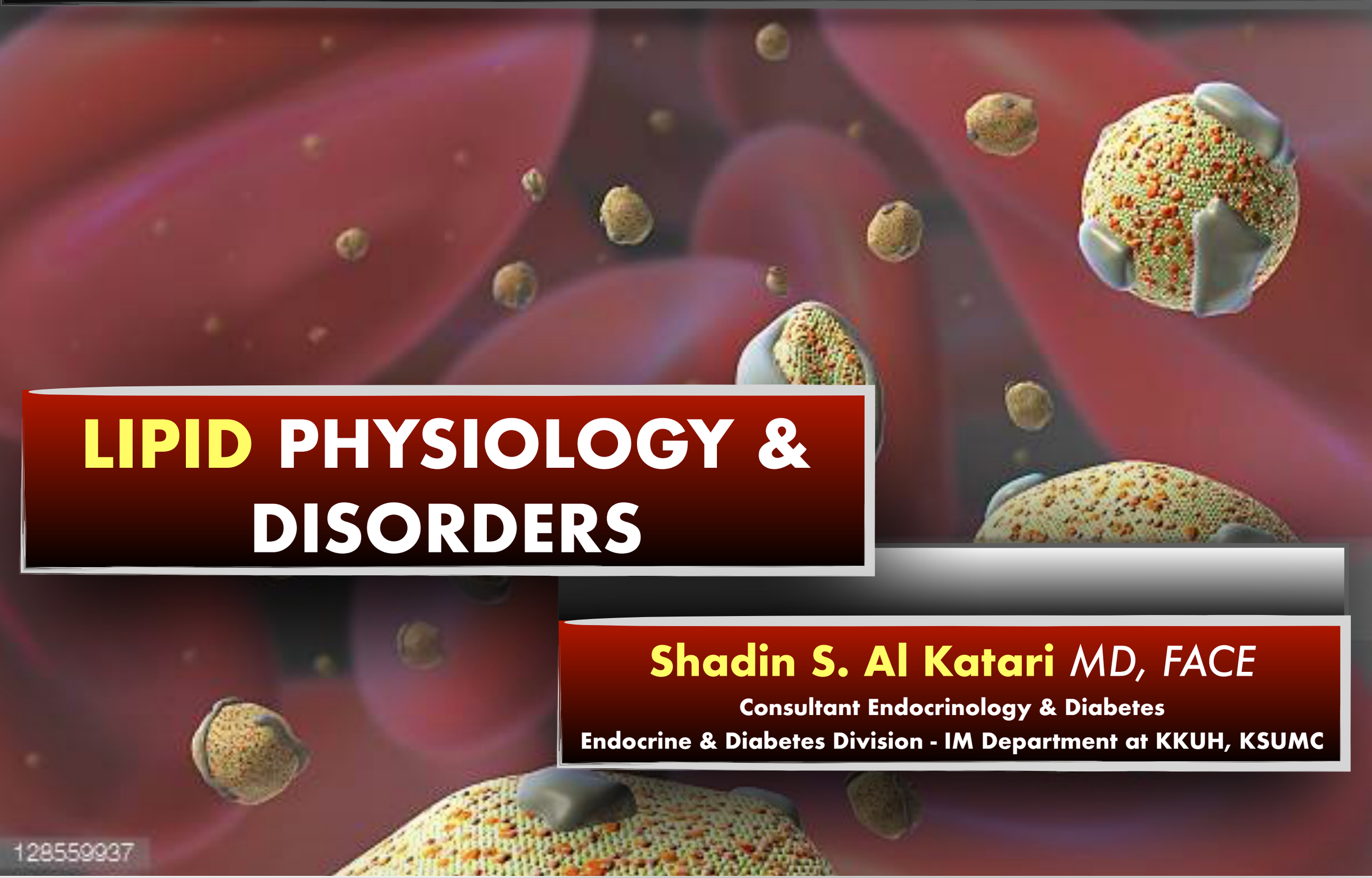

LIPID PHYSIOLOGY & DISORDERS

Shadin S. Al Katari *MD, FACE*

Consultant Endocrinology & Diabetes

Endocrine & Diabetes Division - IM Department at KKUH, KSUMC

AGENDA:

- ➡Introduction
- ➡Lipoprotein classes
- ➡Physiology of lipid metabolism
- ➡Dyslipidemia types & etiology
- ➡Clinical findings & associated risks with types of dyslipidemia
- ➡Management of dyslipidemia

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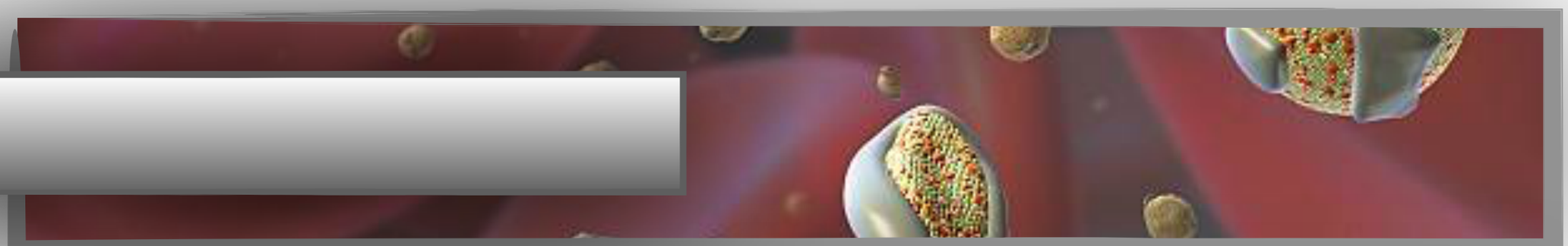
INTRODUCTION:

Lipids, such as cholesterol & triglycerides, are insoluble in plasma.

Circulating lipid is carried in **LIPOPROTEINs** that <u>transport the lipid to various tissues for:</u>

- Energy utilization
- Fat deposition
- Steroid hormone production
- Bile acid formation.

<u>The lipoprotein consists of</u> esterified & unesterified cholesterol, triglycerides, phospholipids, & protein.



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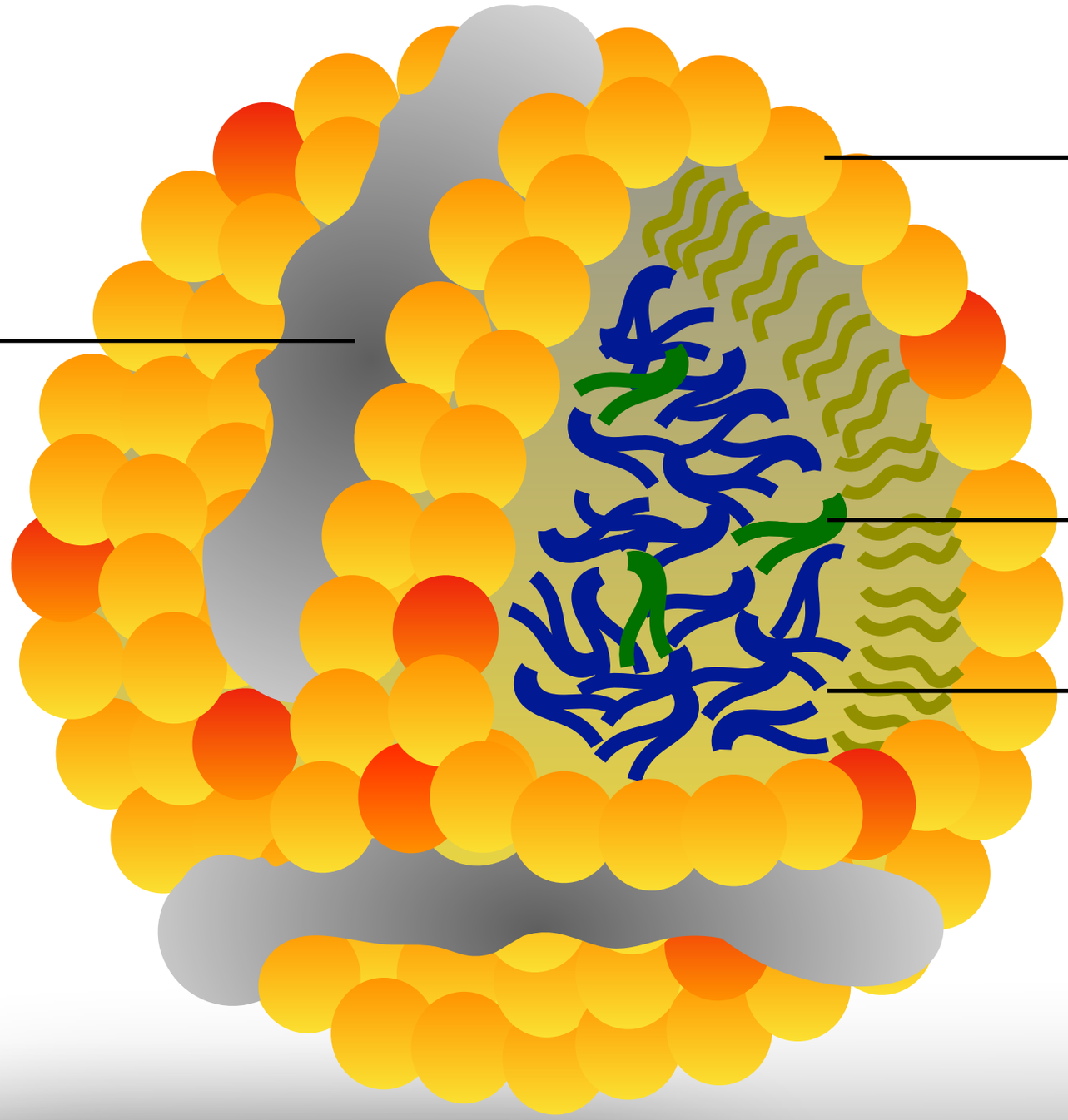
LIPOPROTEIN Particle:



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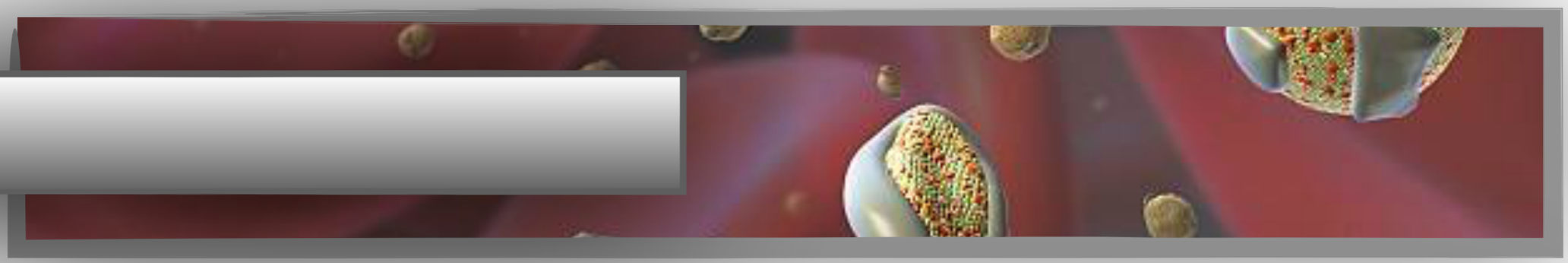
CLASSIFICATION of LIPOPROTEINS:

The five major lipoproteins are presented below:

- **Chylomicrons**
- **Very low density lipoprotein (VLDL)**
- **Intermediate density lipoprotein (IDL)**
- **Low density lipoprotein (LDL)**
- **High density lipoprotein (HDL)**



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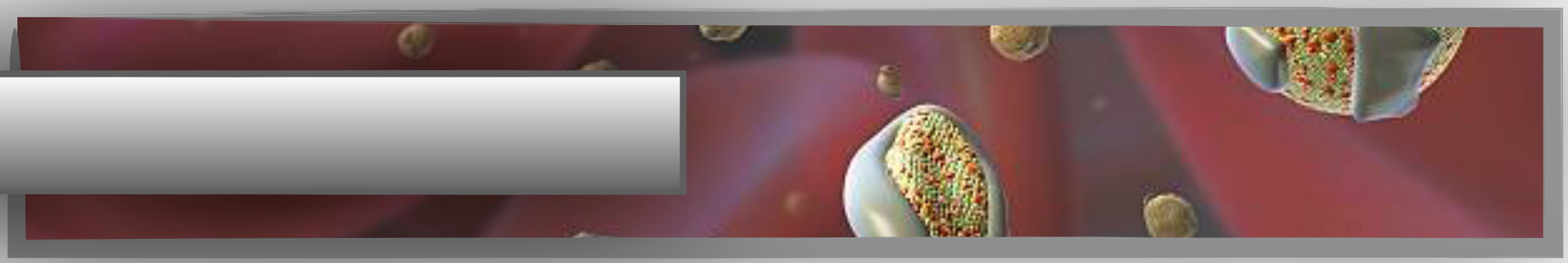
APOLIPOROTINS:

Are presented below:

- **Apolipoprotin A (I, II, IV)**
- **Apolipoprotin B (48, 100)**
- **Apolipoprotin C (I, II, III)**
- **Apolipoprotein E**
- **Apolipoprotein D**
- **Apo(a)**



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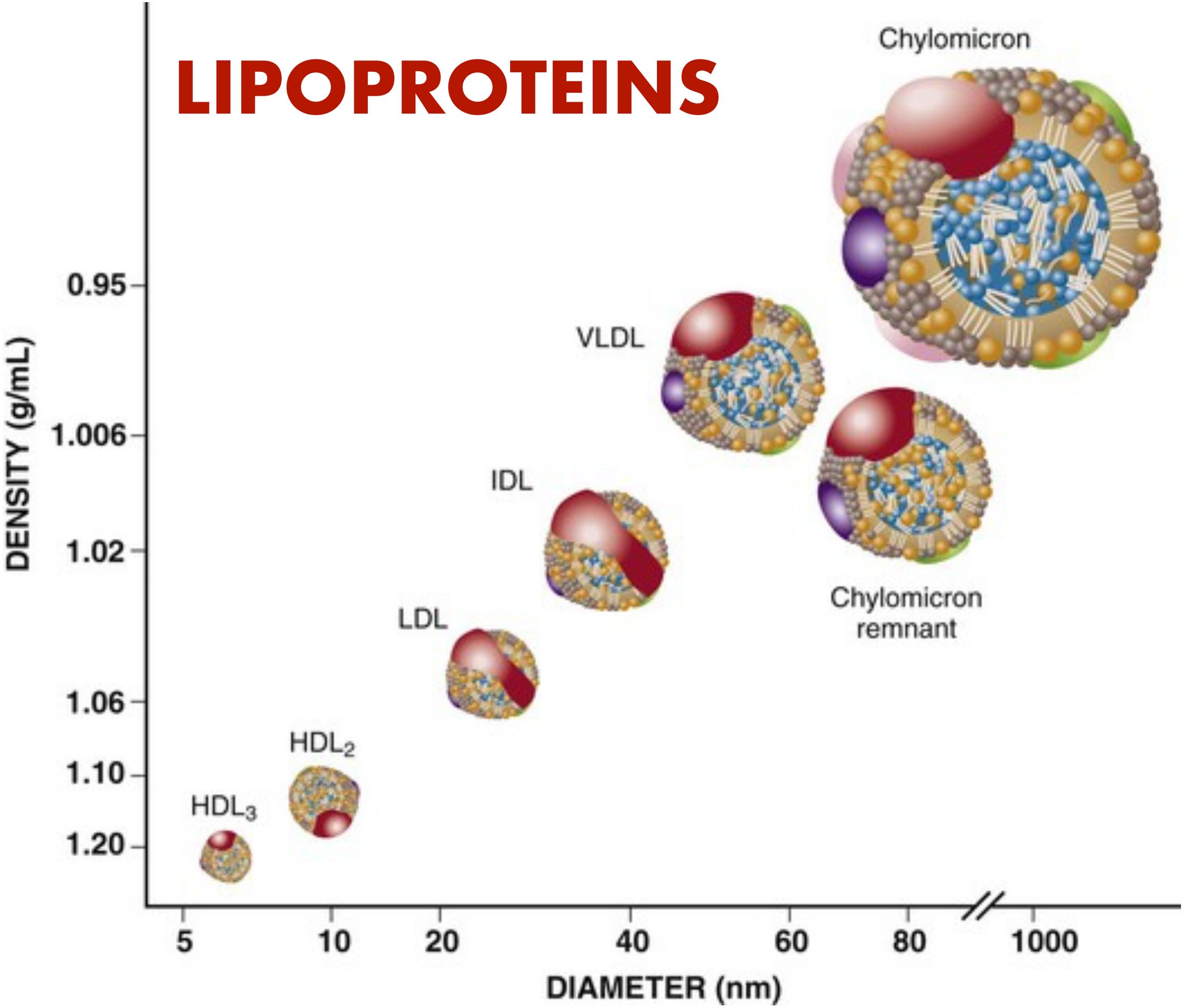
1 LIPOPROTEINS



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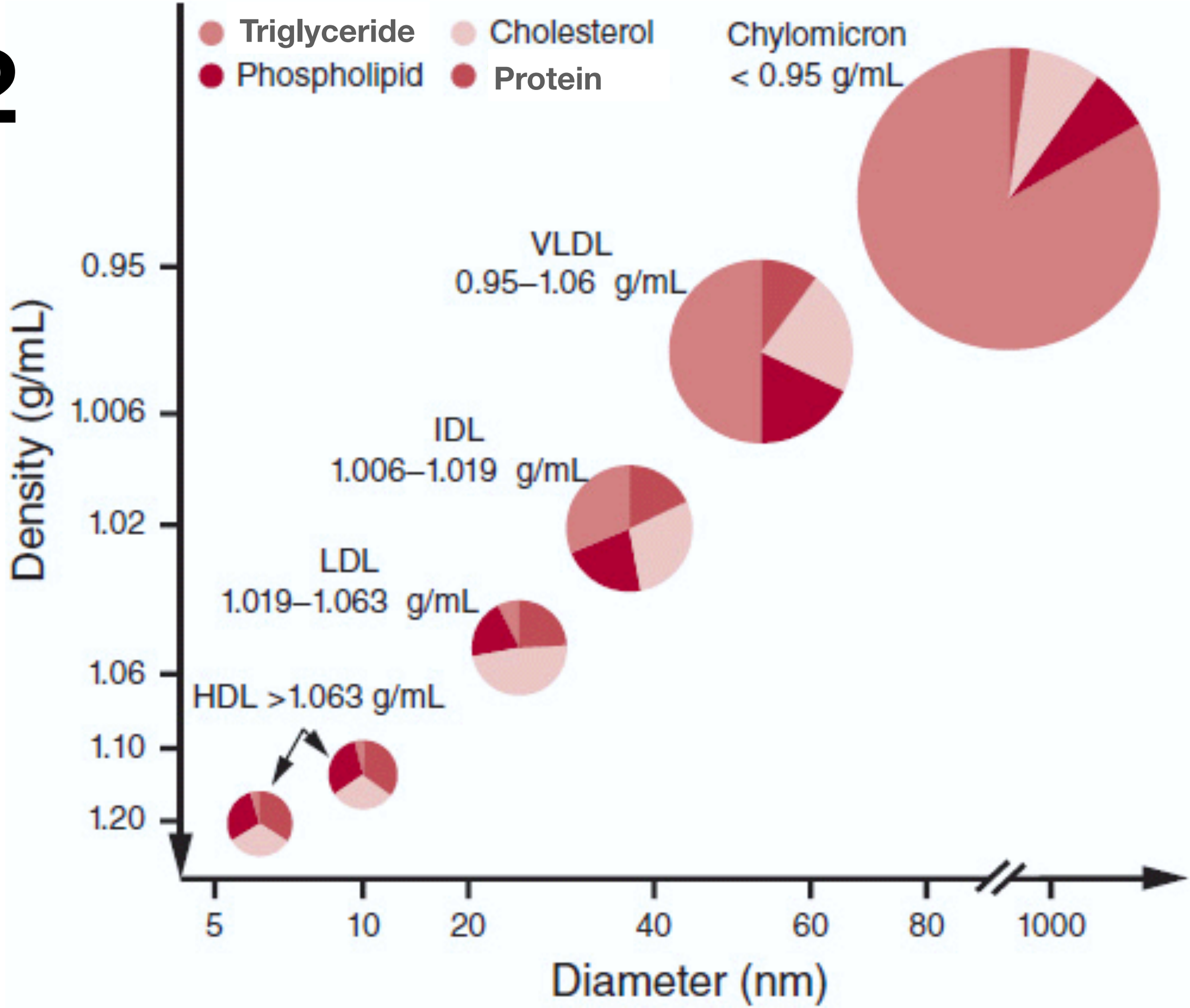
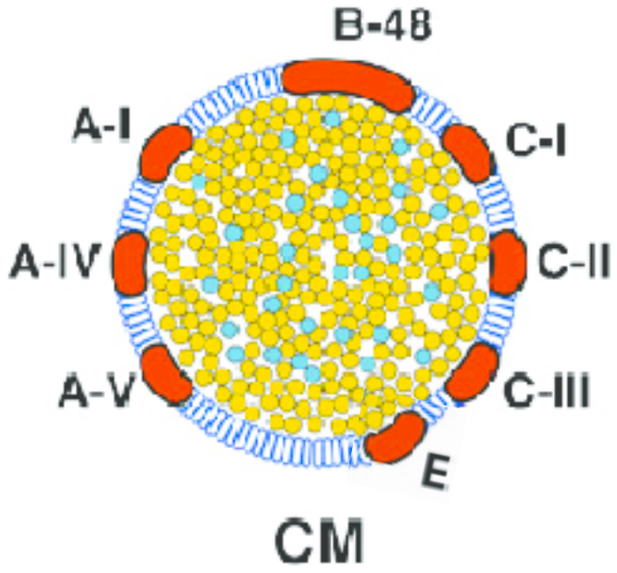
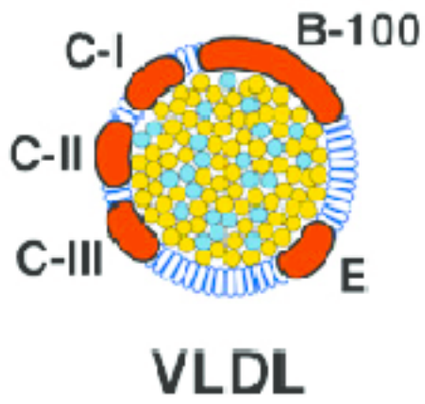

Triglyceride
Cholesterol
Phospholipid
Protein
Chylomicron
< 0.95 g/mL
VLDL
0.95–1.06 g/mL
IDL
1.006–1.019 g/mL
LDL
1.019–1.063 g/mL
HDL >1.063 g/mL
Density (g/mL)
0.95
1.006
1.02
1.06
1.10
1.20
5
10
20
40
60
80
1000
Diameter (nm)

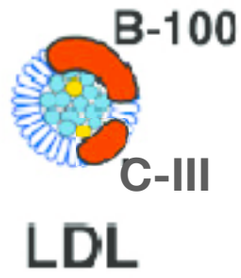
3

Chylomicrons: are very large particles that carry dietary lipid. with a variety of Apo. A-I, A-II, A-IV, B-48, C-I, C-II, C-III, & E.



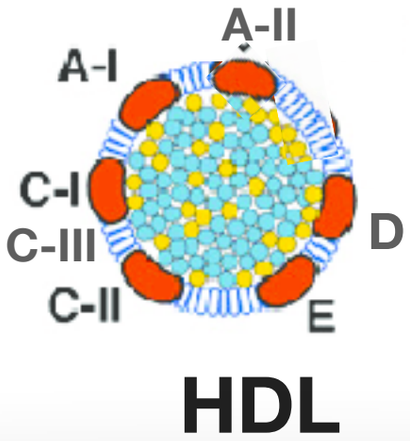
(VLDL): carry endogenous triglycerides & to a lesser degree cholesterol. The App B-100, C-I, C-II, C-III, & E.

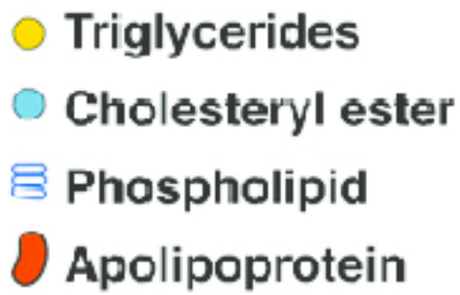




(LDL): carry cholesterol esters with Apo B-100 & C-III.

(HDL): carry cholesterol esters. With Apo. A-I, A-II, C-I, C-II, C-III, D, & E.





(IDL): carry cholesterol esters & triglycerides. with Apo. B-100, C-III, & E.

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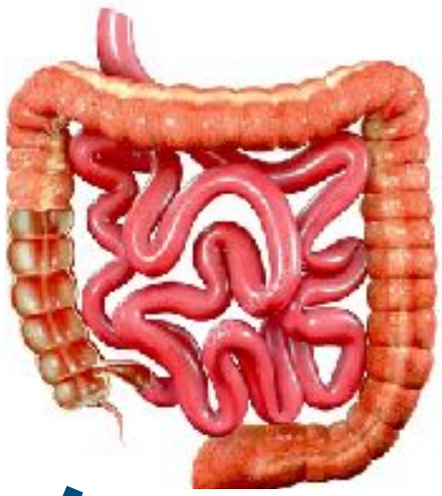
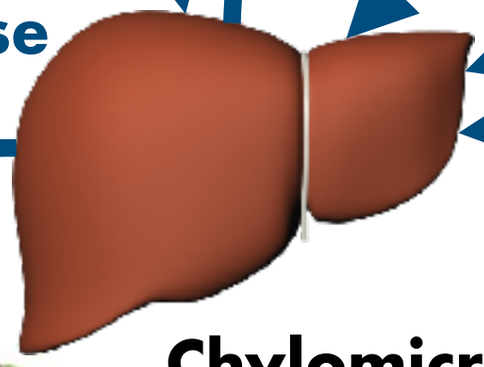
4 Exogenous & Endogenous Pathway for Lipid Metabolism

HDL precursor
Apo A, E
(Liver & insistine)

CTEP/LACT/
ABCA1
HDL
Abo A,C,D,E
reverse
cholesterol
transport

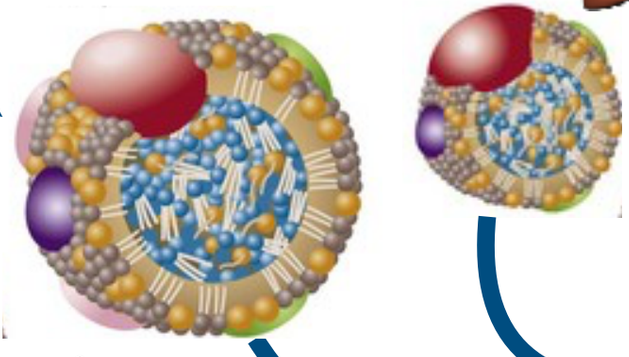


Hepatic lipase

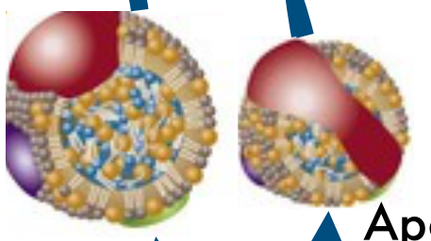


LDL
Apo B100,C

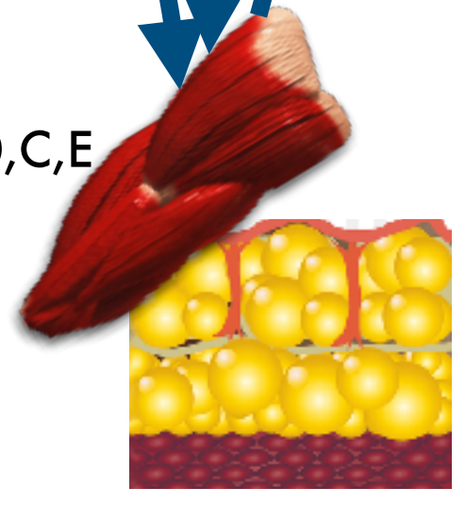
VLDL Apo
B100,C,E



Chylomicron Remnant
Apo B48,C,E



IDL
Apo B100,C,E



Chylomicron
Apo A,B48,C,E

Lipoproteinlipase
Mammary, Fat tissue & muscle

DYSLIPIDEMIAS:

Are disorders of lipoprotein metabolism that result in the following abnormalities:

- High total cholesterol (TC)
- High low-density lipoprotein cholesterol (LDL-C)
- High non-high-density lipoprotein cholesterol (non-HDL-C)
- High triglycerides (TG)
- Low high-density lipoprotein cholesterol (HDL-C)

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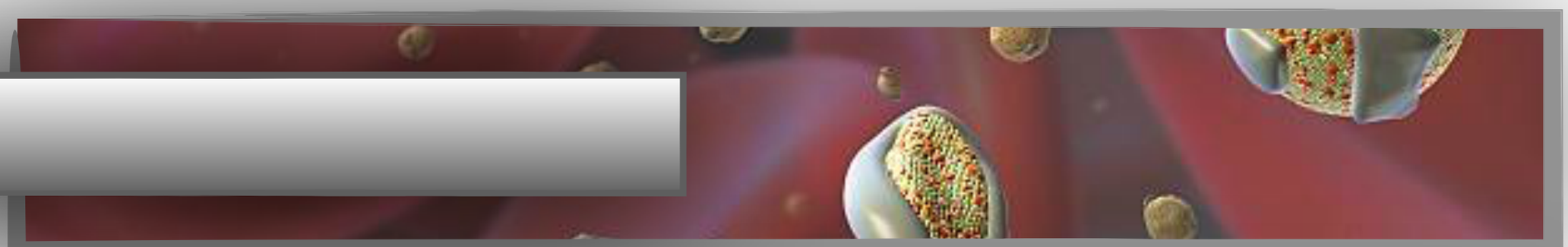
ETIOLOGY:

categorized as follows:

- **Monogenic** conditions due to a single gene defect, such as familial hypercholesterolemia, familial defective apolipoprotein B, & familial hypertriglyceridemia.

- **Secondary dyslipidemia** related to specific diseases, conditions, or exposures, such as obesity, nephrotic syndrome, T2DM, or drugs (eg, alcohol, isotretinoin).

- **Idiopathic**, related to polygenic defects



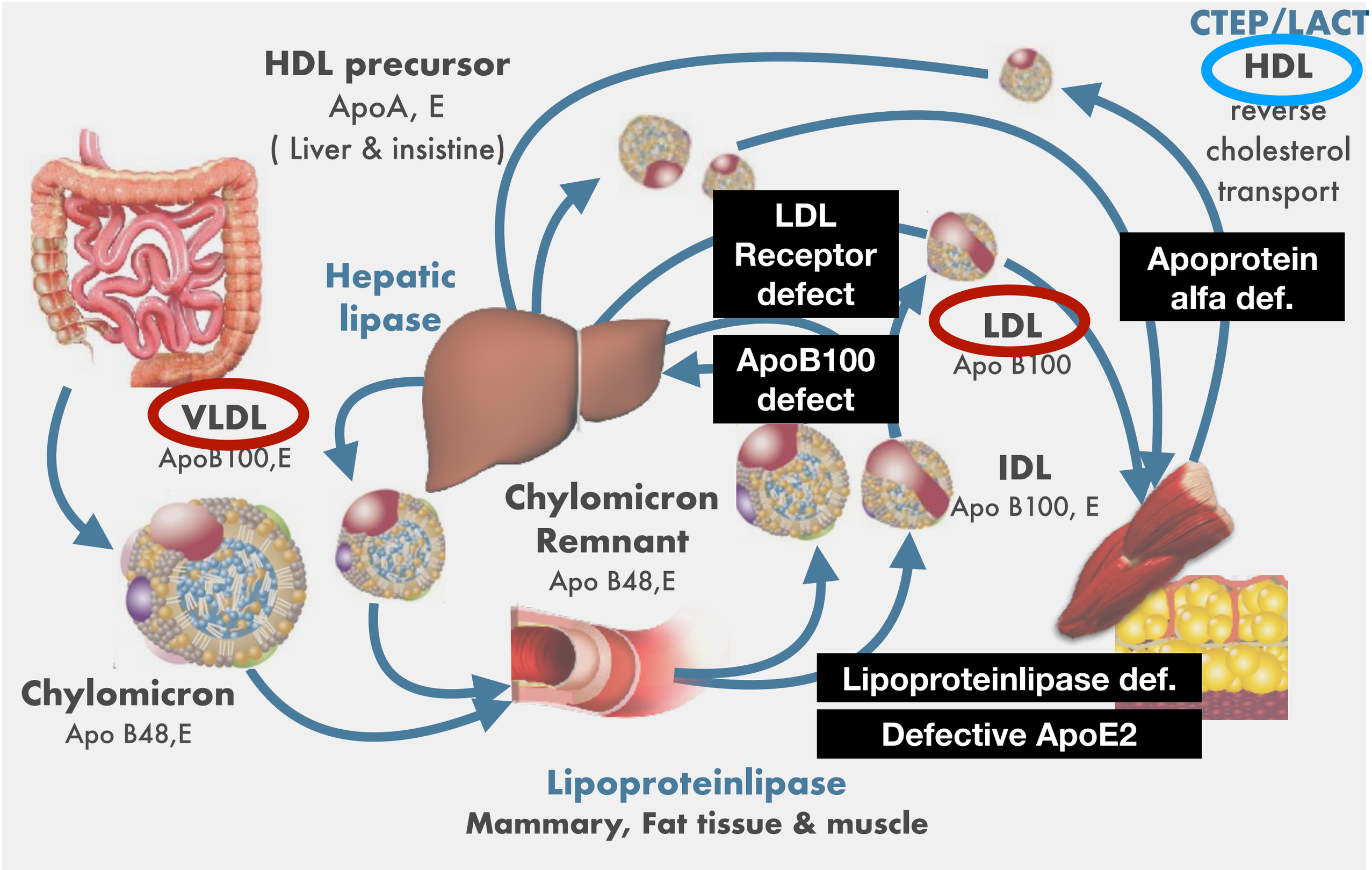
Fredrickson classification of lipid disorders

Frederickson phenotype	Lipoprotein abnormality	Typical lipid levels
I	Chylomicrons	TG >99th percentile
IIa	LDL	TC >90th percentile; depending upon type, may also see apolipoprotein B ≥90th percentile
IIb	LDL and VLDL	Depending upon type, TC and/or TG ≥90th percentile and apolipoprotein B ≥90th percentile
III	Remnants of VLDL and chylomicrons	TC and TG >90th percentile
IV	VLDL	TC >90th percentile; depending upon type, may also see TG >90th percentile or low HDL
V	Chylomicrons and VLDL	TG >99th percentile

Genetic Causes of Dyslipidemia

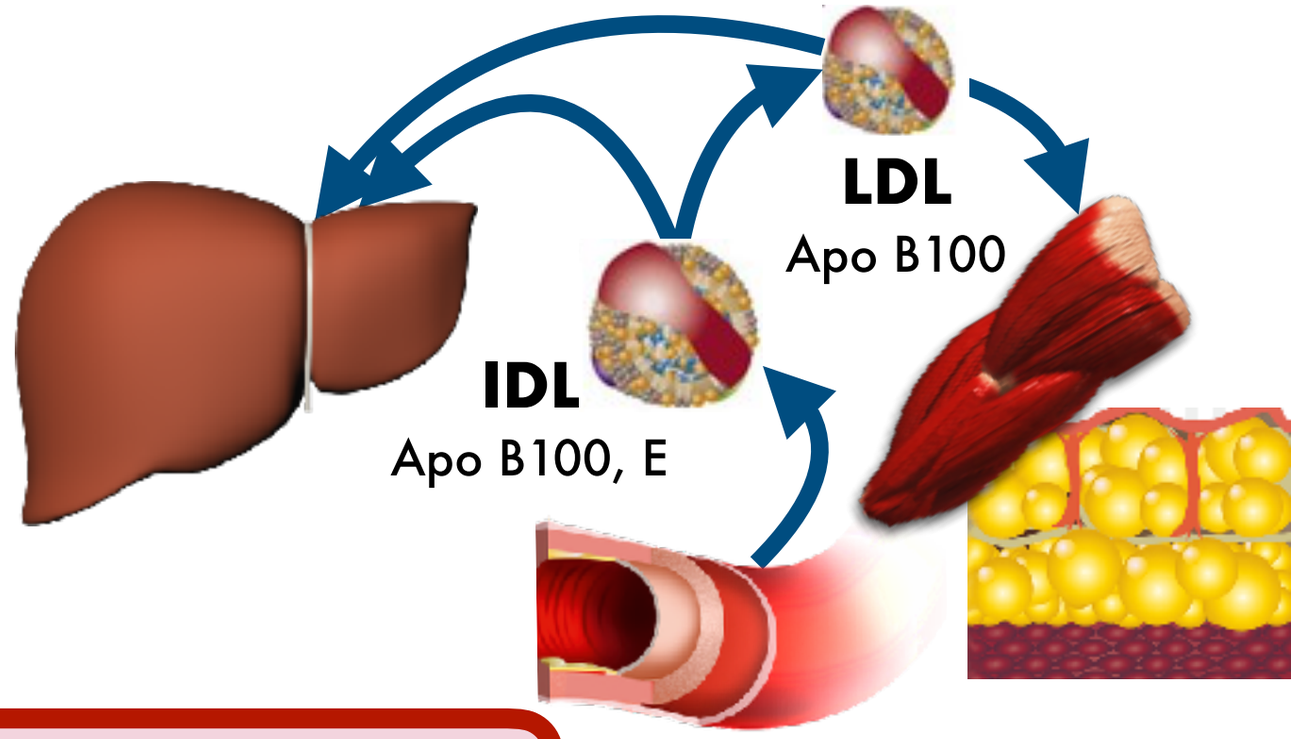
Disease	Lipid Profile	Prevalence	Etiology
Primary Hypercholesterolemia			
Familial Hypercholesterolemia	↑↑ LDL	1:500 (+/-)	↓ LDL Receptor
Familial defective ApoB100	↑↑ LDL	1:100	↓ApoB100 binding to LDLR
Hypercholesterolemia	↑ Chol	Common	unknown
Primary Hypertriglyceridemia			
Familial Hypertriglycredemia	↑TG ↓HDL ↑VLDL	Common	↓VLDL breakdown ↑ VLDL synthesis
Mixed Hyperlipidemia			
Familial Combined Hyperlipidemia	↑LDL↑TG ↓ HDL	1:100	Unknown, dominant inheritance
Disorders of HDL metabolicm			
Polygenic HDL	↓ HDL	Common	Obesity, diabetes high carb diets
Familial Hypoalfalipoproteinemia	↓ HDL	1:100	Unknown, dominant inheritance

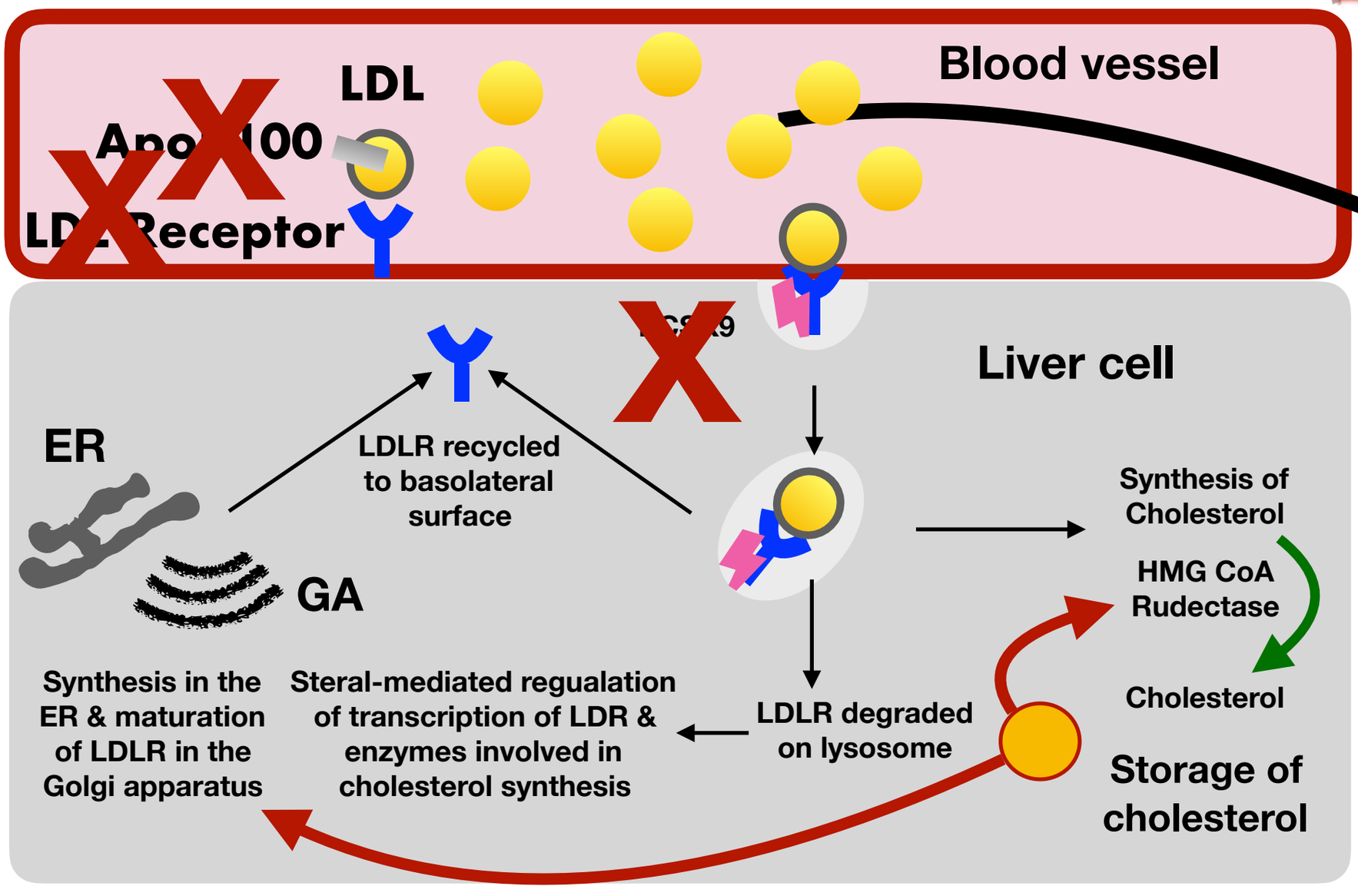
Genetic etiology of DYSLIPIDEMIAs



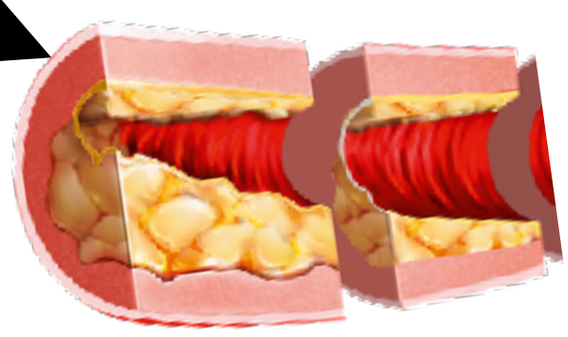
LDL Receptor pathway

FAMILIAL HYPERCHOLESTEROLEMIA



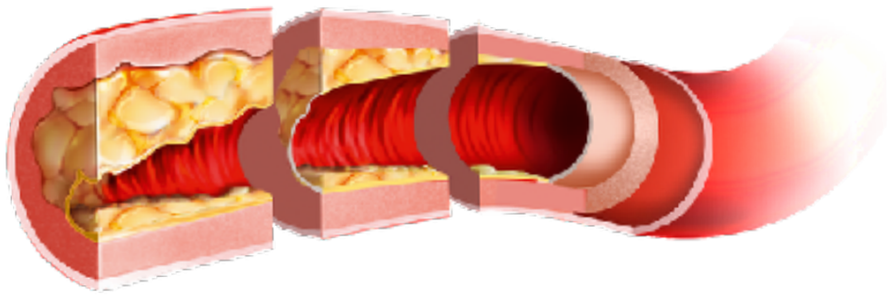


Lipoproteinlipase
Mammary, Fat tissue & muscle



Cell membrane
Steroid hormones
Bile acids

FAMILIAL HYPERCHOLESETROLEMIA



FH is a genetically modulated clinical syndrome characterized by:

- Elevated low-density lipoprotein cholesterol (LDL-C) level from birth
- Xanthomata in untreated adults and patients with homozygous FH
- Early onset coronary heart disease (CHD)

Caused by:

- Mutation in LDL receptor gene (LDLR)
- Mutation in the Genes that code for proportion converts substilisin Kevin 9 (PCSK9)
- Mutation in Apoliporotein B

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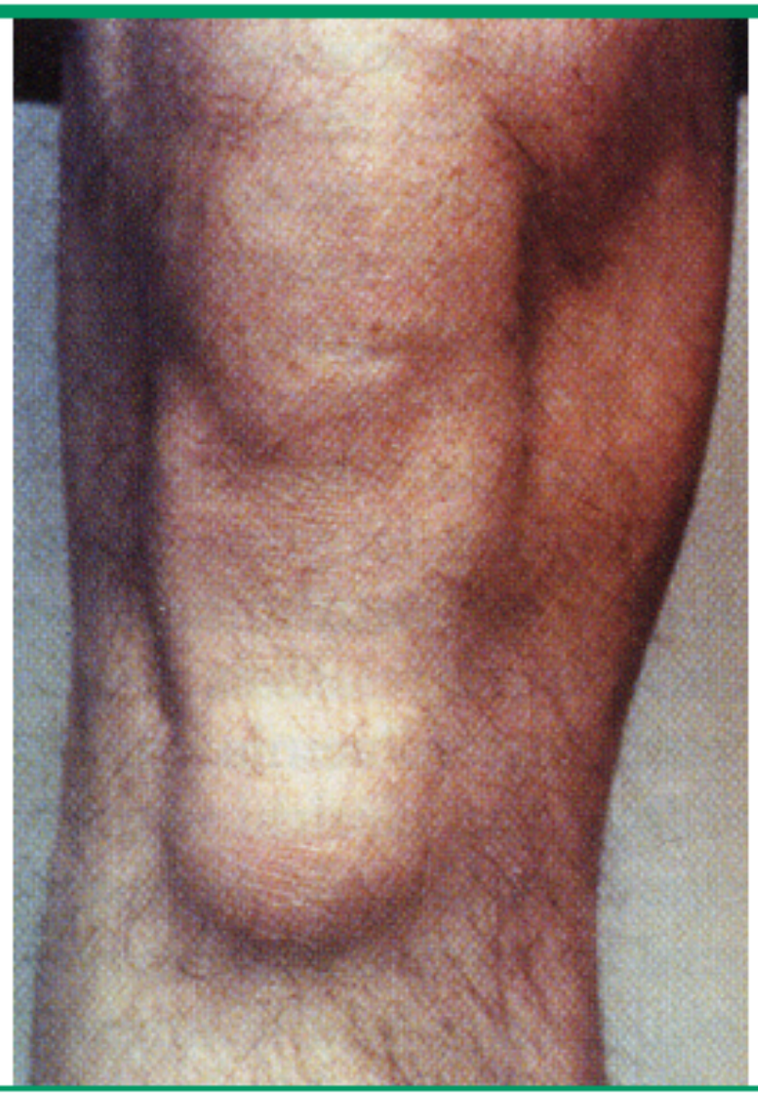
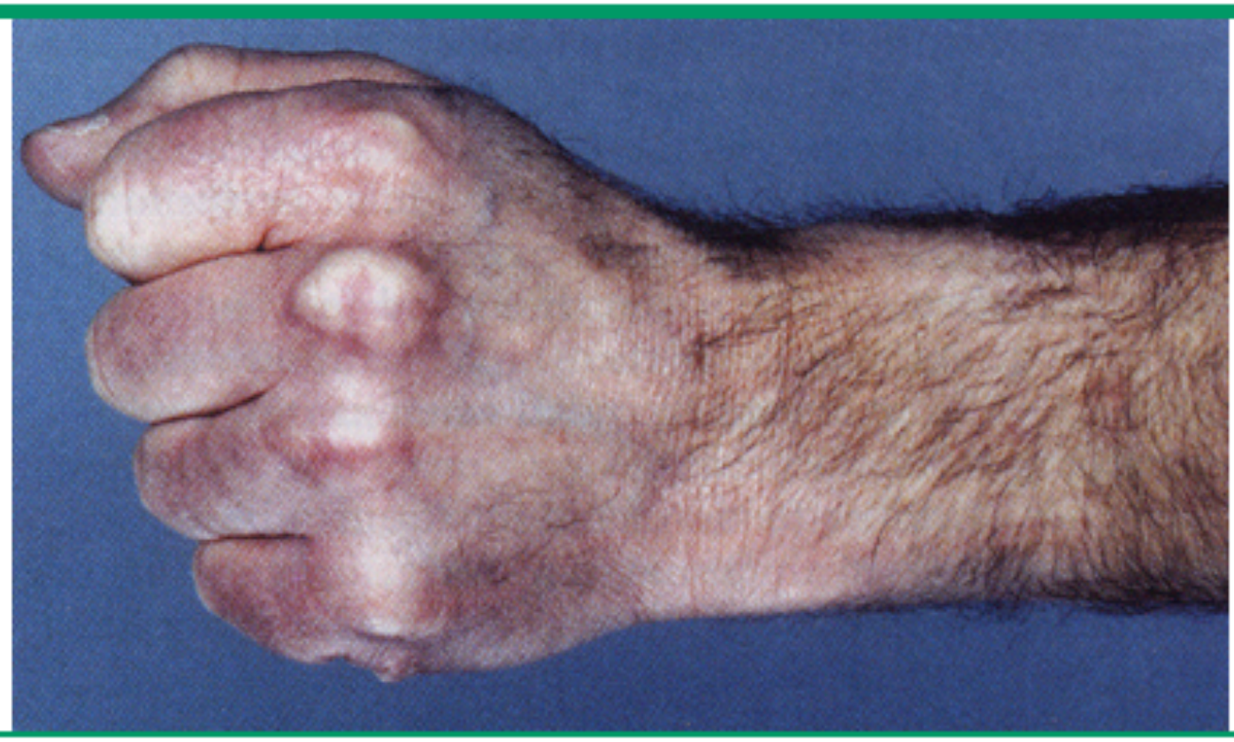
FAMILIAL HYPERCHOLESETROLEMIA

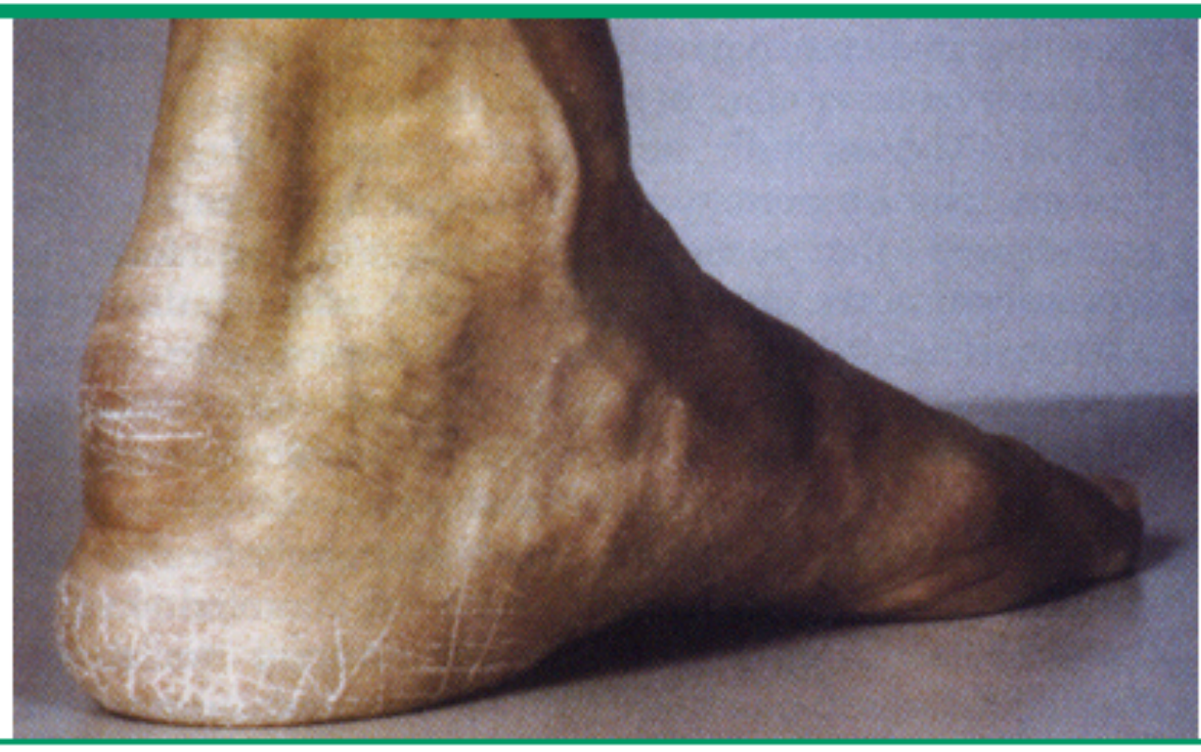
Subperiosteal xanthomata



Tendon xanthomata

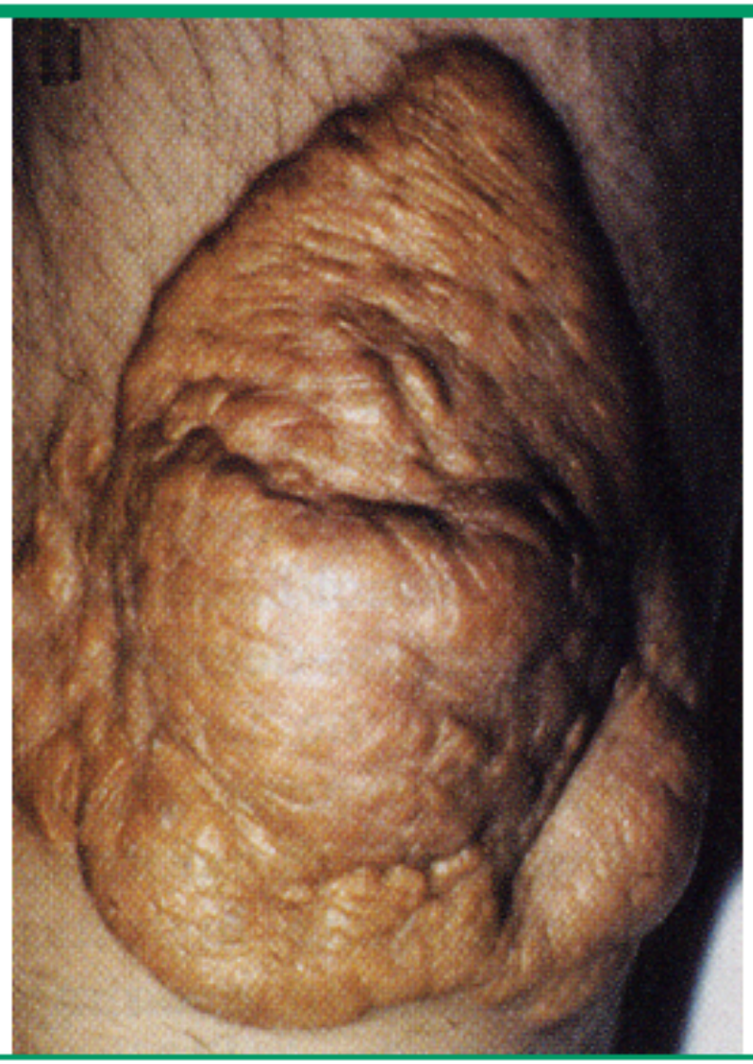


Achilles tendon xanthoma



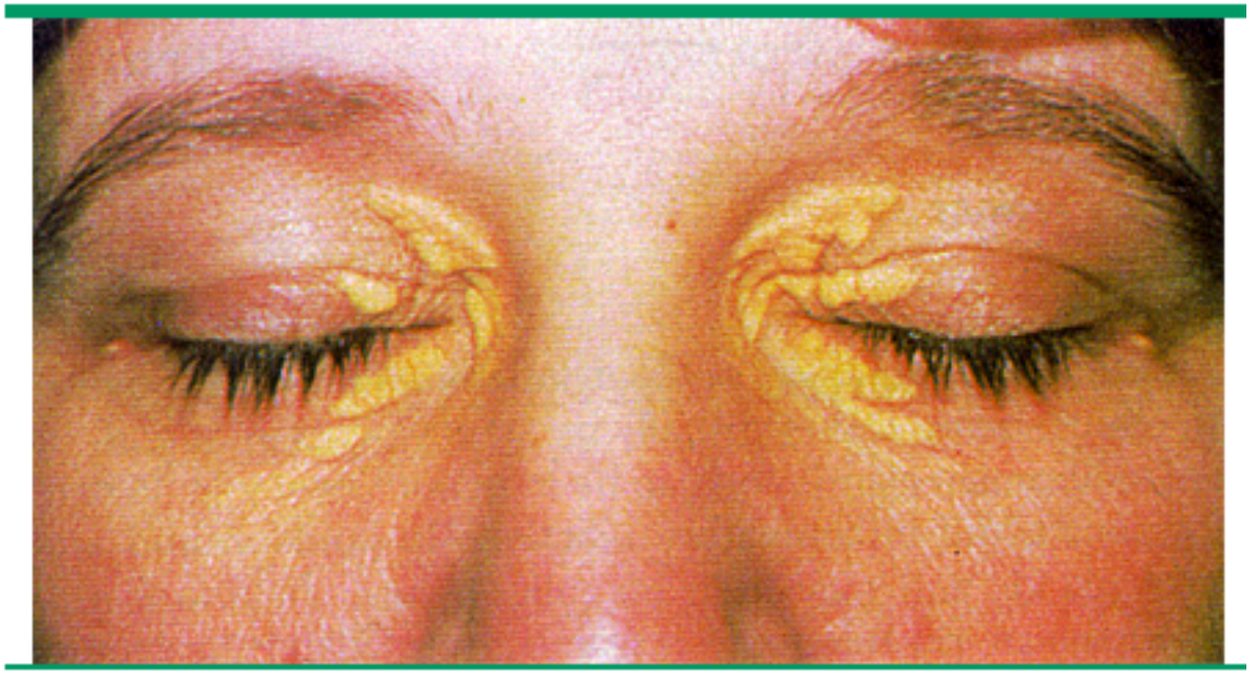
FAMILIAL HYPERCHOLESETROLEMIA

Planar xanthoma



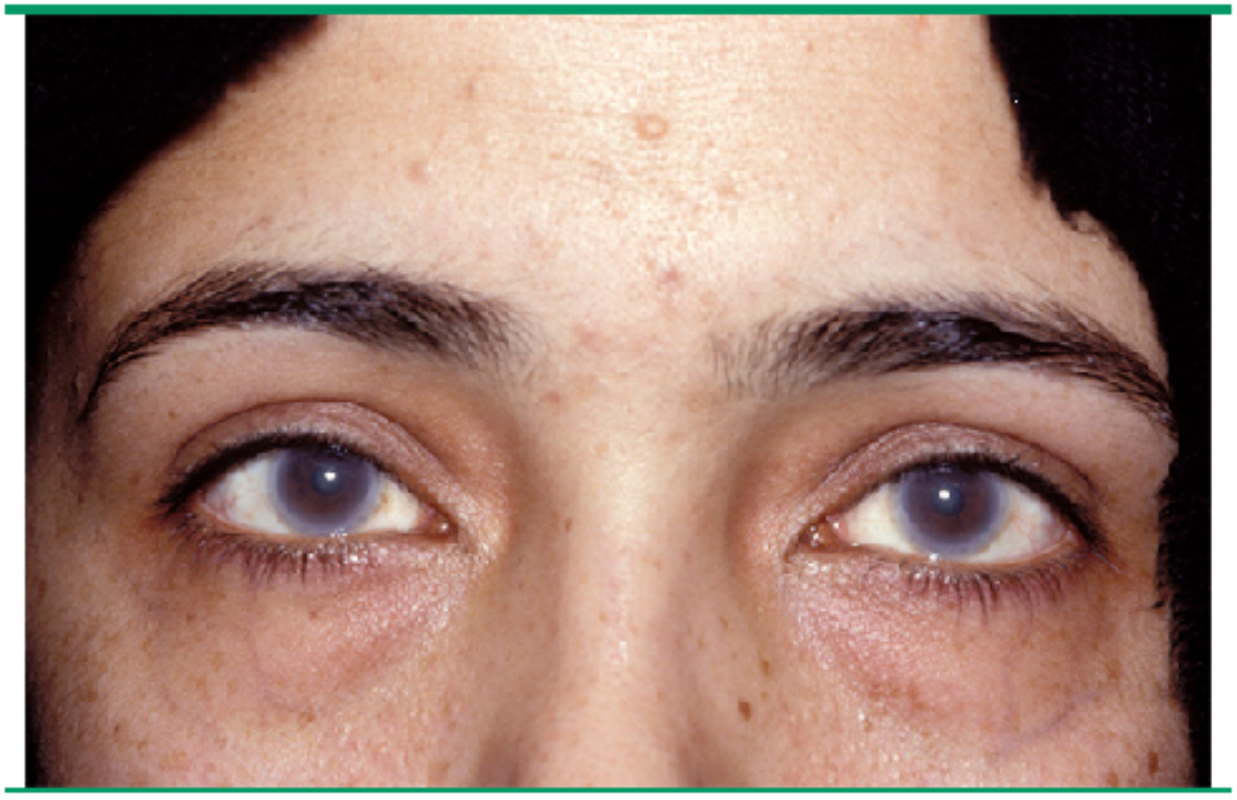
Planar xanthoma in the antecubital fossa of a patient with homozygous familial hypercholesterolemia.

Xanthelasma



Yellow plaques are present bilaterally.

Corneal arcus



Corneal arcus is a white or grey arc or ring around the cornea due to deposition of cholesterol. It is commonly seen in older adults (called arcus senelis), but is an abnormal finding in individuals under age 40.

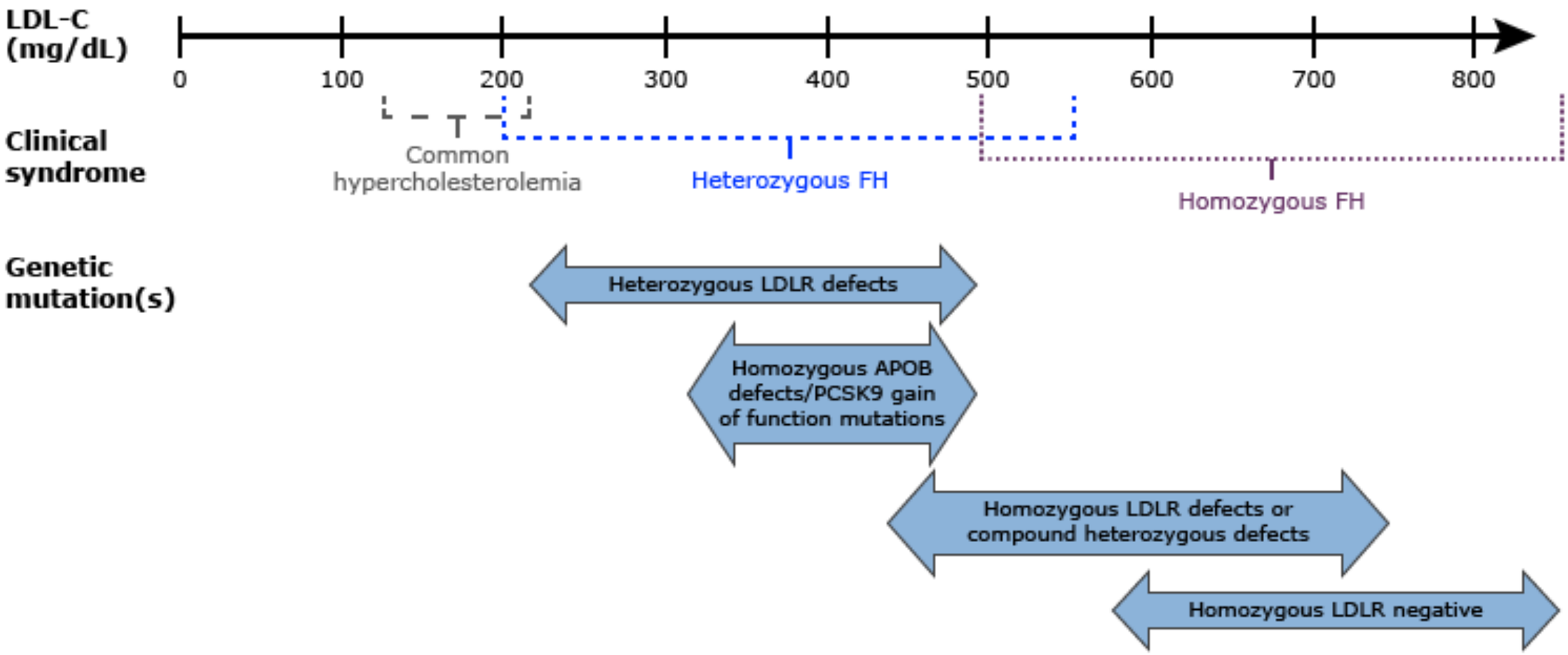
Clinical suspicion:

A diagnosis of FH should be suspected in children with any of the following:

- Elevated plasma LDL-C: The level of LDL-C that warrants further evaluation depends upon whether additional family members have known hypercholesterolemia &/or early cardiovascular disease (CVD).
  - In patients with a negative or unknown family history, a LDL-C level of ≥190 mg/dL (4.9 mmol/L) suggests FH
  - In patients with a positive family history of hypercholesterolemia &/or early CVD, an LDL-C level of ≥160 mg/dL (4.1 mmol/L) is suggestive of FH.

- Family member with known FH or elevated cholesterol ([TC] >240 mg/dL [6.2 mmol/L] in either parent).
- Tendon xanthomas in the child or family member(s).
- Premature CHD in the child or family member(s).
- Sudden premature cardiac death in a family member.

LDL cholesterol levels and genetic mutations in familial hypercholesterolemia



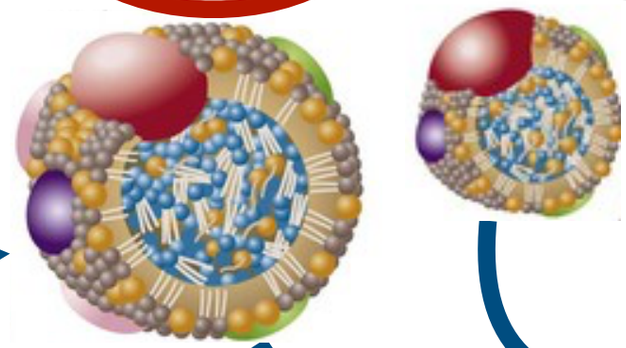
LDL-C units are mg/dL; divide by 38.67 to convert to mmol/L.

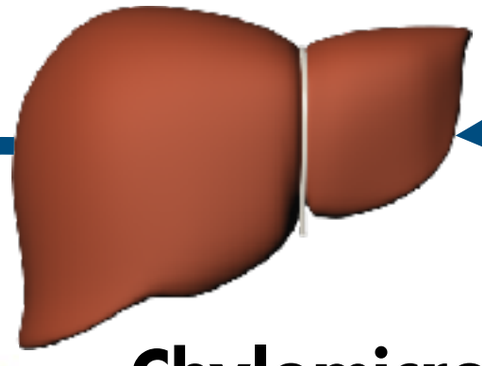
LDL-C: low density lipoprotein cholesterol; FH: familial hypercholesterolemia; LDLR: LDL receptor gene; APOB: apolipoprotein B gene; PCSK9: proprotein convertase subtilisin kexin 9.

Exogenous Pathway for Lipid Metabolism

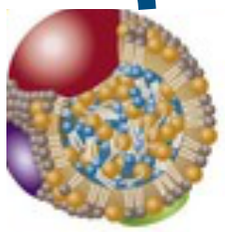
FAMILIAL HYPERTRIGLYCREDEMIA

VLDL
ApoB100,E





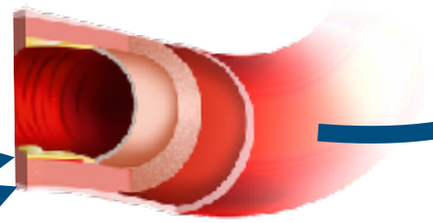
Chylomicron Remnant
Apo B48,E



Chylomicron
Apo B48,E

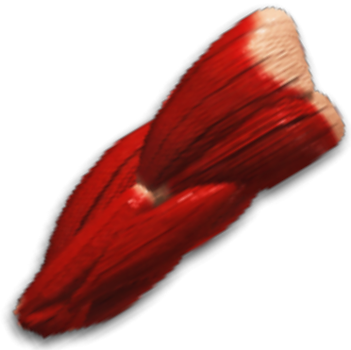
X

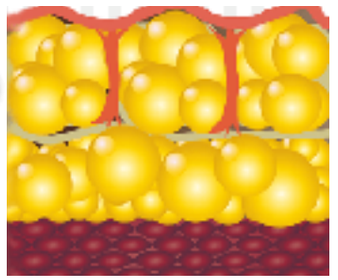
A E



X

Lipopro inlipase
Mammary, F sue & muscle



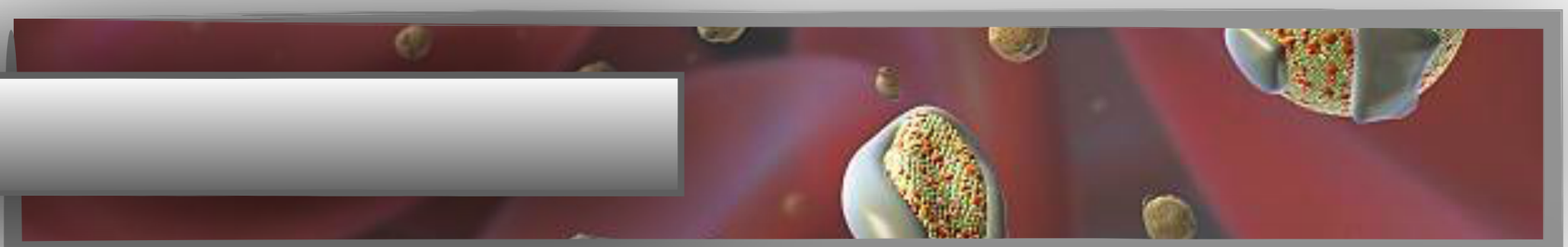


FAMILIAL HYPERTRIGLYCREDEMIA

DEFINITION AND PREVALENCE:

The serum TG concentration can be stratified in terms of population percentiles &/or coronary risk:

- Normal – <150 mg/dL (1.7 mmol/L) **33%**
- Borderline high – 150 to 199 mg/dL (1.7 to 2.2 mmol/L). **18%**
- High – 200 to 499 mg/dL (2.3 to 5.6 mmol/L). **1.7%**
- Very high – ≥500 mg/dL (≥5.6 mmol/L). **0.4%**



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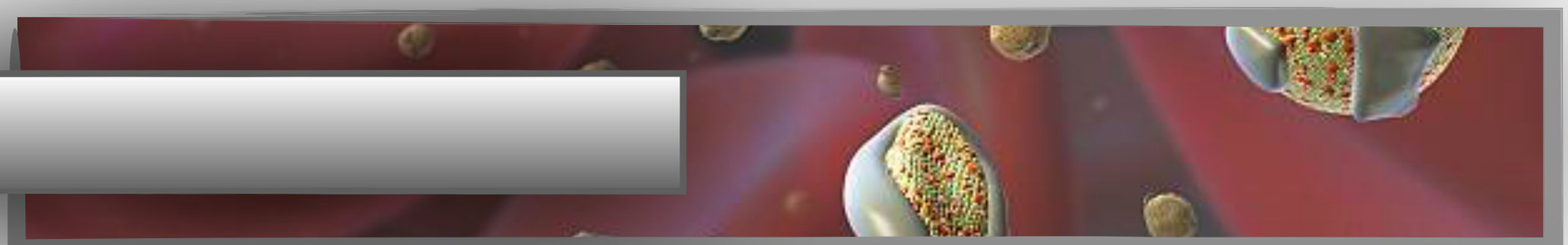
CAUSES:

Acquired disorders

- Obesity
- Diabetes mellitus
- Nephrotic syndrome
- Hypothyroidism
- Pregnancy.
- Estrogen replacement administered orally.
- Tamoxifen
- Beta blockers
- Immunosuppressive medications, such as glucocorticoids & cyclosporine
- HIV antiretroviral regimens
- Retinoids.

Hereditary disorders

- Chylomicronemia
- Familial hypertriglyceridemia
- Familial combined hyperlipidemia
- Familial dysbetalipoproteinemia



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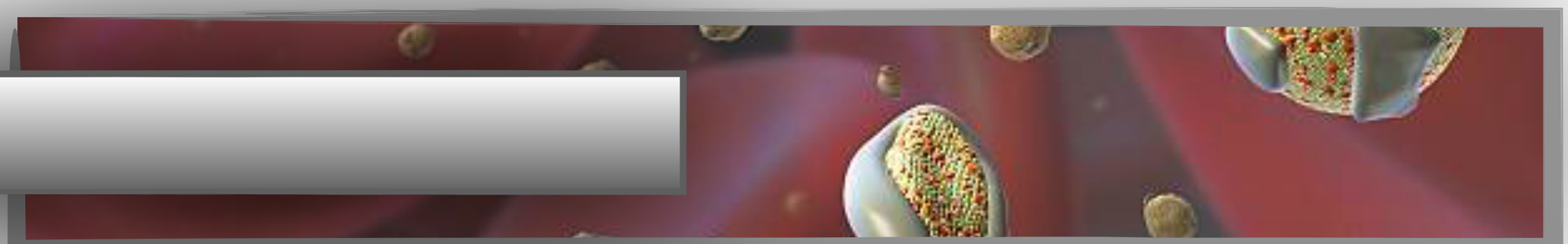
CLINICAL MANIFESTATIONS:

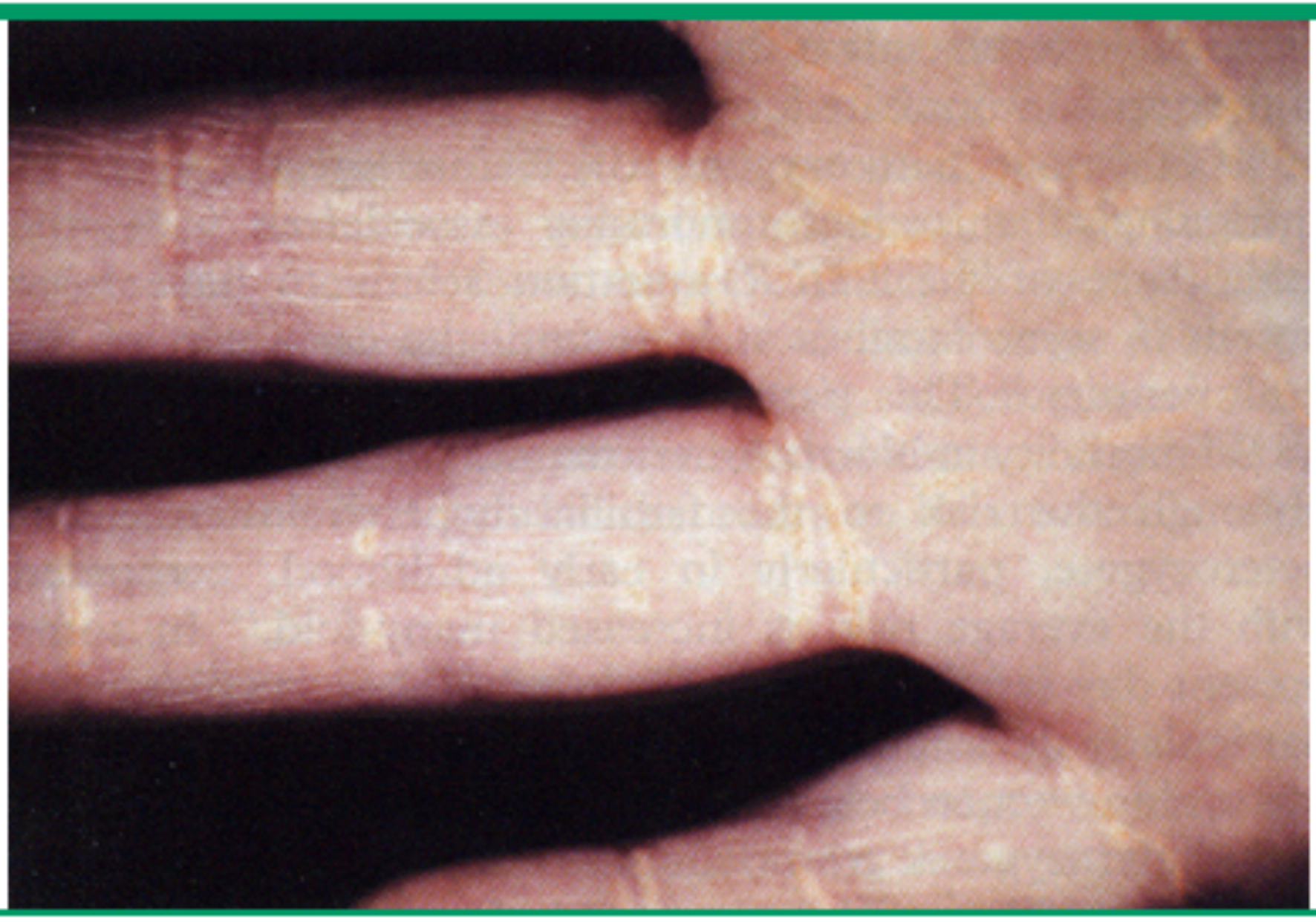
- In patients with **acquired disorders** such as diabetes or obesity, clinical manifestations are usually due to the underlying disorder rather than the lipid abnormality.

- In patients with **hereditary disorders,** skin lesions such as xanthomas & xanthelasmas may be present.
- In patients with very high TG levels (above 1000 mg/dL [11 mmol/L]), pancreatitis may develop.



FAMILIAL DYSBETALIPOPROTEINEMIA

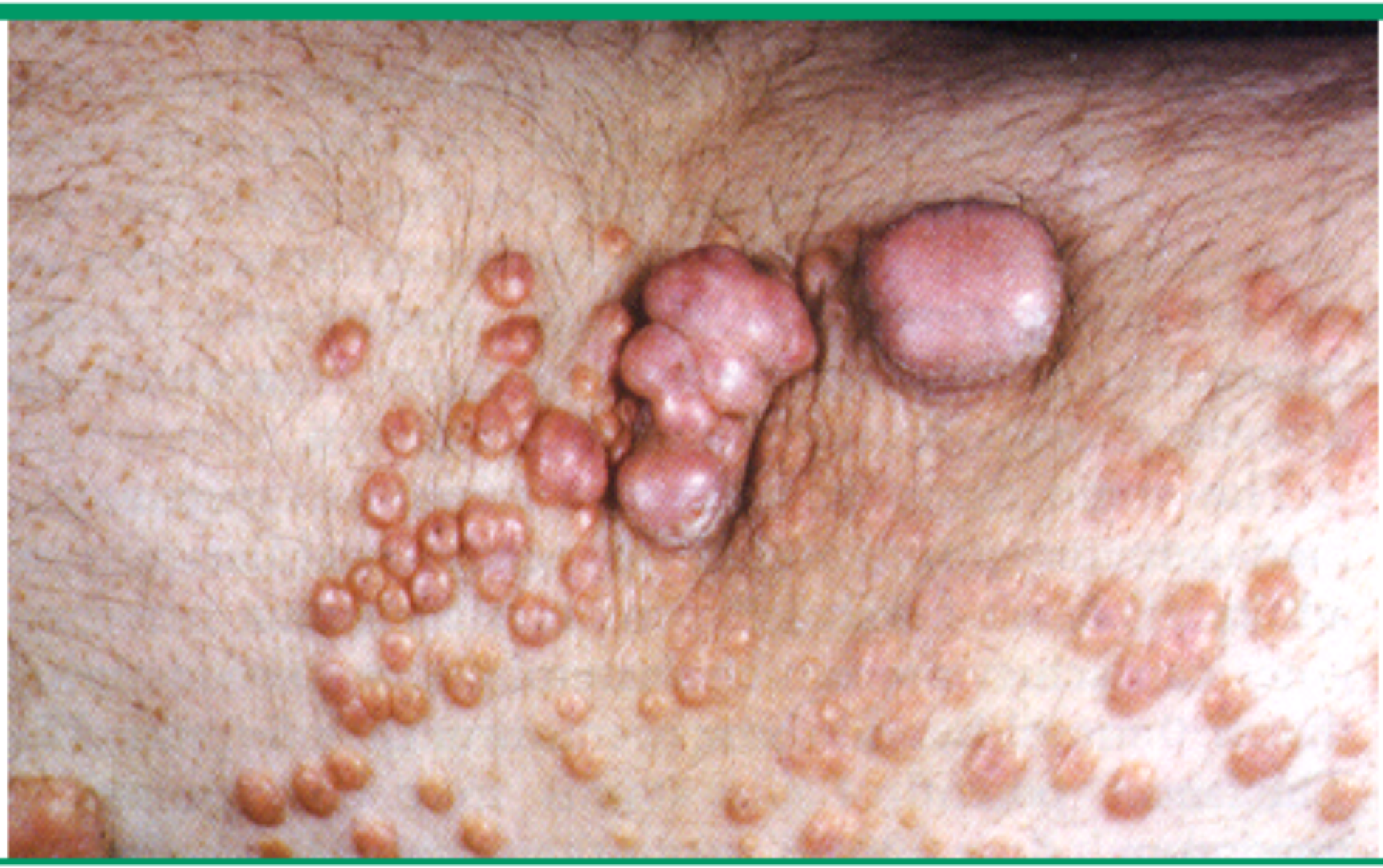
Palmar xanthomata



Striate xanthomata of the palmar creases in a patient with type III hyperlipoproteinemia.

FAMILIAL DYSBETALIPOPROTEINEMIA

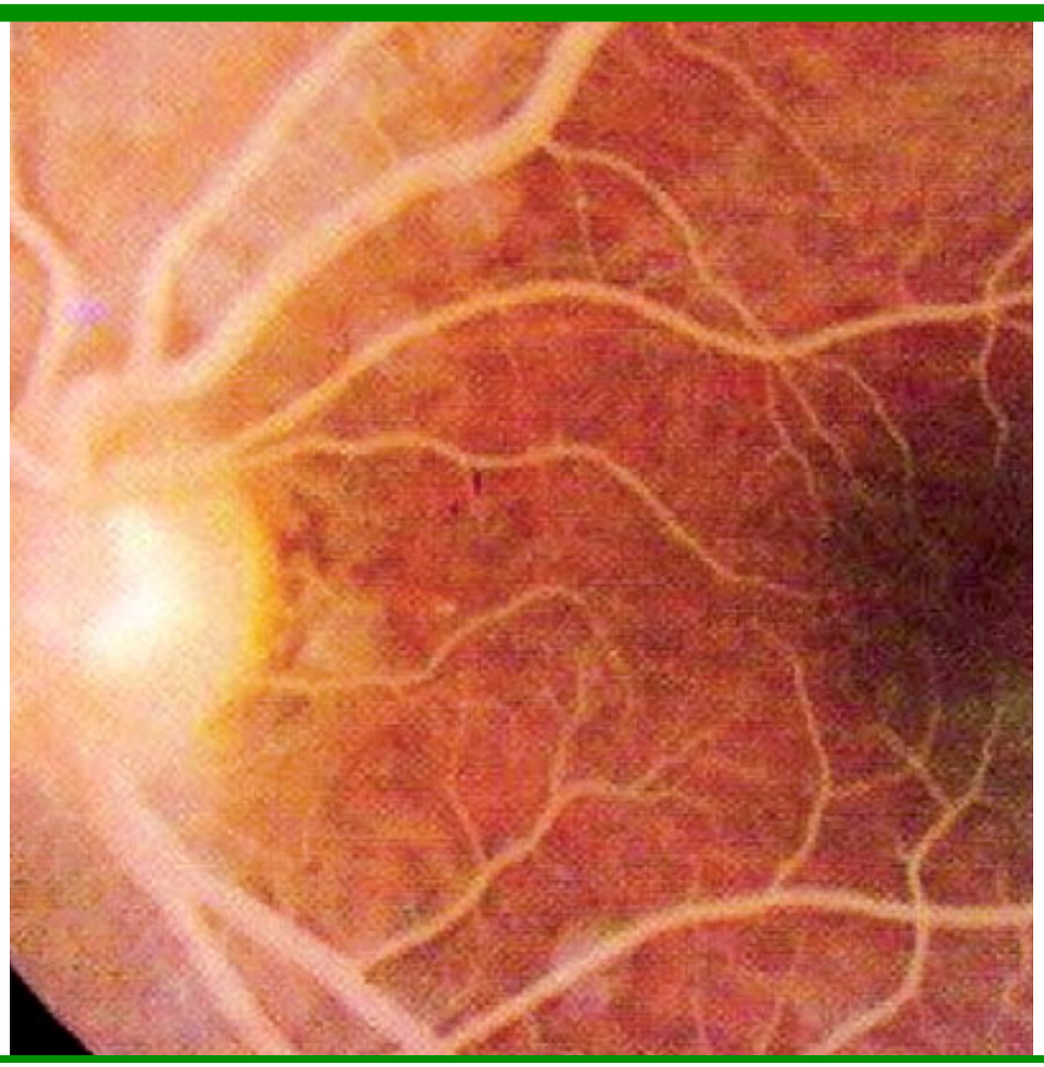
Tuberoeruptive xanthomata



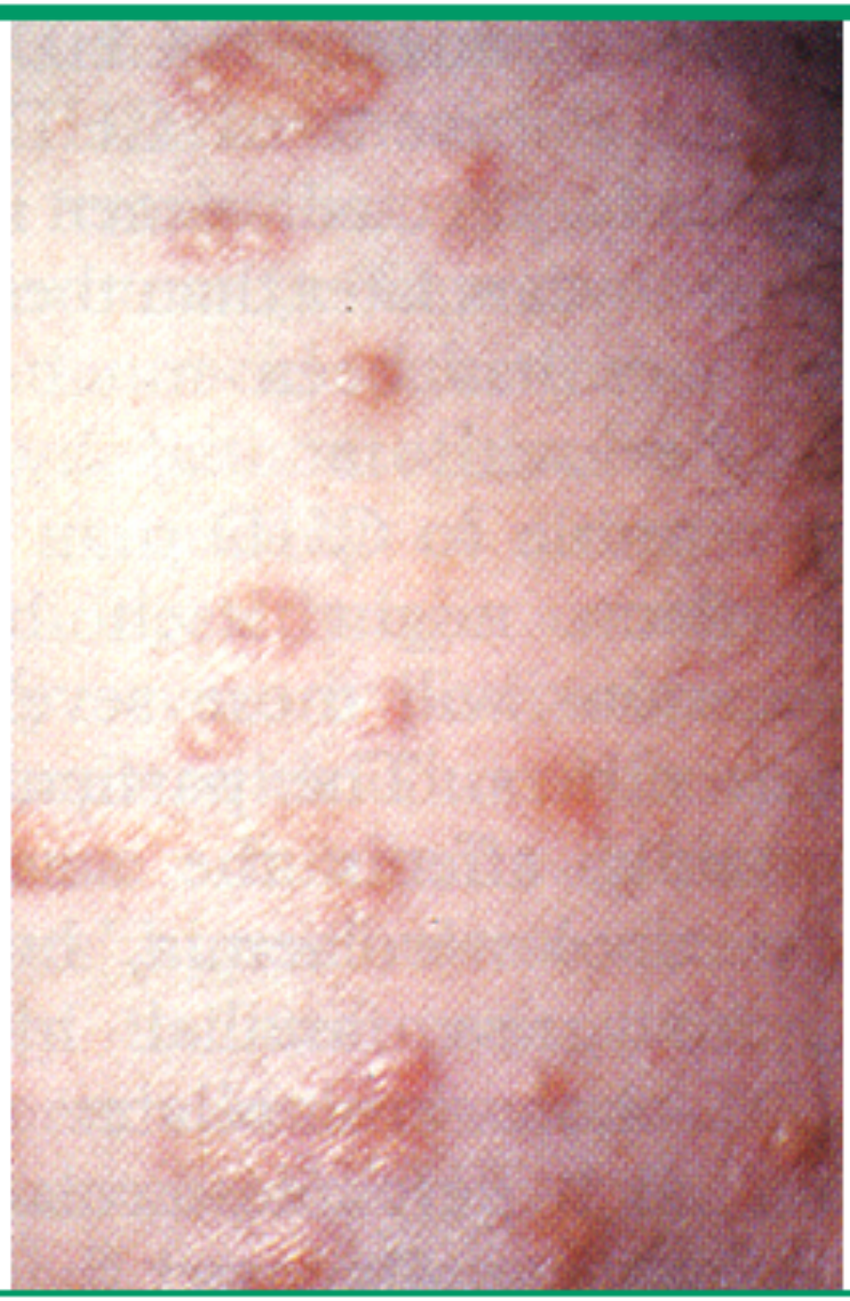
Tuberoeruptive xanthomata on the elbow and extensor surface of the arm in a patient with type III hyperlipoproteinemia.

FAMILIAL HYPERTRIGLYCEREDEMIA

Lipemia Retinalis

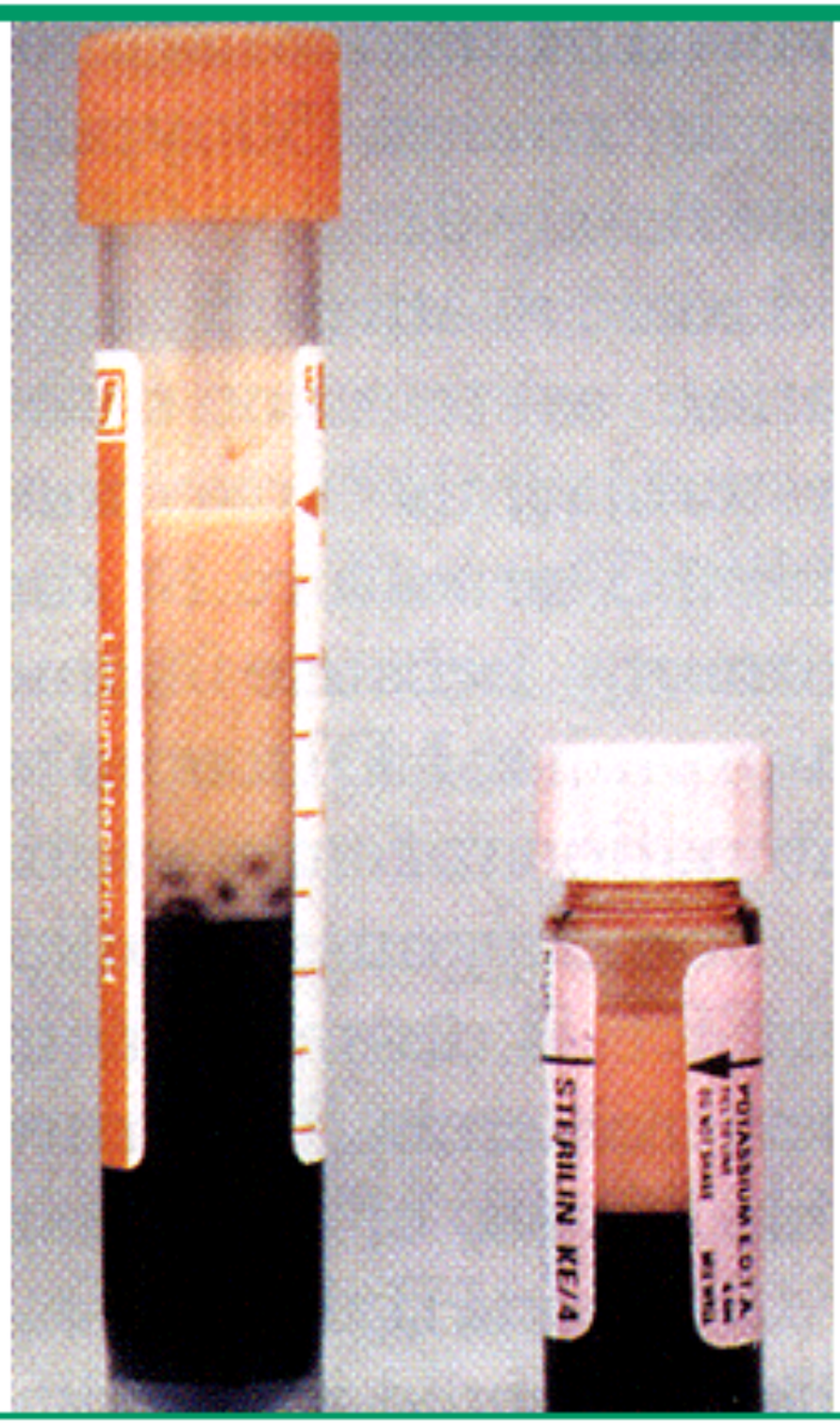


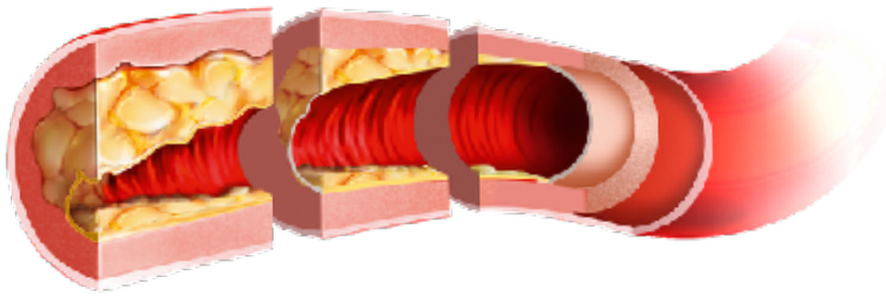
Eruptive xanthomata



FAMILIAL HYPERTRIGLYCEREDEMIA

Milky plasma



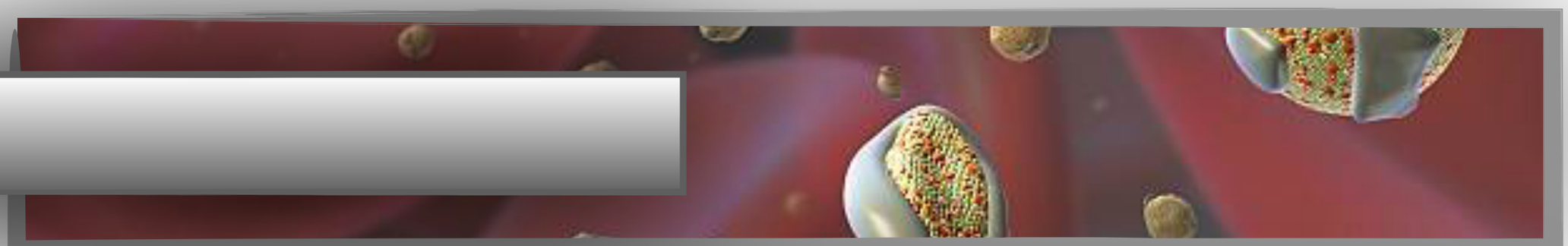


• TRIGLYCERIDES AND CVD RISK:

- Studies generally show a positive relationship between hypertriglyceridemia & atherosclerotic burden
- *<u>Abnormalities that predispose to atherosclerosis or are associated with increased CVD risk. These include:</u>*
  - Low levels of high density lipoprotein cholesterol (HDL).
  - Small, dense low density lipoprotein particles (LDL)
  - Atherogenic triglyceride-rich lipoprotein remnants (VLDL).
  - Insulin resistance
  - Increases in coagulability & viscosity; triglyceride-mediated hyperviscosity may contribute to endothelial dysfunction, tissue ischemia, & the chylomicronemia syndrome.

Table 2. ATP III Classification of LDL, Total, and HDL Cholesterol (mg/dL)

LDL Cholesterol	
<100	Optimal
100-129	Near optimal/above optimal
130-159	Borderline high
160-189	High
≥190	Very high
Total Cholesterol	
<200	Desirable
200-239	Borderline high
≥240	High
HDL Cholesterol	
<40	Low
≥60	High



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MANAGEMENT OF HYPERLIPIDEMIA

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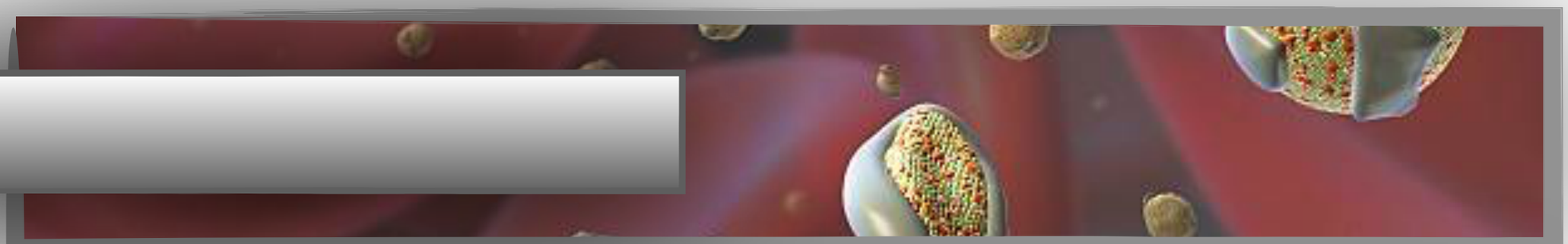


(LDL-C) LOWERING

RATIONALE FOR LDL-C LOWERING

The approach of aggressive (LDL-C) lowering

- LDL-C plays a key **role** in the pathogenesis & perpetuation of atherosclerotic CVD.

- Elevated levels of LDL-C are associated with an increased risk of CVD events & lowering of LDL-C is associated with a reduction in events.

- Mendelian randomization analysis has shown that a lifelong very low LDL-C is associated with a much lower risk of CVD.

- Randomized trials of many classes of LDL-C lowering drugs, including Statins, Ezetimibe, PCSK9 inhibitors, & cholesteryl ester transfer protein CETP inhibitors, have shown reductions in CVD events

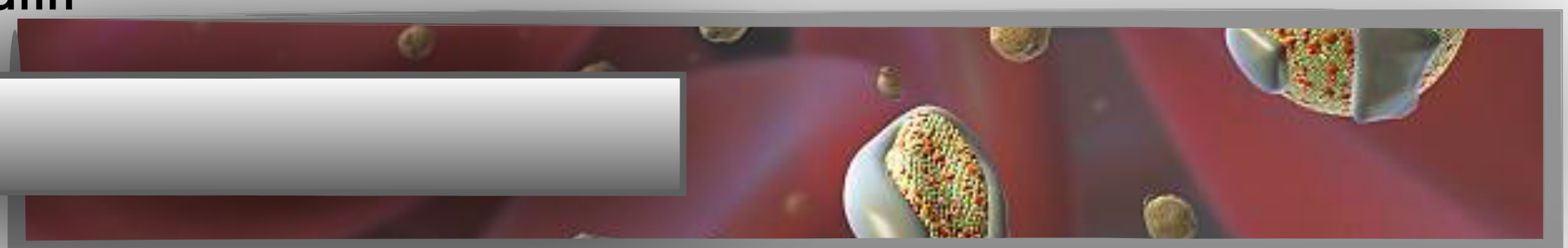
RISK GROUPS:

Patients with established cardiovascular disease (CVD) include those with stable or unstable coronary artery disease, ischemic stroke, transient ischemic attack, or peripheral arterial disease.

Prevention of CVD events in these **high-risk individuals** is referred to as **Secondary prevention.**

There is a spectrum of risk among individuals with CVD. We consider the CVD individuals with the following characteristics to be **at very high risk:**

- Acute coronary syndrome within the past year
- Familial hypercholesterolemia
- Diabetes, HTN, smoking
- Chronic kidney disease stages 3, 4, & 5.
- Recurrent atherosclerotic CVD event, need for revascularization while on statin

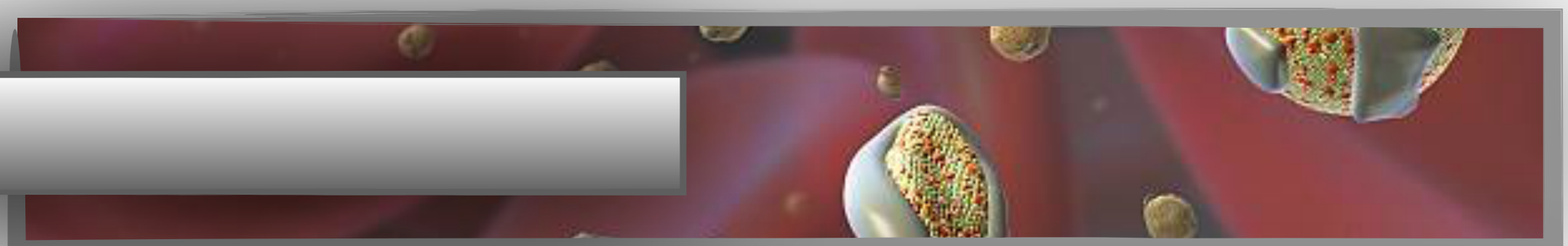


MANAGEMENT:
Patients with (CVD) or at high risk

BENEFITS ASSOCIATED WITH LDL-C LOWERING

- Across a broad range of baseline cardiovascular disease (CVD) risk & low density lipoprotein cholesterol (LDL-C) baseline levels, most therapies that lower LDL-C **lead to** a clinically important reduction in the risk of myocardial infarction (MI) & ischemic stroke.

- Among therapies that lower LDL-C & thus CVD risk, the best evidence of benefit in the past 30 years comes from studies of
  - ➡Statins
  - ➡Ezetimibe
  - ➡PCSK9 inhibitors.

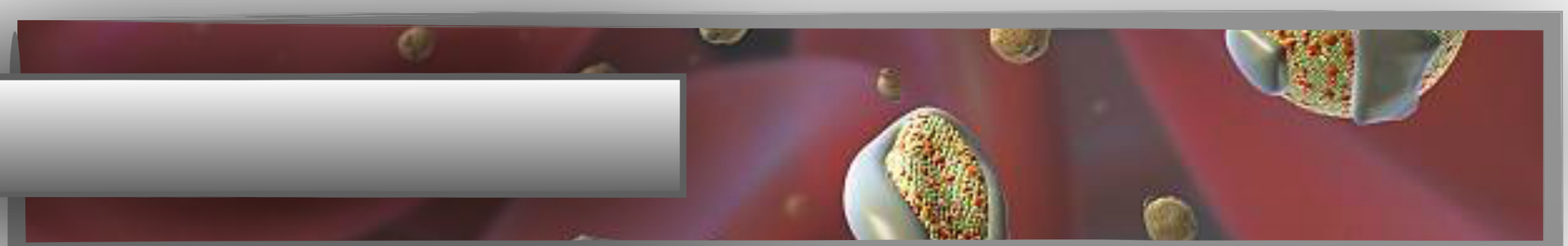


HYPERLIPIDEMIA MANAGEMENT

LIFE STYLE MODIFICATIONS:

FIRST LINE OF THERAPY

- **Weight loss** in obese patients
- **Aerobic exercise**
- Avoidance of medications that raise serum triglyceride levels& alcohol overuse
- Strict glycemic control in diabetics
- Other risk factors for cardiovascular disease, such as hypertension & smoking, should also be addressed
- **Dietary modification:**
  - Low saturated fat diet: limits total fat intake to 30 % of total calories, saturated fat to 7-10 %, & T.C to 300 mg/day
  - Fiber, Avoidance of concentrated sugars



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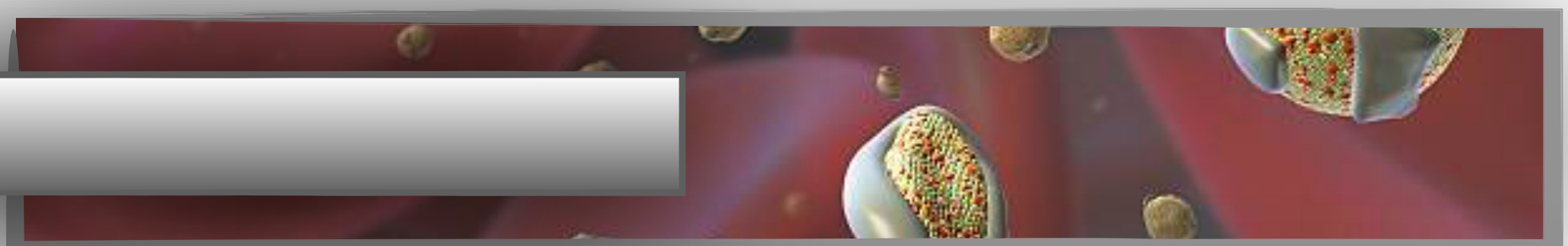
HYPERCHOLESETROLEMIA (LDL-C) MANAGEMENT

PHRAMCOTHERAPY

SECOND LINE OF THERAPY

- **Statins**
- **Ezetimibe**
- **PCSK9 inhibitors.**



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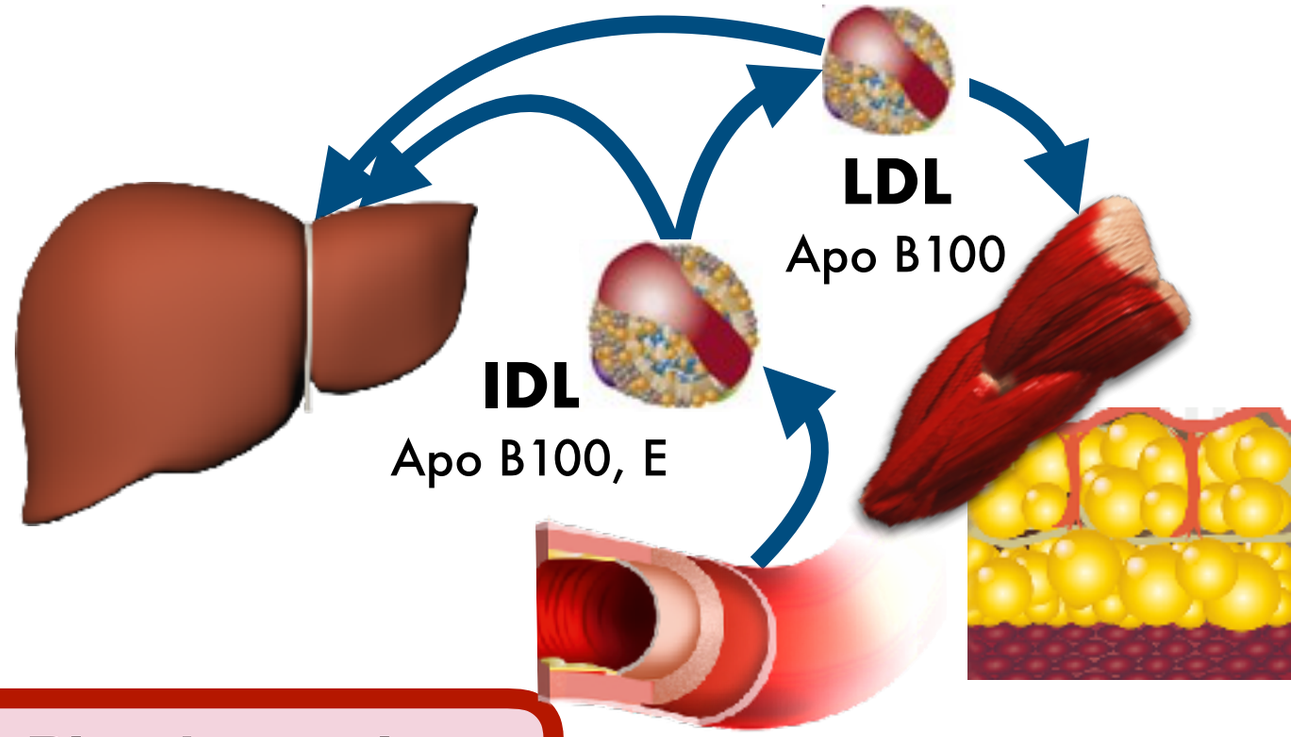
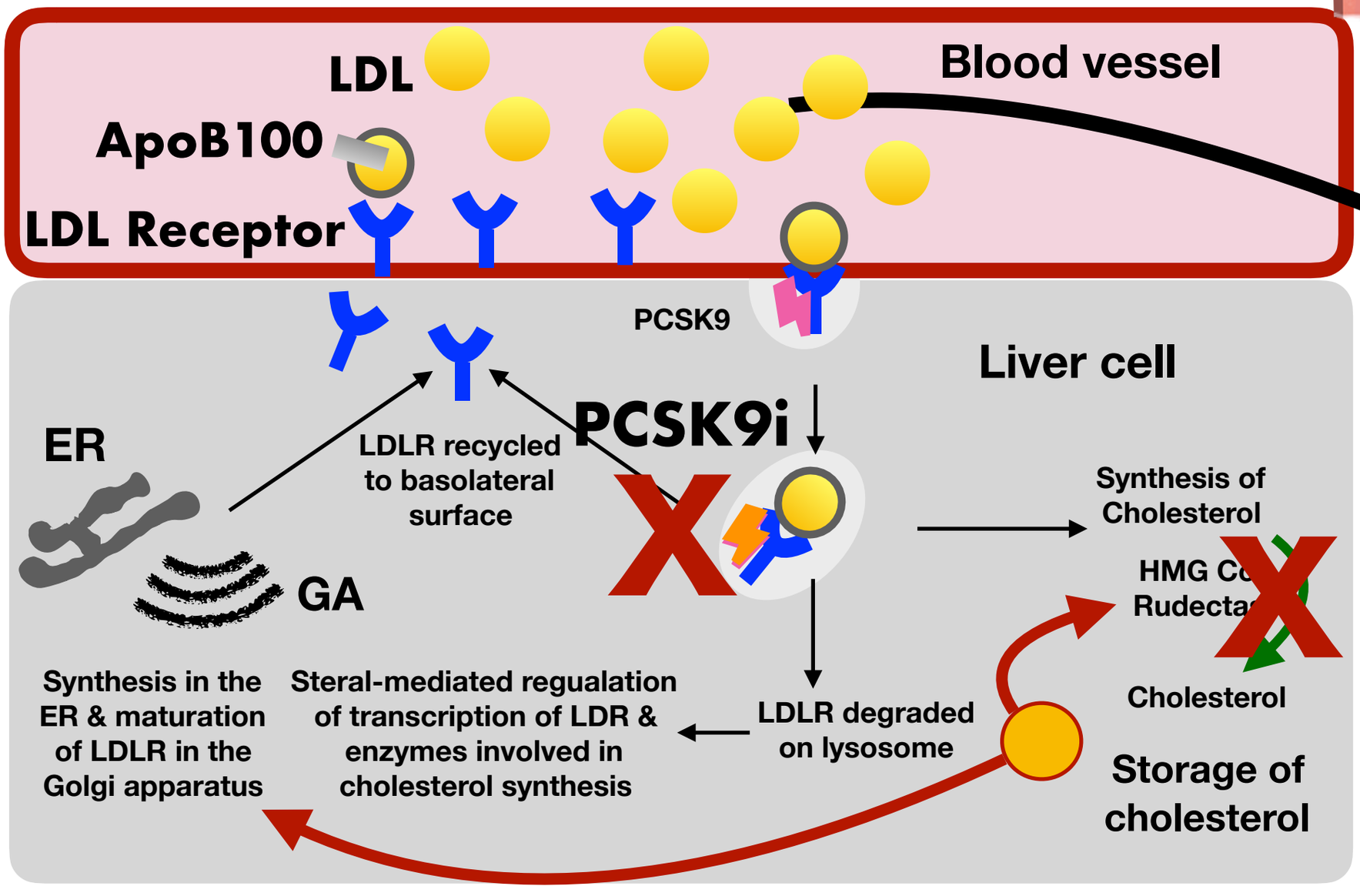
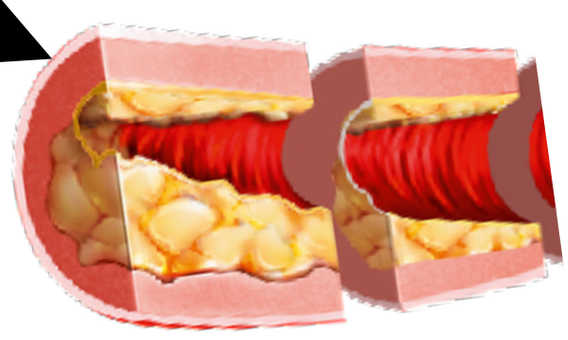
Mechanism of action of LDL Lowering agents



LDL Receptor pathway



Lipoproteinlipase
Mammary, Fat tissue & muscle



Statin

Cell membrane
Steroid hormones
Bile acids

Patients with (CVD) or at high risk MANAGEMENT

INTENSITY OF STATIN THERAPY:

Moderate-intensity statin therapy (30-50 % LDL-C reduction) includes daily treatment with:

- Lovastatin 40 mg
- Pravastatin 40 mg
- Simvastatin 40 mg
- Atorvastatin 10 to 20 mg
- Rosuvastatin 5 to 10 mg.

High-intensity statin therapy (≥50 % LDL-C reduction) includes daily treatment with:

- Atorvastatin 40 to 80 mg
- Rosuvastatin 20 to 40 mg.

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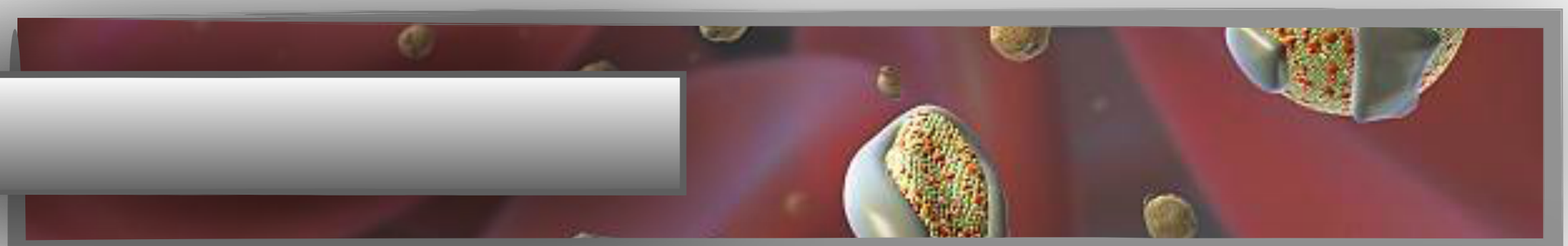
GOAL OF THERAPY FH/High risk group with CVD:

Targeted values of LDL-C depend on the presence of associated risk factors & are generally as follows:

- Minimal value, LDL-C <130 mg/dL (3.35 mmol/L)
- Optimal value, LDL-C <110 mg/dL (2.85 mmol/L)
- Some providers target values of LDL-C <100 mg/dL (2.59 mmol/L) for high-risk patients, such as those with diabetes mellitus or chronic renal insufficiency



ESTABLISHING A TREATMENT GOAL Patients with (CVD) or at high risk

The use of three classes of LDL-C lowering drugs in Statin-treated patients has been shown to lead to an additional reduction in CVD events in study populations that achieved a mean LDL-C < 55 mg/dL:

- In the FOURIER trial (PCSKi9): start LDL-C of 90 mg/dL; final LDL-C of 30 mg/dL.
- In the IMPROVE IT trial (Ezetimibe): start LDL-C of 69 mg/dL; final LDL-C of 54 mg/dL.
- In the REVEAL trial (Anacetrapib): start LDL-C of 61 mg/dL; final LDL-C of 53 mg/dL.

HYPERTRIGLYCREDEMIA MANAGEMENT

INDICATIONS FOR DRUG THERAPY:

SECOND LINE OF THERAPY

The two potential indications for pharmacologic therapy to lower triglyceride levels are prevention of episodes of pancreatitis & lowering of cardiovascular risk.

- If triglyceride levels persistently > 886 mg/dL (10.0 mmol/L), we start drug therapy to lower the risk of pancreatitis.

PHRAMCOTHERAPY

- **Fenofibrate**
- **Niacine**
- **Fish oil**

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Mechanism of action for Lipid lowering agents

Ezetimibe

Bile acid sequestrate

CTEP

HDL
Apo A,C,D,E

Fish Oil

VLDL
ApoB100,E

IDL
Apo B100,E

Chylomicron Remnant
Apo B48,E

Chylomicron
Apo B48,E,A,C

LDL
Apo B100

ApoE ApoA ApoC

Lipoproteinlipase
Mammary, Fat tissue & muscle

Fenofibric acid

Niacin

Average effects of different classes of lipid lowering drugs on serum lipids

Drug class	Serum LDL cholesterol (% change)	Serum HDL cholesterol (% change)	Serum triglycerides (% change)
Bile acid sequestrants	↓ 15 to 30	0 to slight increase	No change or increase
Cholesterol absorption inhibitors	↓ 17	↑ 1	↓ 7 to 8
Fenofibrate (micronized form)	↓ 6 to 20	↑ 5 to 20¶	↓ 41 to 53
Gemfibrozil◇	↓ 10 to 15	↑ 5 to 20¶	↓ 35 to 50
Neomycin	↓ 20 to 25	No change	No change
Nicotinic acid (niacin)	↓ 10 to 25	↑ 15 to 35	↓ 25 to 30
Omega 3 fatty acids△	↑ 4 to 49	↑ 5 to 9	↓ 23 to 45
PCSK9 inhibitors	↓ 38 to 72	↑ 4 to 9	↓ 2 to 23
Statins	↓ 20 to 60	↑ 5 to 10	↓ 10 to 33

Adult dosing, side effects, and drug interactions of lipid-lowering drugs

Drug class	Dose	Dosing	Major side effects and drug interactions
Statins			
Atorvastatin	10 to 80 mg/day		Headache; nausea; sleep disturbance; elevations in hepatocellular enzymes and alkaline phosphatase. Myositis and rhabdomyolysis, primarily when given with gemfibrozil or cyclosporine; myositis is also seen with severe renal insufficiency (CrCl <30 mL/min). Lovastatin, atorvastatin, rosuvastatin, and simvastatin potentiate effect of warfarin; this interaction is not seen with pravastatin, fluvastatin, or pitavastatin. Most statins can also affect digoxin metabolism and levels.
Fluvastatin	IR: 20 to 80 mg/day	IR take in the evening. Divide dose twice per day (morning and evening) if dose >40 mg/day.	
	XR: 80 mg/day	XR take any time	
Lovastatin	IR: 20 to 80 mg/day	IR take with evening meal. Divide dose twice per day with meals if dose >20 mg/day.	
	XR: 20 to 60 mg/day	XR take any time	
Pitavastatin	1 to 4 mg/day		
Pravastatin	10 to 80 mg/day		
Rosuvastatin	5 to 40 mg/day		
Simvastatin	5 to 40 mg/day	Take in the evening	
PCSK9 inhibitors			
Alirocumab	75 to 150 mg every two weeks	Subcutaneous injections	Injection site reactions
Evolocumab	140 mg every two weeks or 420 mg every month Homozygous familial hypercholesterolemia: 420 mg every month to 420 mg every two weeks		

Fibric acid derivatives			
Fenofibrate	Nanocrystal 145 mg/day Micronized 160 to 200 mg/day	Micronized taken with meals. Use lower doses with renal insufficiency.	Skin rash, gastrointestinal (nausea, bloating, cramping) myalgia; lowers blood cyclosporine levels; potentially nephrotoxic in cyclosporine treated patients. Avoid in patients with CrCl <30 mL/min.
Gemfibrozil	600 mg twice per day	30 to 60 minutes before meals	Potentiates warfarin action. Absorption of gemfibrozil diminished by bile acid sequestrants.
Nicotinic acid (niacin)	IR: 1 to 6 g/day	IR: Taken with meals. Start with 100 mg twice per day and titrate to 500 mg three times per day. After six weeks, check lipids, glucose, liver function, and uric acid. Increase dose as needed.	Prostaglandin-mediated cutaneous flushing, headache, warm sensation, and pruritus; hyperpigmentation (particularly in intertriginous regions); acanthosis nigricans; dry skin; nausea; vomiting; diarrhea; and myositis
	XR (Niaspan): 0.5 to 2 g/day	XR: Taken at bedtime; adjust dose every four weeks as needed.	
Bile acid sequestrants			
Cholestyramine	4 to 24 g/day	Take within 30 minutes of a meal. A double dose with dinner produces same lipid-lowering effect as twice per day dosing.	Nausea, bloating, cramping, and constipation; elevations in hepatic transaminases and alkaline phosphatase. Impaired absorption of fat soluble vitamins and coadministered medications including: Amiodarone, digoxin, warfarin, thiazides, beta blockers, levothyroxine, others; interaction can be minimized by taking other medications at least one hour before or four hours after bile acid sequestrant.
Colestipol	5 to 30 g/day		
Colesevelam	3.75 g/day	Take with meals once daily or in two divided doses.	Similar
Cholesterol absorption inhibitors			
Ezetimibe	10 mg/day		Increased transaminases in combination with statins
Neomycin	1 g twice per day		Ototoxicity; nephrotoxicity
Probucol (not available in United States)	500 mg twice per day		Loose stools; eosinophilia; QT prolongation; angioneurotic edema

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King Saud University

THANK YOU

Shadin S. Al Katari *MD, FACE*

Consultant Endocrinology & Diabetes

Endocrine & Diabetes Division - IM Department at KKUH, KSUMC