Atherosclerosis, Lipids and Lipoproteins

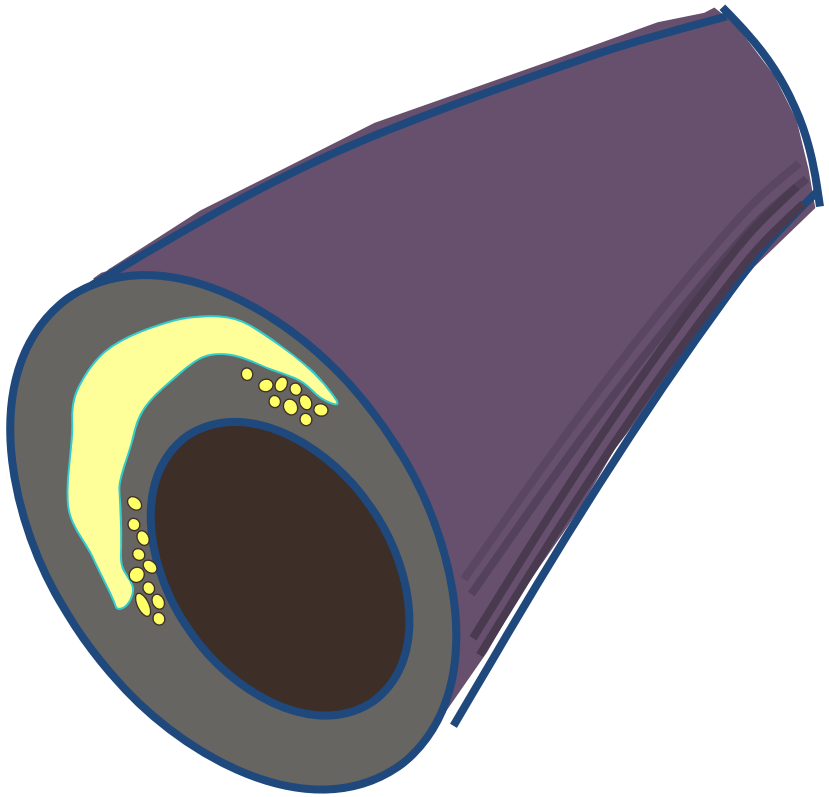
Objectives

- Describe the functions and sources of cholesterol and triglycerides
- Describe the functions and role of lipoproteins in atherosclerosis
- Explain the pathogenesis of atherosclerosis
- Identify the role of inflammation in atherosclerotic process

Presentation Outline

- Pathophysiology of Atherosclerosis
  - Early, Middle and Late Stages
  - Interaction among key elements: endothelial dysfunction, lipoprotein B particle infiltration and oxidation, inflammation, plaque rupture, thrombosis
- Lipid and Lipoprotein Metabolism
  - Key principles
  - Key lipoproteins
  - Key enzymes and transfer proteins
- Common Atherogenic Dyslipidemias
  - Elevated LDL & related (↑LDL-C, non-HDL-C, apo B, LDL-P)
  - Elevated TG, low HDL, small, dense LDL
  - Elevated Lp(a)
  - Mixed dyslipidemias

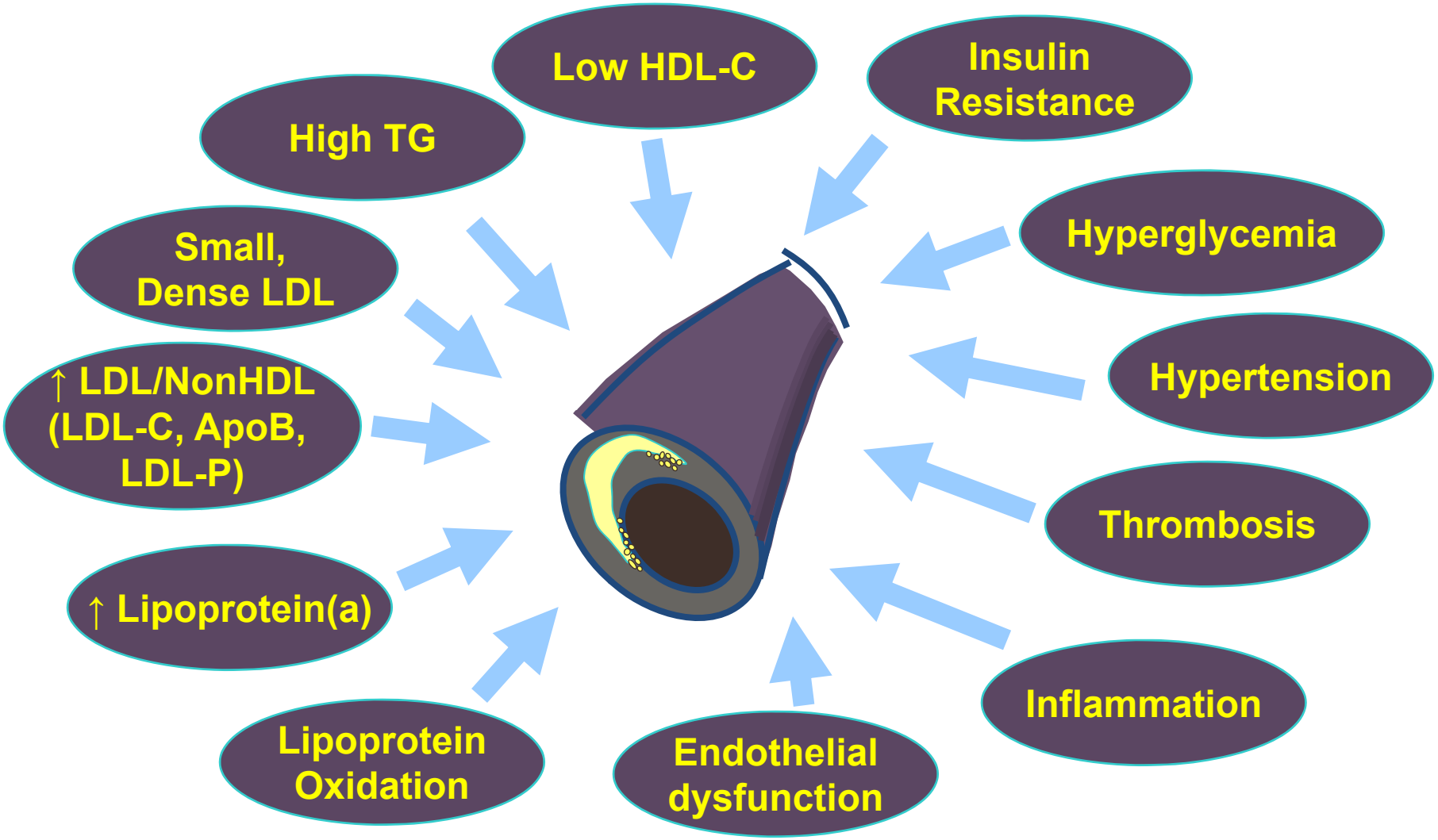
ATHEROGENESIS OVERVIEW



Atherosclerosis:

A *single* pathologic process beginning early in life, potentially in utero that progresses throughout the lifetime and is the *greatest* cause of death and disability in the Western world (~1/3 of all US mortality)

Atherogenesis Overview



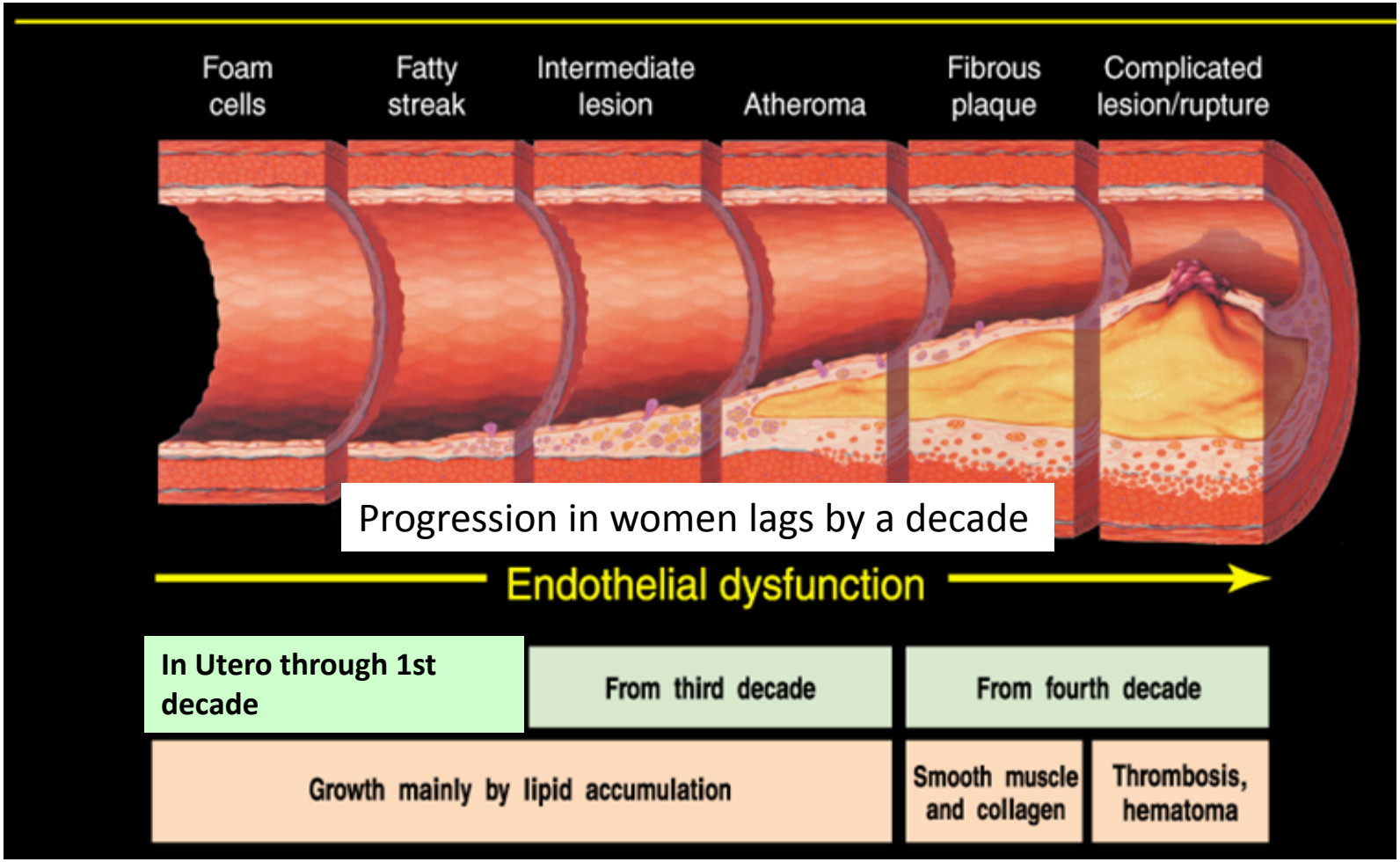
Most atherosclerosis/CVD risk factors are <u>lipoproteins</u> or are <u>lipoprotein-related</u>

Atherogenesis: Overview

Atherogenesis involves a cascade of events (mainly top to bottom of this list, but with some feedback in reverse)

- *High* plasma apo B lipoproteins (Lp B= *All* non-HDL) *PLUS* focal endothelial *trauma/dysfunction*
- ↑ *Infiltration* of Lp B into the subendothelium (SE)
- ↑ *Retention* of Lp B in the SE
- ↑ *Modification* of Lp B in the SE
- ↑ *Inflammation*
- Plaque *rupture*
- *Thrombosis*
- ↓↓↓ *Blood flow*
- *Ischemic event*

Atherosclerosis Timeline



Adapted from Pepine CJ. *Am J Cardiol*. 1998; 82(suppl.10A):23S-27S.

Early Stages of Atherogenesis: Arterial Endothelium

Healthy

Causes

- Laminar flow
- *Lack* of Subendothelial Lp accumulation

Effects

- Anti-inflammatory
- Anti-oxidative
- Anti-thrombotic
- (*normal* vasodilatation)

*Dys*functional

Causes

- *Turbulent* flow
- Subendothelial Lp *accumulation*

Effects

- Pro-inflammatory
- Pro-oxidative
- Pro-thrombotic
- (*abnormal* vasodilatation)

Adapted from N. Omoigui, VJ Dzau *J Vasc Med Biol*, 1991 3:382-391.

Early Stages of Atherogenesis: Apo B Lipos in Subendothelial Space

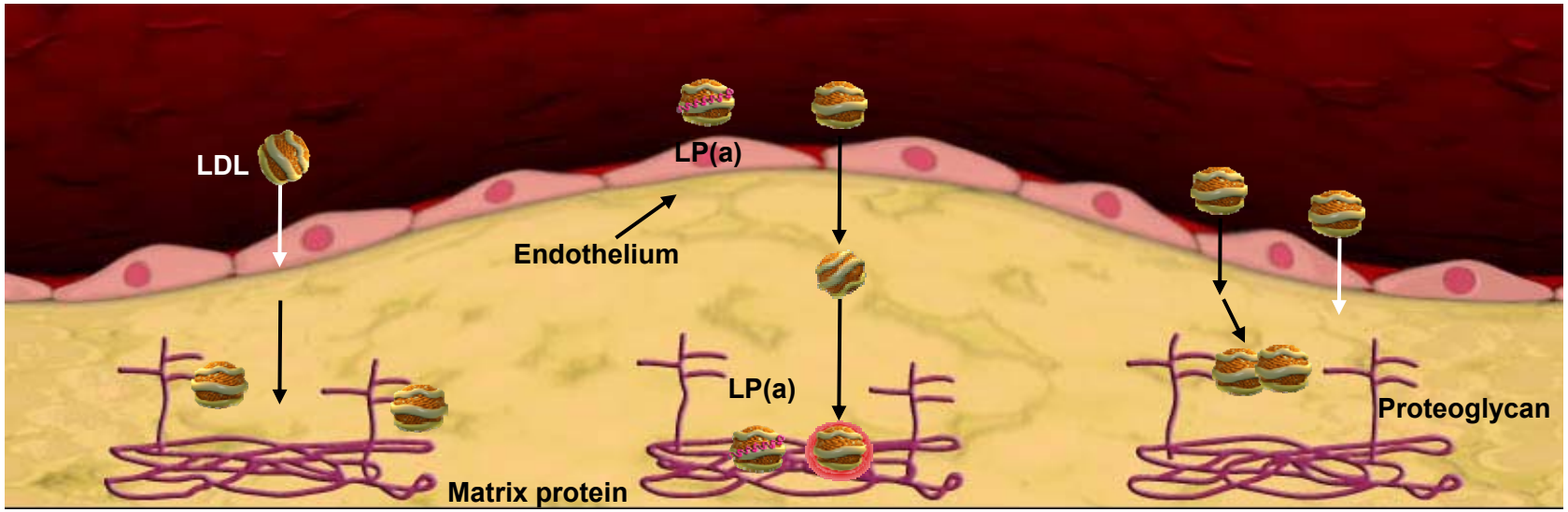
<u>Contributions of Lp B (=LDL+ other Non-HDL Particles)</u>

- ***Lp B entry*** into subendothelium ↔ ***endothelial dysfunction***.
- ***Lp B retention/binding*** to subendothelial matrix – (proteoglycans, elastin, collagen)
- ***Lp B Modification***
  - Lipolysis
  - Aggregation/fusion
  - Oxidation
- ***Lp B uptake*** by macrophages

Modified from: "Response-to-Retention Hypothesis" Kevin Williams, Ira Tabas, *ATVB* 1995; 15:551-61.

Mechanism of Lipoprotein Retention: Role of Extracellular Matrix

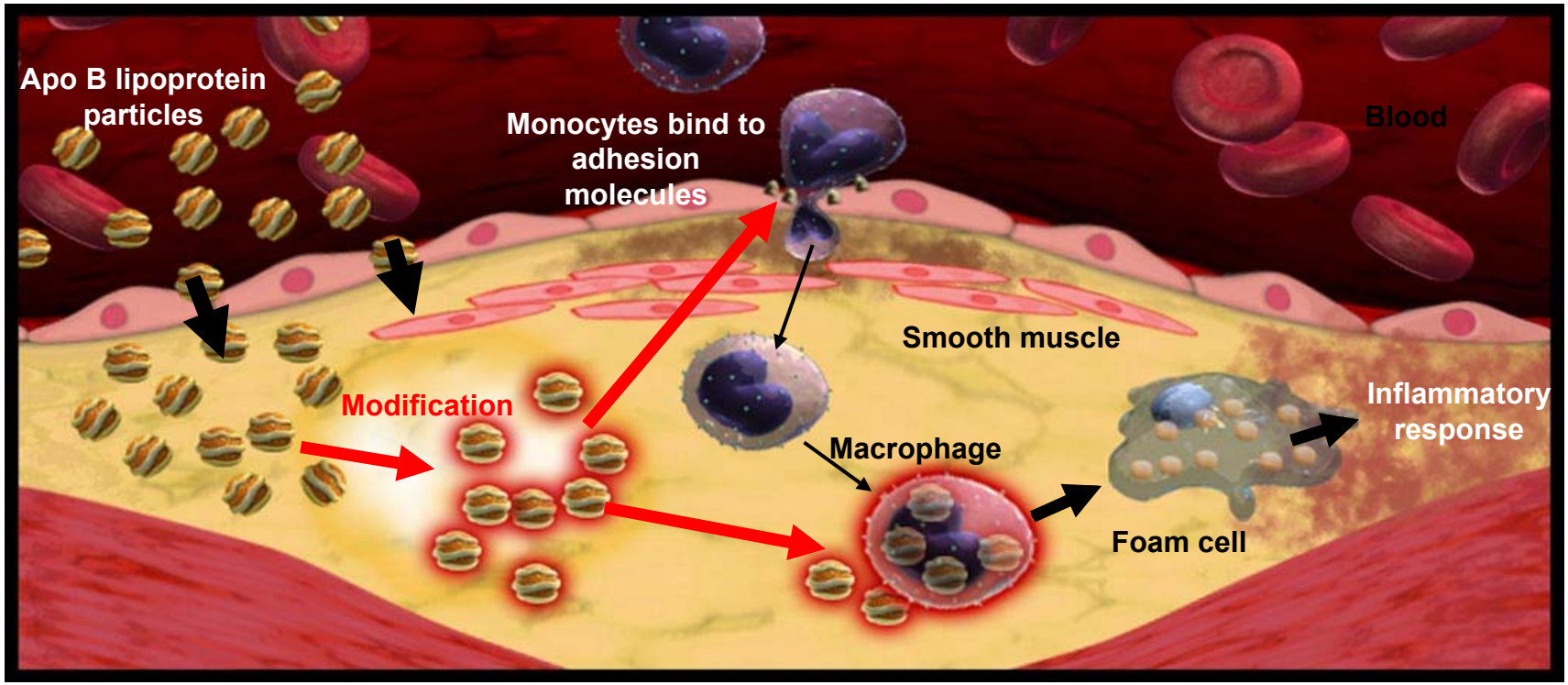
- Lipoprotein retention is mediated by physical interaction between lipoproteins and matrix molecules[1,2]
  - Proteoglycans, collagen, elastin, fibronectin, vitronectin, etc
- Accessory molecules promote lipoprotein retention[1,2]
  - Lipoprotein lipase, secretory sphingomyelinase, secretory phospholipase A_2



[1] Adapted from Tabas I et al. *Circulation*. 2007;116(16):1832–1844.
[2] Adapted from Khalil MF et al. *Arterioscler Thromb Vasc Biol*. 2004;24(12):2211–2218.

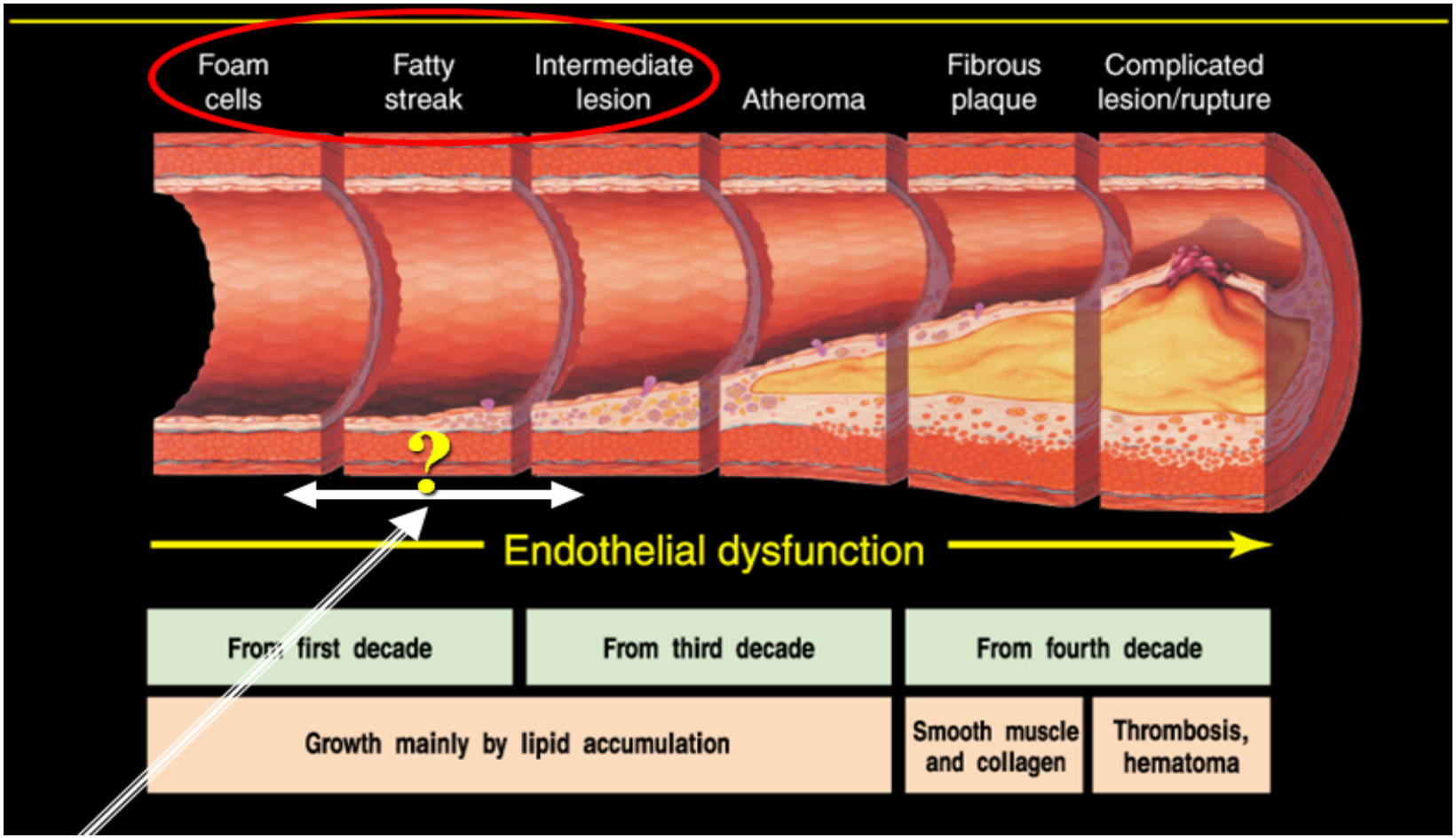
Cardiovascular Risk Increases With Increased Plasma Apo B Lipoproteins

Rationale for therapeutic lowering of Lp B: to decrease the inflammatory response to retention



Adapted from Tabas I, et al. *Circulation.* 2007;116(16):1832–1844.
Williams KJ ,et al. *Arterioscler Thromb Vasc Biol.* 1995;15(5):551–561.
Williams KJ, et al. *Arterioscler Thromb Vasc Biol.* 2005;25(8):1536–1540.
Hoshiga M, et al. *Circ Res.* 1995;77(6):1129–1135.
Merrilees MJ, et al. *J Vasc Res.* 1993;30(5):293–302.
Nakata A ,et al. *Circulation.*1996;94(11):2778–2786.
Steinberg D et, al. *N Engl J Med.* 1989;320(14):915–924.

Atherosclerosis Timeline - *Early Lesions*



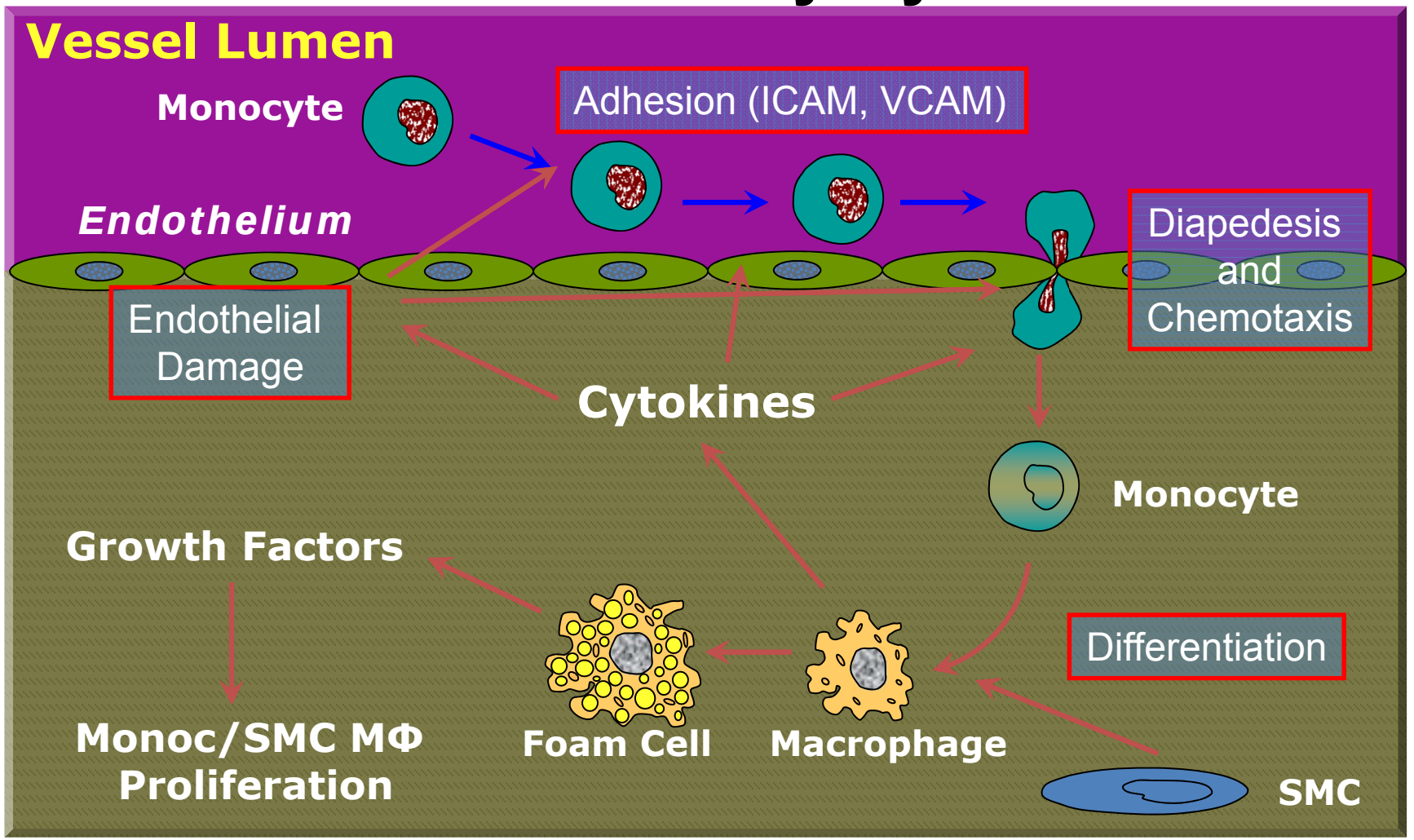
***Not* clear *what* determines *progression* vs. *regression* from fatty streak -Potentially reversible in utero**

Adapted from Pepine CJ. *Am J Cardiol*. 1998; 82(suppl.10A):23S-27S.

Middle Stages of Atherogenesis

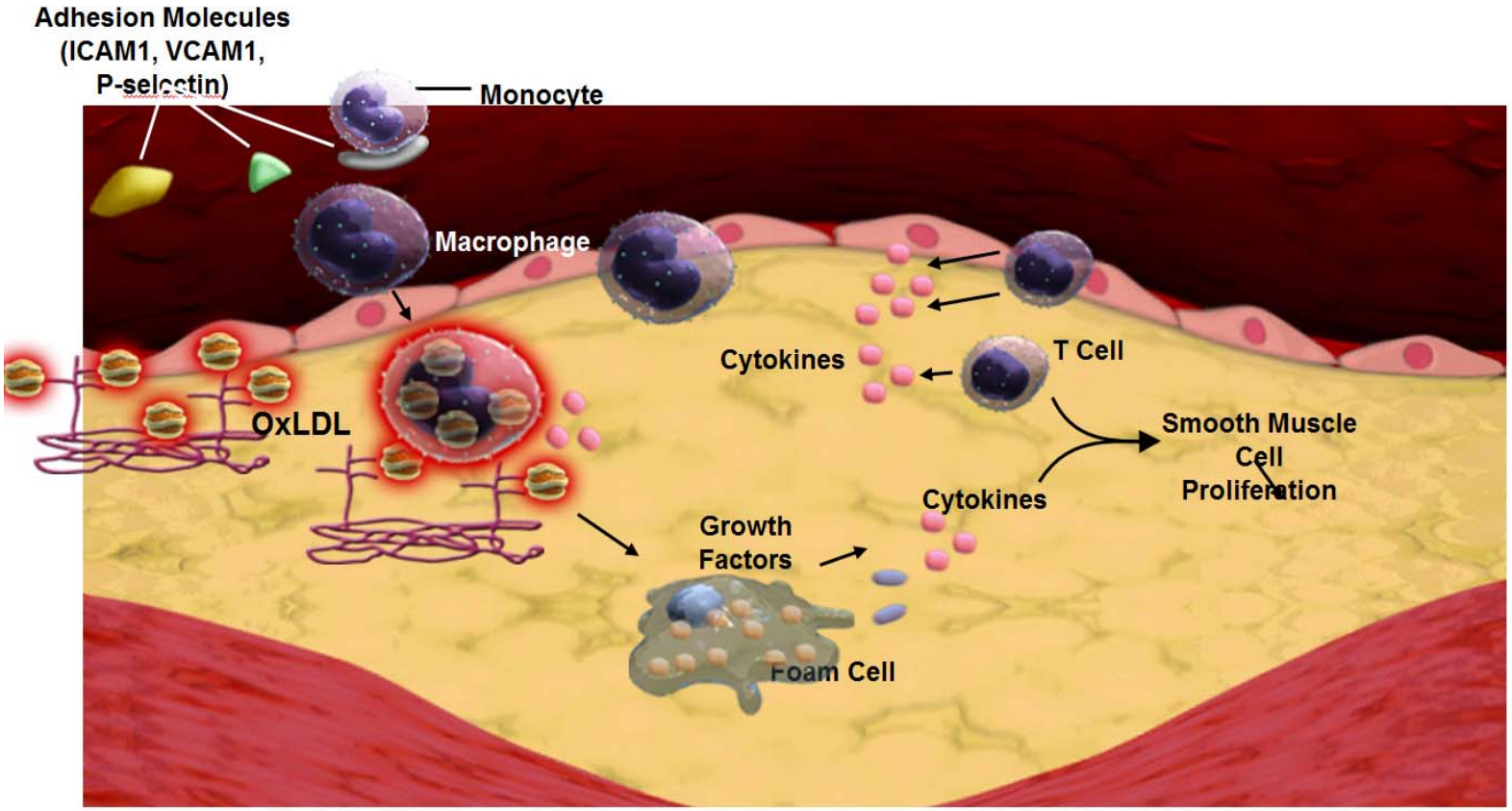
- Lipid-laden macrophages = foam cells
- Foam cells undergo apoptosis
- Foam cell apoptosis triggers:
  - ↑Macrophage recruitment
    - Monocyte adhesion and diapedesis thru endothelium
    - SMC chemotaxis and transformation
  - ↑Inflammation ↔ ↑Oxidation
  - ↑Lp B (=all Non-HDL) retention
  - ↑Lp B modification (various enzymes)
  - ↑Macrophage Lp B ingestion → foam cell
  - *More* foam cell apoptosis

Atherosclerosis: A Self-Feeding Inflammatory Cycle



Adapted from Ross R. *N Engl J Med* 1999;340:115-126.

Inflammatory Response to Atherogenic Lipoproteins



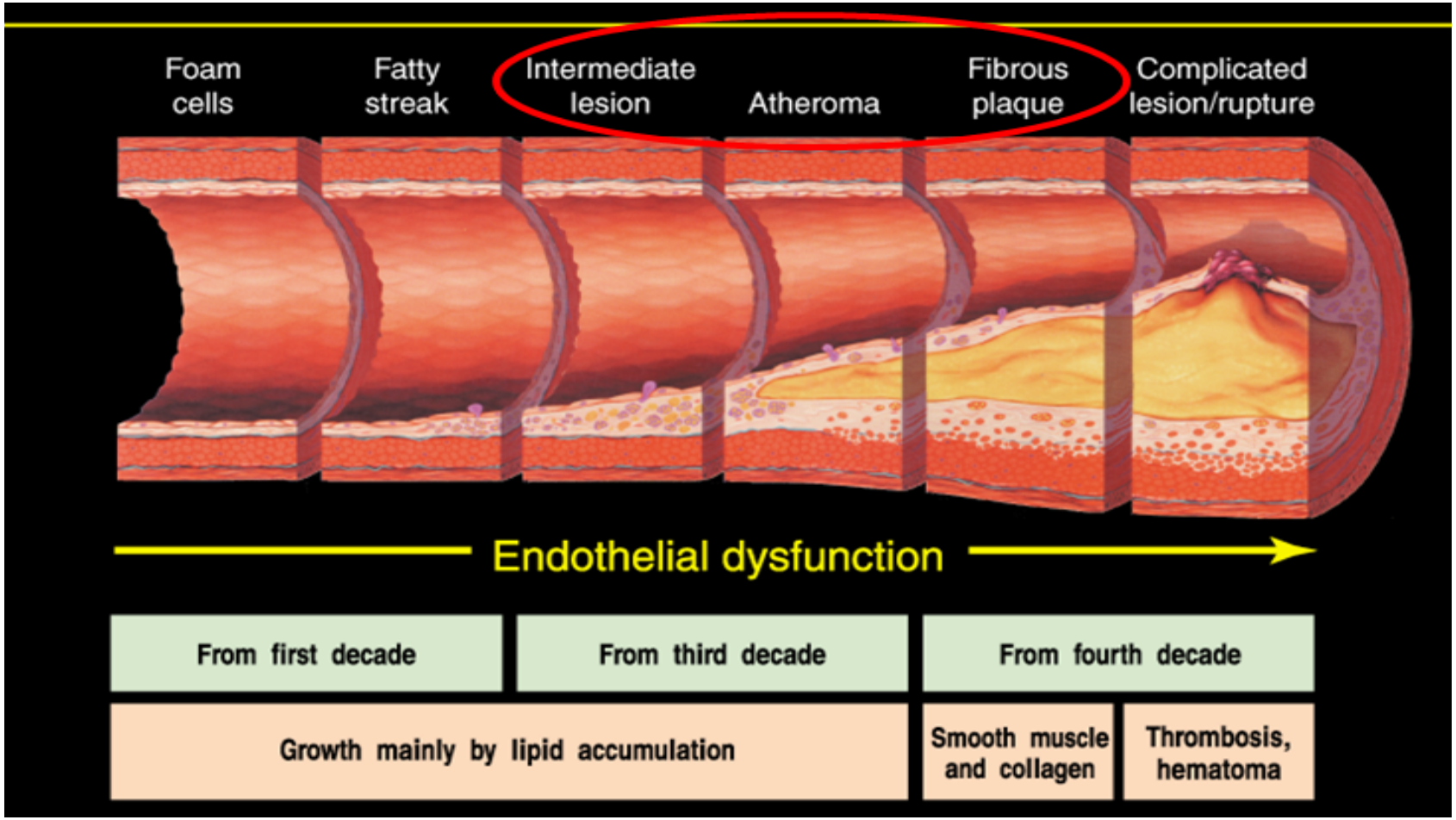
ICAM1 = intercellular adhesion molecule 1; oxLDL = oxidized low-density lipoprotein; VCAM1 = vascular cell adhesion molecule 1.

Sherer Y, et al. *Nat Clin Pract Rheumatol*. 2006;2(2):99–106.

Middle-Late Atherosclerosis: Complex and Vulnerable Plaques

- Inflamed/apoptotic macrophages secrete matrix metalloproteases (MMP-9, etc)
- MMP effects:
  - Outward: remodeling of adventitia → vessel enlargement
  - Inward: erosion of collagen and elastin → thinning and weakening of the fibrous cap (plaque instability)

Atherosclerosis Timeline -*Middle Lesions*



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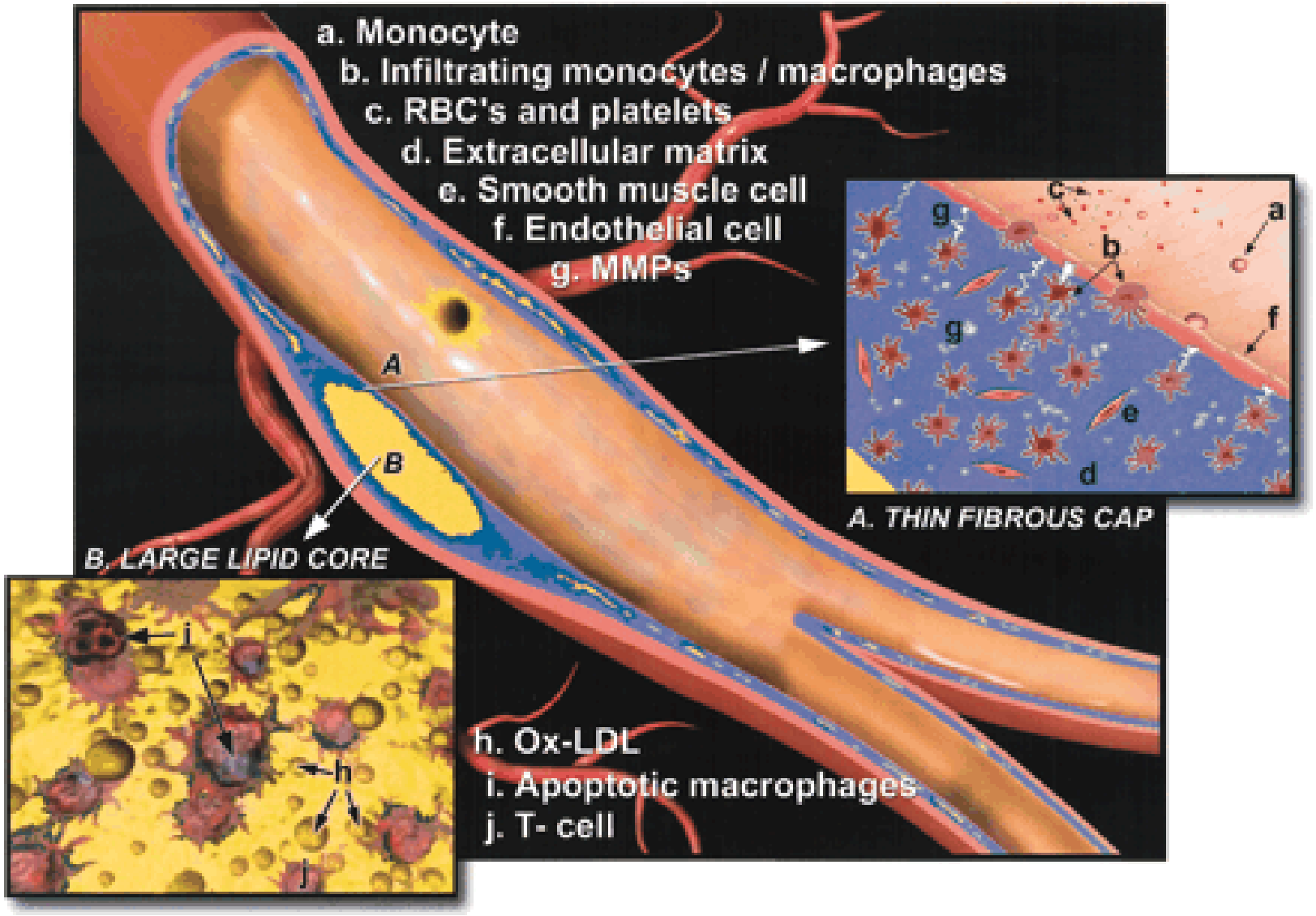
Arterial Remodeling



Naghavi, M, et al. *Circulation* 2003;108:1664-1672.

Late-Stage Atherosclerosis: Plaque Rupture and Acute Vascular Events

- Plaque rupture* due to
  - Matrix metalloproteases (MMP-9, etc)
  - Other inflammatory processes
  - Angiogenesis/neovascularization *within* the plaque
  - Mechanical effects
- Intra-arterial thrombosis:
  - Exposure of highly prothrombotic material (SE matrix, inflammation, etc.)
  - Pro-thrombotic state (plt. activation, increased soluble coag. factors)
- Acute ischemic event (MI, USA, CVA, sudden death, critical limb ischemia)

*Endothelial *erosion* may cause thrombosis w/o prior rupture, but these are *mural* thrombi, which are less likely to cause an acute CV event.

Unstable vs. Stable Plaque

*Un*stable Plaque

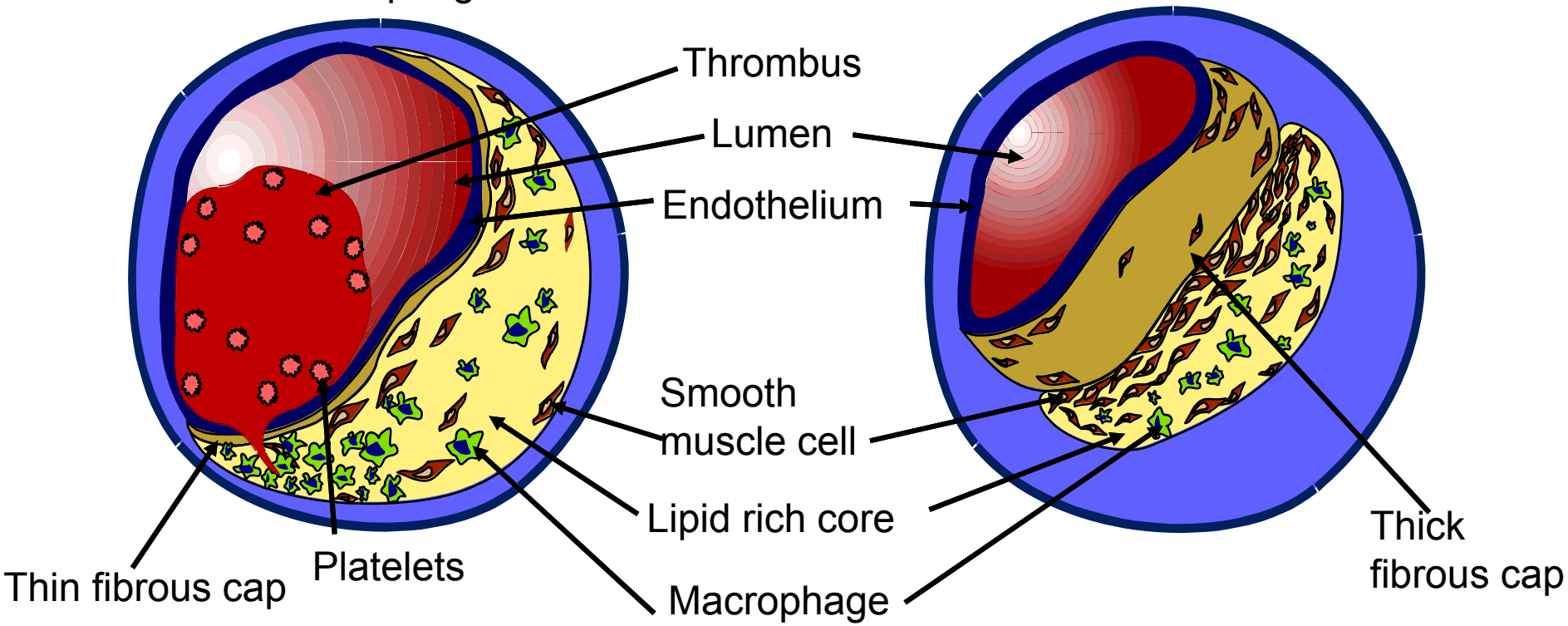
86% of Fatal MIs:
< 70% prior stenosis

- Large lipid core
- Thin fibrous cap,
- ++macrophages

Stable Plaque

14% of Fatal MIs:
> 70% prior stenosis

- Small lipid core
- Thick fibrous cap,
- ++SMCs



Adapted from Libby P. *Circulation* 1995;91:2844-50. Falk, et al. *Circulation* 1995; 92:657–671.

Clinical Manifestations of Different Types of Coronary Atherosclerosis

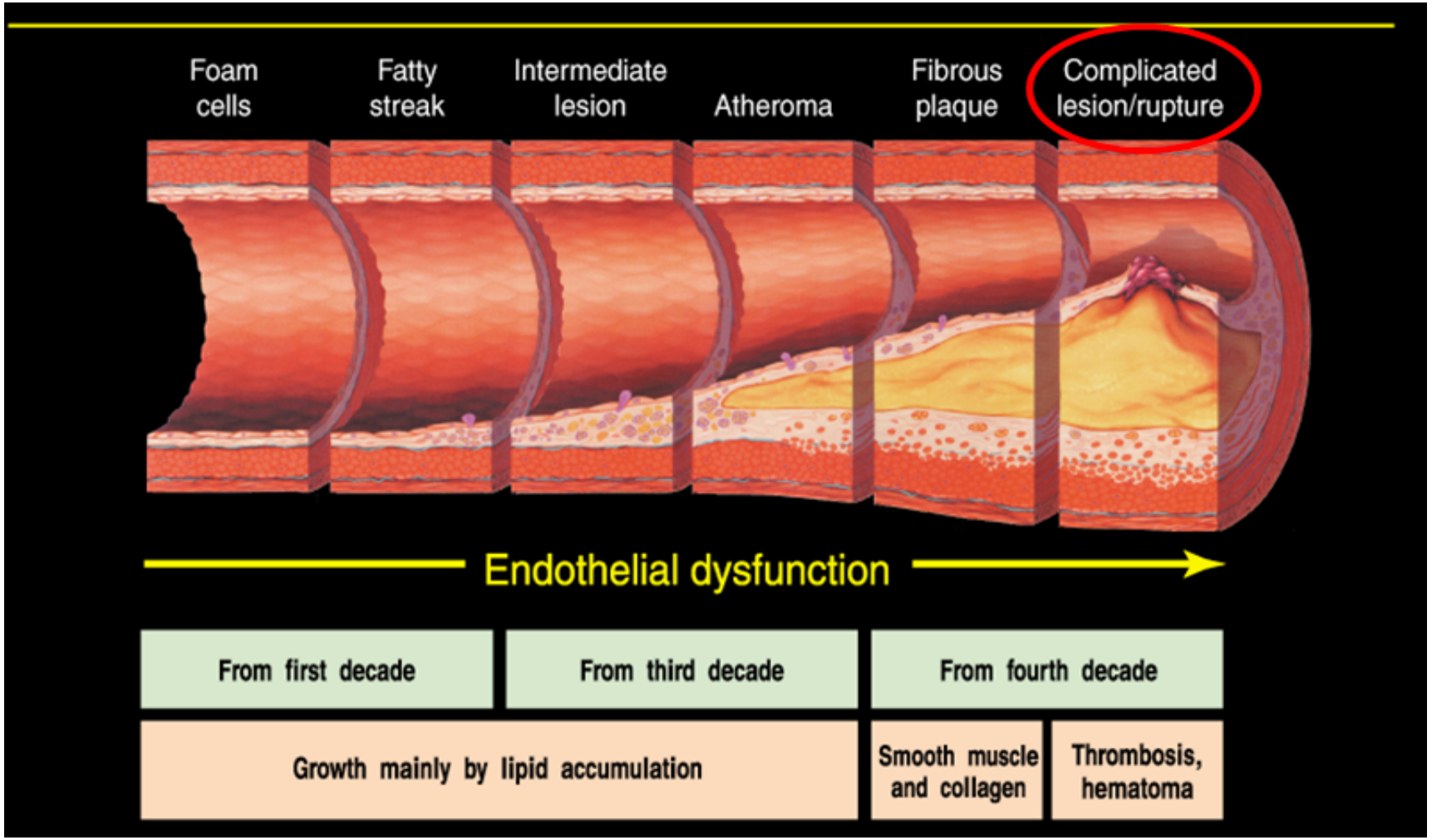
Fixed stenosis → **Stable angina**

***Gradual* Progression—Less common**

Plaque rupture → **Unstable angina**
Myocardial infarction
Sudden Death

***Rapid* Progression—More Common**

Atherosclerosis timeline *Late Lesions*



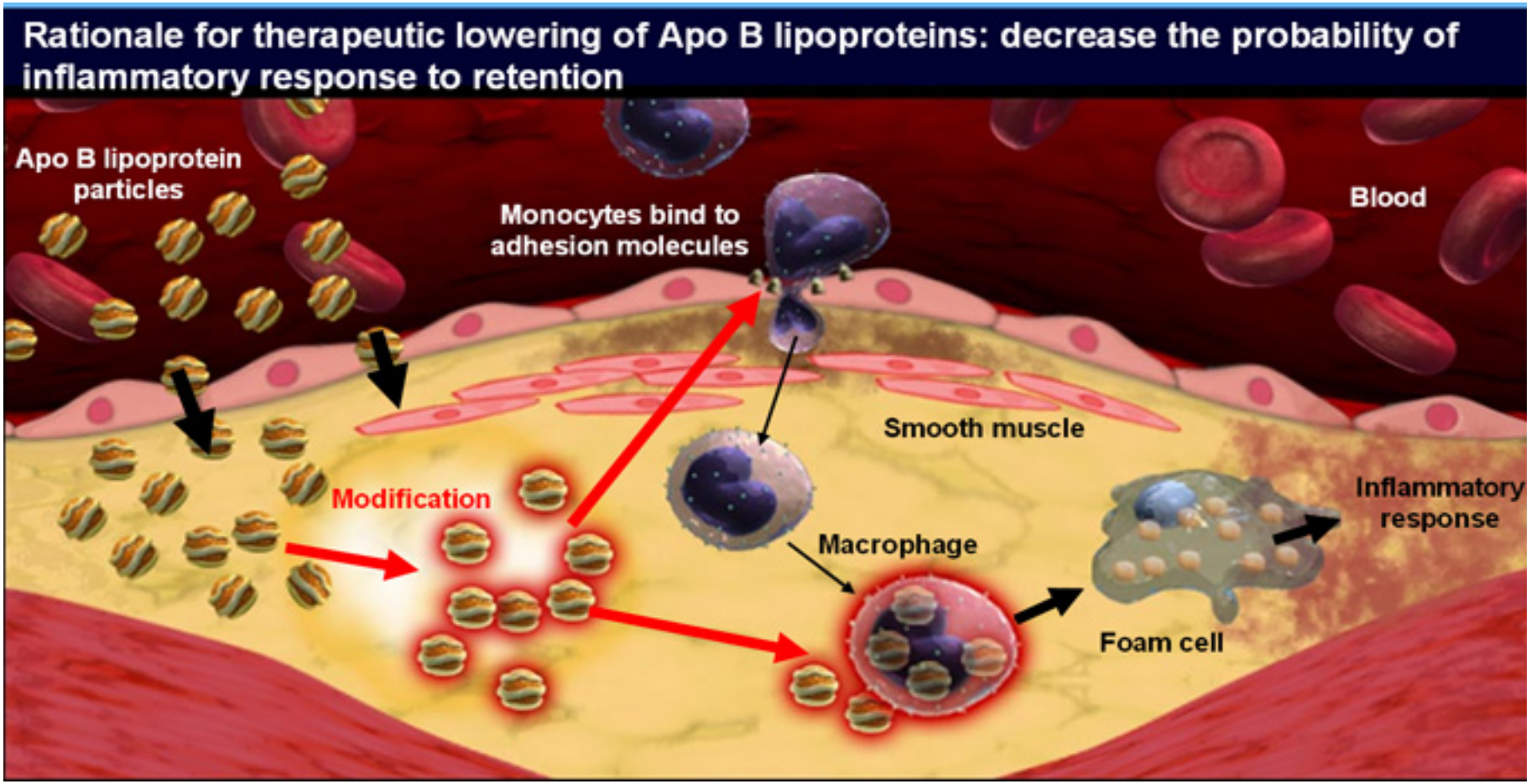
Up to 90% of AMI may be due to plaque rupture; *AmHeartJ* 1977;93:468.

Adapted from Pepine CJ. *Am J Cardiol*. 1998; 82(suppl.10A):23S-27S.

Regression of Atherosclerosis

- "Holy Grail" of atheroprevention (!?)
  - Plaque regression="Nirvana"
  - Debates over "magic threshold" of LDL-C, non-HDL-C, HDL-C, CRP, etc.
- *Not* very useful if looking only at plaque thickness/size
  - *Stability* more important than *size*
  - Events can *still* occur with *little or no stenosis*
  - Events may be *avoided* just by *stopping progression* or ↓ *growth*
- Regression is a reasonable goal, but may be *neither* necessary *nor* sufficient to prevent CVD events

How Decreasing Plasma Lp B Levels Can Decrease Atherosclerosis and CV Risk



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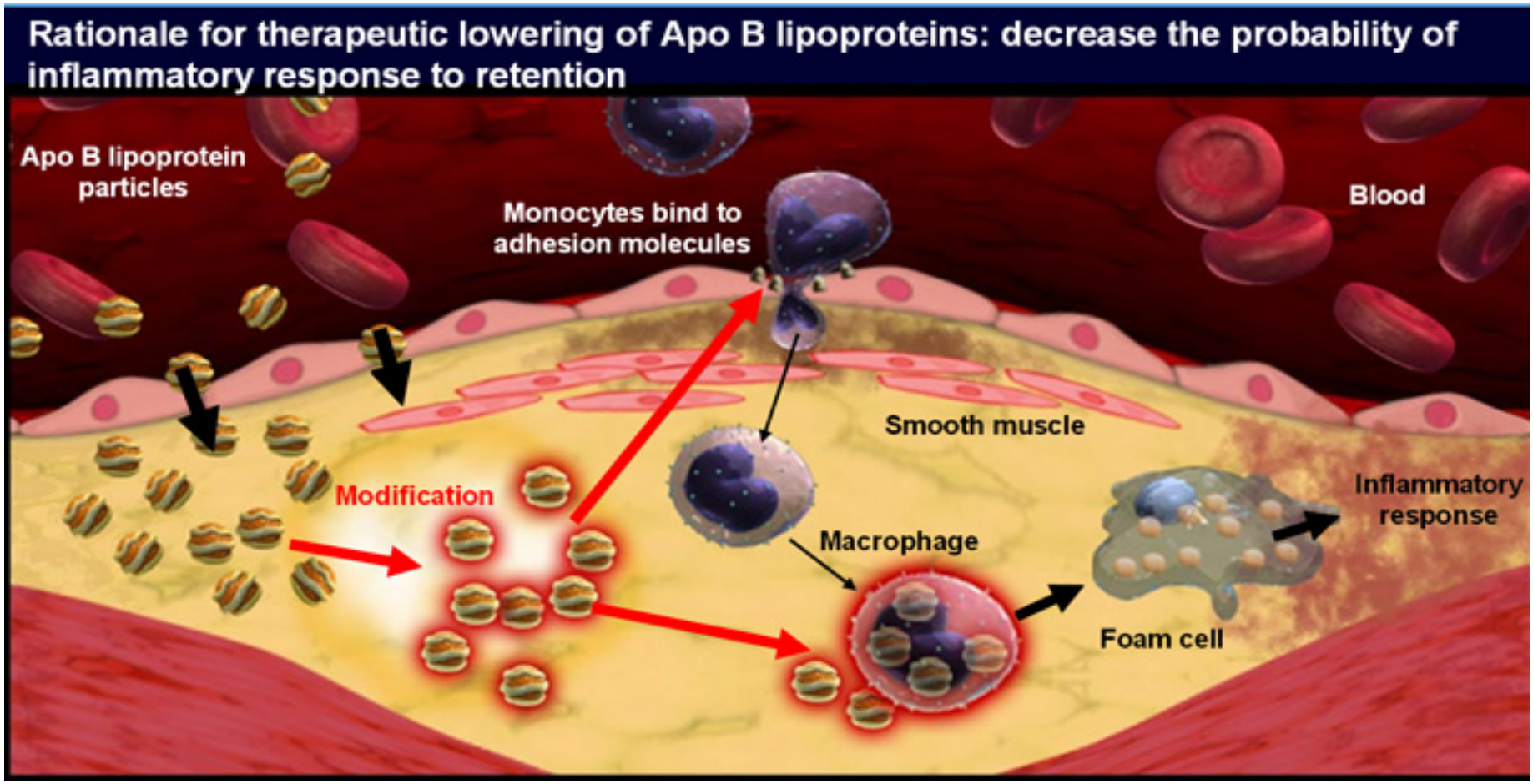

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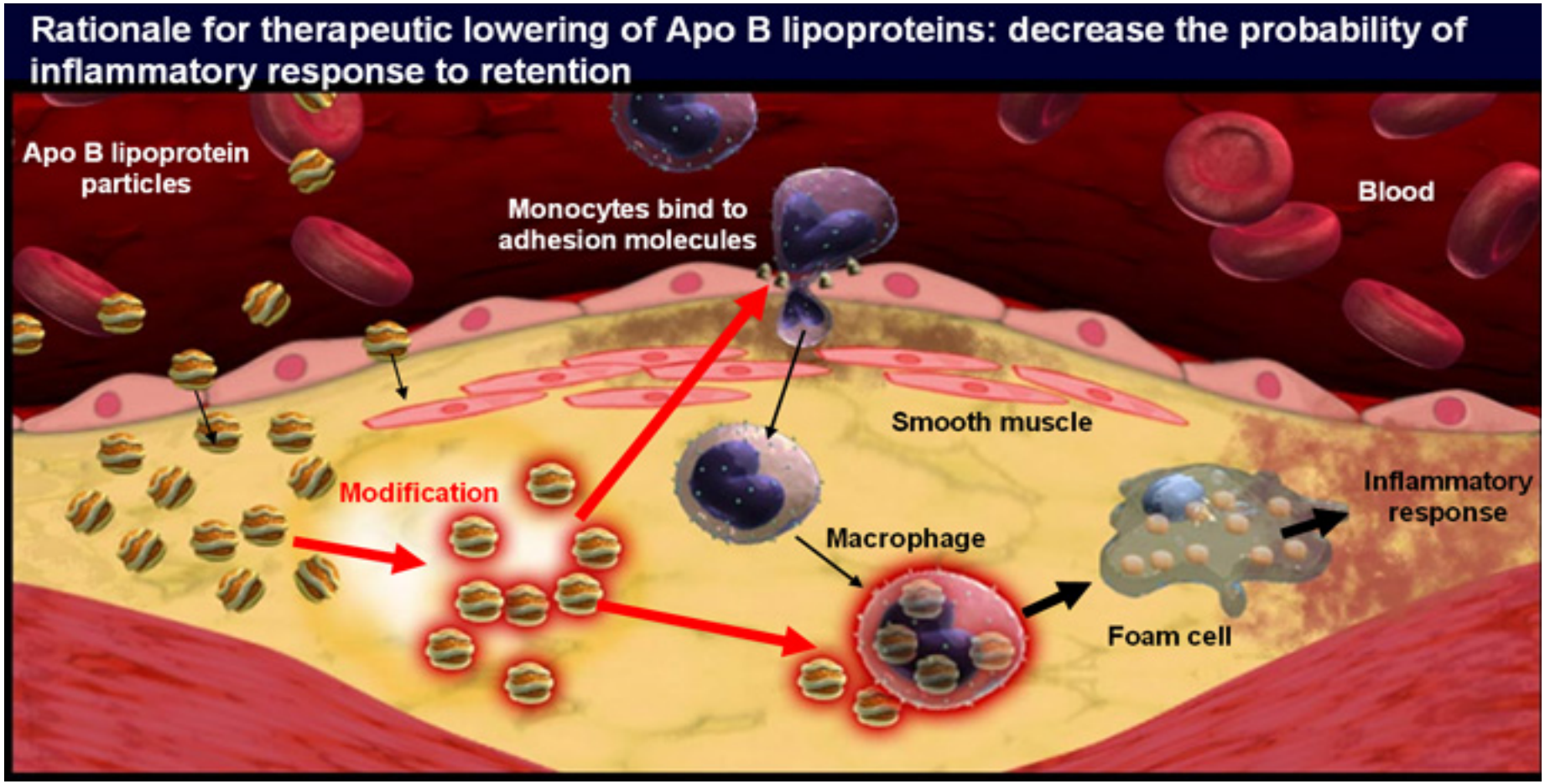

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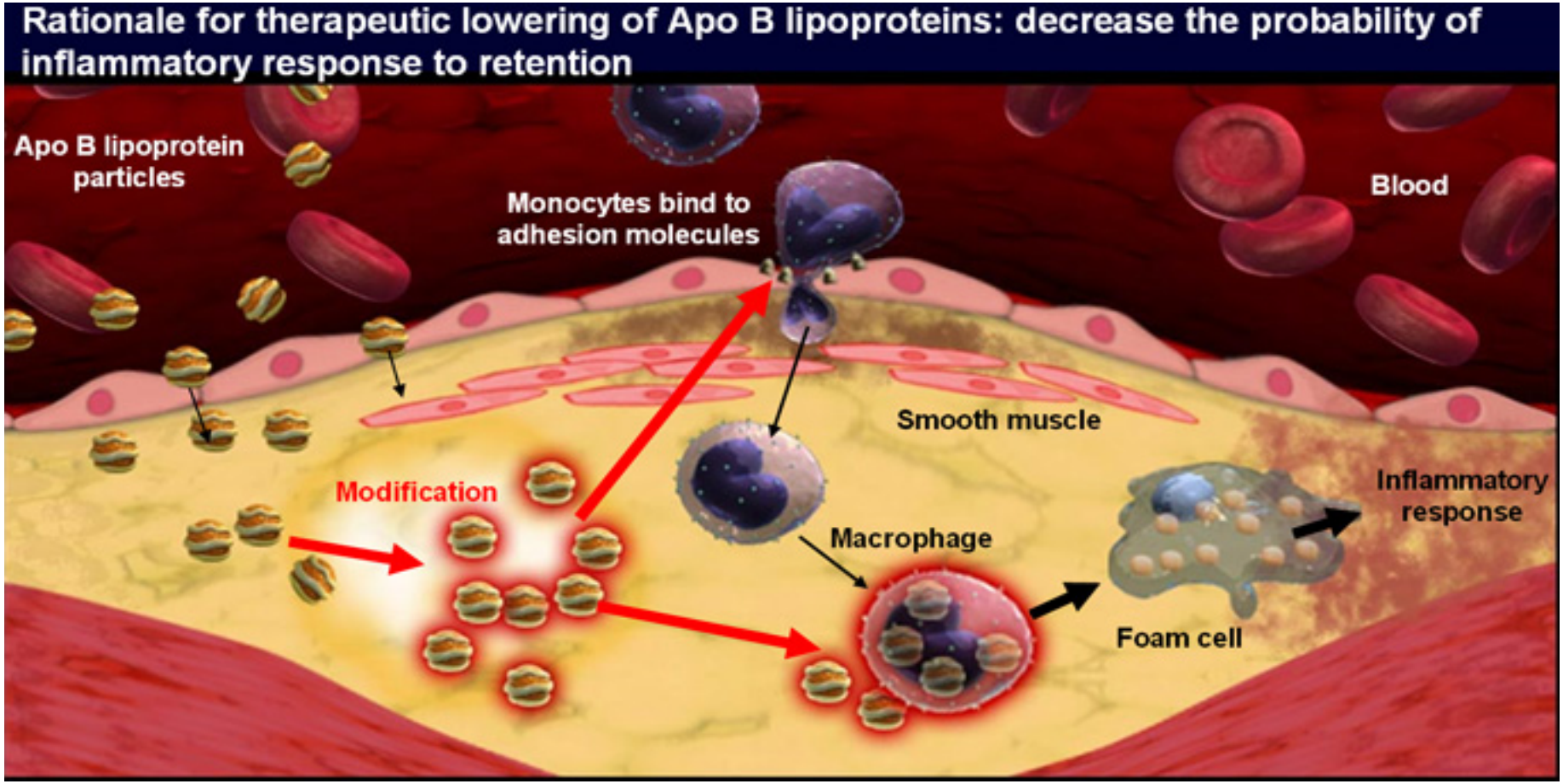

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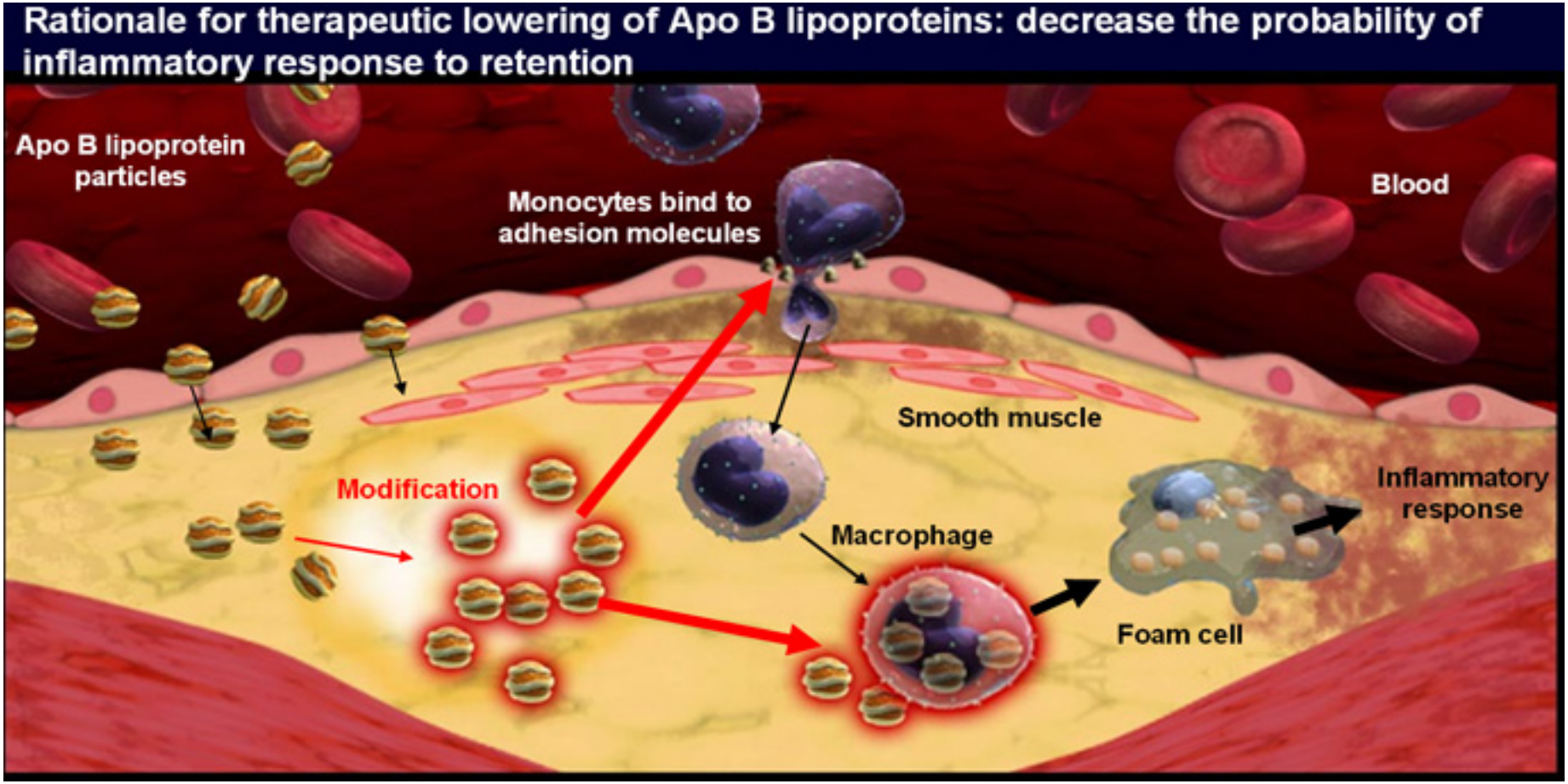

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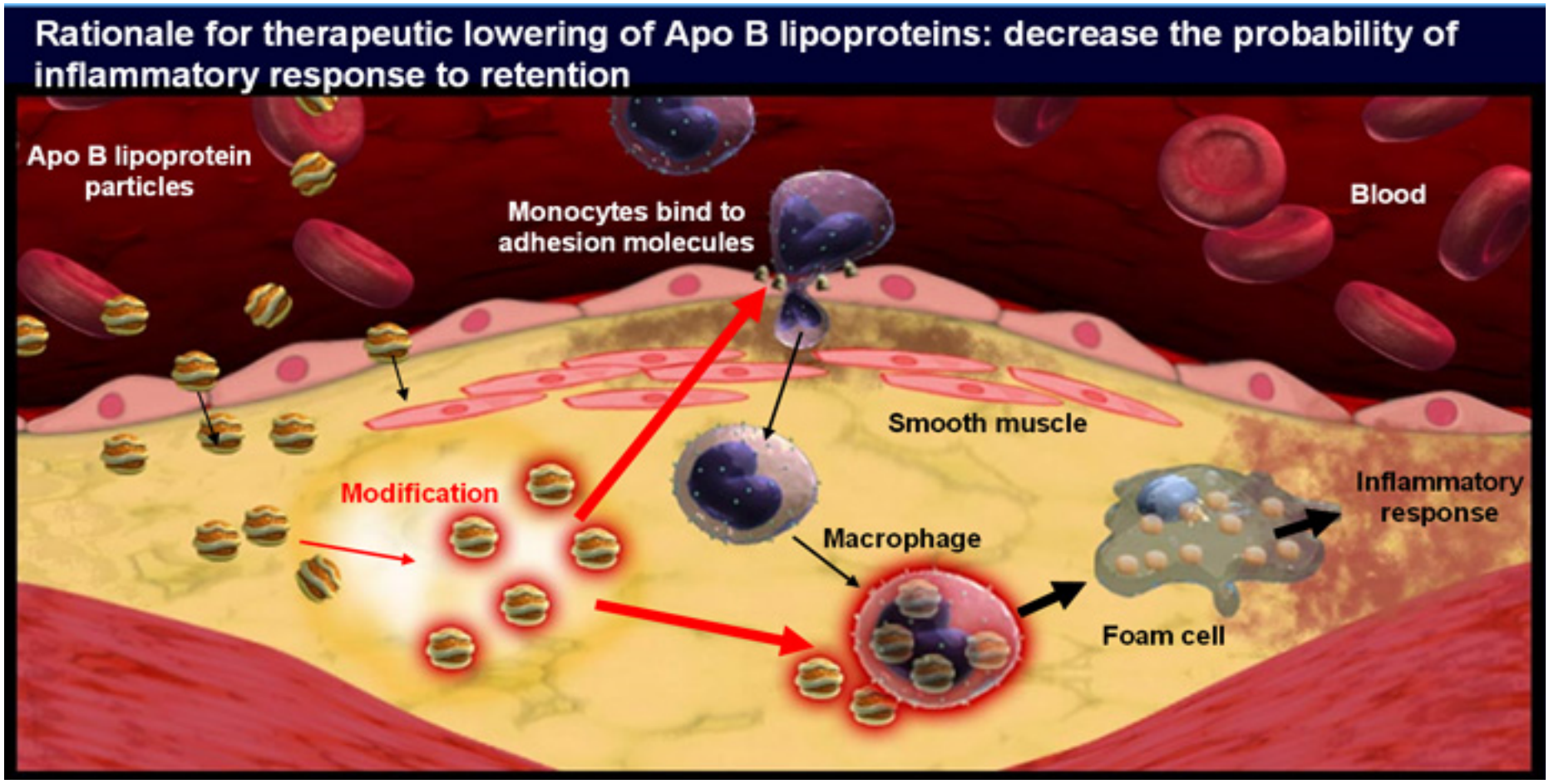

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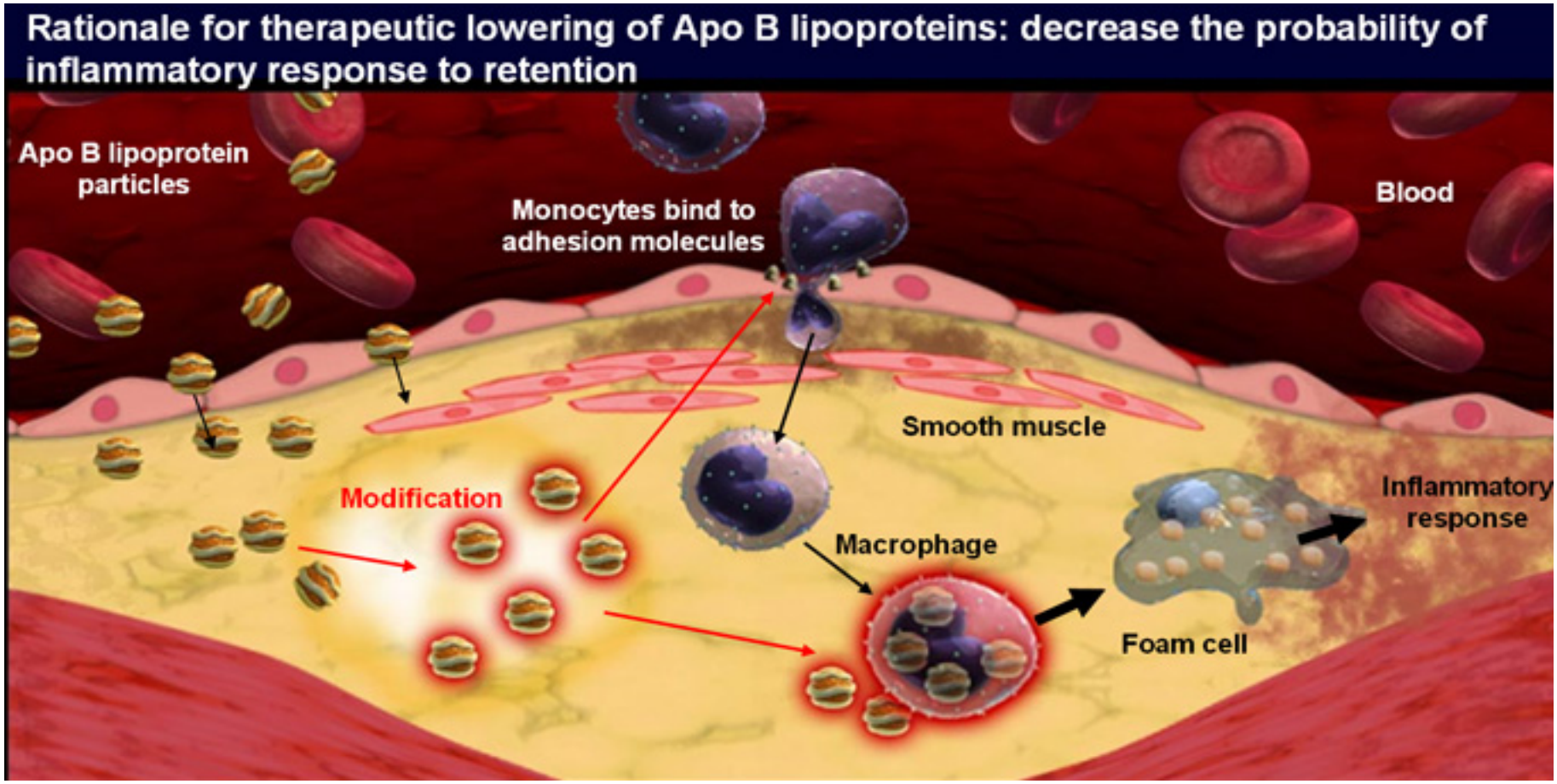

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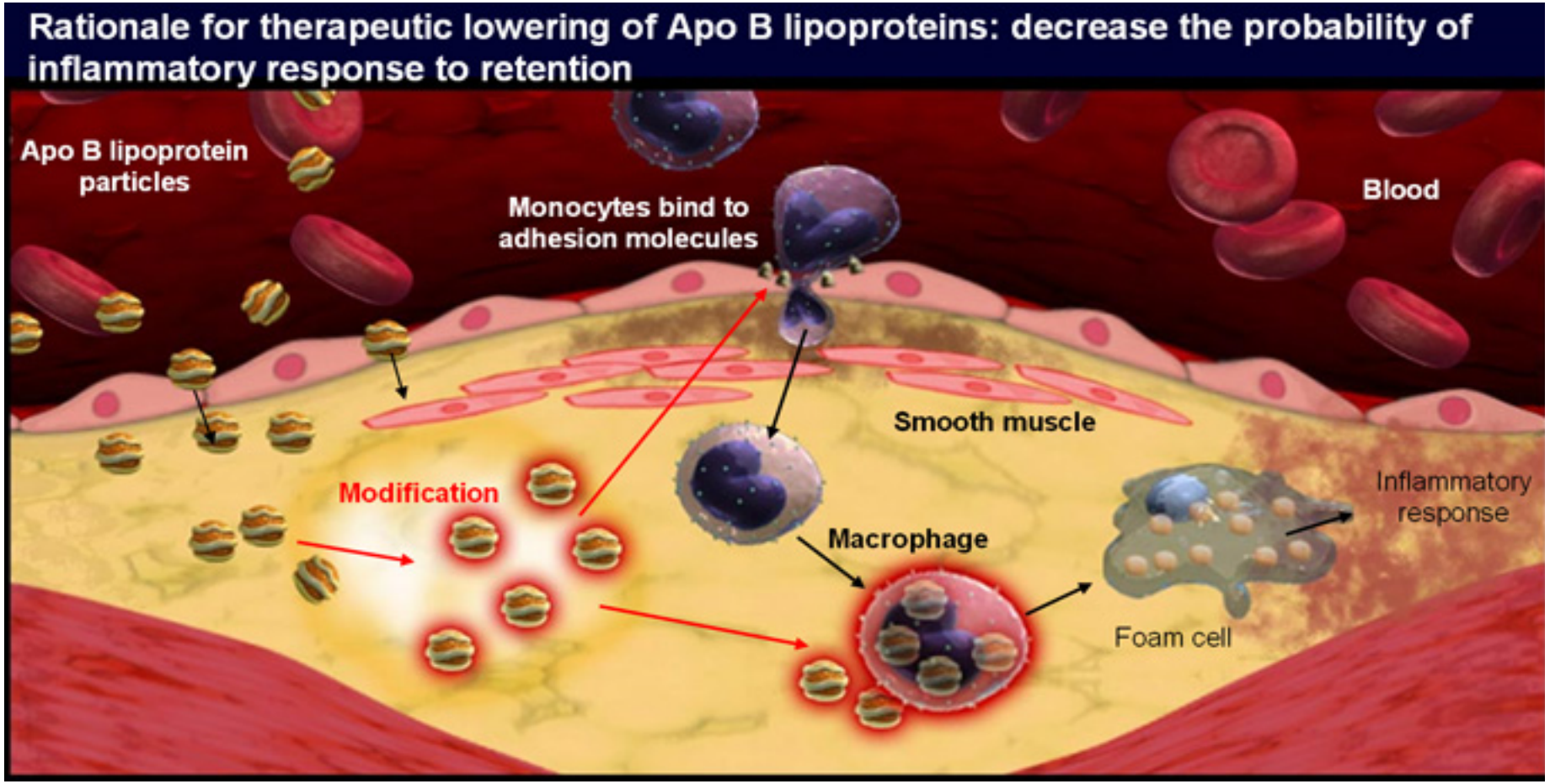

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Atherogenesis: Prevention/Regression

- ↓ **Plasma apo B lipoproteins (Lp B)** ***PLUS***
  ↓ focal endothelial trauma?
- ↓ Infiltration of Lp B into subendothelium (SE)
  PLUS increase LDL size
- ↓ Retention of Lp B in SE
- ↓ Modification of Lp B in SE
- ↓ Inflammation
- ***Prevention*** of plaque rupture
- ***Prevention*** of thrombosis
- ***No*** ↓↓ Blood flow
- ***No*** ischemic event

Summary: Pathophysiology of Atherosclerosis

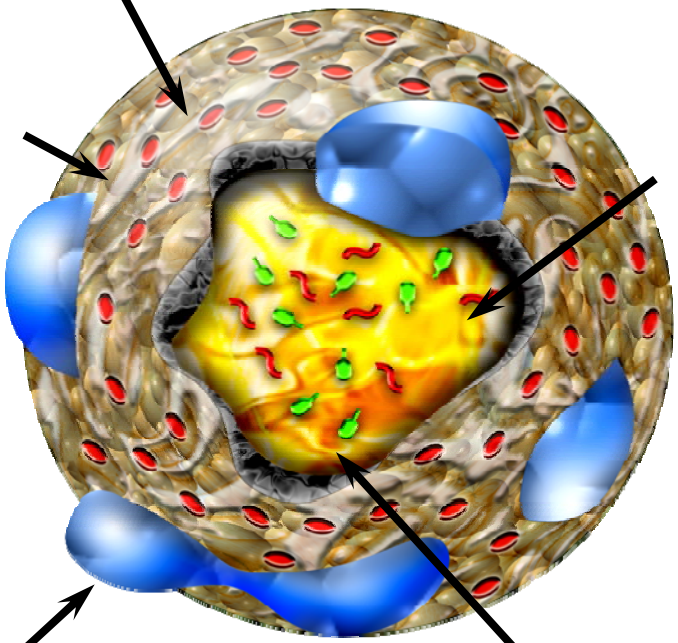
- Main elements are *all* interactive (multiple adverse feedback loops)
- Key areas of focus:
  - Apo B lipoproteins
  - Retention
  - Oxidation/modification
  - Inflammation
  - HDL to block/reverse above
- Stages:
  - Early—probably reversible
  - Middle—goal: regression vs. stabilization?
  - Late—main goal: stabilization of vulnerable plaques, prevention of new plaques

LIPID AND LIPOPROTEIN METABOLISM

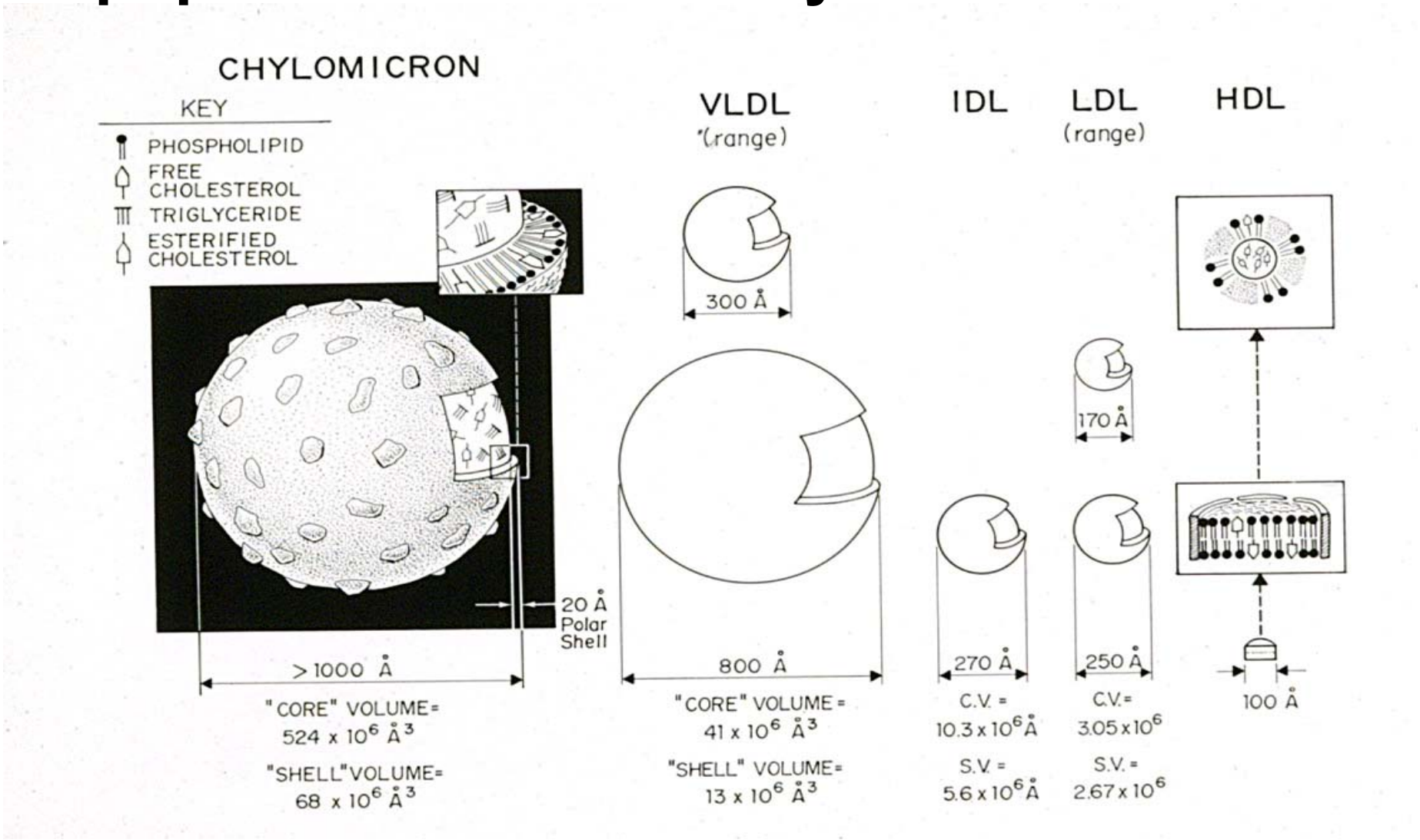
Why Lipoproteins?

- Oil and water *don't* mix
- *Lipids* (triglycerides, phospholipids, sterols) need vehicles (lipoproteins) to travel through *aqueous* media:
  - Lymph
  - Plasma
- Lipid transport (via lipoproteins) helps:
  - Absorb/distribute *dietary/intestinal* lipids
  - Re-distribute *endogenous* lipids
  - Energy use/storage—TG only
  - Cell structure—Chol, PL?
  - Cell function—Apo A-I, other?

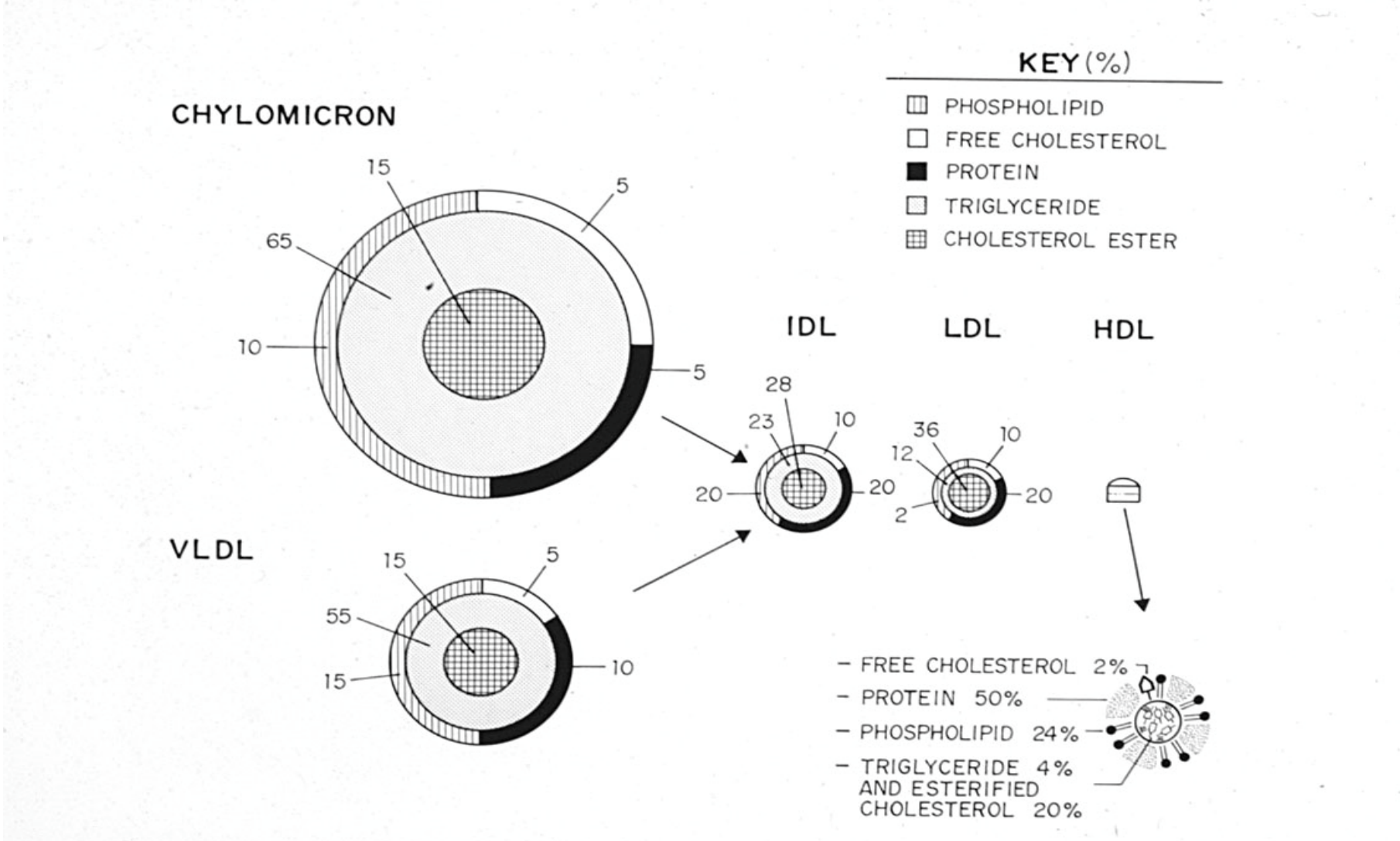
Structure of a Typical Lipoprotein



Lipoprotein Classes: Physical Dimensions



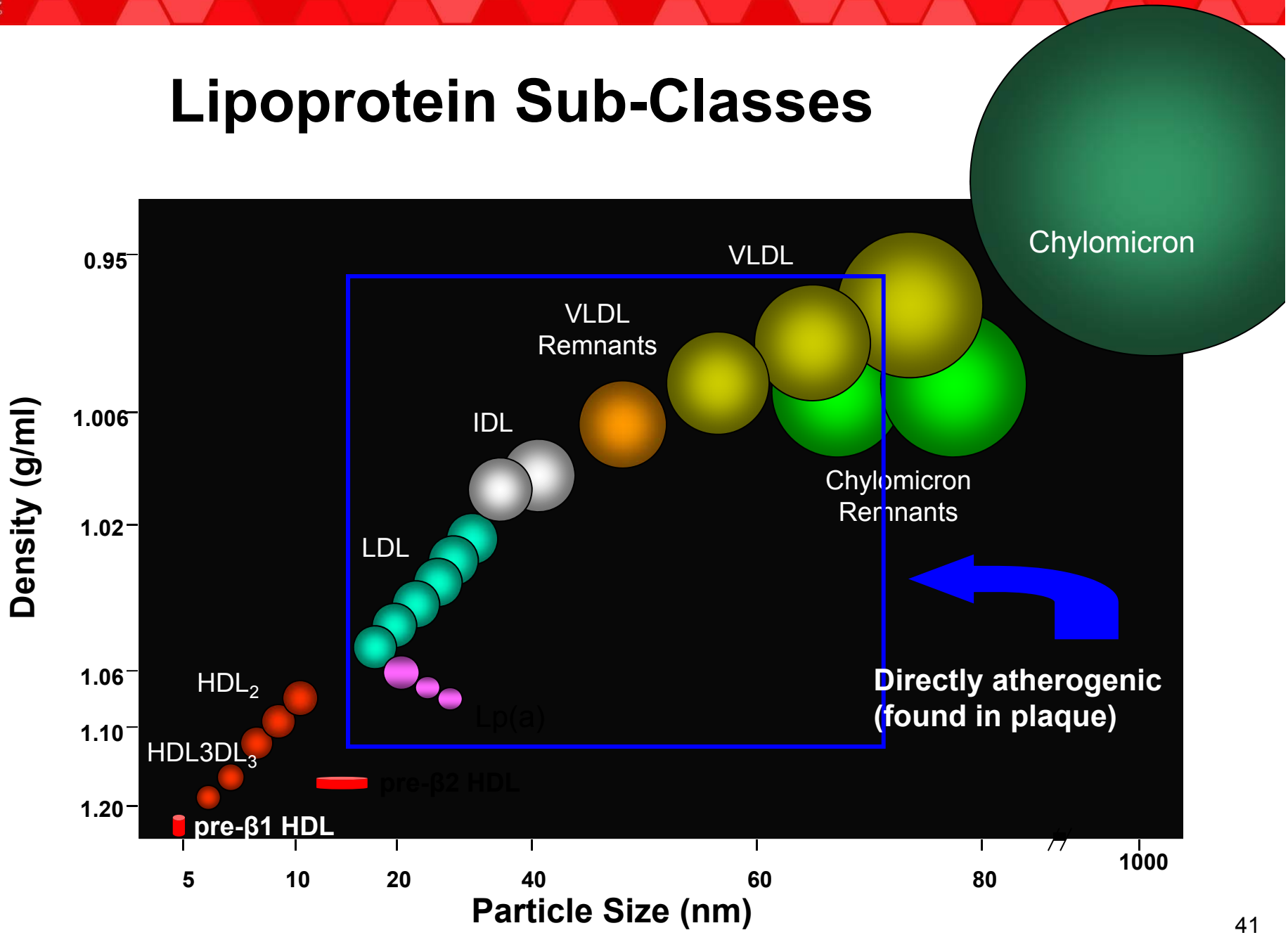
Lipoprotein Classes: Chemical Composition



Lipids

Lipid	Lipophil.	Function	Location in Lipoprotein	Prevalence
TG	+++	Energy	Core	Common
Free fatty acids	+++	Energy	*Not* in lipo; w/ albumin	Common
Chol-Ester	+++	Chol. storage	Core	Common
Free Chol	++	Membranes hormones	Inner shell + core	Common
Oxid Chol	+	Signaling?	Inner shell?	Rare
Plant Sterol	+	??	Inner shell?	Rare
Phospholipid	+++/-- (amphip)	Structure	Shell	common

Lipoprotein Sub-Classes



Major Apolipoproteins

Apo	Location	Function	Plasma Levels	Athero
A-I	HDL (Chyl)	Multi anti-athero	High	↓ ↓ ↓
A-II	HDL	??	Moderate	↓ ?
B-48	Chyl	Exog. TG & Ch transp	Moderate (post-prandial only)	↑ ?
B-100	VLDL, LDL	Deliver endog. cholesterol	High	↑ ↑ ↑
C-II	VLDL, HDL	↑ LPL activity	Low	↓
C-III	VLDL, HDL	↓ LPL, plq rupt?	Low	↑ ↑
E	VLDL, HDL	Remn Lp Catab, Chol Efflux?	Low	↑ ↑ ↑ / ↓ ?
(a)	Lp(a)	Ox FFA scaveng	Low	↑ ↑ ↑

Apo B-100 and Apo A-I are most important clinically, but all are important.

Lipoprotein Composition and Function

Lipoprotein	Apolipoproteins	Function
Chylomicrons, Chylo-remnants	B-48 (A-I, C-II, C-III, and E)	Delivers TG & Chol (intestinal or exog. path)
VLDL, IDL	B-100 (C-II, C-III, E)	Delivers TG & Chol (endogenous path)
LDL	B-100	Delivers Chol (endogenous path)
Lp(a)	B-100, apo (a)	Delivers Chol (endogenous path)
HDL	A-I, A-II (C-II, C-III, E)	Steroid horm. synth. Anti-infect, Anti-athero

It is important to know all of these major lipoprotein fractions.

Fredrickson Hyperlipidemia Classification *Plus 2*

Type	Lipoprotein in excess	Frequency	Athero	T Chol (mg/dL)	TG (mg/dL)
I	Chylomicrons	v. rare	sl ↑?	~1/6 TG	>1000
IIa	**LDL**	**common**	**↑ to ↑↑↑**	**>200**	**<150**
IIb	**LDL, VLDL**	**common**	**↑ to ↑↑↑**	**>200**	**200-500**
III	βVLDL, IDL	rare	↑↑↑	200-500	200-500
IV	**VLDL**	**common**	**↑ to ↑↑**	**<200**	**200-500**
V	VLDL, Chylo	*un*common	↑ to ↑↑	~1/4 of TG	>500
---	**Lp(a)**	*un*common	**↑ to ↑↑↑**	**nl**	**nl**
---	***Low* HDL**	**common**	**↑ to ↑↑↑**	**↓ to ↑**	**>200**

All are worth remembering, but focus most on the common ones.

Dyslipidemia and Disease

A. Pancreatitis—(↑↑↑TG + non-lipid causes *only*)

1. ↑↑↑plasma TG + sl. leak of pancreatic lipase →
2. Lipolysis →
3. ↑↑↑FFA →
4. Damage to pancreatic exocrine cells →
5. Further leak of pancreatic lipase →
6. Further lipolysis = vicious cycle

B. Atherosclerosis (#1 cause of death and disability)—*most* dyslipidemias are causal (adverse)

Major Lipid/Lipoprotein Modifying Factors

Name	Class	Function	Location
CETP	*Shuttle*	*CE for TG*	*Plasma*
PLTP	Shuttle	PL transfer (HDL recombin.)	Plasma
LPL	*Lipase*	*TG lipol. (Chyl, VLDL, IDL)*	*Vascular endothelium*
HL	*Lipase*	*TG&PL hydrol (LDL, HDL)*	*Hepatic endothelium*
EL	Lipase	Like HL?	Vascular endothelium
LpPLA2	Lipase	Cleaves Ox PL	LDL, HDL
LCAT	*Esterifier*	*Chol ester.*	*HDL*

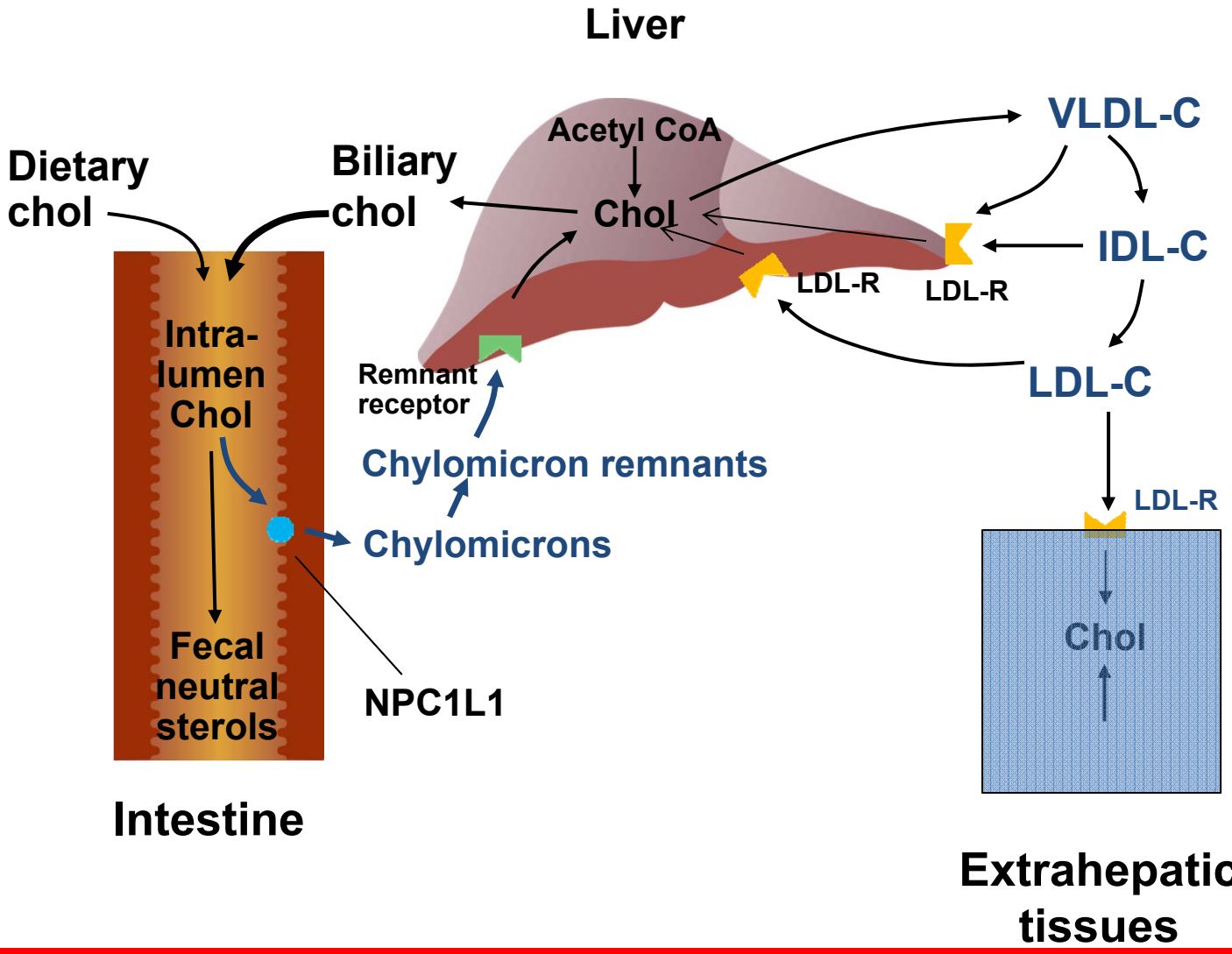
Focus on CETP, LPL, HL and LCAT only. Others are FYI.

Cell-Surface/Intracellular Lipid/Lipoprotein Factors

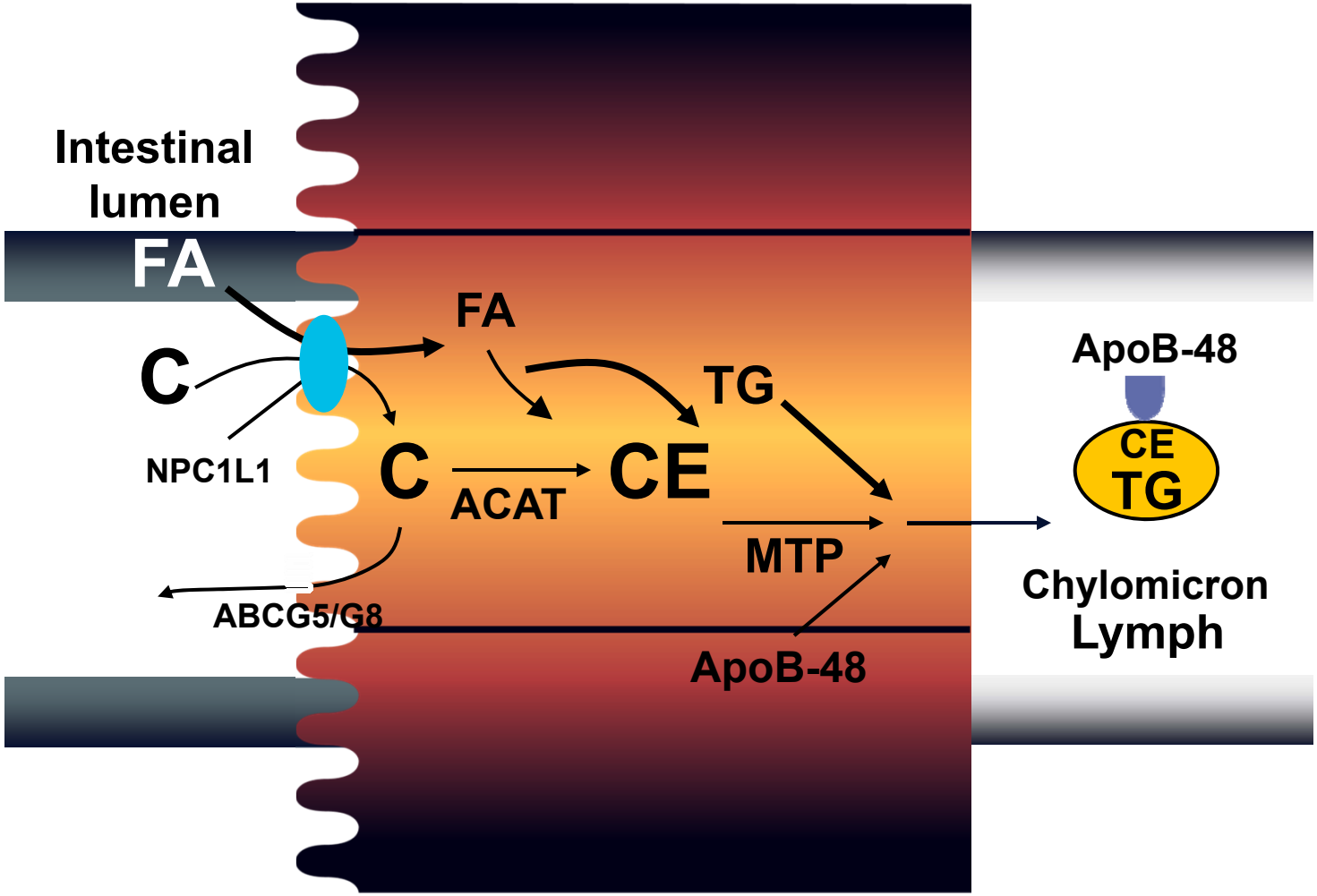
Name	Class	Function	Location
NPC1L1	Sterol transporter	Sterols into Enterocyte	Enterocyte
ABCG5/8	Sterol transporter	Plant Sterol out of enterocyte	Enterocyte
ACAT	Esterifier	FC to CE (C storage)	Intracellular
CEH	CE Hydrolase	CE to FC (C release)	Intracellular
ABCA1	Chol. Efflux	Chol to lipid poor Apo A-I particle	Cell surface
ABCG1	Chol. Efflux	Chol efflux to spherical HDL, etc.	Cell surface
SR-B1	Chol. Influx	Accepts chol from HDL (also donor?)	Cell surface
HSL	Lipase	Hydrolyze TG (rel. from adipocytes)	Intracellular (adipocytes)
PCSK9	LDL-R Chaperone protein	Targets LDL receptor for lysosomal degredation	Intra and extra-celluar

All are given FYI only: you do not need to memorize these!

Enterohepatic Cholesterol Transport (intestine to liver)

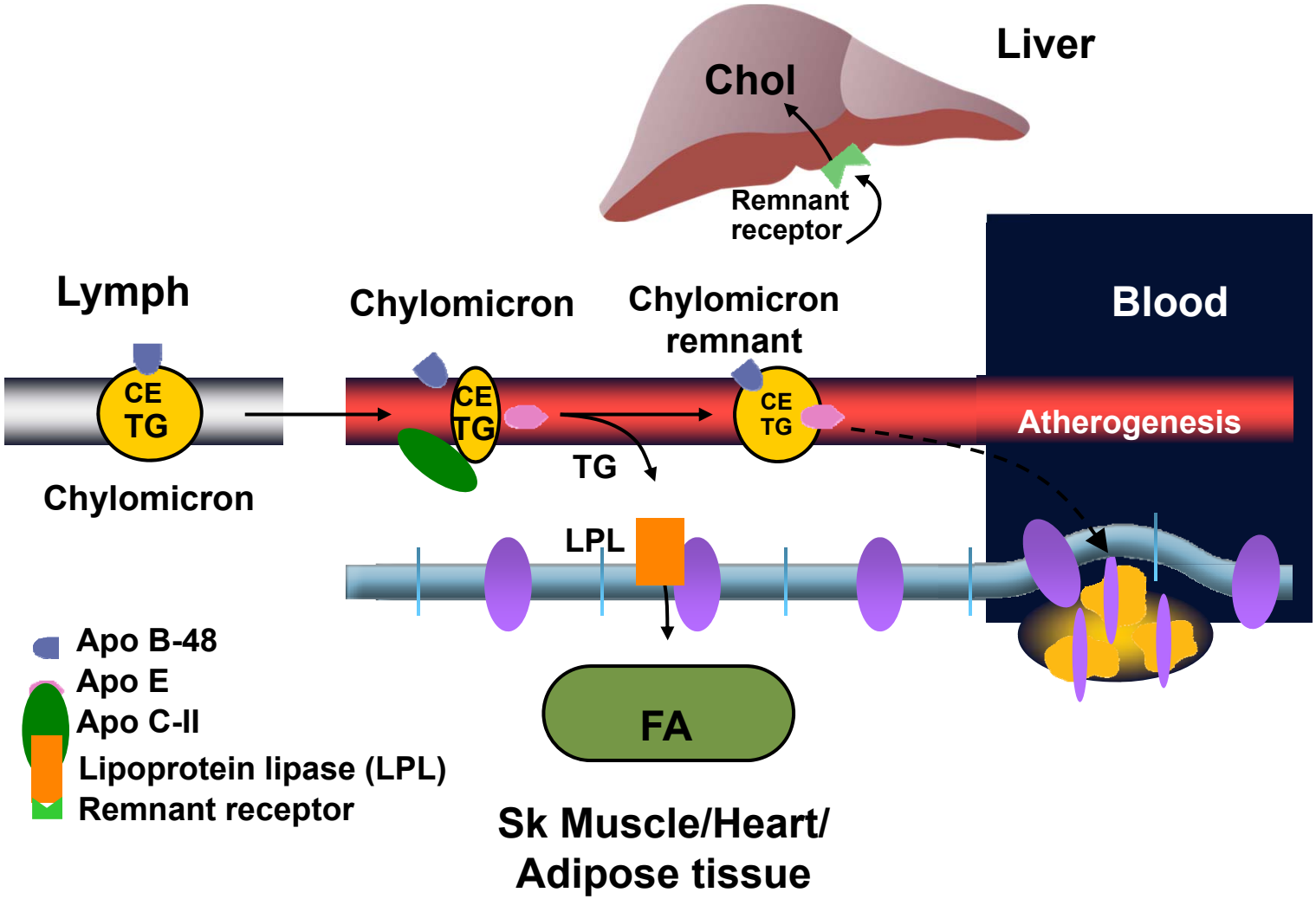


Enterocyte Transport of Luminal Cholesterol (diet + bile)

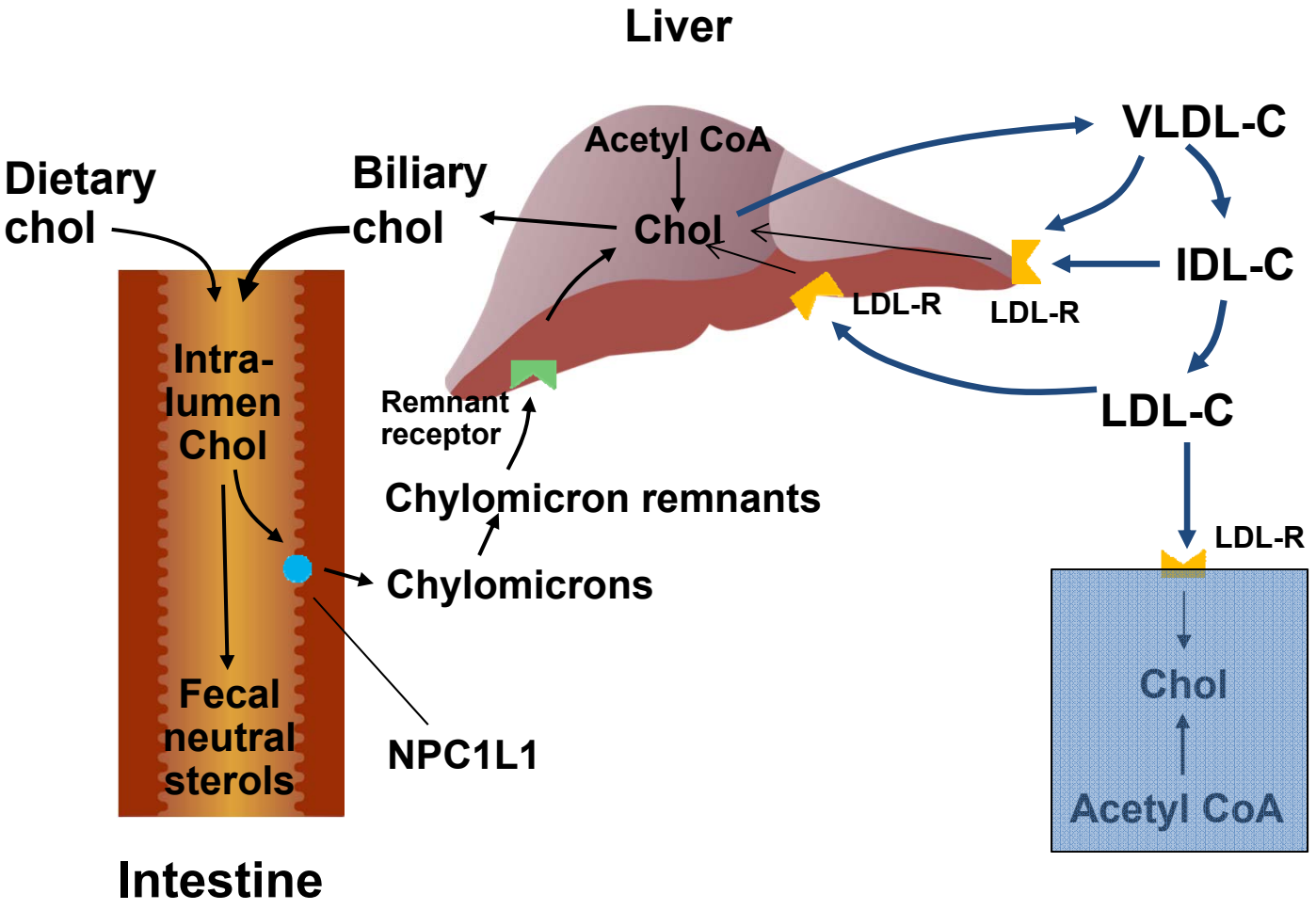


Plant sterol has same paths as cholesterol (C) but <u>much</u> less net absorption

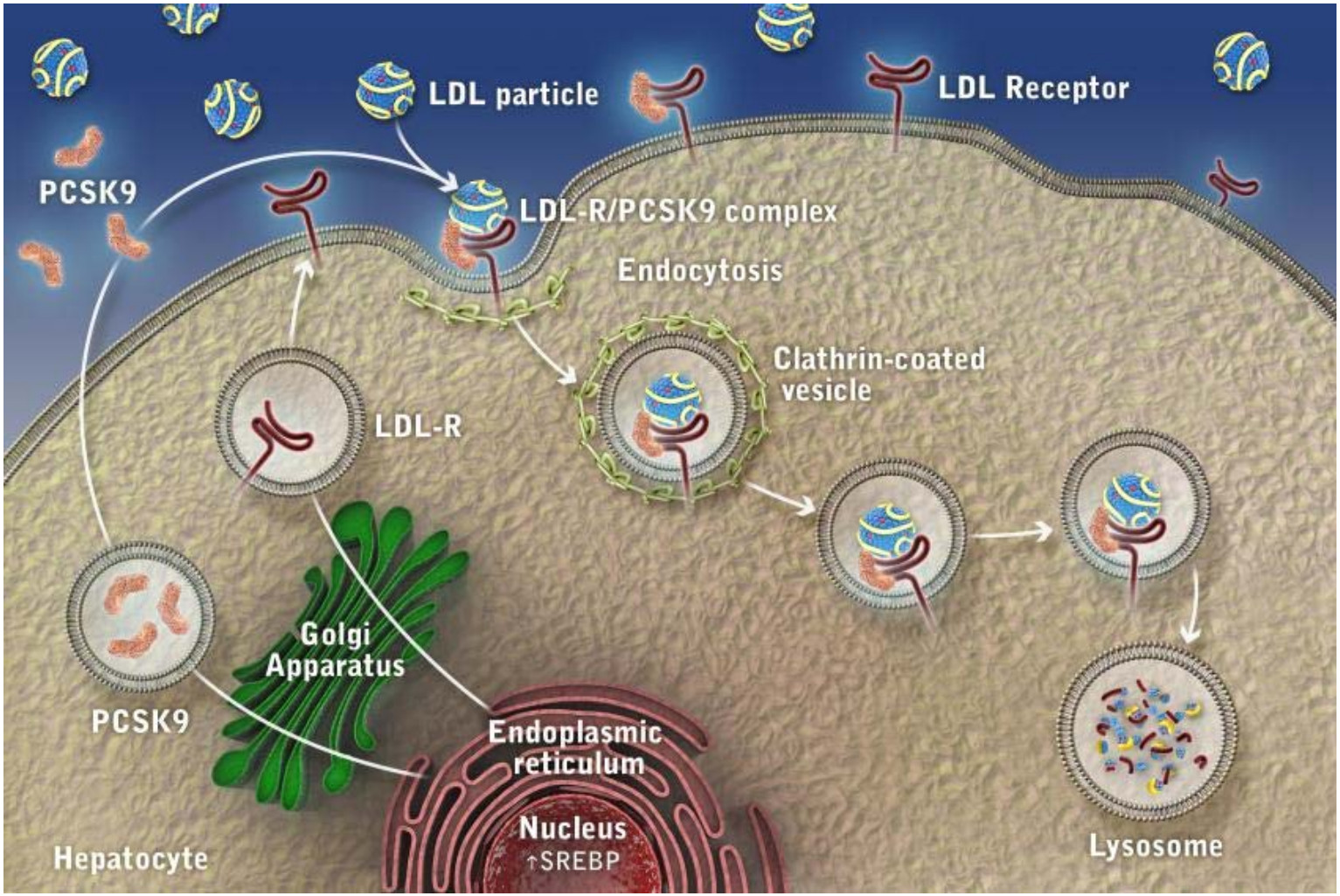
Plasma Metabolism of Intestinally-Derived Cholesterol



Endogenous Cholesterol Transport (liver to periphery to liver)



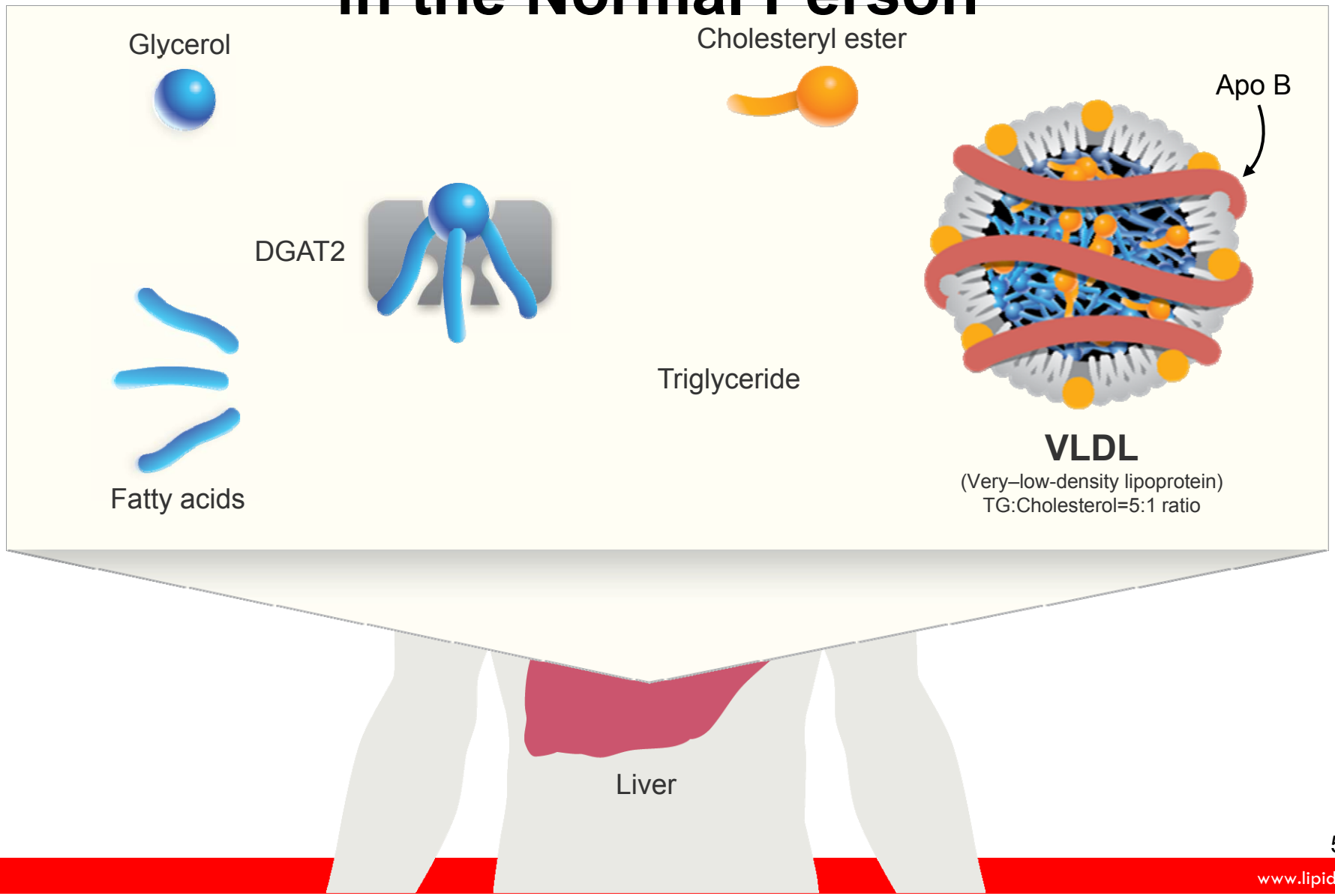
The Role of PCSK-9 in the Regulation of LDL Receptor Expression



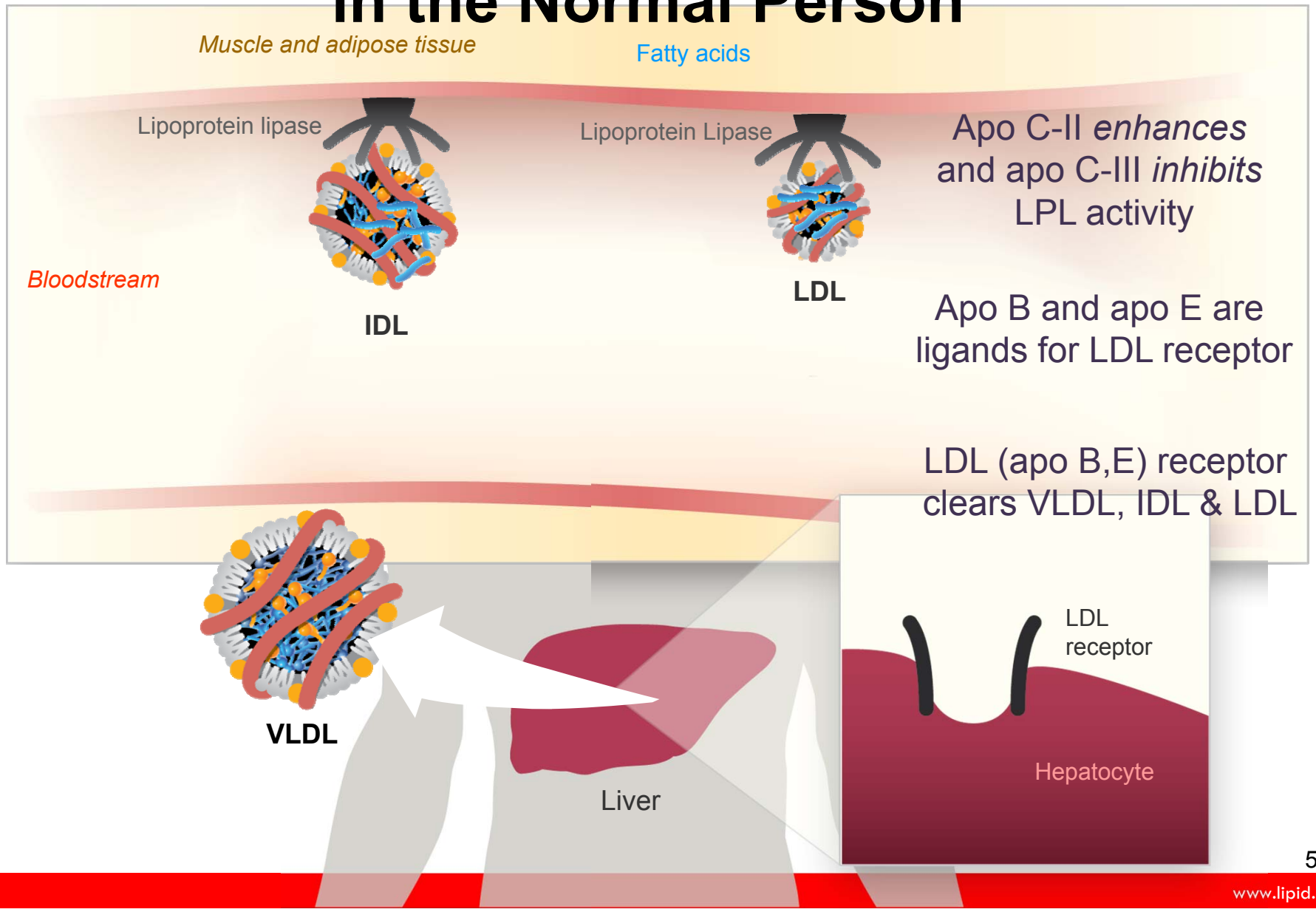
LDL=low-density lipoprotein; LDL-R=LDL receptor; PCSK9=proprotein convertase subtilisin/kinexin type 9; SREBP-2=sterol regulatory element-binding protein-2.

Lambert G et al. *J Lipid Res.* 2012;53:2515–2524.

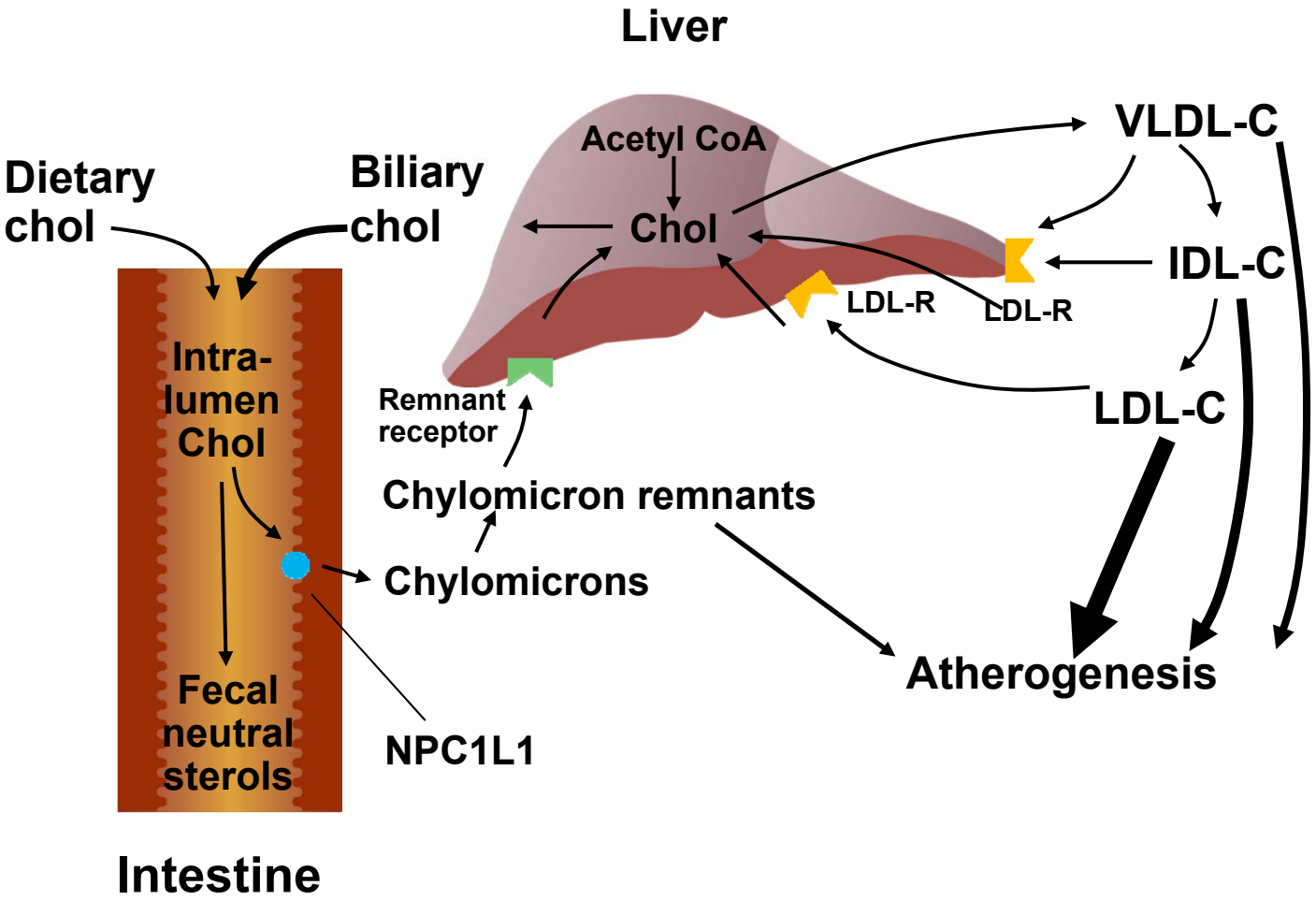
Lipid and Lipoprotein Metabolism in the Normal Person



Lipid and Lipoprotein Metabolism in the Normal Person



Metabolism and Atherogenicity of Apo B–Containing Lipoproteins[1-4]



Adapted from 1 Shepherd J. *Eur Heart J Supplements.* 2001;3(suppl E):E2–E5. 2 Dietschy JM. *Am J Clin Nutr*. 1997;65(suppl):1581S–1589S. 3Turley SD et al. *Prev Cardiol*. 2003;6:29–33,64. 4 Homan R et al. *Curr Pharm Design*. 1997;3:29–44.

Summary: Lipid and Lipoprotein Metabolism

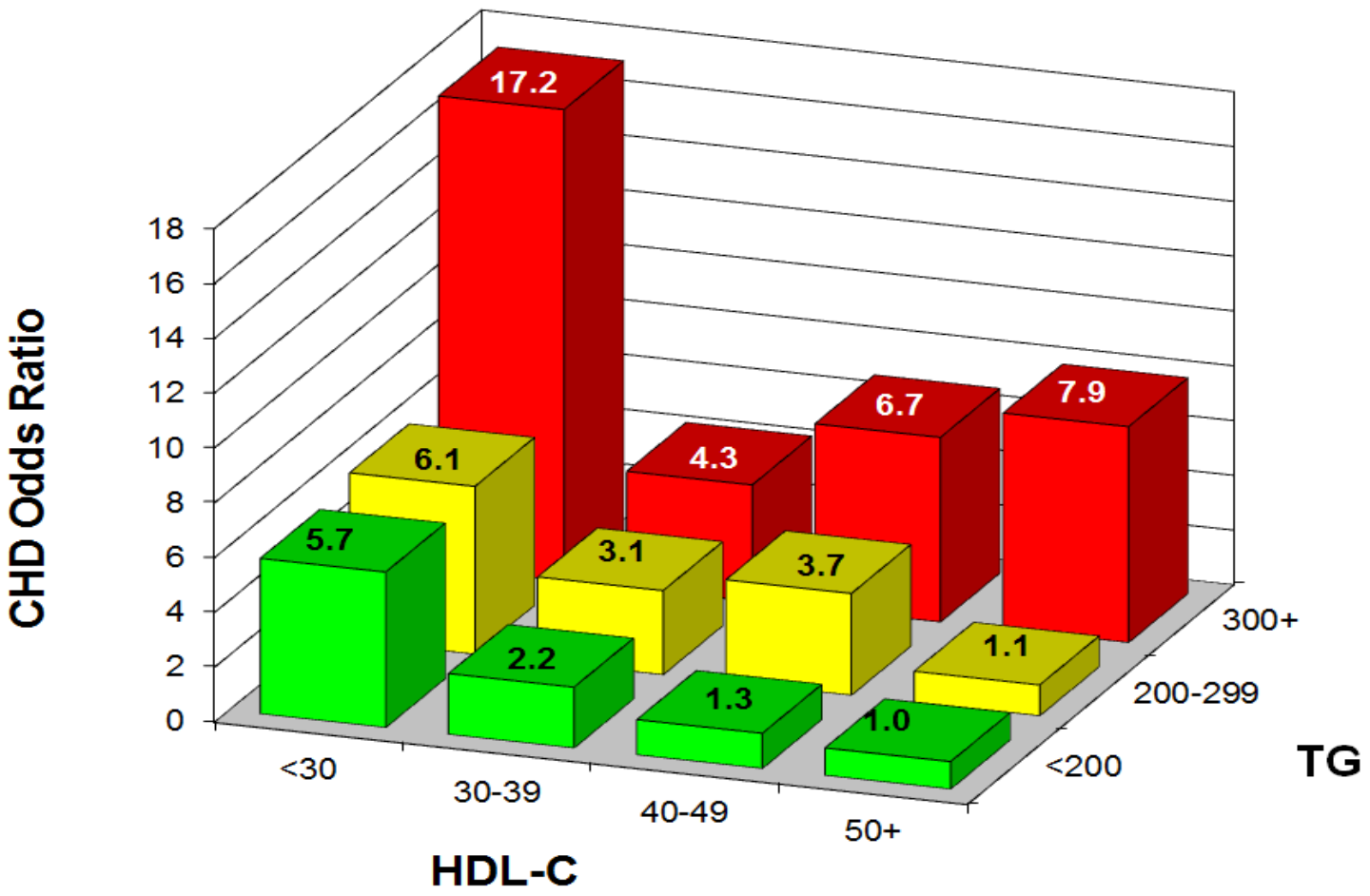
- Major Lipoproteins
  - Chylomicrons
  - VLDL→IDL →LDL
  - Lp(a) (origin/metabolic relationship to LDL *un*known)
  - HDL
- Major Functions
  - TG transport (energy)—mainly Chylomicrons and VLDL
  - Cholesterol transport (cellular functions, hormone & bile synthesis) —mainly LDL and HDL
  - Anti-infective (anti-inflam, anti-athero)—mainly HDL
  - No known "primary" function for Lp(a)
- Disease Relationships
  - Pancreatitis
  - **Atherosclerosis**
  - Other?

Common Types of Atherogenic Dyslipidemia

Common Types of Atherogenic Dyslipidemia

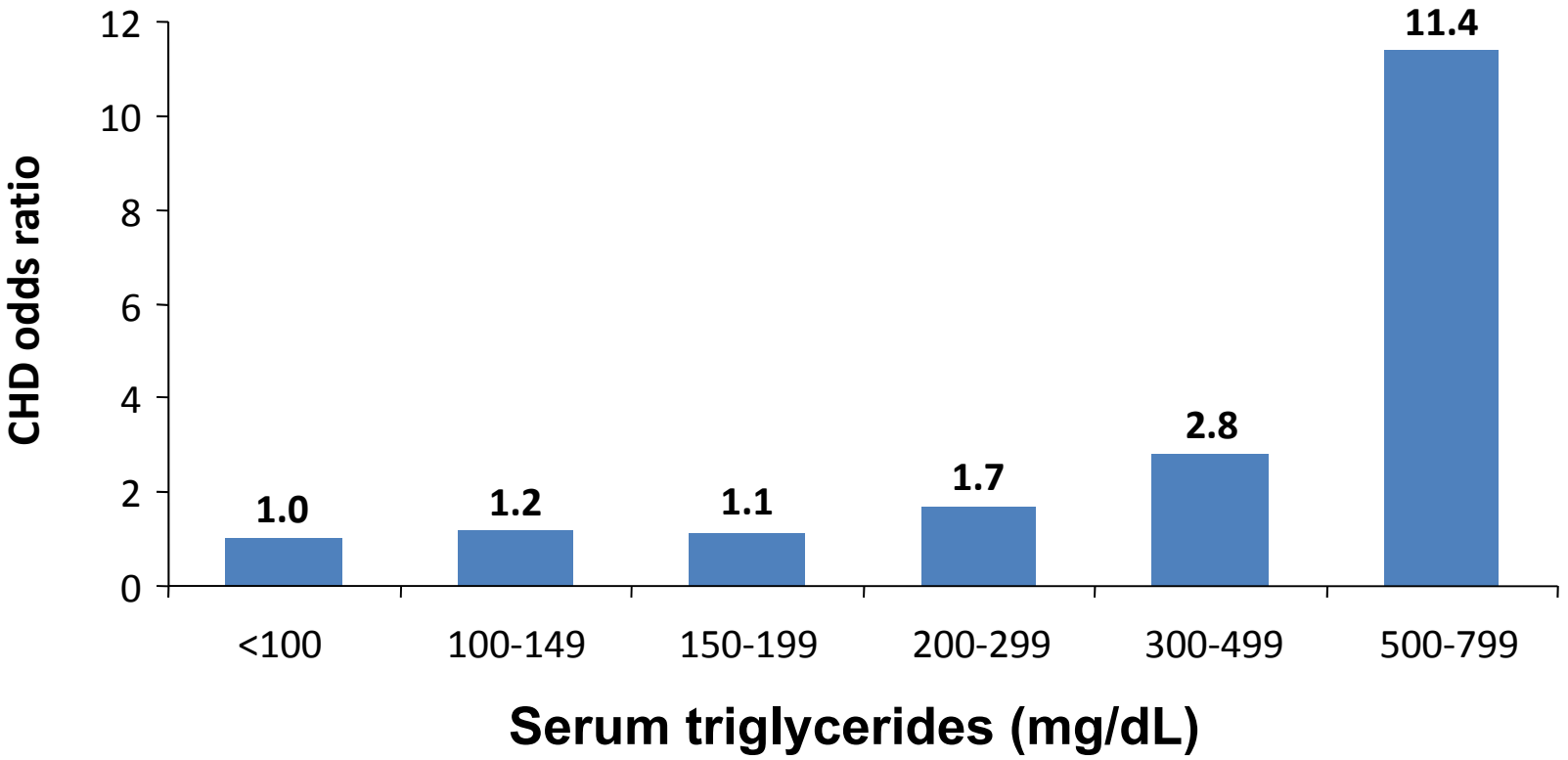
- ↑TG + ↓HDL-C + small, dense LDL
  - 1º: few *mono*genic
  - 1º + 2º: many factors + polygenic
  - 2º: many factors (↑Glucose, ↓thyroid, etc, etc.)
- ↑LDL-C
  - 1º: FH and other *mono*genic
  - 1º + 2º: Bad diet + polygenic
  - 2º: *few* other factors
- Combination = mixed dyslipidemia

TG and HDL-C *Both* Contribute to CHD Risk



Adapted from Hopkins PN, et al. *JACC* 2005 Apr 5;45(7):1003-12.

Triglycerides Are Independently Associated With Premature Familial CHD*



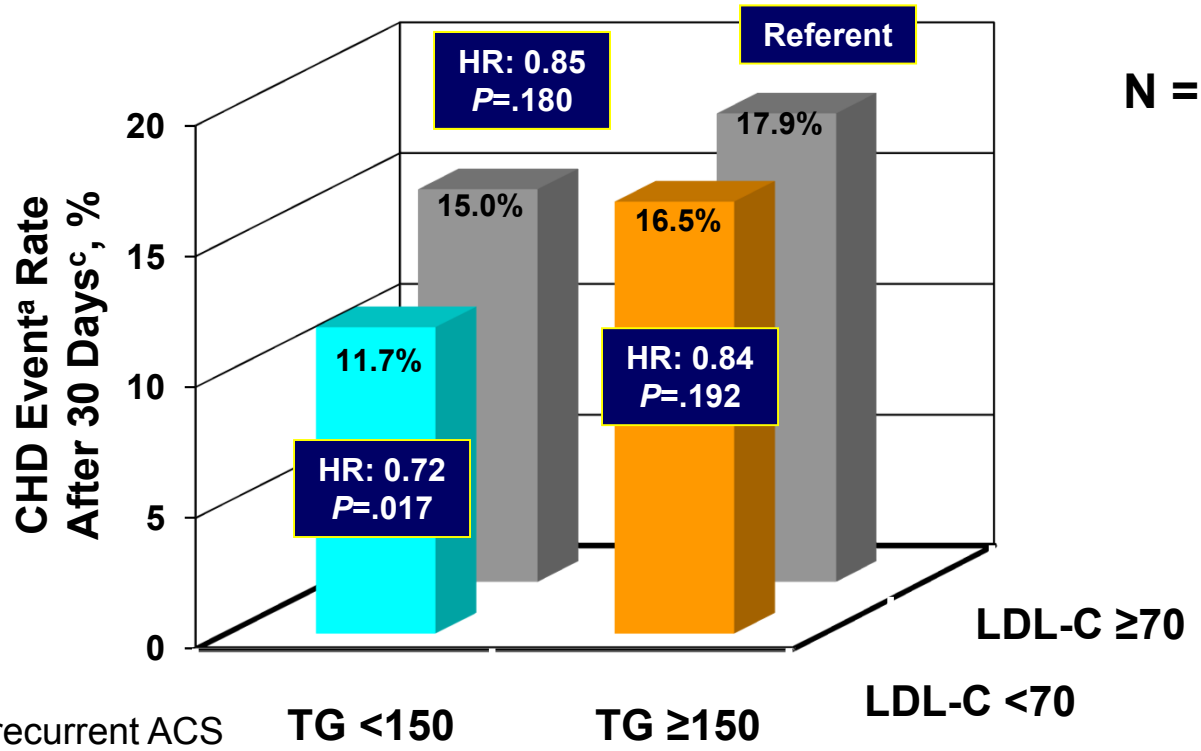
*Triglyceride odds ratio adjusted for HDL-C; n=653 (Family History=early CHD), n=1029 (control).
CHD=coronary heart disease; HDL-C=high-density lipoprotein cholesterol.

Adapted from Hopkins PN, et al. *J Am Coll Cardiol.* 2005;45:1003-1012.

TG >150 mg/dL Increases CHD Risk Independent of LDL-C Level[a]

PROVE IT-TIMI 22 Trial[b]

- Achieving *optimal TG* (<150 mg/dL) may help reduce residual CVD risk in statin-treated post-ACS patients



N = 4162

[a]Death, MI, and recurrent ACS

[b]ACS patients on atorvastatin 80 mg or pravastatin 40 mg

Adjusted for age, gender, low HDL-C, smoking, HBP, obesity, diabetes, prior statin Rx, prior ACS.

Adapted from Miller M, et al. *J Am Coll Cardiol.* 2008;51:724-730.

1 Compared with LDL-C ≥70 mg/dL and TG ≥150 mg/dL, lower CHD risk was observed with low on-treatment TG (<150 mg/dL) and LDL-C (<70 mg/dL) (HR = 0.72; P=.017

James Underberg, 4/15/2014

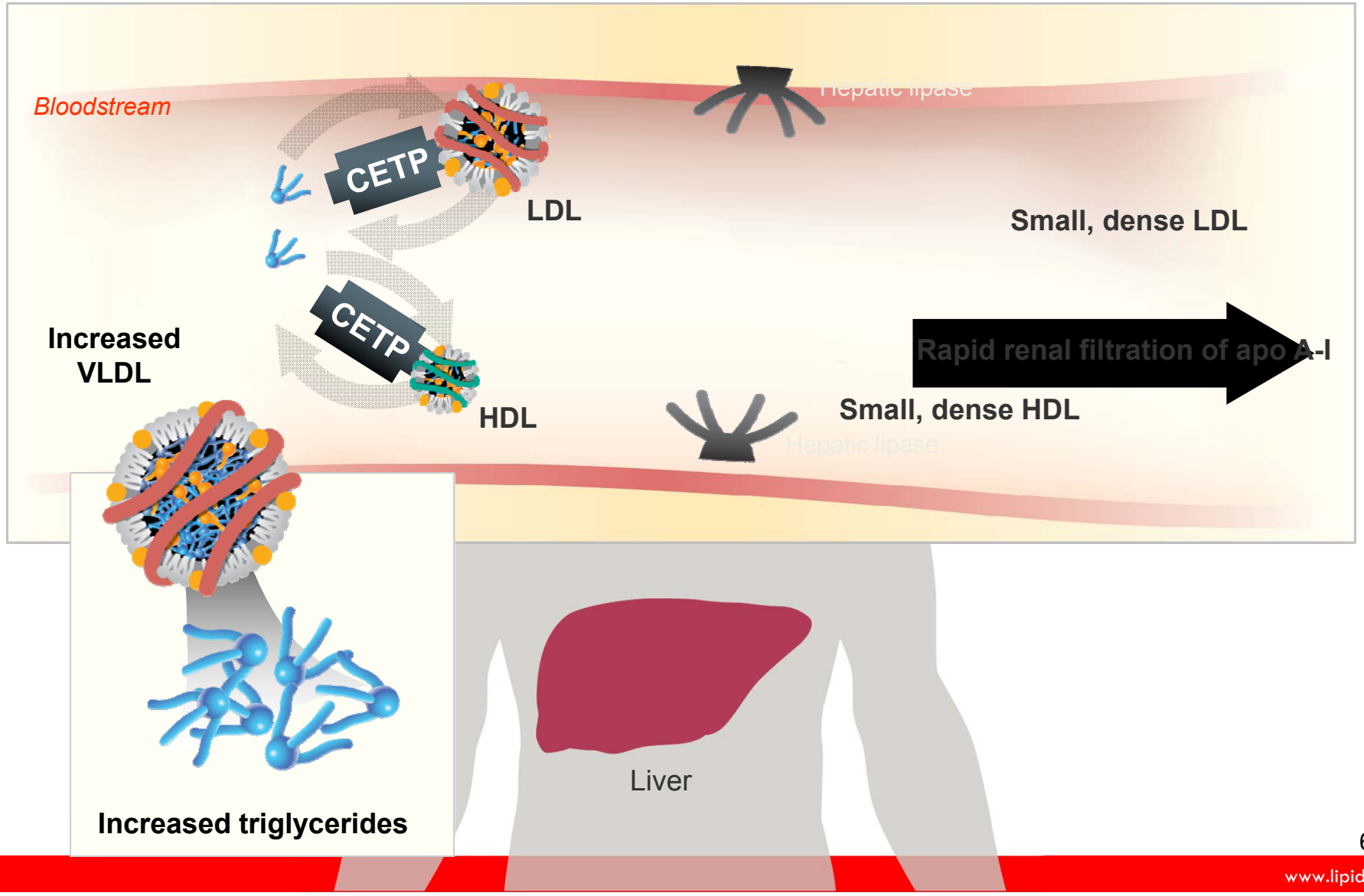
How Can Hypertriglyceridemia (HTG) Be Atherogenic?

- TGRL carry cholesterol and promote atherosclerosis (especially remnants)*
- VLDL is precursor to LDL (pro-atherogenic)
- HTG drives:
  - CE enrichment of VLDL (*more* atherogenic)*
  - ↓ LDL size (small, dense LDL are *more* atherogenic)*
  - ↓ LDL-C (small, dense LDL carry less cholesterol)*
  - ↓ HDL size (small, dense HDL are unstable and *less* anti-atherogenic)
- HTG is linked to other pro-atherogenic states*
  - Insulin resistance
  - Endothelial dysfunction
  - Pro-oxidative state
  - Pro-inflammatory state
  - Prothrombotic state

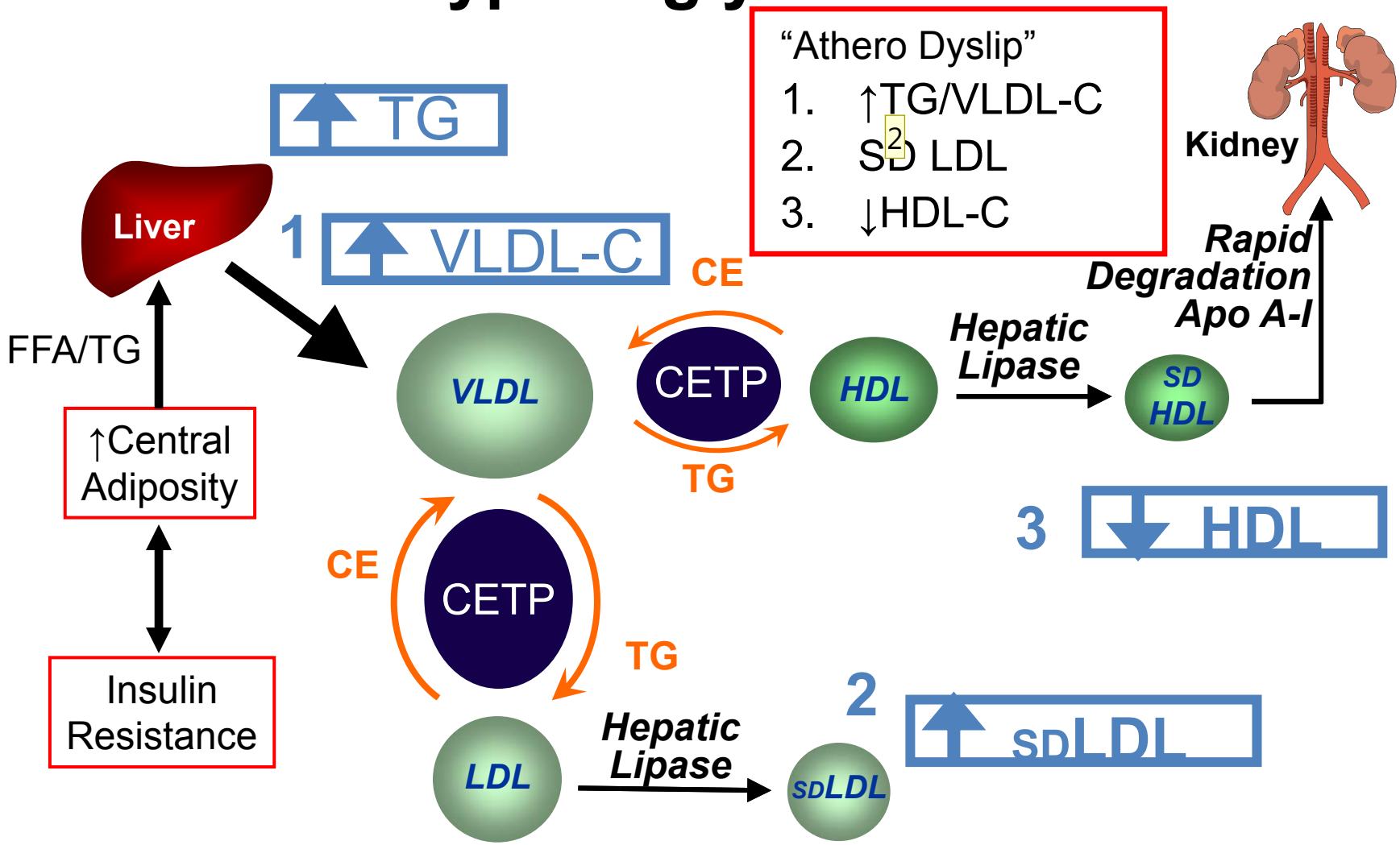
***Reasons why *non-HDL-C* is *stronger than LDL-C* as CVD factor.**

CE=cholesteryl ester; TGRL=triglyceride-rich lipoproteins; VLDL=very low-density-lipoprotein.

Dyslipidemias *Secondary* to Hypertriglyceridemia



Three Atherogenic Consequences of Hypertriglyceridemia

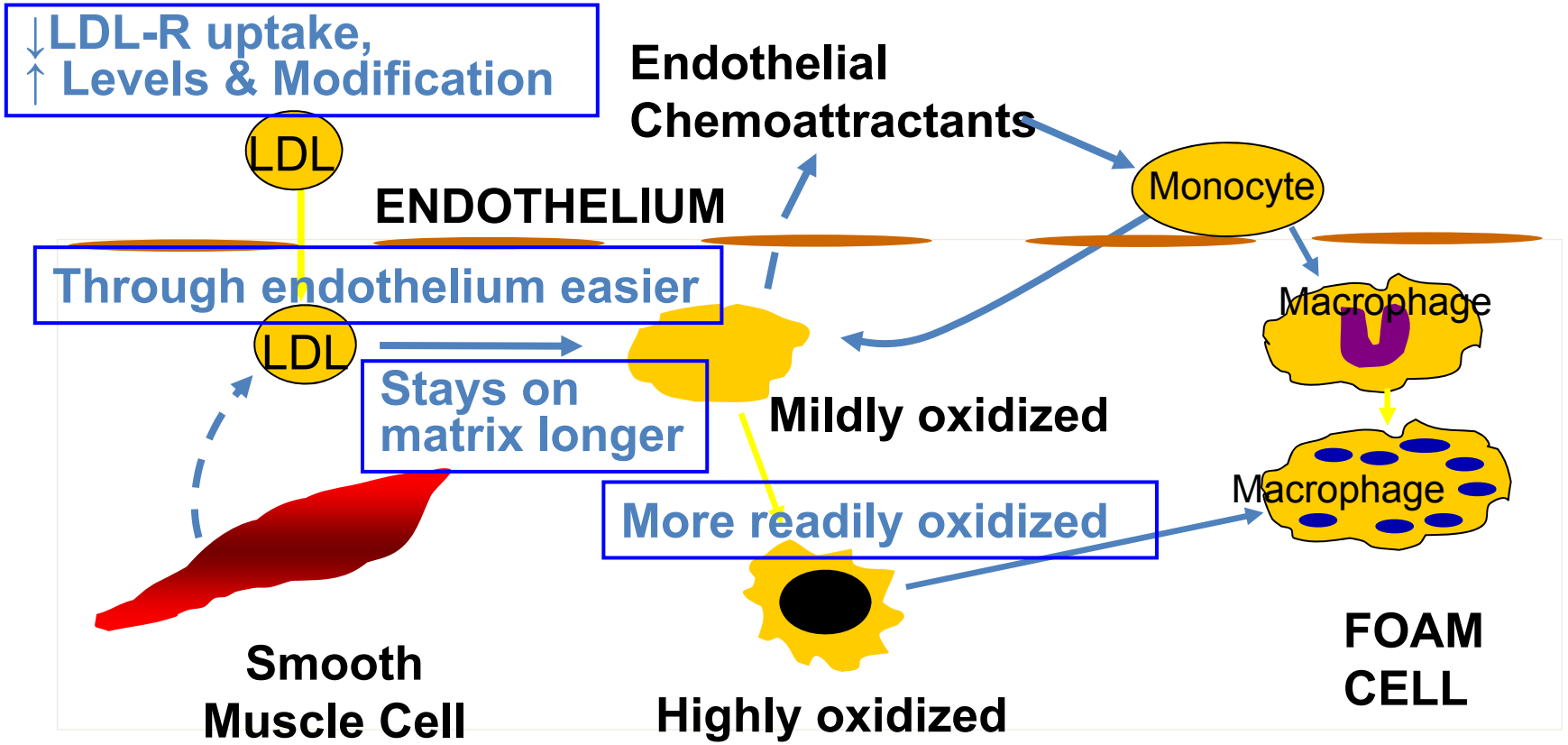


Adapted from Ginsberg HN. *J Clin Invest*. 2000;106:453-458.

CETP = cholesterol ester transfer protein

2 no arrow needed here. Small dense LDL formed but not necessarily more of them so woiuld be hesitant to add the upward arrow.
James Underberg, 4/15/2014

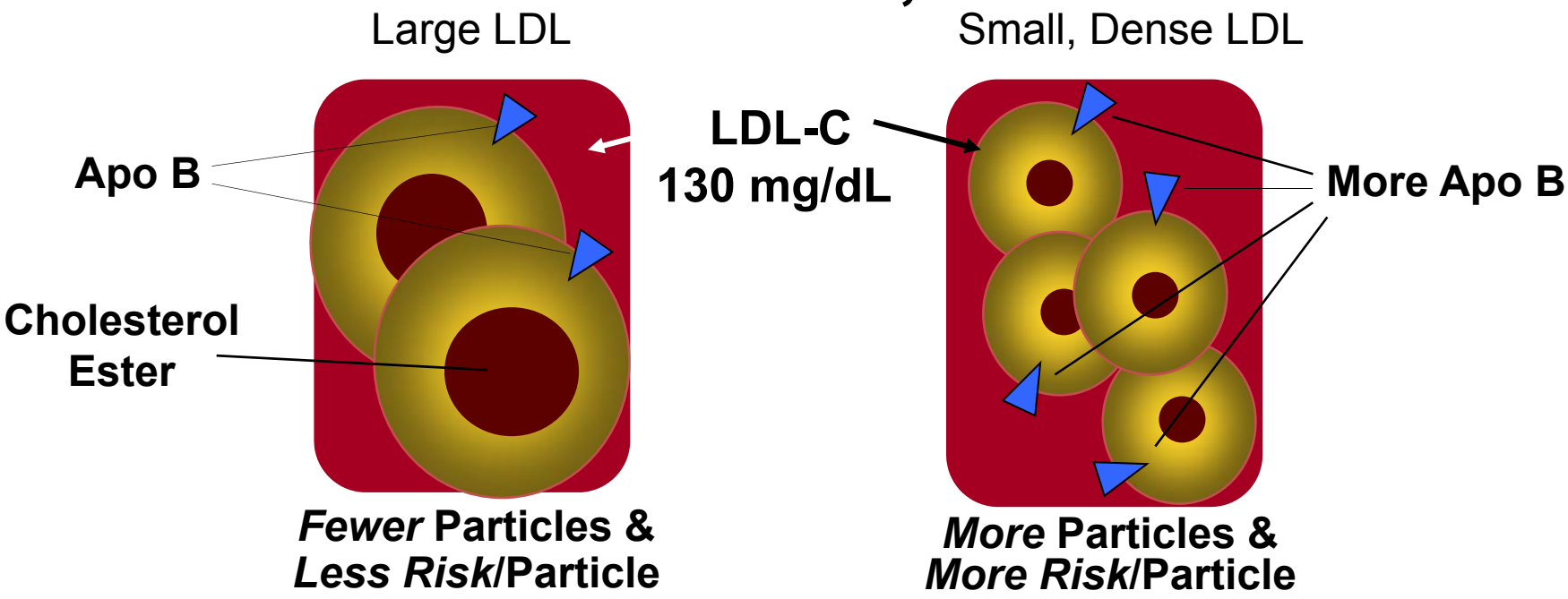
Potential Impact of *Small Dense* LDL (pattern B)



And **Associates with Metabolic Syndrome/DM: ↓HDL, ↑TG, ↑Inflam., ↑Thromb., ↑Oxid.**

Adapted from Carmena et al. *Circulation.* 2004;109(23 Supplement 1):111-112.

LDL-C Doubly *Underestimates* CVD Risk in Cases of Small, Dense LDL



***Fewer* Particles & *Less Risk*/Particle**

Lipid profile:

TC	198 mg/dL
LDL-C	130 mg/dL
TG	90 mg/dL
HDL-C	50 mg/dL
Non–HDL-C	148 mg/dL

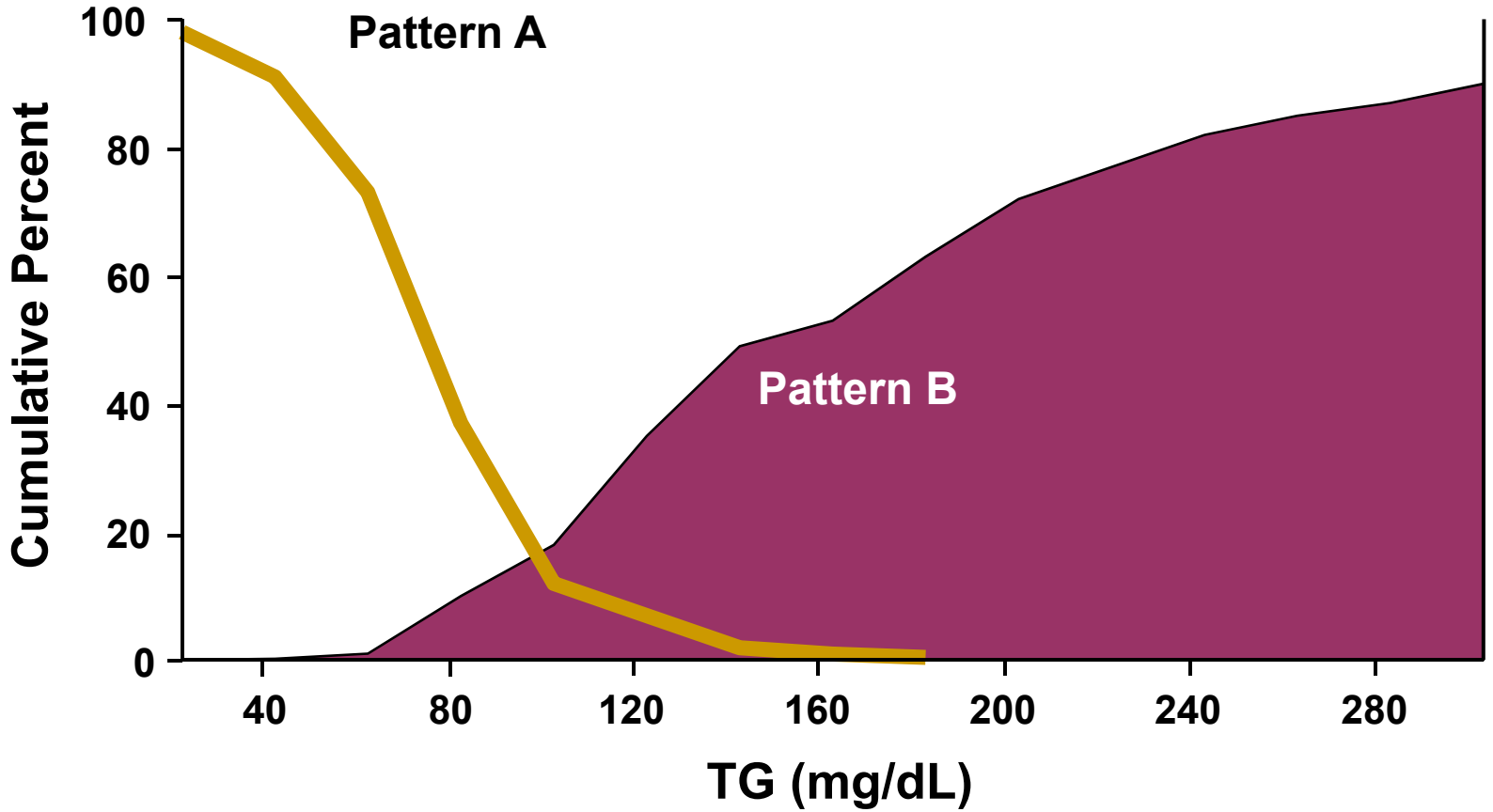
***More* Particles & *More Risk*/Particle**

Lipid profile:

TC	210 mg/dL
LDL-C	130 mg/dL
TG	250 mg/dL
HDL-C	30 mg/dL
Non–HDL-C	180 mg/dL

Adapted from Otvos JD, et al. *Am J Cardiol*. 2002;90:22i-29i.

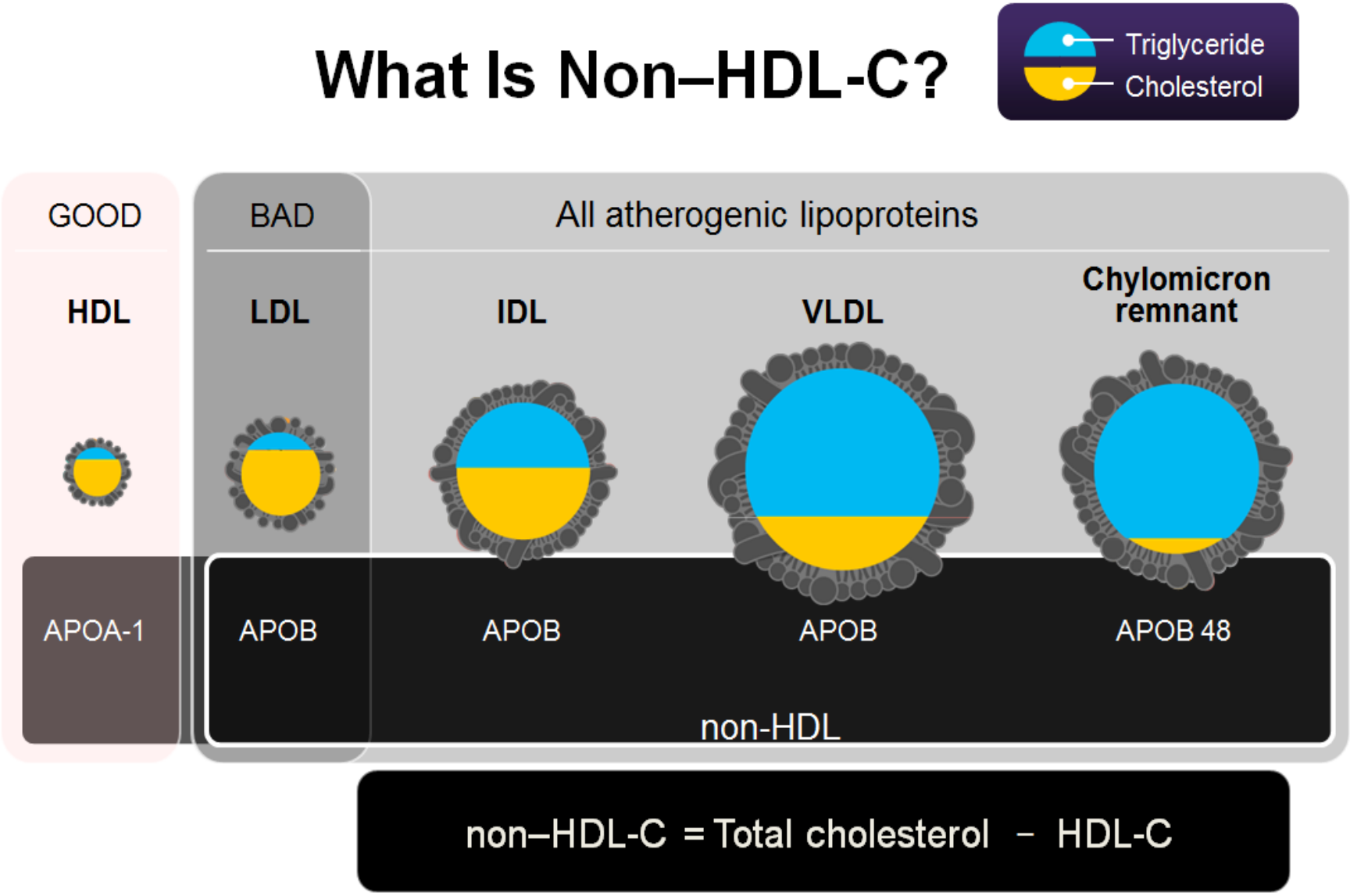
High Triglycerides Are Strongest Predictor of Small, Dense LDL (Pattern B)



LDL=low-density lipoprotein; TG=triglyceride.

Adapted from Austin MA, et al. *Circulation.* 1990;82:495-506.

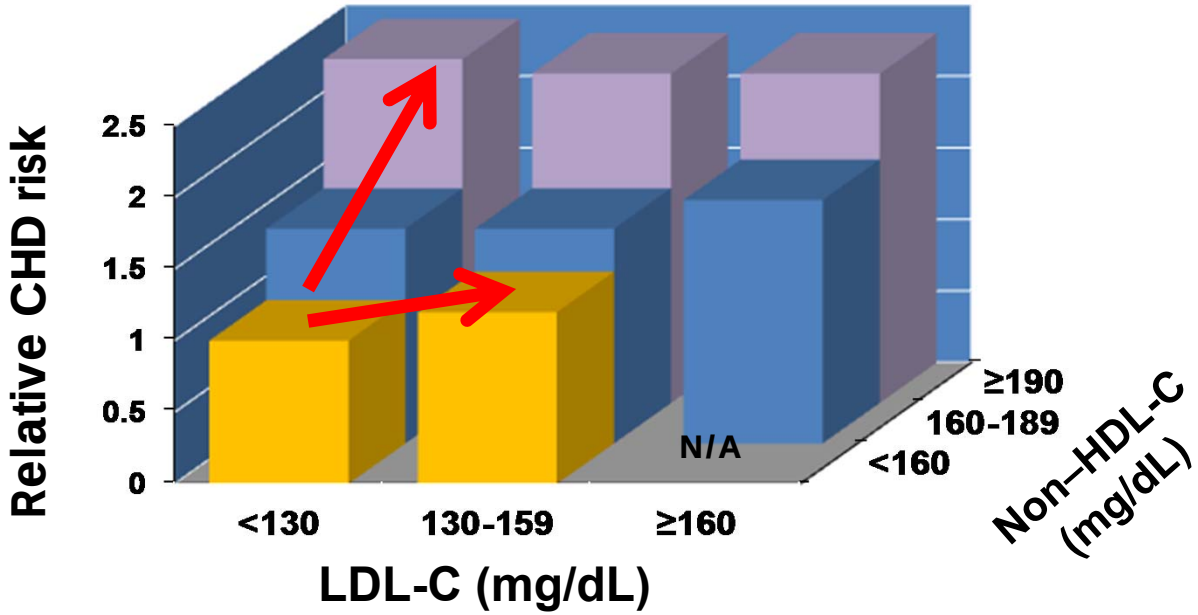
What Is Non–HDL-C?



NCEP Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults Adult Treatment Panel III). *Third Report Executive Summary*. 2001; NIH Publication No. 01-3670.

Non–HDL-C Is Stronger than LDL-C in Predicting CHD Risk The Framingham Study

(Average follow-up time was about 15 years)



- Within non–HDL-C levels, no association was found between LDL-C and the risk for CHD
- Strong, positive, graded association of non–HDL-C w/ CHD seen at every LDL-C level

HDL-C=high-density lipoprotein cholesterol; LDL-C=low-density lipoprotein cholesterol.

Adapted from Liu J, et al. *Am J Cardiol.* 2006;98:1363-1368.

Testing for Atherosclerosis/CVD Risk in HTG Patients

Required/Routine

- ↑TG level
- ↓HDL-C

Other Measures

- ↓LDL size (GGE, ultracentrifuge, NMR)
- ↑Non-HDL-C (=Total C – HDL-C)
- ↑Apo B-100
- ↑LDL-P (particle concentration, NMR *only*)
- ↑Remnant lipoproteins (RLP-C vs subfract)
- ↑VLDL-C & VLDL-C/TG (UC, “beta-quant”)
- ↑hsCRP (MetSynd surrogate)

LDL-C and Non HDL-C

LDL-C

- Focus of most research
- Focus of current guidelines
- Always *reported* in lipid profile

Non-HDL-C

- Conceptually better (*all pro*-athero lipos)
- Stronger CVD factor
- Valid in HTG
- Valid non-fasting
- Always *measured* in lipid profile ("free")

Bottom line: Non-HDL-C is much better (no unique advantages of LDL-C) but we are stuck with LDL-C for now!

Non-HDL-C and Apo B

Non-HDL-C

- *Cholesterol* content conceptually better (*causal* role)
- *Free* with lipid profile (*no* extra testing needed)
- Well standardized
- Already incorporated in guidelines

Apo B

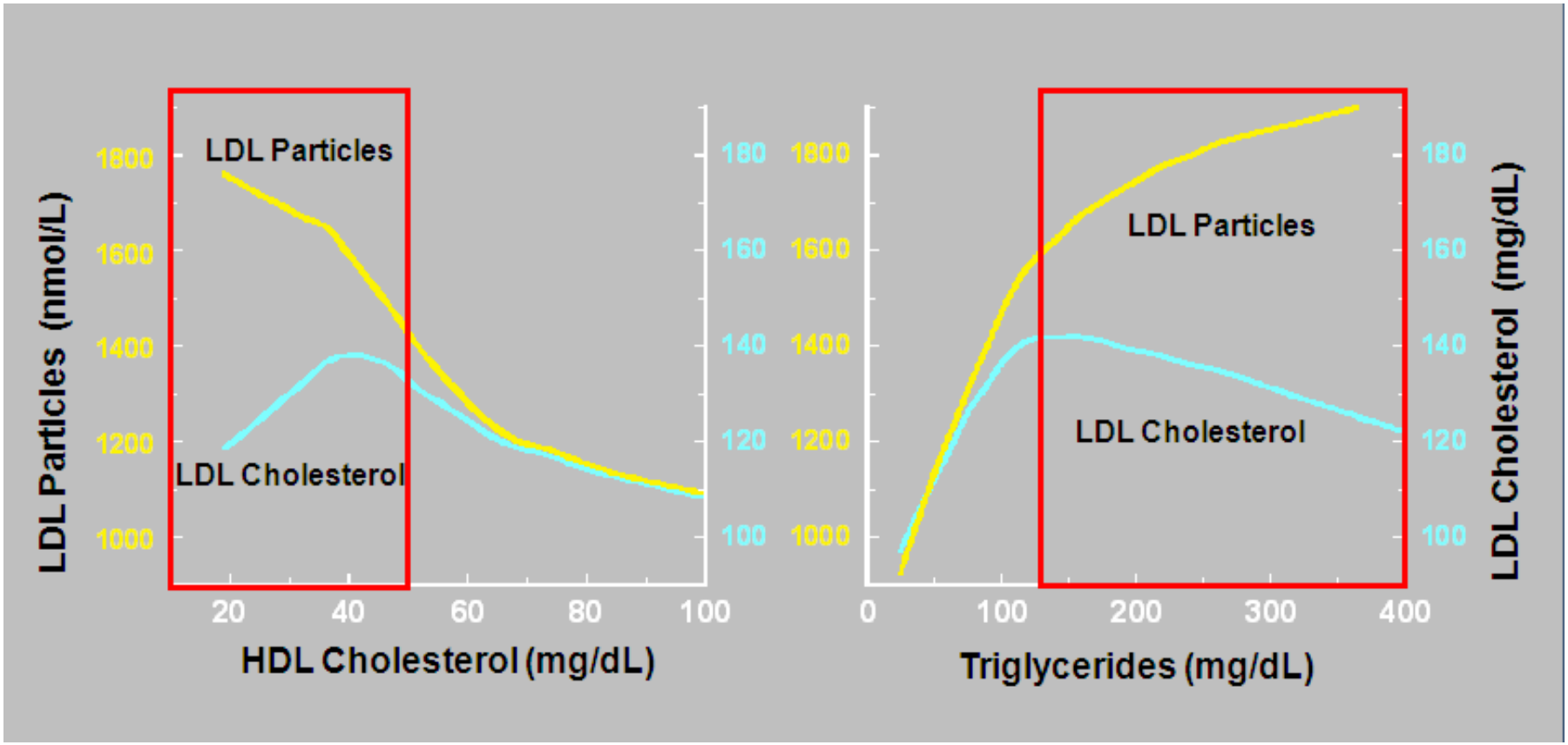
- Apo B *may* play *causal* athero role
- Gives non-HDL particle count
- Good standardization
- Stronger CVD factor? (some dyslipidemias)
- Complementary to non-HDL-C?

Bottom line: Non-HDL-C cheaper/easier, best routine
Apo B likely gives ↑info but at ↑cost, ok as adjunct

Relations of LDL Particles and LDL Cholesterol to Levels of HDL Cholesterol and Triglycerides

LDL-P Includes Remnants, Pools Lipid Risk in Metabolic Syndrome

Framingham Offspring Study



Adapted from Clarenbach, Grundy, et al. J Int Med 2007; 55:237-247;
Kathiresan, S, et al. Circulation. 2006;113:20-29.
Otvos JD. J Lab Medicine 2002;26(11/12):555-556.

LDL-P and Non-HDL-C

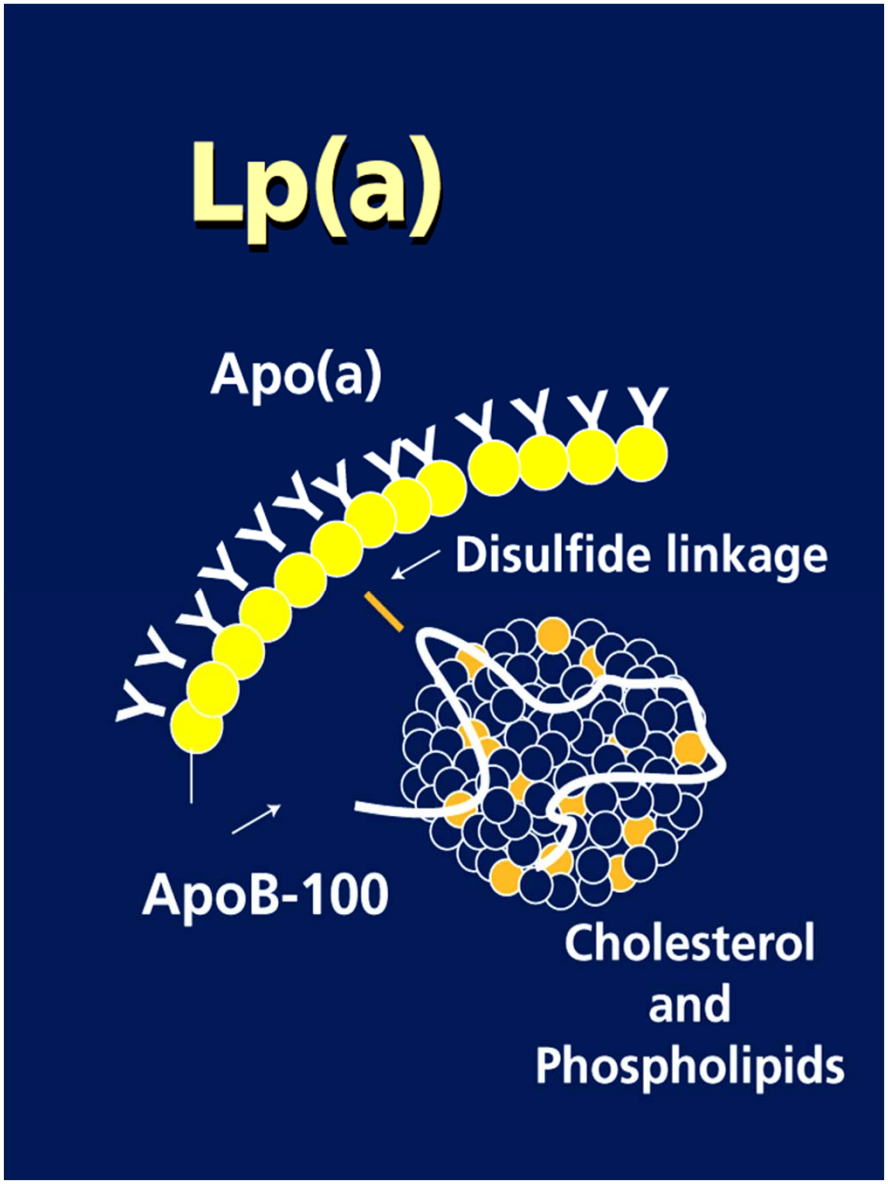
Non-HDL-C

- Includes all atherogenic particles
- *Free* with lipid profile
- Universally available
- Already incorporated into guidelines
- ***Better*** than LDL-P (w/ best apo B assay)

LDL-P

- *Well* studied
- Good CVD risk prediction (incl. some remnants)
- Well standardized
- *Beats* non-HDL-C (*some* studies)
- May suggest more aggressive Rx

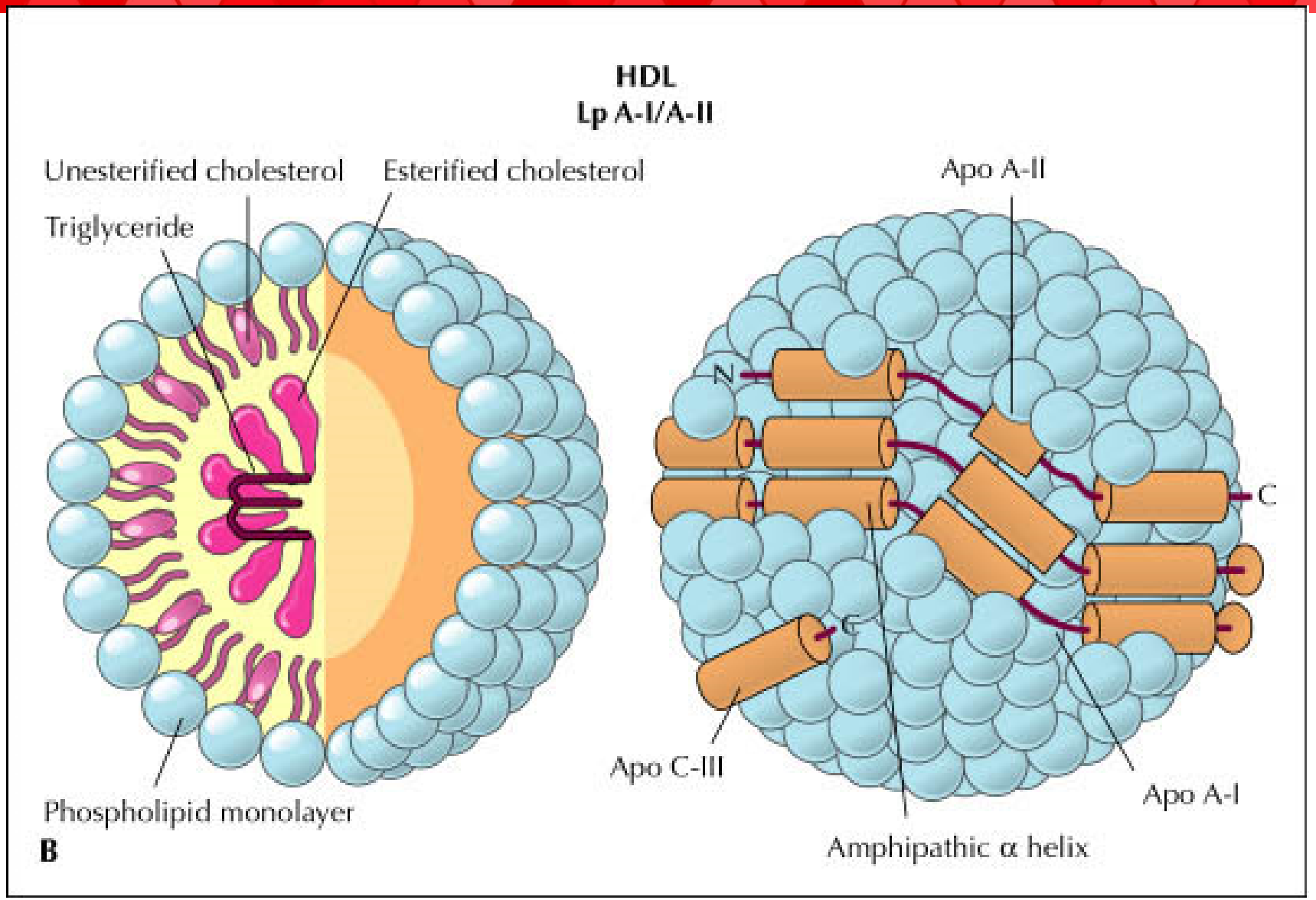
Bottom line: Non-HDL-C cheaper/easier, best routine
LDL-P gives ↑info but at ↑cost, ok as adjunct



- Lp(a) levels are *genetically* determined
  - more kringle-repeats in gene→
  - longer apo(a) →
  - less apo(a) synthesis →
  - lower apo(a) levels
- Measurement important but difficult (protein vs chol?)
- Pro-athero mechanisms of Lp(a):
  - More oxidized (=more atherogenic) vs LDL
  - Scavenges and spreads oxidized FFAs
  - Pro-thrombotic? (plasmin competitor, ↑PAI-1 synth)
  - Slow LDL-R clearance (poor binding)
- ↑in Acute Coronary Syndrome (why?)

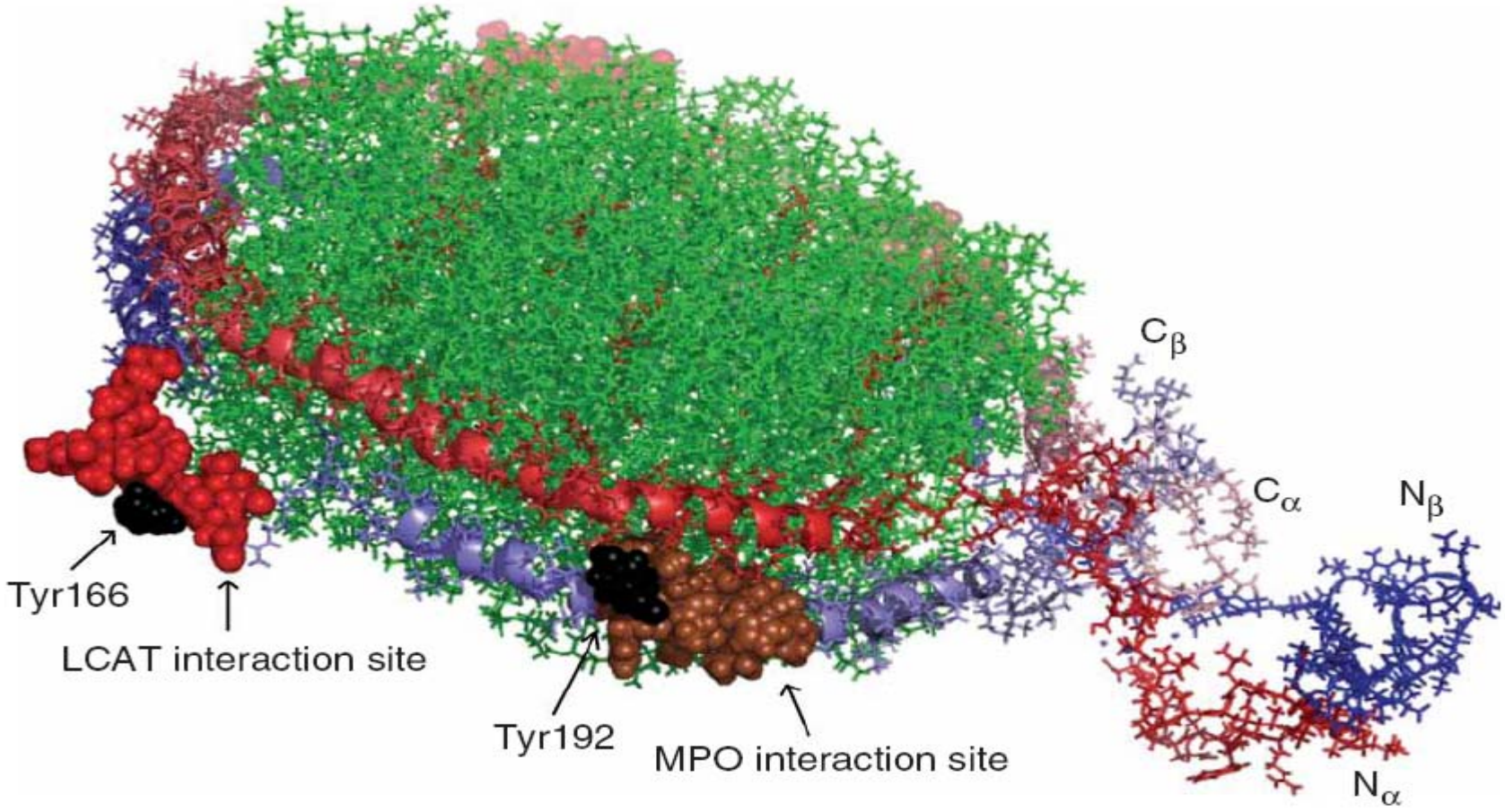
Modified from Stein, JH and Rosenson, RS. *Arch Int Med* 1997;157:1170.

HDL: Protective but Clinically Difficult



In HDL and all lipoproteins, unesterified cholesterol partitions between the core and inner aspect of the surface

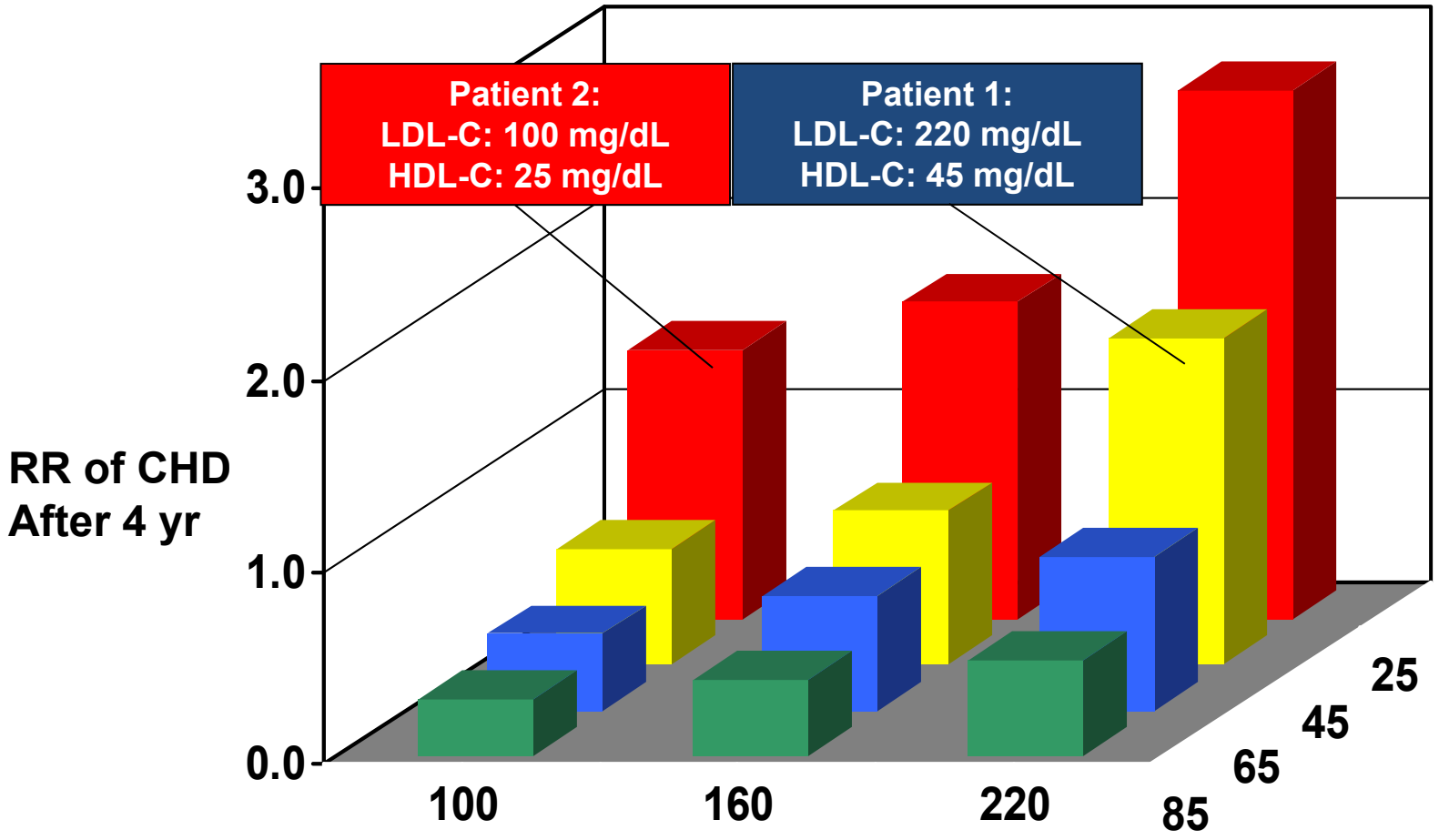
Proposed Structure of Discoidal HDL



Pre-beta HDL is unique among lipoproteins in being non-spherical. Smaller, pre-beta-1 HDL is globular and has almost no lipid. Pictured here is pre-beta-2 HDL which is discoidal with apolipoproteins wrapped around a circular PL bilayer.

Wu Z, Wagner MA, Zheng L, et al. Nat Struct Mol Biol. Sep 2007;14(9):861-868.

Low HDL-C *associated with increased* CHD Risk in observational data

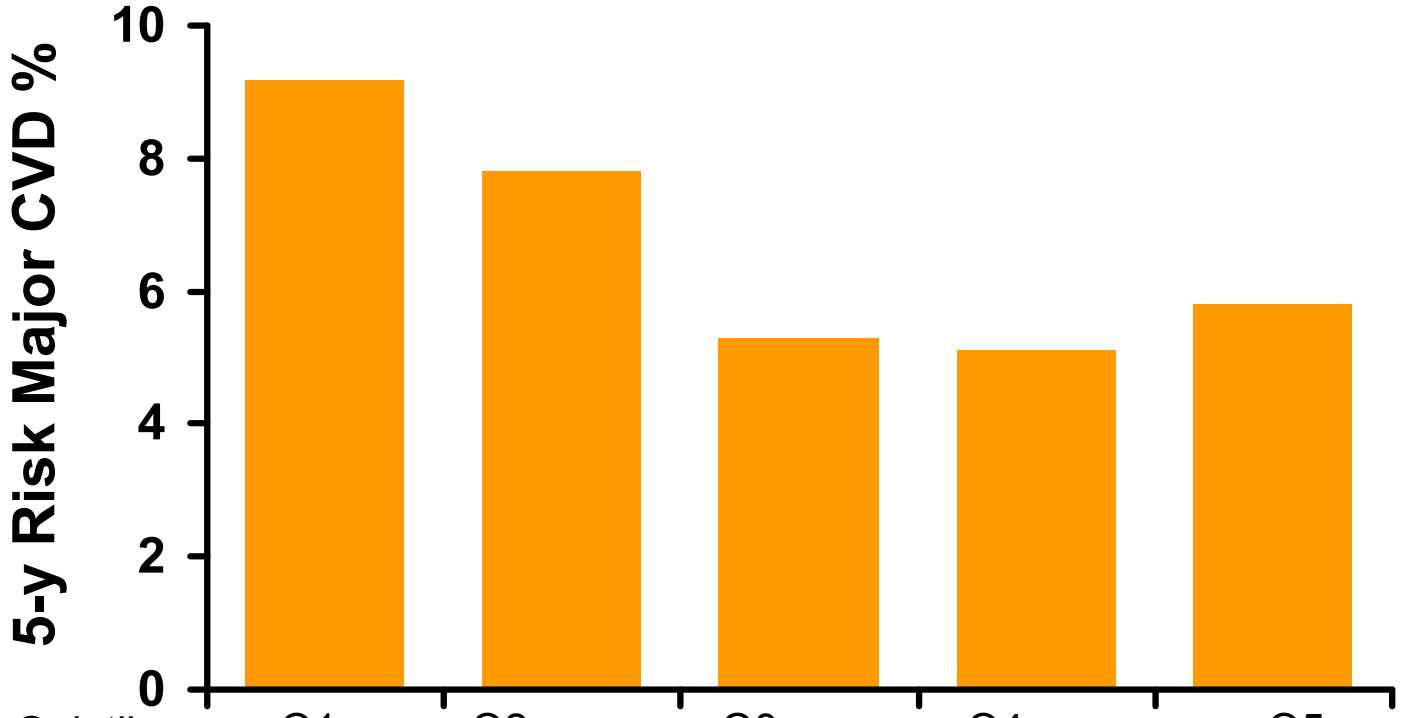


***Data represent men age 50–70 yr from the Framingham Study.**

Adapted from and reprinted with permission from Castelli WP. *Can J Cardiol*. 1988;4(suppl A):5A.

Low HDL-C & CVD events in TNT
In patients with LDL-C lowered to <70 mg/dL

Post-hoc, TNT Subjects w/ LDL-C ≤70 mg/dL on Statin[a,b]



HDL-C Quintiles[a] mg/dL	Q1 <37	Q2 37 to <42	Q3 42 to <47	Q4 47 to <55	Q5 ≥55
Hazard Ratio Versus Q1*		0.85	0.57	0.55	0.61

[a]On-treatment level (3 months statin therapy); n = 2661
[b]Mean LDL-C, 58 mg/dL; mean TG, 126 mg/dL
**P*=.03 for differences among quintiles of HDL-C

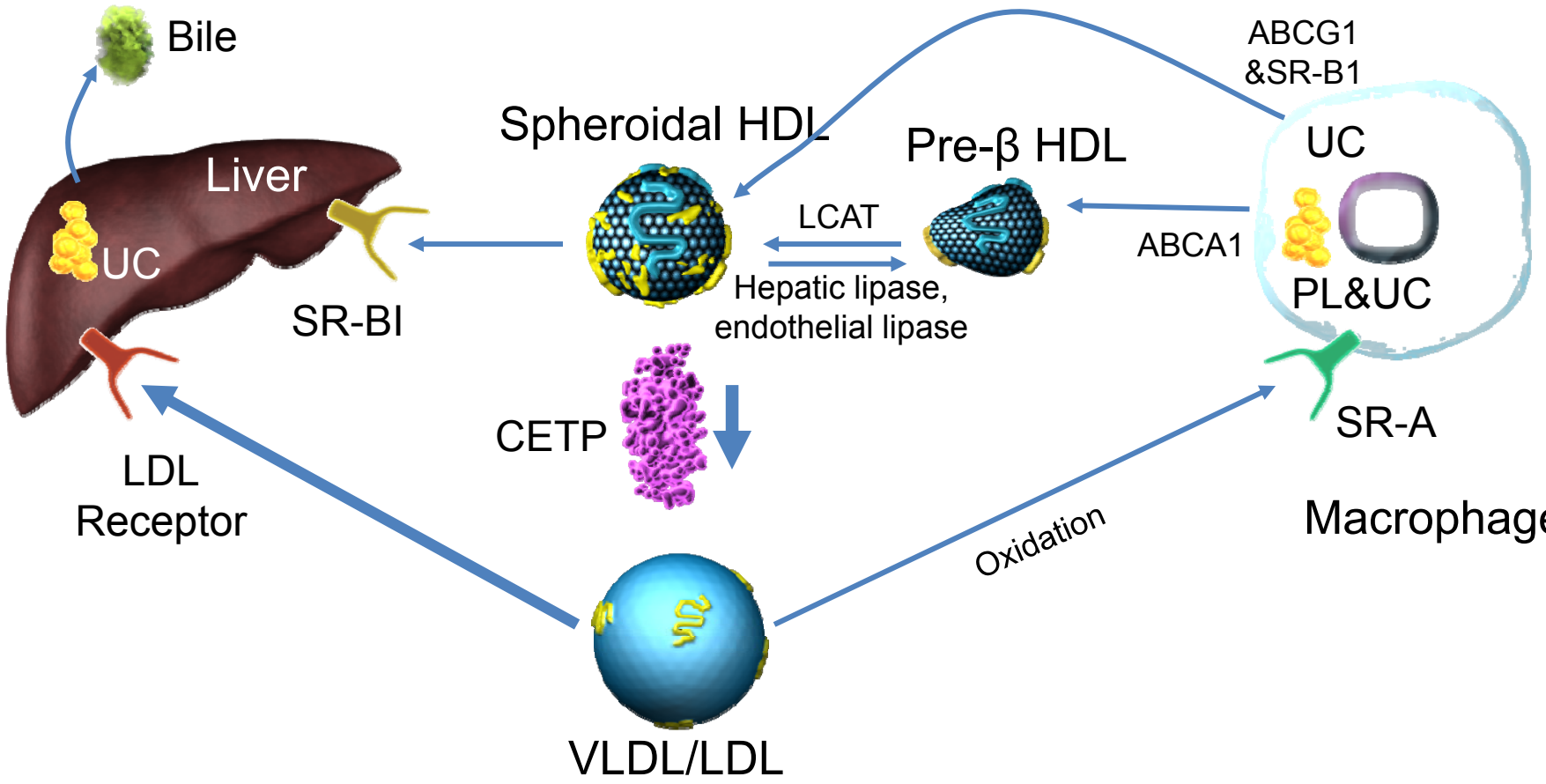
Adapted from Barter P, et al. *New Engl J Med.* 2007;357:1301-1310.

Suggested Anti-atherogenic Mechanisms of HDL

- Promotes ***reverse cholesterol transport***
- Partner in TG metabolism
- ***Antioxidant***
  - Oxidized *in place of* apo B particles?
  - *Reverses oxidation* of apo B particles?
- *Pro*-endothelial
  - ↑ NO production
  - ↑ Endothelial repair (↑EC progenitors, other?)
- *Anti*-coagulant
  - Anti-thrombotic (↓plt. membr cholesterol)
  - Pro-fibrinolytic
- ↑ Prostacyclin production
- ***Anti-inflammatory***
  - ↓ Cell-adhesion molecules
  - Scavenges acute-phase reactants
  - ↓ Neutrophil degranulation
  - Anti-complement?
  - Anti-T-cell effect?
- *Anti*-apoptotic (prevents death of MΦ, EC, SMC)
- Blocks other adverse effects of apo B particles?

Phillips M et al. *Atherosclerosis* 1998;137(suppl):S13-7. Avarim M et al. *Circulation* 2000;101:2252-7. Cockerill G et al. *Arterioscler Thromb Vasc Biol* 1995;15:1987-94; Li X et al. *Int J Cardiol* 2000;73:231-6. Griffin J et al. *J Clin Invest* 1999;103:219-27. Blackburn W et al. *J Lipid Res* 1991;32:1911-8. Fleisher L et al. *J Biol Chem* 1982;257:6653-5. Brewer H. *Am J Cardiol* 1999;83:3F-12F.

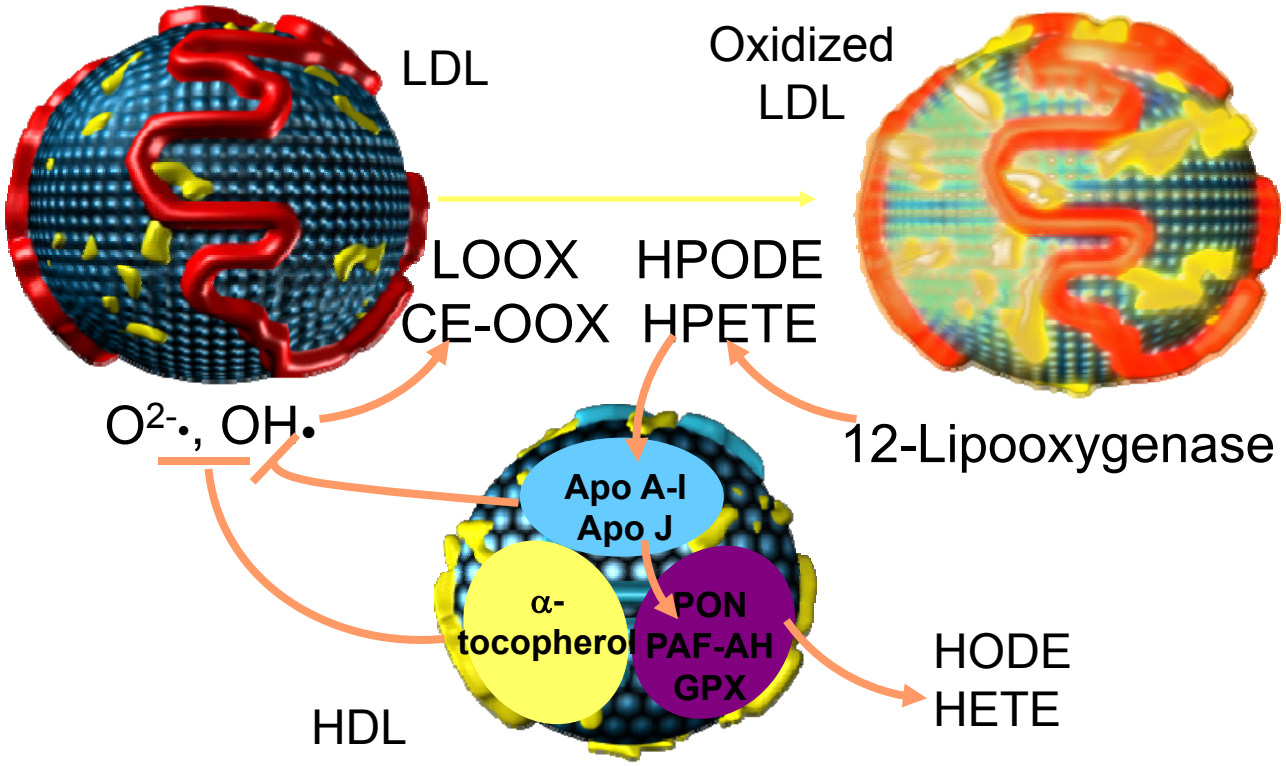
The Role of HDL in Reverse Cholesterol Transport



ABCA1, ATP-binding cassette protein A1; CETP, cholesterol ester transfer protein; FC, free cholesterol; LCAT, lecithin:cholesterol acyltransferase; SR-A, scavenger receptor class A; SR-BI, scavenger receptor class B type I.

Adapted from Cuchel C et al. *Arterioscler Thromb Vasc Biol*. 2003;23:1710–1712.

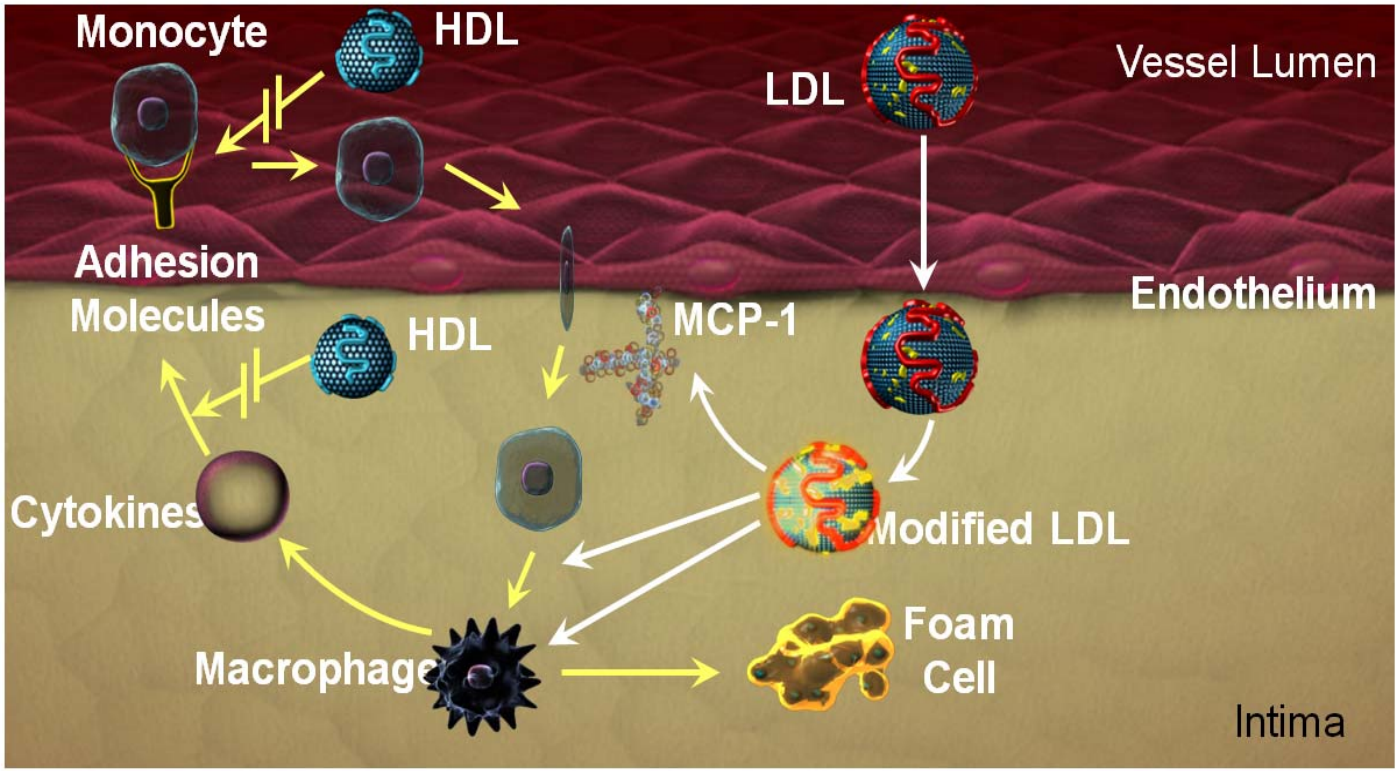
Antioxidant Effects Mediated by HDL



CE-OOX, oxidized cholesterol esters; GPX, glutathione peroxidase; HETE, hydroxyeicosatetraenoic acid; HPETE, hydroperoxyeicosatetraenoic acid; HODE, hydroxyoctadecadienoic acid; HPODE, hydroperoxyoctadecadienoic acid; LOOX, lipid hydroperoxides; PAF-AH, platelet-activating factor acetylhydrolase; PON, paraoxonase.

Adapted from Assmann G et al. *Annu Rev Med*. 2003;54:321–341. Adapted from *Annual Review of Medicine*, Volume 54 ©2003 by Annual Reviews www.annualreviews.org.

HDL–Mediated Inhibition of Adhesion Molecule Expression



MCP-1 = monocyte chemoattractant protein-1

Adapted from Nofer J-R et al. *Atherosclerosis* 2002;161:1–16.

Summary: HDL

Diagnosis

- HDL-C level likely best/sufficient
- Apo A-I, HDL-P, HDL_2-C good, *not* needed

Causes

- *Common*: insulin resistance, HTG (mod-sev), *poor* lifestyle (cigarettes, sedentary, central obesity), polygenic factors
- *Rare*: monogenic, androgen abuse

Consequences

- HTG (mild-moderate)
- Athero/CVD (most *common* dyslip. in CHD)

Treatment *difficult* (by TLC *or* drug)

Key Take-Away Messages: Major *Dyslipidemias*

- Chylomicrons and chylomicron remnants (apo B-48, etc.)
  - Mainly for transport of *dietary* TG (energy)
  - Seen in fasting plasma *only* if TG > 1000 (T ½=mins)
  - Increased risk of *pancreatitis* when TG > 1000
  - ~Always due to *decreased clearance* (↓LPL)
  - *Minor* role in atherogenesis (chylo remnants only)
- VLDL+IDL (apo B-100, apo Cs, apo E)
  - Common/moderate TG increase (TG 200-500)
  - Due to ↑*production* (fatty liver) + ↓*clearance* (↓LPL)
  - *Moderate* role in atherogenesis
- LDL (apo B-100)—also Lp(a) variant
  - Mainly for cholesterol transport
  - *Major* atherogenic factor
    - Oxidation/Inflammation
    - Endothelial dysfunction
- HDL (apo A-I, etc)
  - Major atheropreventive (blocks/reverses ~all adverse effects of VLDL, IDL, LDL)

Key Take-Away Messages: Major *Dyslipidemias* (cont.)

***Not* associated** w/-Insulin-resistance

- ↑LDL alone (Type IIa)—common *and* high-risk

Associated w/ Insulin-resistance

- ↑VLDL (usually w/ ↓HDL; if w/o ↑LDL = type IV)—common *and* high-risk
- ↓HDL-C (usually w/ ↑VLDL)—common *and* high-risk
- Mixed dyslipidemia: ↑LDL + ↑VLDL + ↓HDL (IIb, IV or V) —common *and* high-risk