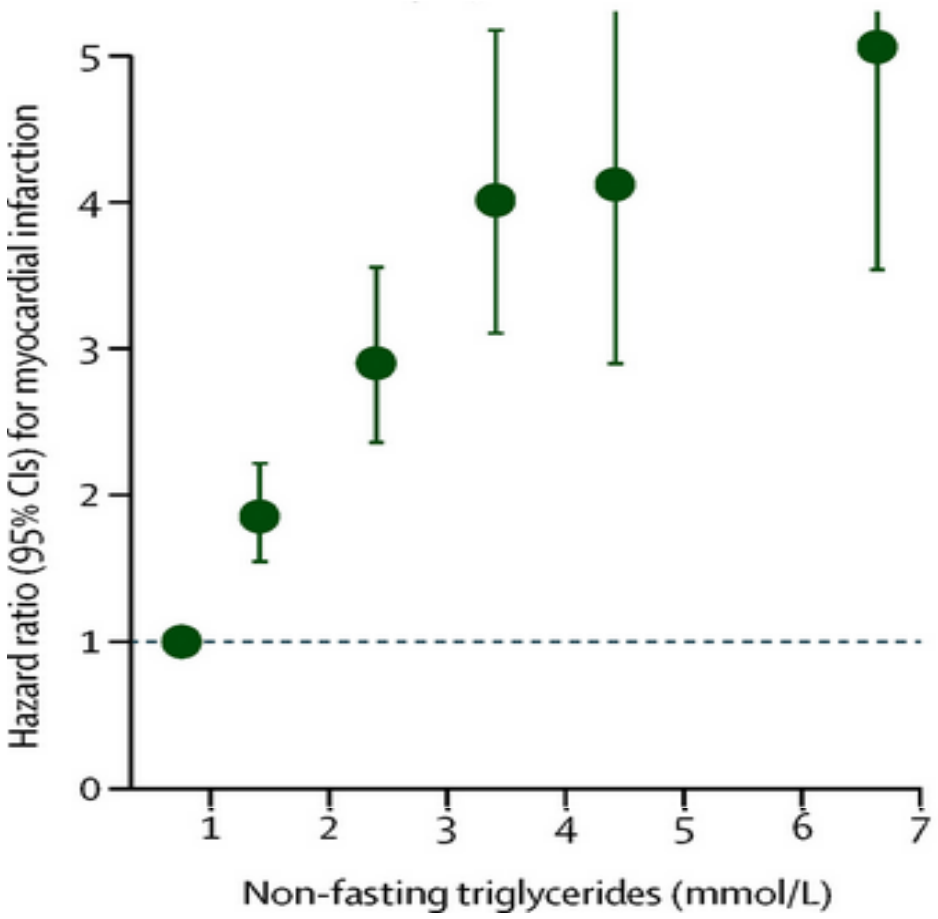
Do et al, Nat Genet 2013;45: 1345-52

Mendelian Randomization Study using 185 SNPs affecting Lipoproteins



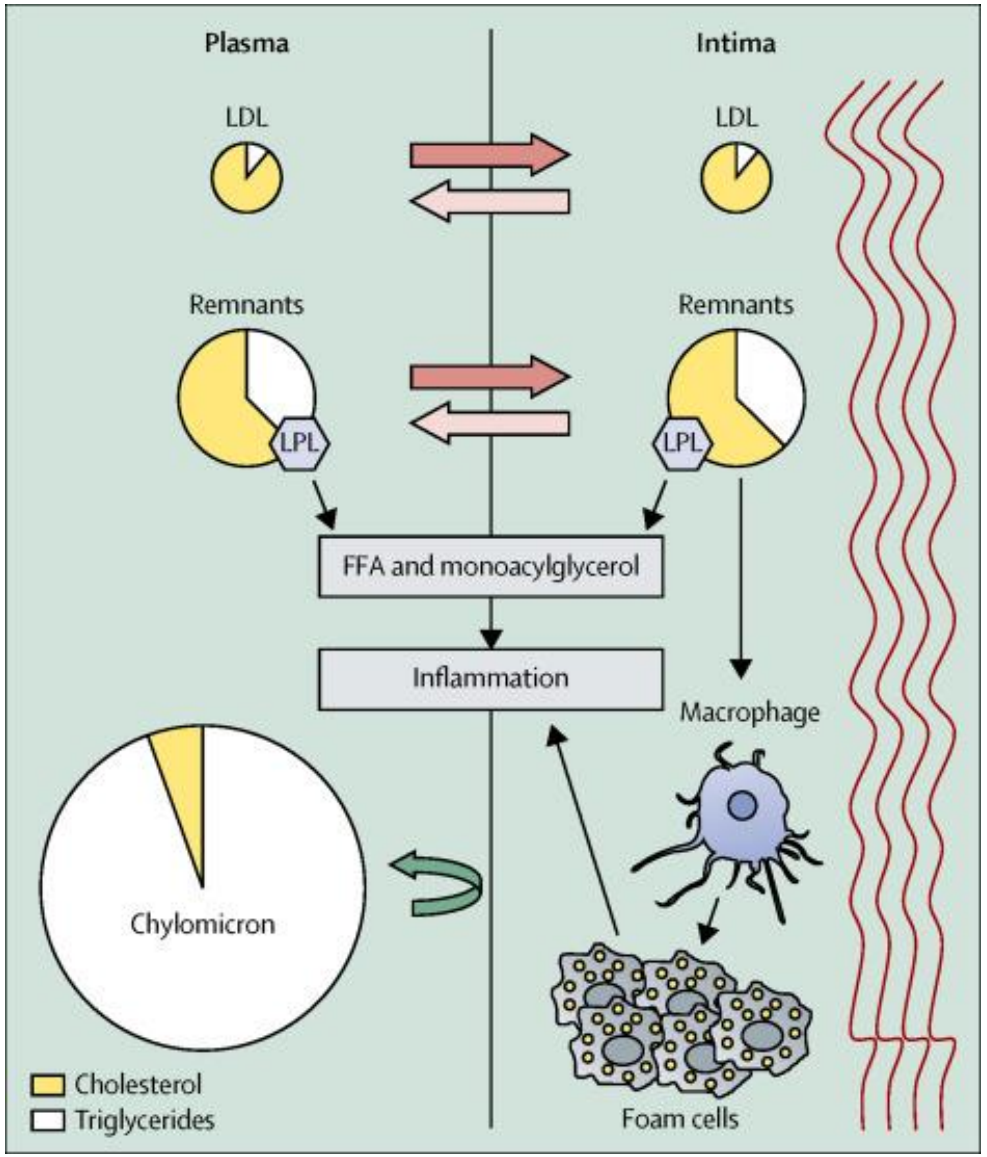
Do et al, Nat Genet 2013;45: 1345-52

Relationship Between Non-fasting TGs and MI risk



Nordestgaard and Varbo. Lancet 2014; 384:626-635

Potential Mechanisms by Which TRL Might Cause CVD



Nordestgaard and Varbo et al Lancet 2014

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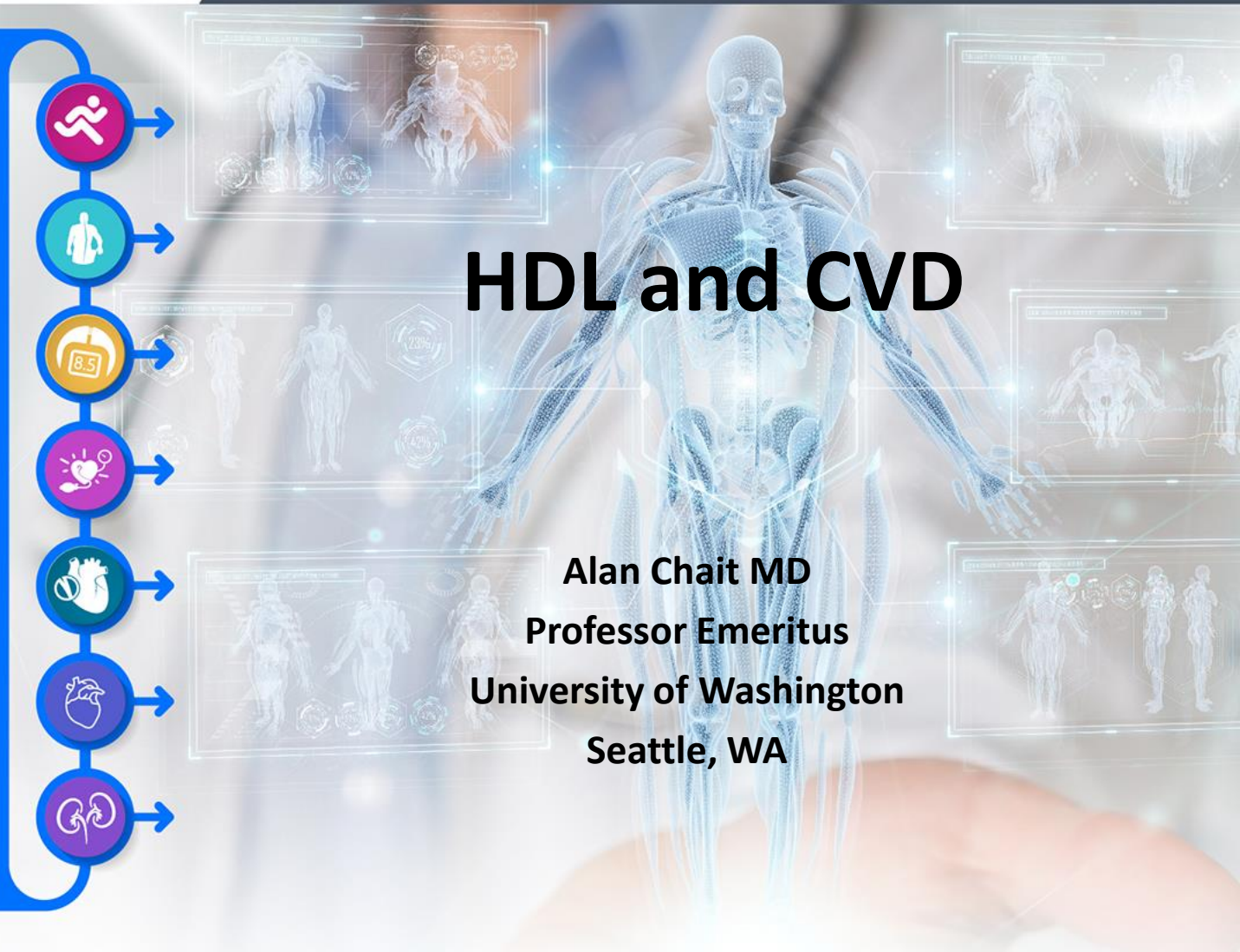

HDL and CVD

Alan Chait MD

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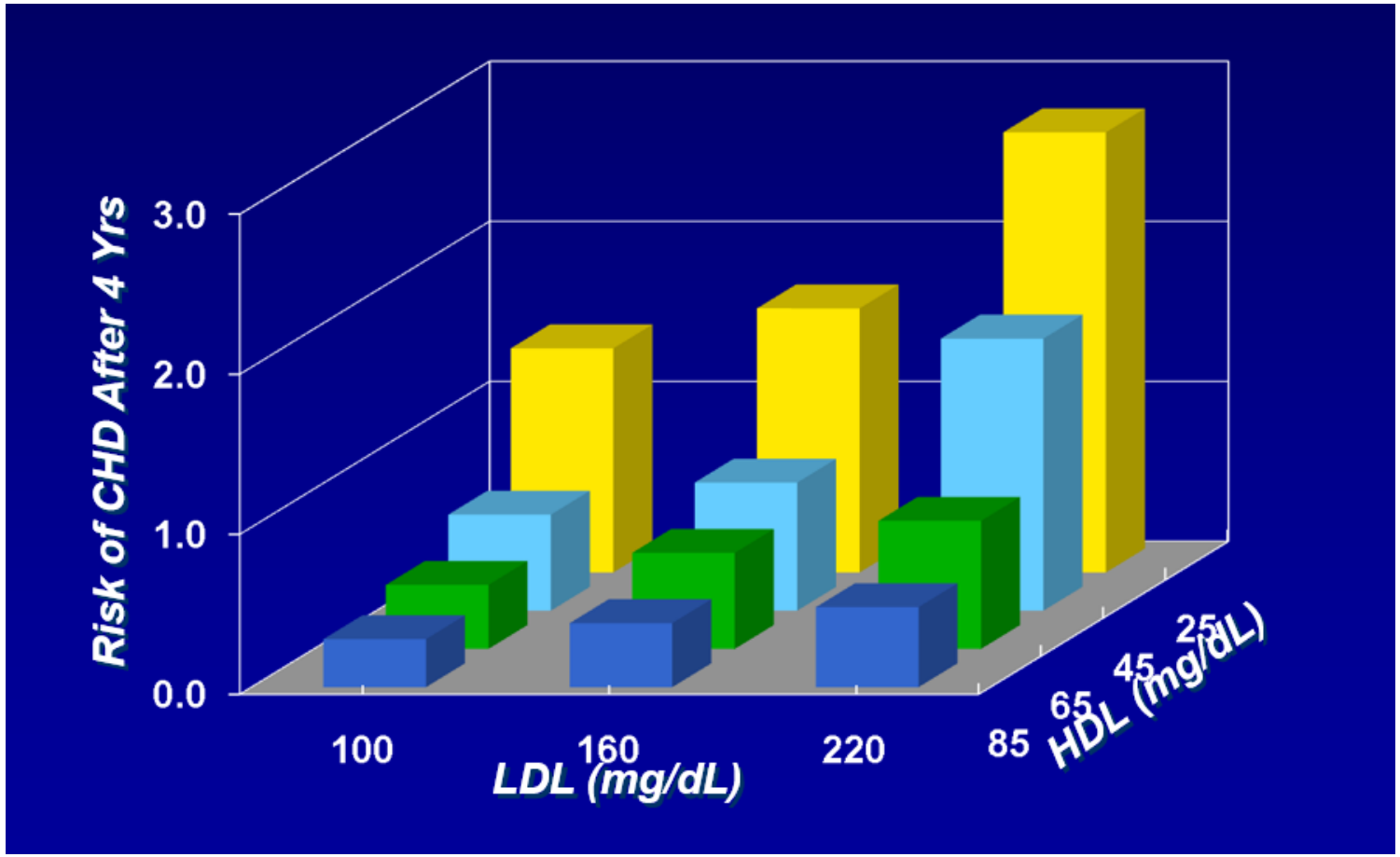
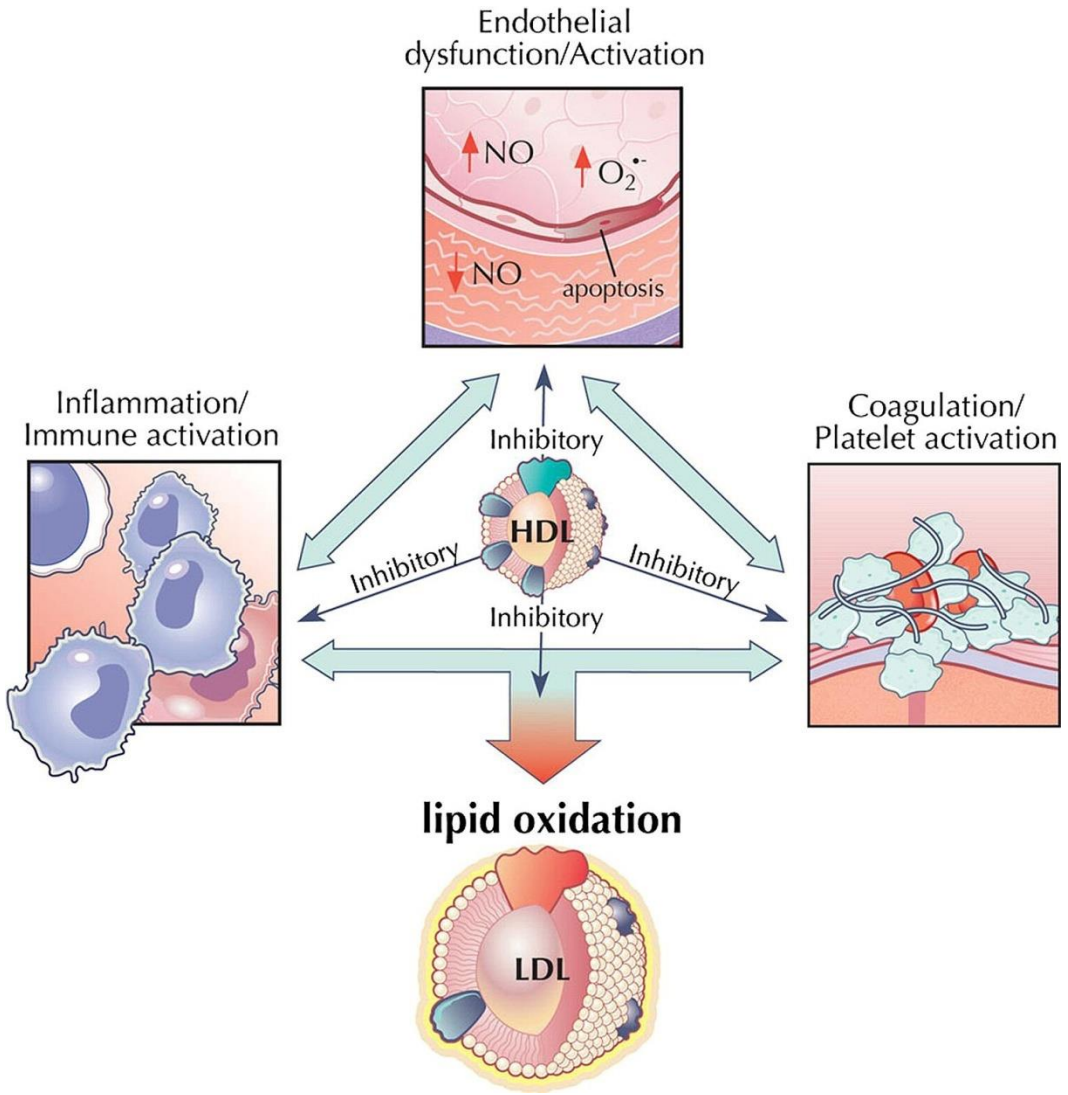
Seattle, WA

HDL is a Stronger Predictor of CAD Risk Than LDL



Gordon T et al. Am J Med 1977;62:707-714.

HDL Functions Other than Reverse Cholesterol Transport



DeGoma, DeGoma and Rader, JACC 51: 2199-11, 2008

However:

- Some animal studies show a dissociation between low HDL-C and atherosclerosis
- Some new genetic data not consistent with HDL-cholesterol being a negative CVD risk factor
- Clinical trials have failed to show a benefit of raising HDL-cholesterol
  - CETP inhibitors
  - Niacin

HDL – Time for a rethink?

- Can HDL become dysfunctional?
- Are we using the wrong metric, i.e., HDL cholesterol, rather than HDL particle number or HDL functionality?
- Is HDL a marker rather than a mediator of CVD?
- Can cardioprotective drugs be developed that increase functional HDL and RCT and reduce atherosclerosis risk?