THE CHOLESTEROL DILEMMA

Cholesterol Metabolism and Plaque Formation

Focus on FH Individuals

Lourdes Ella G. Santos, M.D.

Preventive Cardiology, Clinical Lipidology and Hypertension

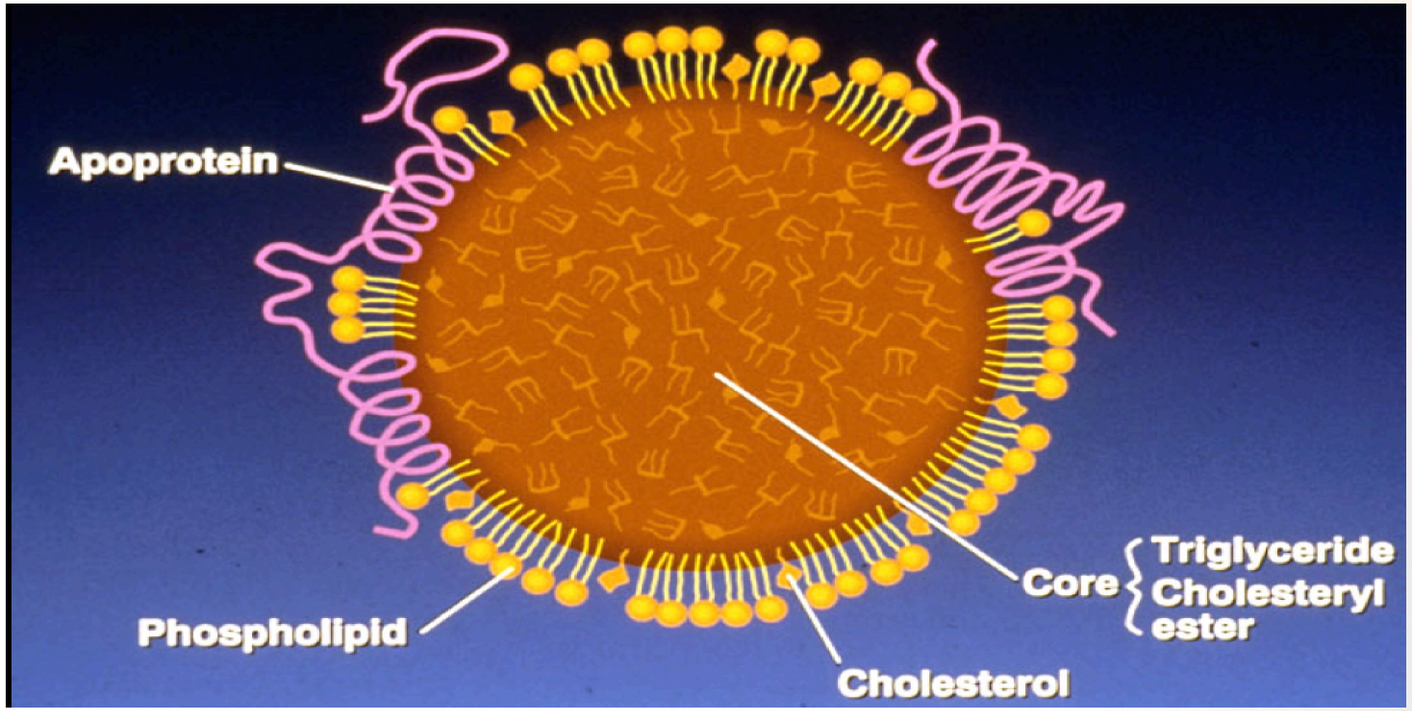
Outline

- Lipoprotein structure
- Cholesterol Pathways
- Identifying Proatherogenic Molecules
- Molecular Basis for FH
- Impact of Elevated LDL-C levels on Plaque Formation
- Value of Diagnosis : Prevention of CV Events

Lipoprotein Structure

Outer coat:
- Apoproteins
- Phospholipids
- Cholesterol (Unesterified)

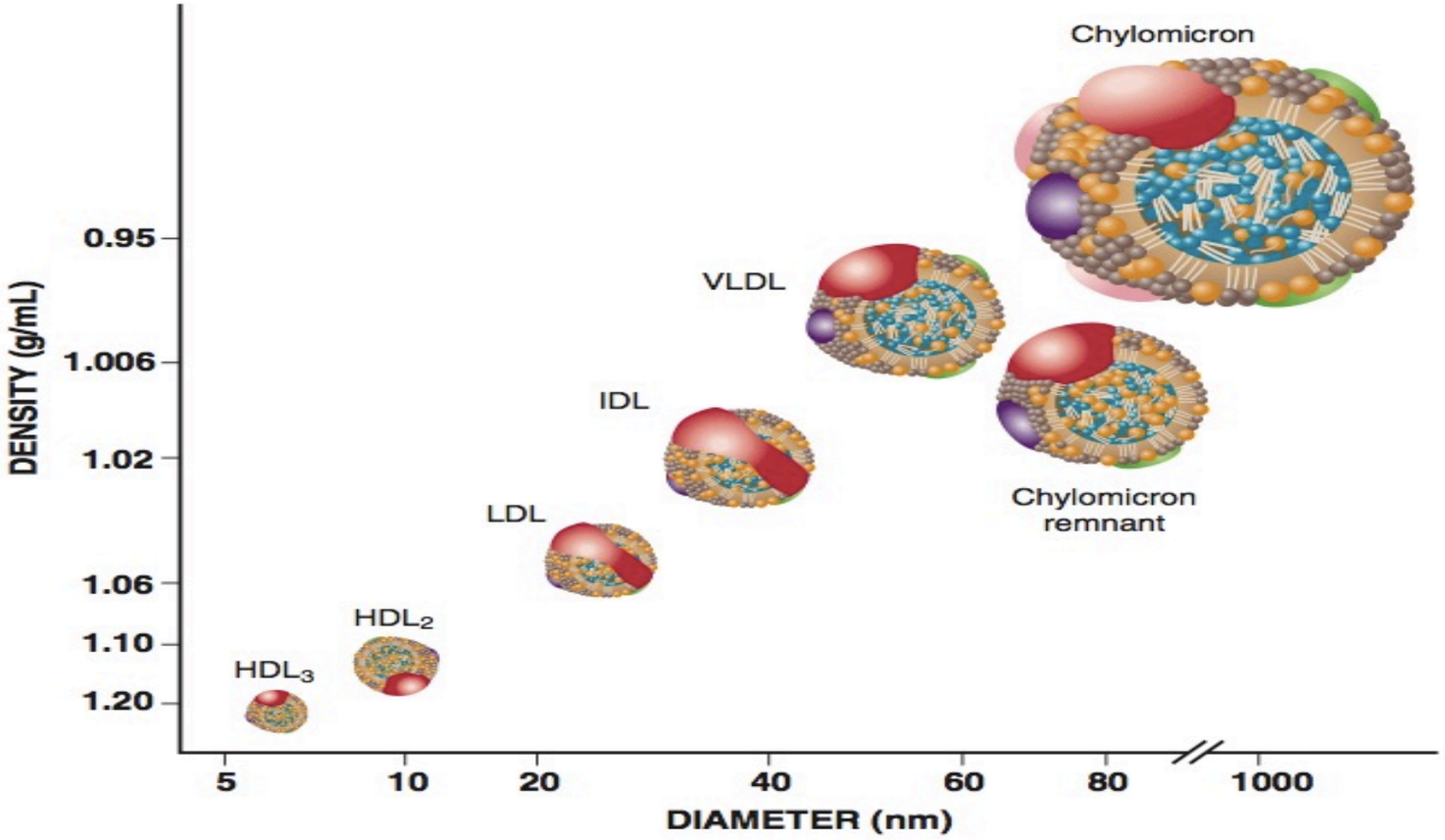
Inner core:
- TG
- Cholesterol ester (CE)

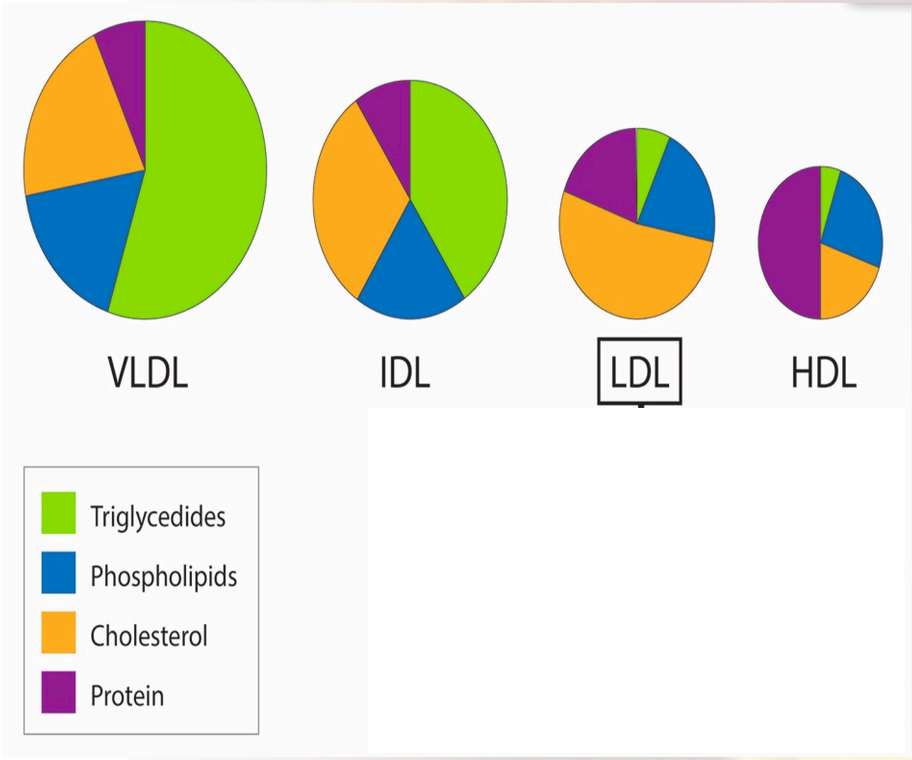


Spherical molecules of lipids and proteins (apoproteins) = amphipathic molecules

Feingold KR. Introduction to Lipids and Lipoproteins. [Updated 2021 Jan 19]. In: Feingold KR, Anawalt B, Boyce A, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000

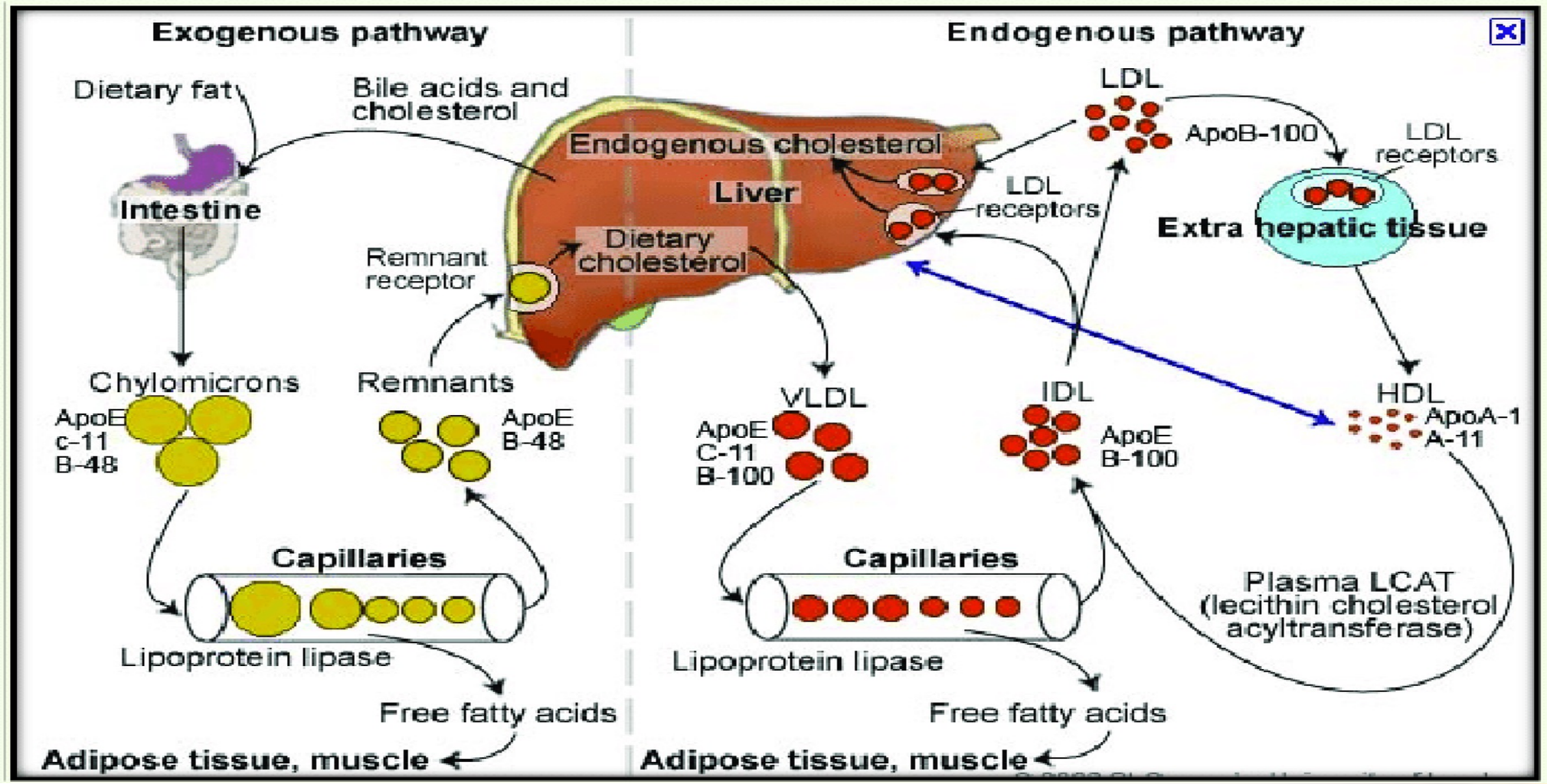
Lipoproteins Vary in Size and Composition





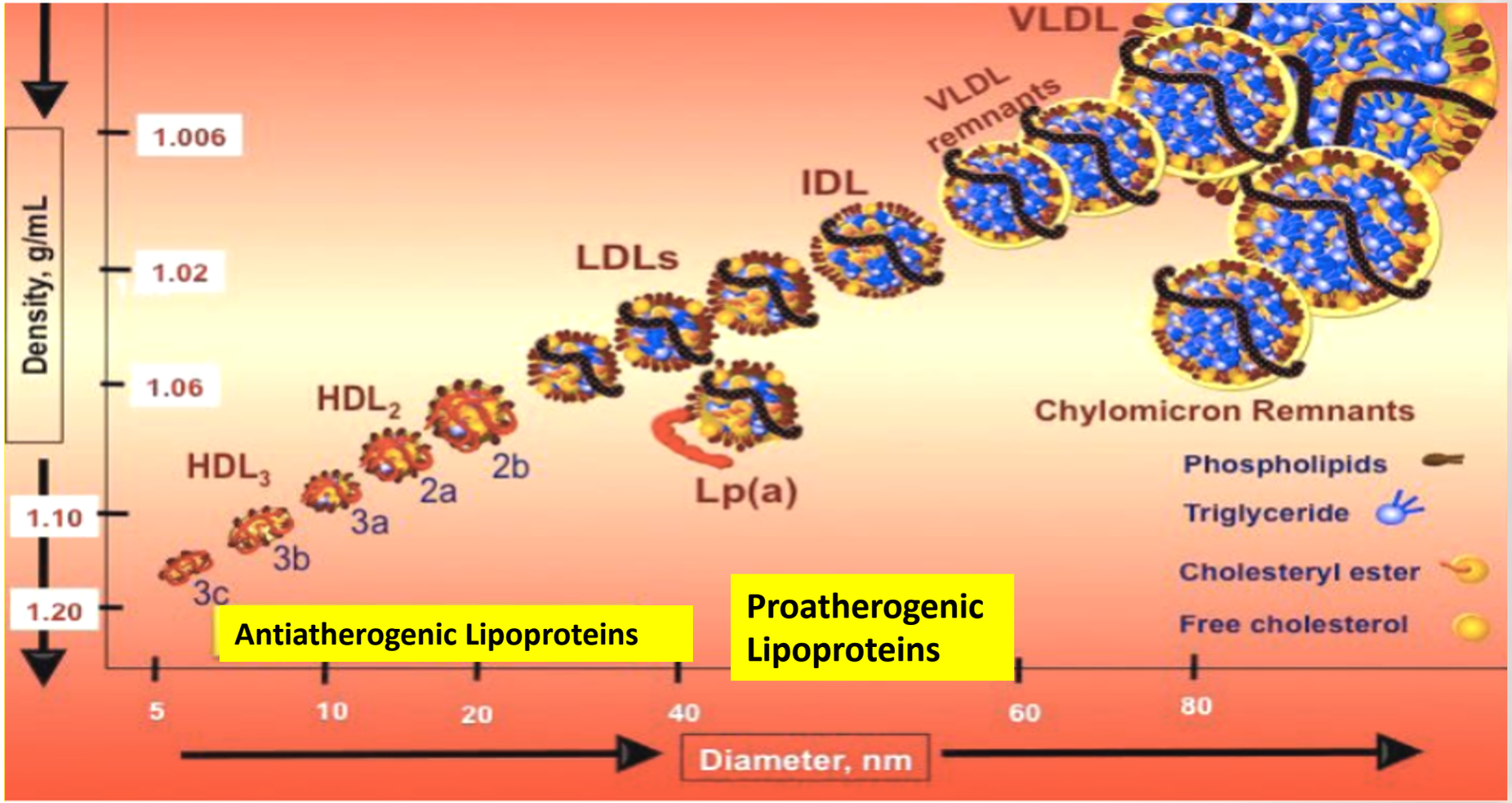
March 2020 Archives of Medical Science 16(2):1-16

Cholesterol Synthesis



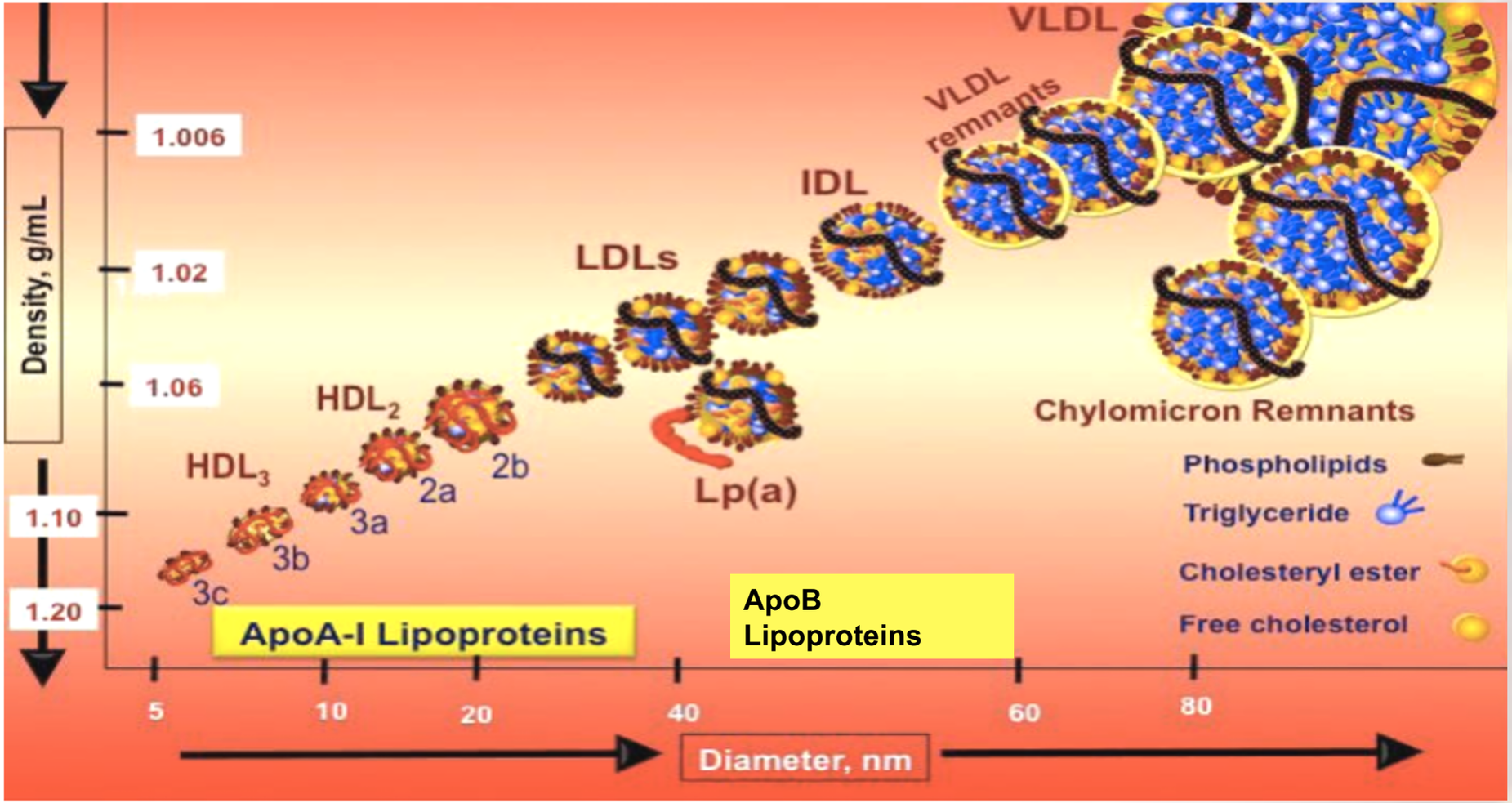
Karam I, Yang YJ and Li JY. Hyperlipidemia Background and Progress. SM Atheroscler J. 2017; 1(1): 1003.

Identifying Pro-atherogenic Lipoproteins



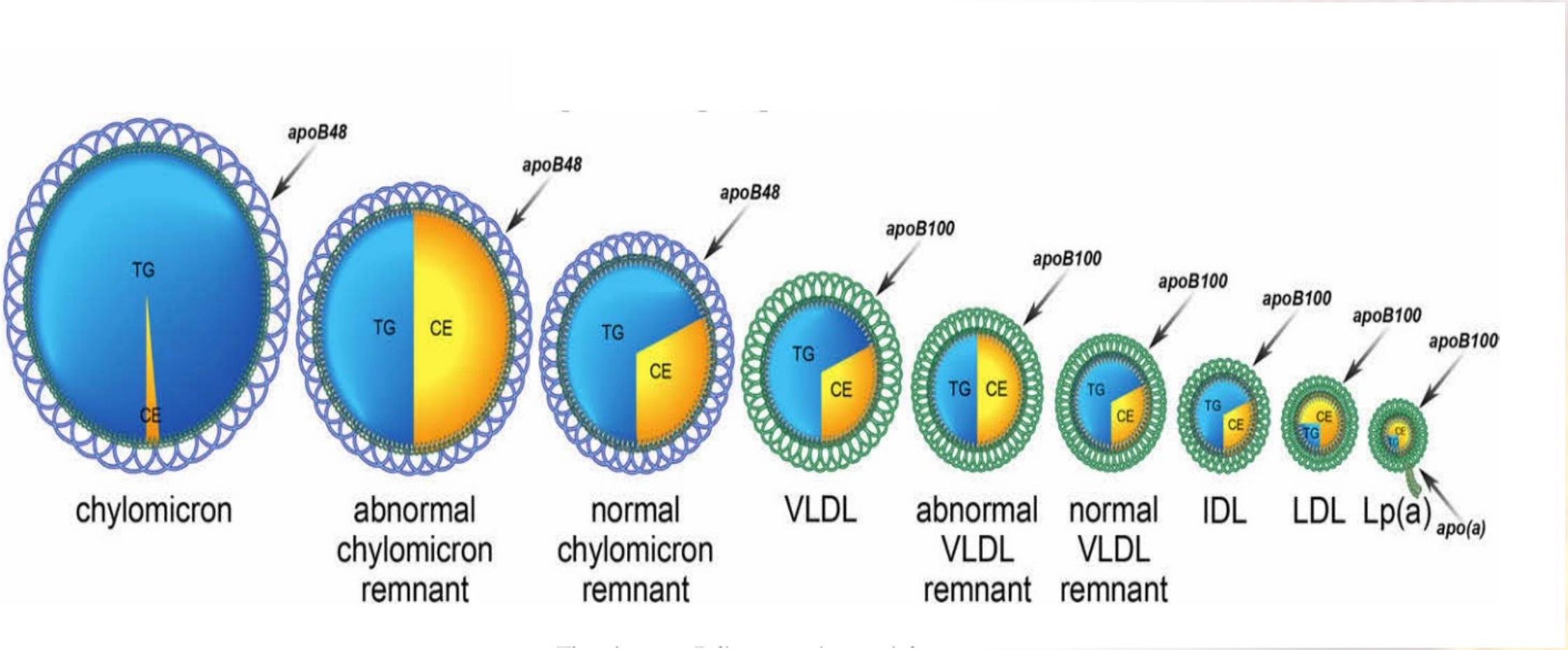
Classes of Lipoproteins (figure modified from Advances Protein Chemistry 45:303, 1994)

Identifying Pro-atherogenic Lipoproteins



Classes of Lipoproteins (figure modified from Advances Protein Chemistry 45:303, 1994)

ApoB-Containing Proatherogenic Particles



J Lipid Res 2018. 59 : 1266-1275

Apolipoproteins

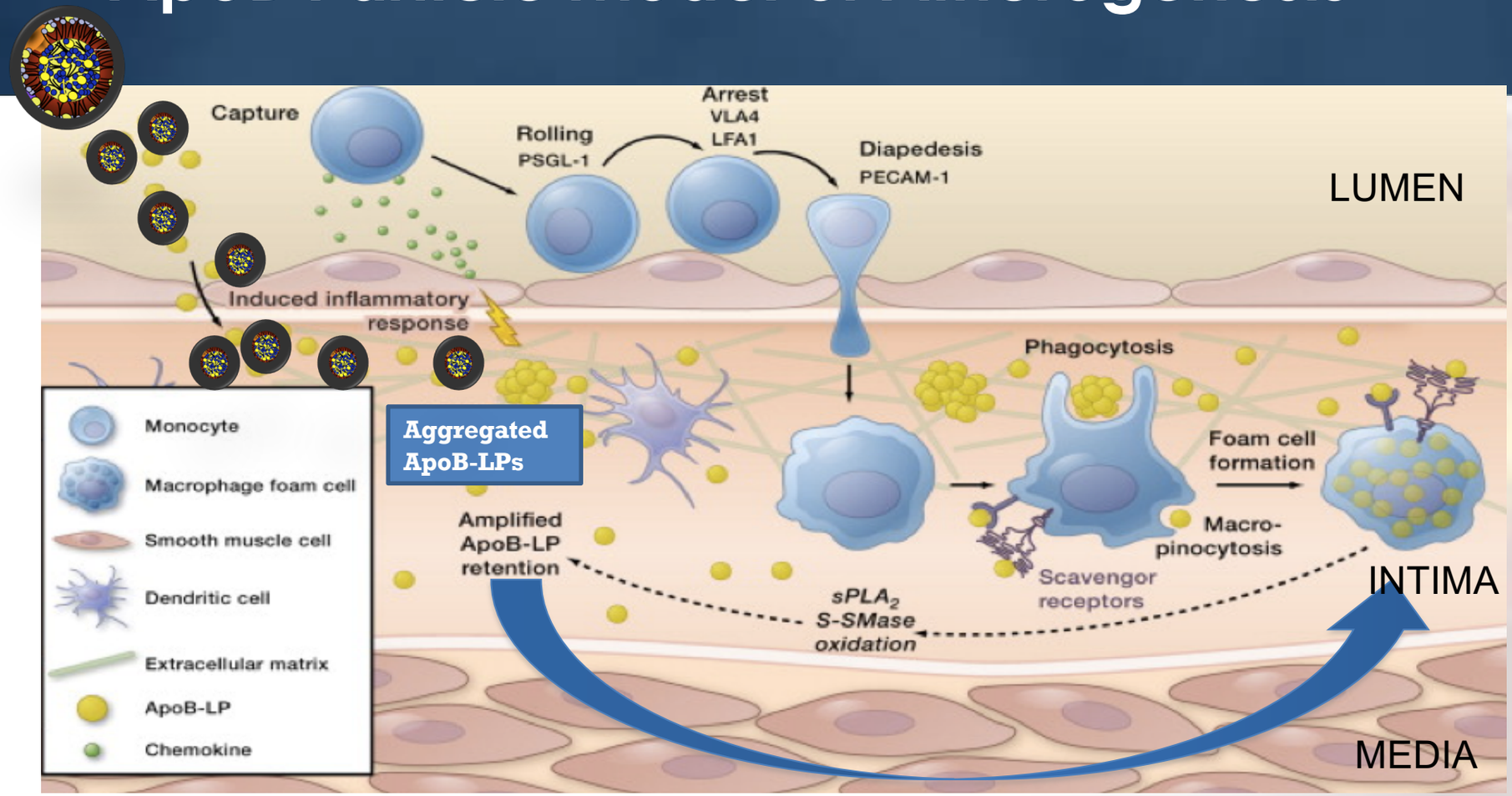
apoA-I	HDL structural protein; LCAT activator;RCT
apoA-II	HL activation
apoA-IV	Tg metabolism; LCAT activator; diet response
apoB-100	Structural protein of all LP except HDL Binding to LDL receptor
apoB-48	
apoC-I	Inhibit Lp binding to LDL R; LCAT activator
apoC-II	LpL activator
apoC-III	LpL inhibitor; antagonizes apoE
apoE	B/E receptor ligand *E2:IDL; *E4: Diet Responsivity

Functions

Some are required as structural proteins
Some are activators,
Some are recognition sites.

Chiang J. (2014) Liver Physiology: Metabolism and Detoxification. In: Linda M. McManus, Richard N. Mitchell, editors. *Pathobiology of Human Disease*. San Diego: Elsevier; p. 1770-1782.

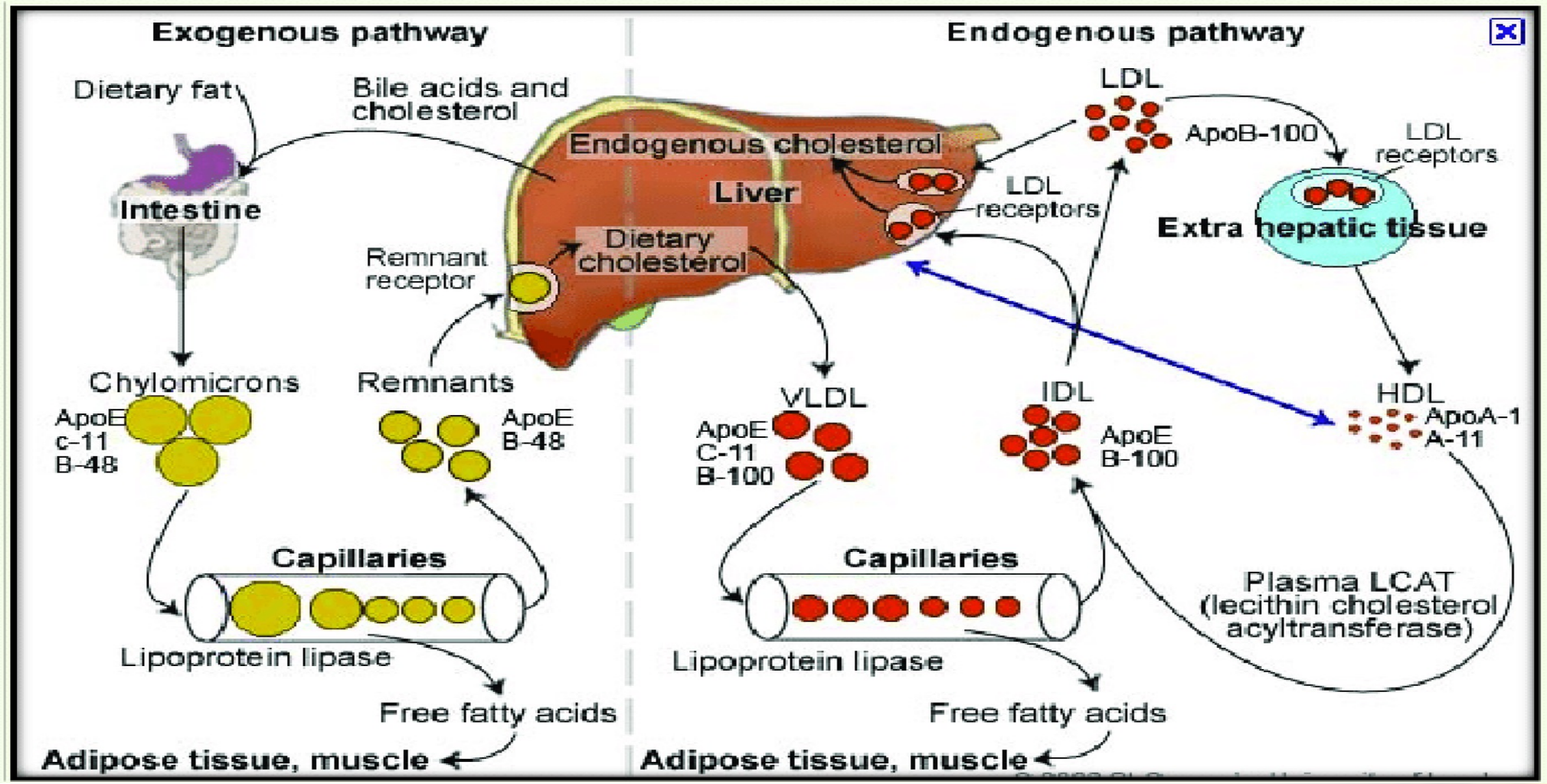
ApoB Particle Model of Atherogenesis



Atherosclerosis is initiated by the trapping of Apo B particles within sub-intimal space

Sniderman AD, Thanassoulis G, Glavinovic T, Navar AM, Pencina M, Catapano A, Ference BA. Apolipoprotein B Particles and Cardiovascular Disease: A Narrative Review. JAMA Cardiol. 2019 Dec 1;4(12):1287-1295. doi: 10.1001/jamacardio.2019.3780. PMID: 31642874; PMCID: PMC7369156.

Cholesterol Synthesis



Karam I, Yang YJ and Li JY. Hyperlipidemia Background and Progress. SM Atheroscler J. 2017; 1(1): 1003.

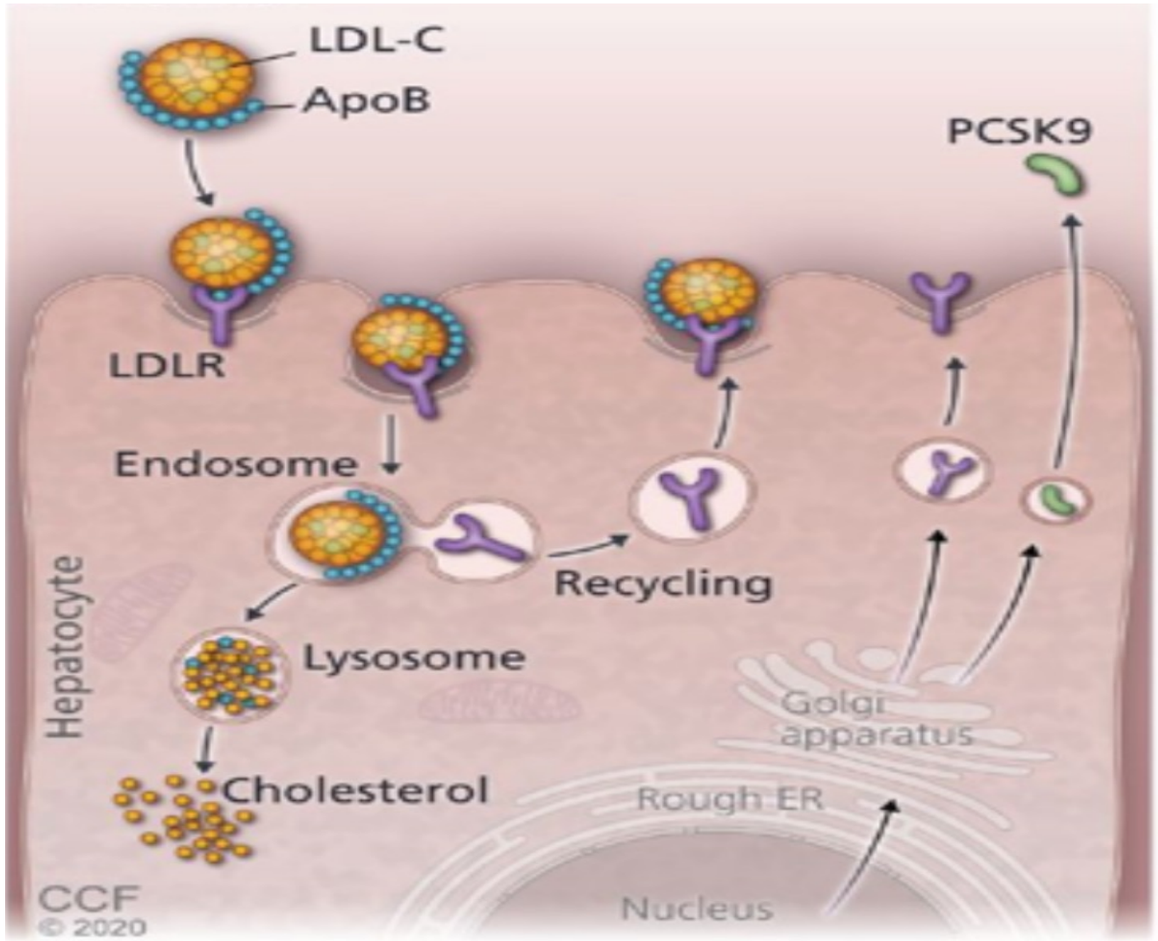
WHO Fredrickson Classification of Dyslipidemia

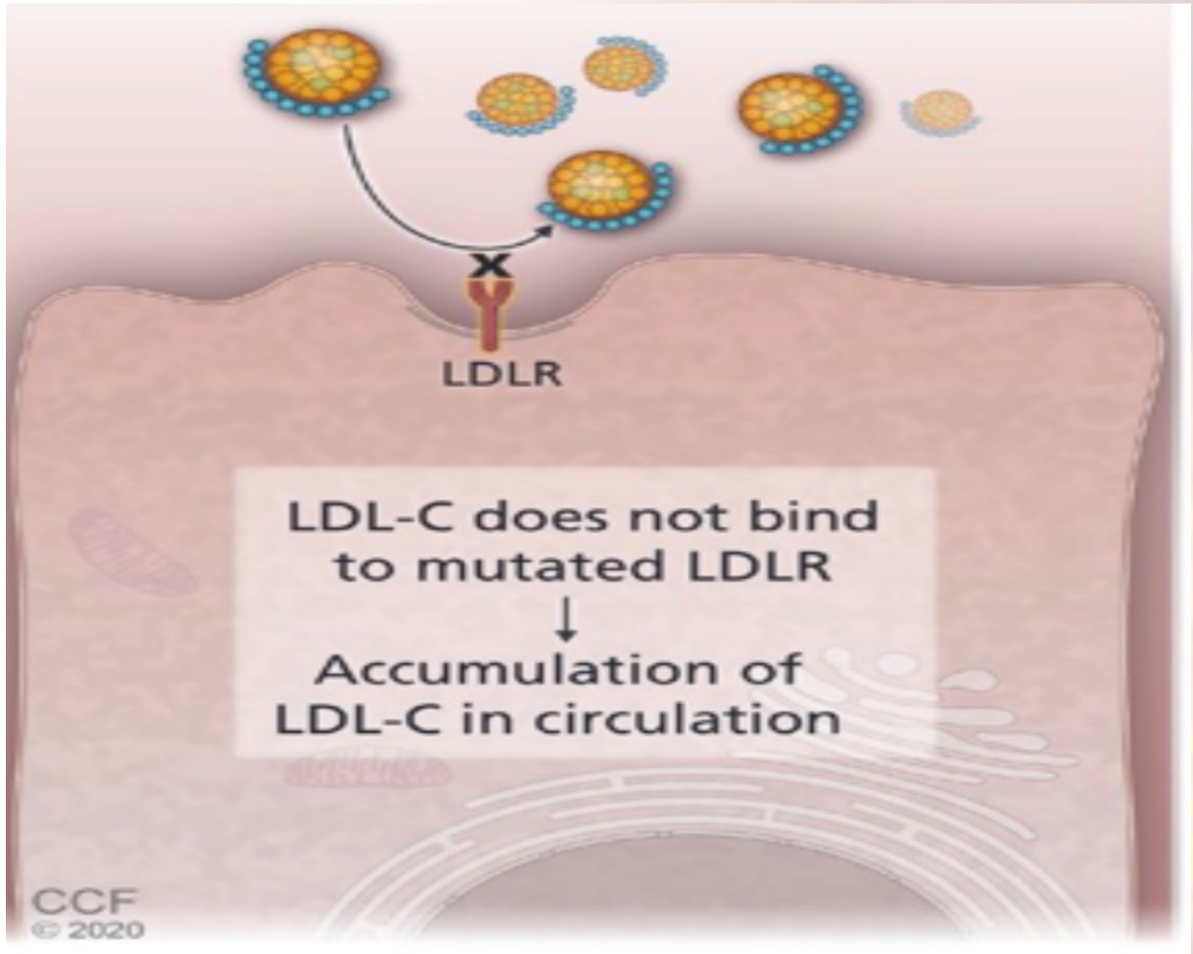
Hyperlipo-proteinaemia		Synonym	Genetic Causes/Defect Type	Elevated lipo-protein	Main Symptoms	Serum appearance
Type II	a	Familial hypercholesterolemia	1. LDL receptor mutations 2. ApoB mutations 3. PCSK9 mutations	LDL	Xanthelasma, arcus senilis, tendon xanthomas	Clear

Sampson, M., Ballout, R.A., Soffer, D. *et al.* A new phenotypic classification system for dyslipidemias based on the standard lipid panel. *Lipids Health Dis* **20,** 170 (2021).

LDL-R Mutation

Normal Physiology

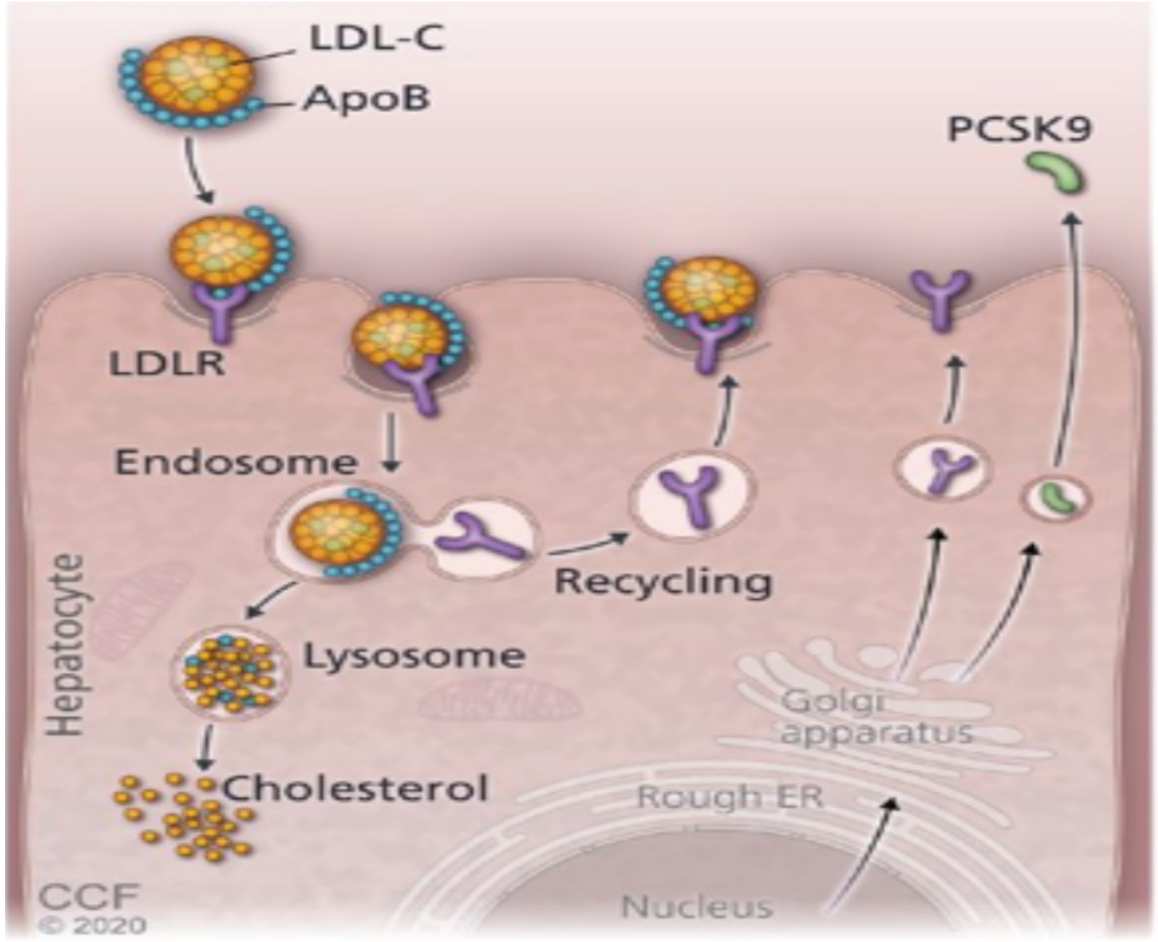


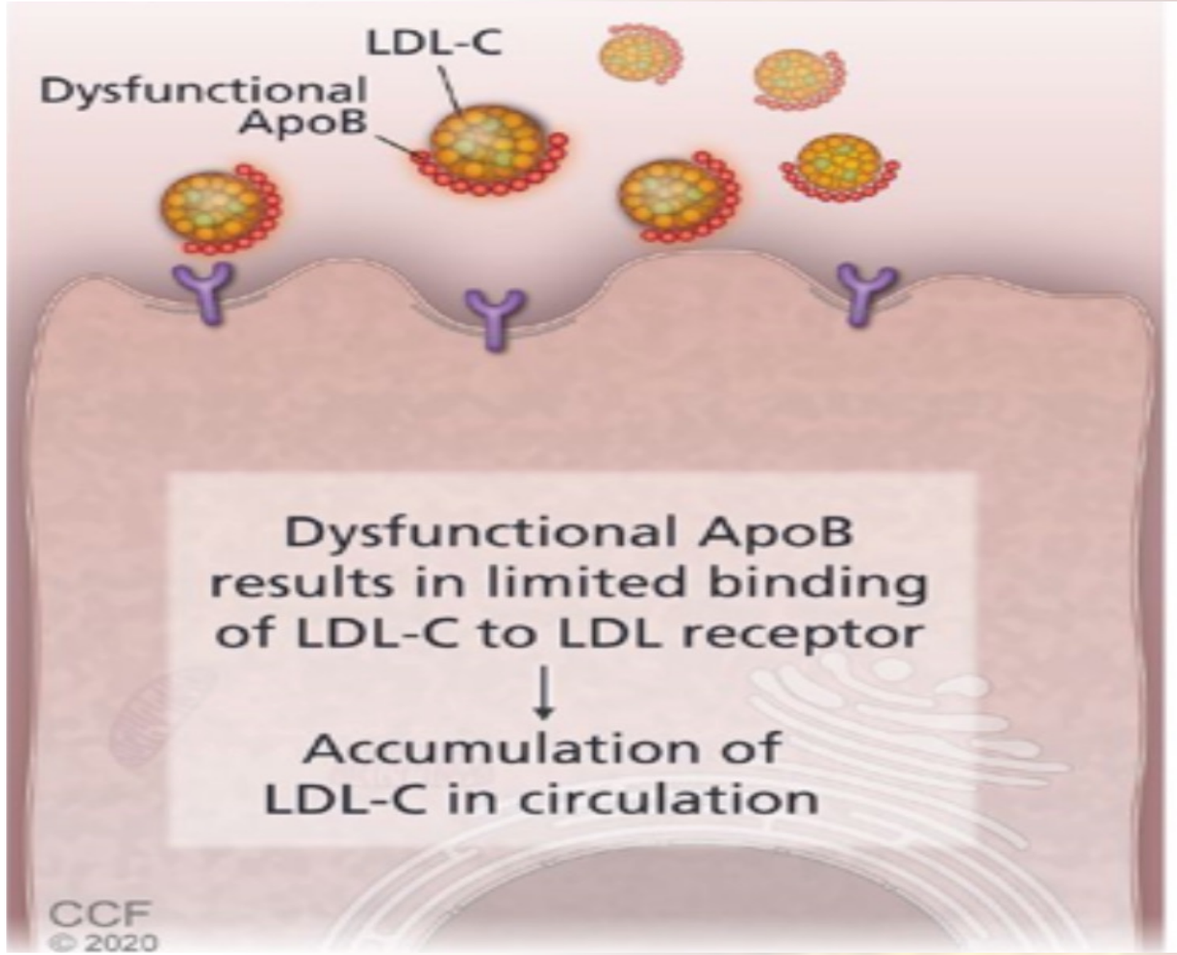


Adapted from Shah et al. CCJM 2020;87:109-120 with permission. CCF © 2020

ApoB Dysfunction

Normal Physiology

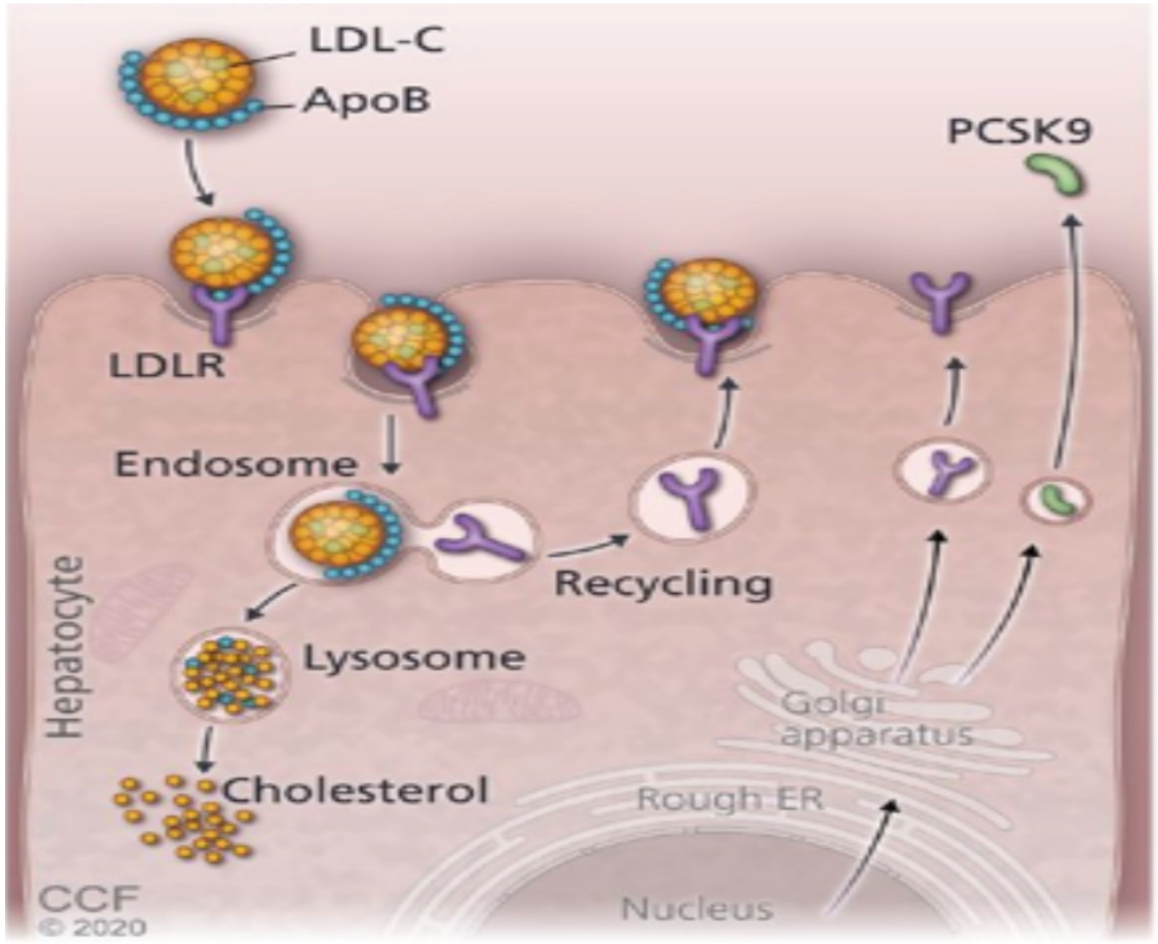


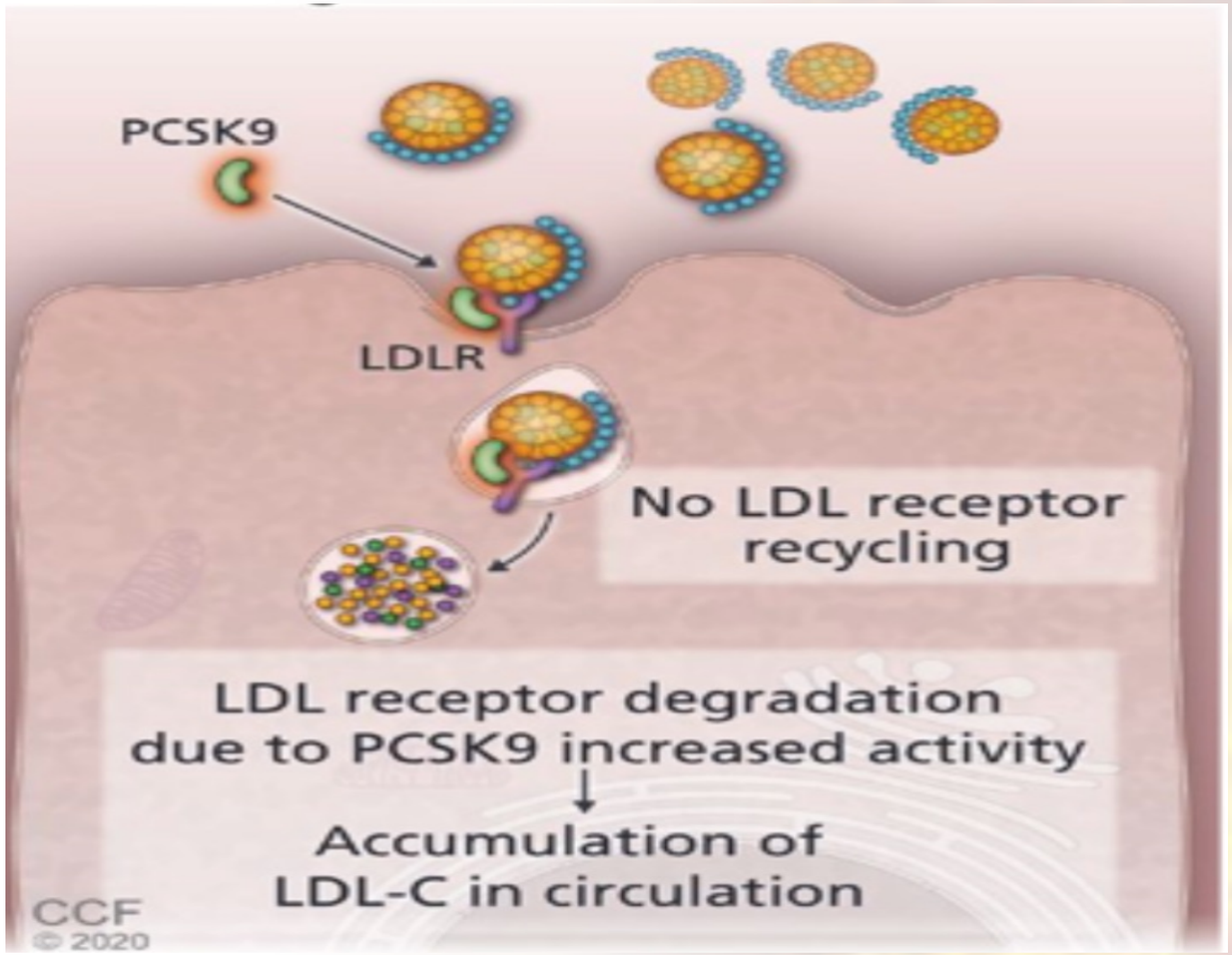


Adapted from Shah et al. CCJM 2020;87:109-120 with permission. CCF © 2020

PCSK9 Gain of Function

Normal Physiology





Adapted from Shah et al. CCJM 2020;87:109-120 with permission. CCF © 2020

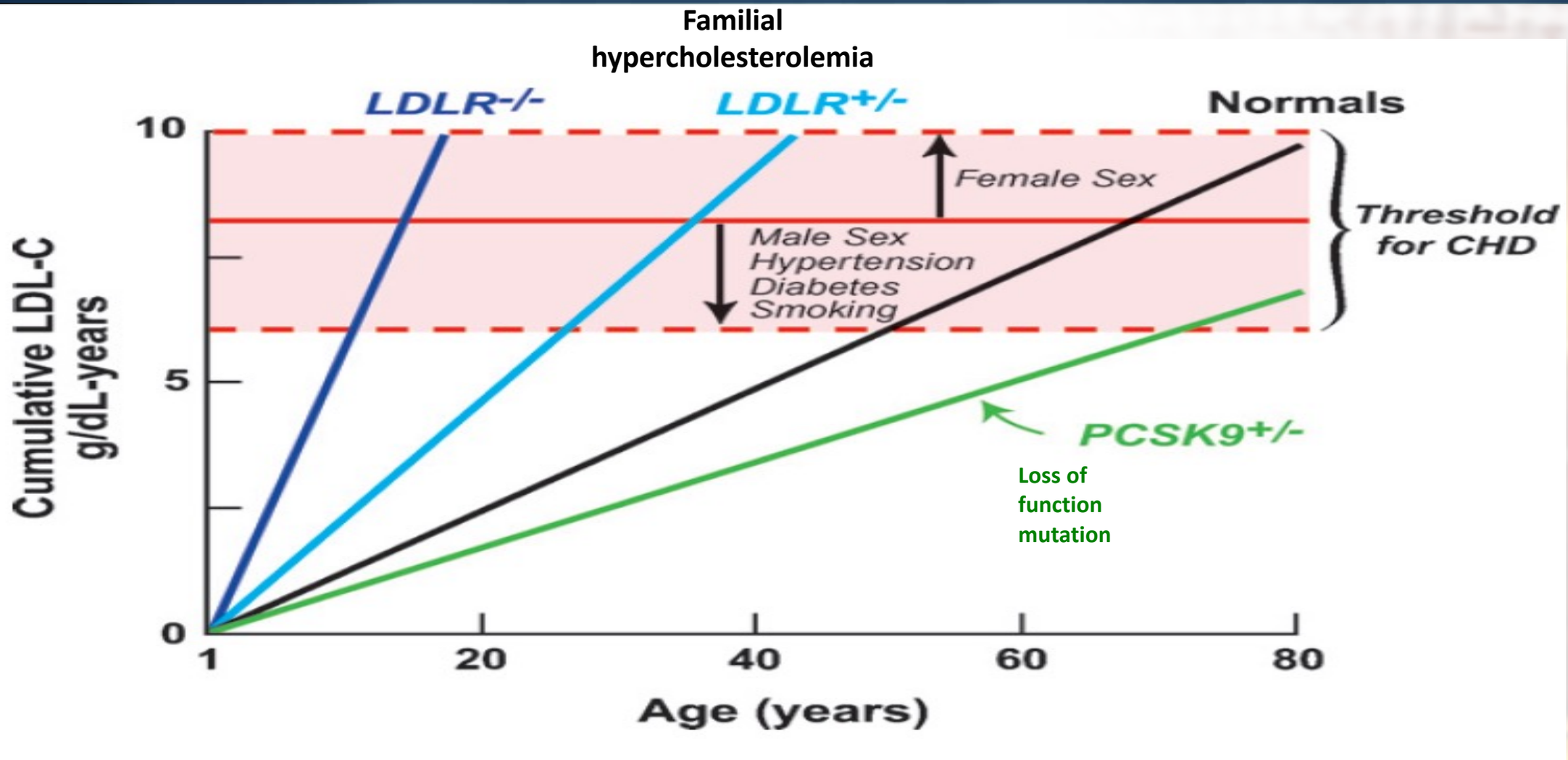
Prevalence of Mutations in Genes Encoding Proteins Involved In LDL Uptake

Types of Mutations Causing FH[1-4]		
Gene	**Mechanism of gene mutation**	**Prevalence**
LDLR	LDLR is absent or has decreased capacity to clear LDL from the circulation	85–90%
ApoB	Mutations impair binding of LDL to the LDLR, reducing LDL uptake	5–10%
PCSK9	Gain of function mutations increase PCSK9 activity leading to increased LDLR degradation and decreased surface expression of LDLR, thus reducing uptake of LDL-C	Rare
LDLRAP1	Loss of function mutations in the protein required for clathrin-mediated internalization reduce uptake of the LDLR–LDL-C complex	Rare (autosomal recessive hypercholesterolemia [ARH])

Although over 1,250 distinct *LDLR* mutations have been described,[1,3] novel FH mutations continue to be identified[3,5]

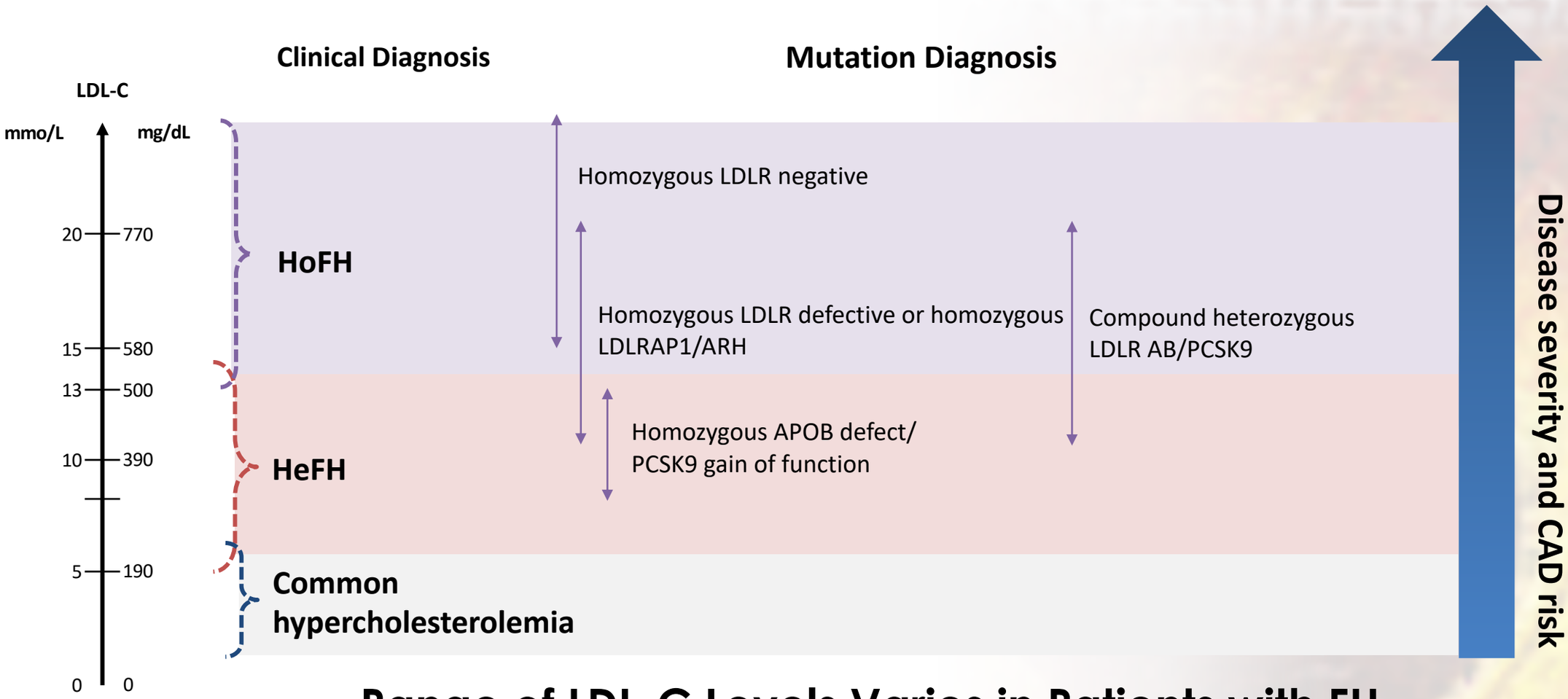
1. Nordestgaard BG, et al. *Eur Heart J*. 2013;34:3478a-3490a. 2. de Castro-Orós I, et al. *Appl Clin Genet*. 2010;3:53-64.
3. Foody JM, et al. *J Clin Lipidol*. 2016;10:970-986. 4. Goldberg AC, et al. *J Clin Lipidol*. 2011;5:S1-S8. 5. Ahmad Z, et al. *Circ Cardiovasc Genet*. 2012;5:666-675.

Prolonged LDL Exposure Over a Lifetime in FH Patients and Normal Individuals



Horton JD et al. *Journal of Lipid Research 2009*;50:S172-S177.

FH Genotype Determines LDL-C Levels



Range of LDL-C Levels Varies in Patients with FH

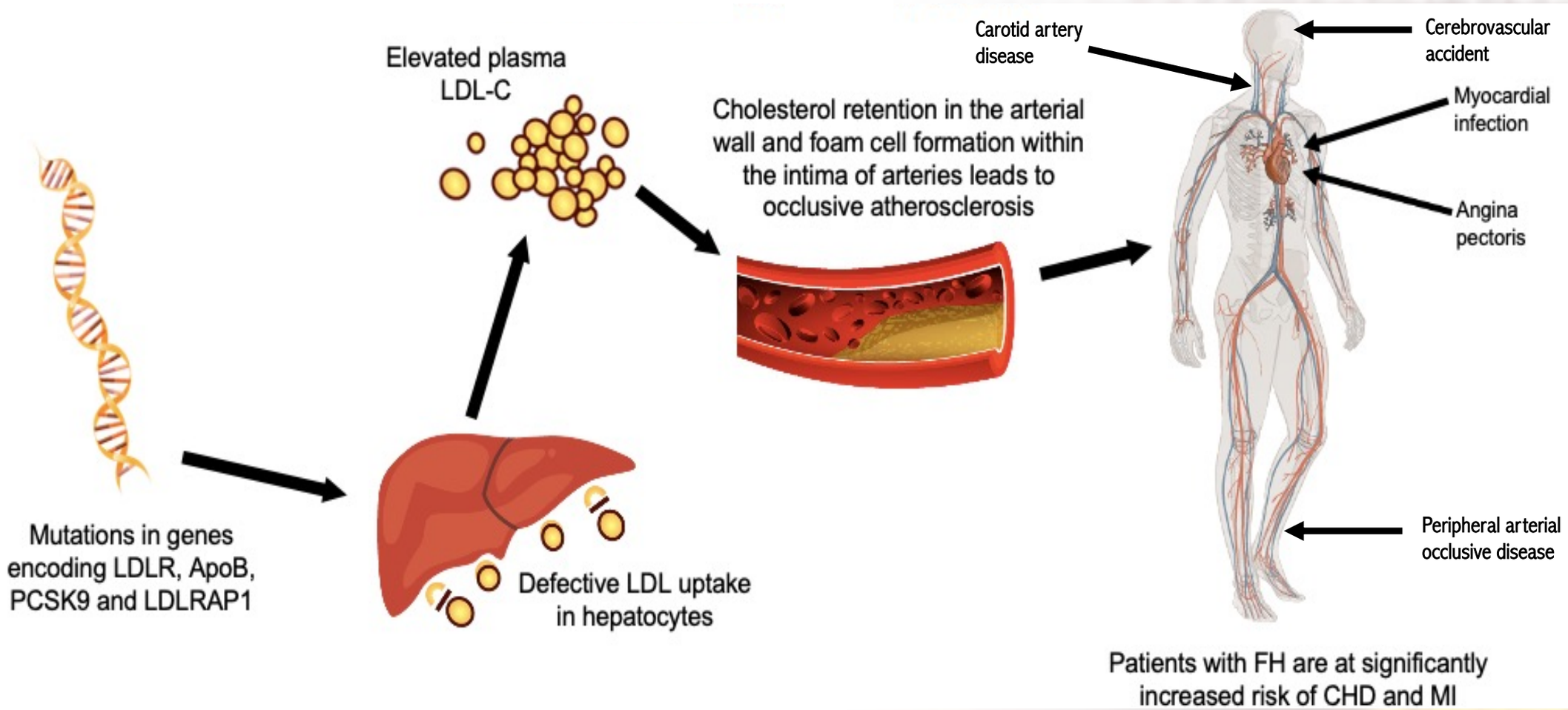
1. Cuchel M, et al. *Eur Heart J*. 2014; 35:2146-2157. 2. Sturm AC, et al. *J Am Coll Cardiol*. 2018;72:662-680.

Characteristics of Homozygous and Heterozygous FH

	HeFH	HoFH
Genetic mutation[1]	One mutated allele	Two mutated alleles
Prevalence[1-4]	More prevalent	Less prevalent
Total cholesterol[1,5]	310–580 mg/dL	460–1160 mg/dL
LDL-C levels[1-4]	≥ 190 mg/dL	> 500 mg/dL
Physical presentation[1-3,6]	Xanthomas[a] or corneal arcus	Xanthomas[a] or corneal arcus in childhood
Acute Myocardial Infarction[2,6,7]	Usually > 30 years old	Early childhood/adolescence[b]
CHD development[1-3,5]	< 55–60 years	Childhood/adolescence[c]

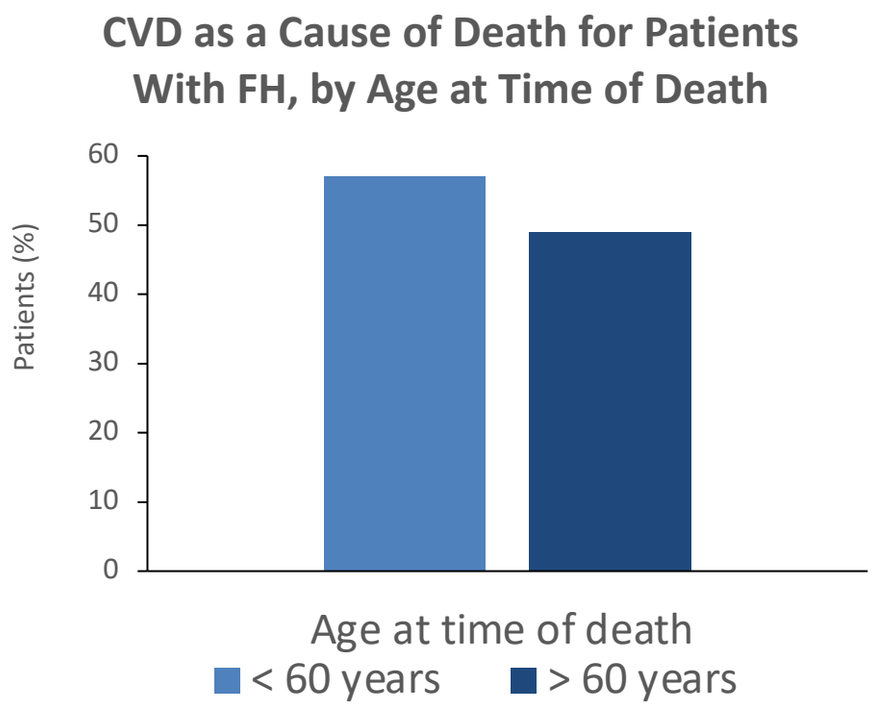
1. NCEP. *Circulation*. 2002;106:3143-3421. 2. Raal FJ, et al. *Atherosclerosis.* 2012;223:262-268. 3. Reiner Z. *Nat Rev Cardiol.* 2015;12:565-575. 4. Robinson JG. *J Manag Care Pharm.* 2013;19:139-149. 5. Nordestgaard BG, et al. *Eur Heart J*. 2013;34:3478-3490a. 6. Cuchel M, et al. Eur Heart J. 2014;35:2146-2157. 7. Goldstein JL, et al. *Arterioscler Thromb Vasc Biol*. 2009;29:431-438. 8. Soutar AK and Naoumova RP. *Nat Clin Pract Cardiovasc Med.* 2007;4(4):214-225.

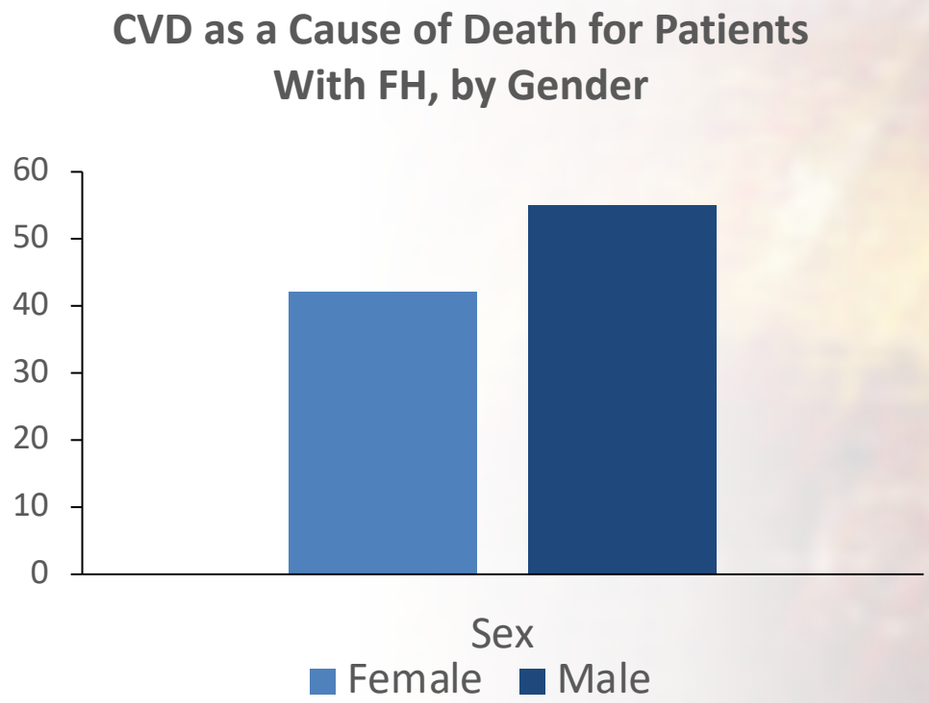
Elevated LDL-C Exposure Promotes Retention Leading to Atherosclerosis



1. Nordestgaard BG et al. *Eur Heart J*. 2013;34:3478-3490. 2. Soutar AK and Maoumova RP. *A Nat Clin Cardiovasc Med*. 2007;4(4):214-225. 3. Perak AM, et al. *Circulation*. 2016;134:9-19.

CVD Is the Major Cause of Death in Patients With FH



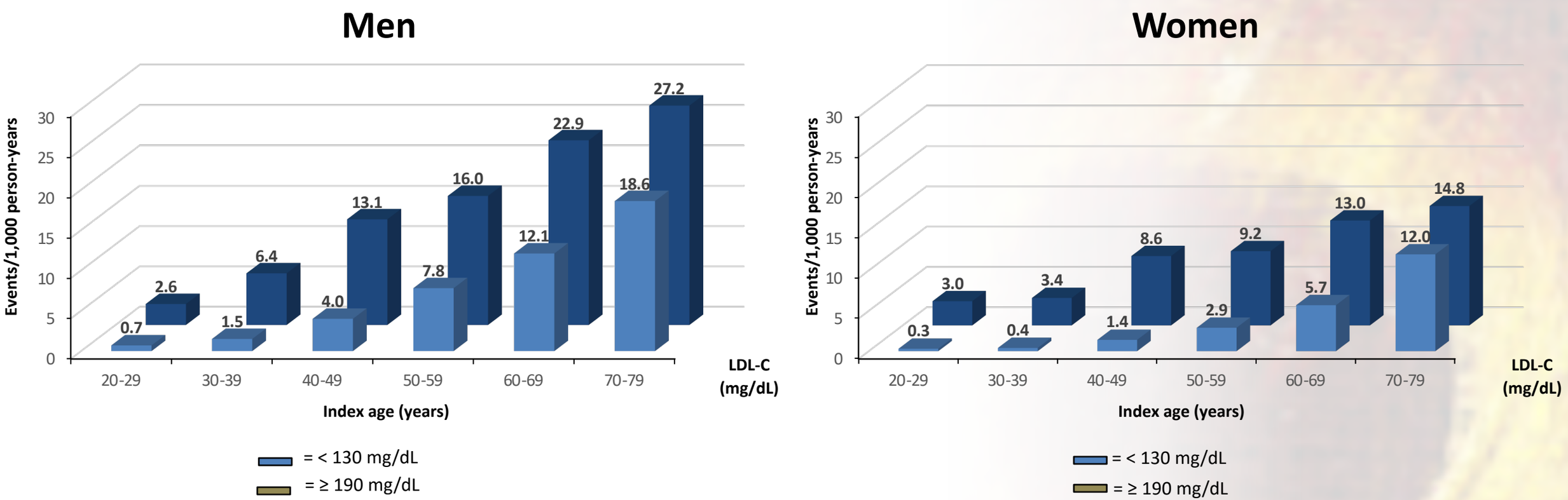


- **Untreated FH increases the risk of premature atherosclerosis and CVD**
- **CVD was the main cause of death for 50% of patients and was present in 93% of patients at the time of death**
- **Importance of diagnosing high risk population**

Krogh HW, et al. *Eur Heart J*. 2016; 37:1398-1405.

Adults With FH Have Increased Long-Term CHD and ASCVD Risk

Unadjusted Rates of CHD or Nonfatal MI*

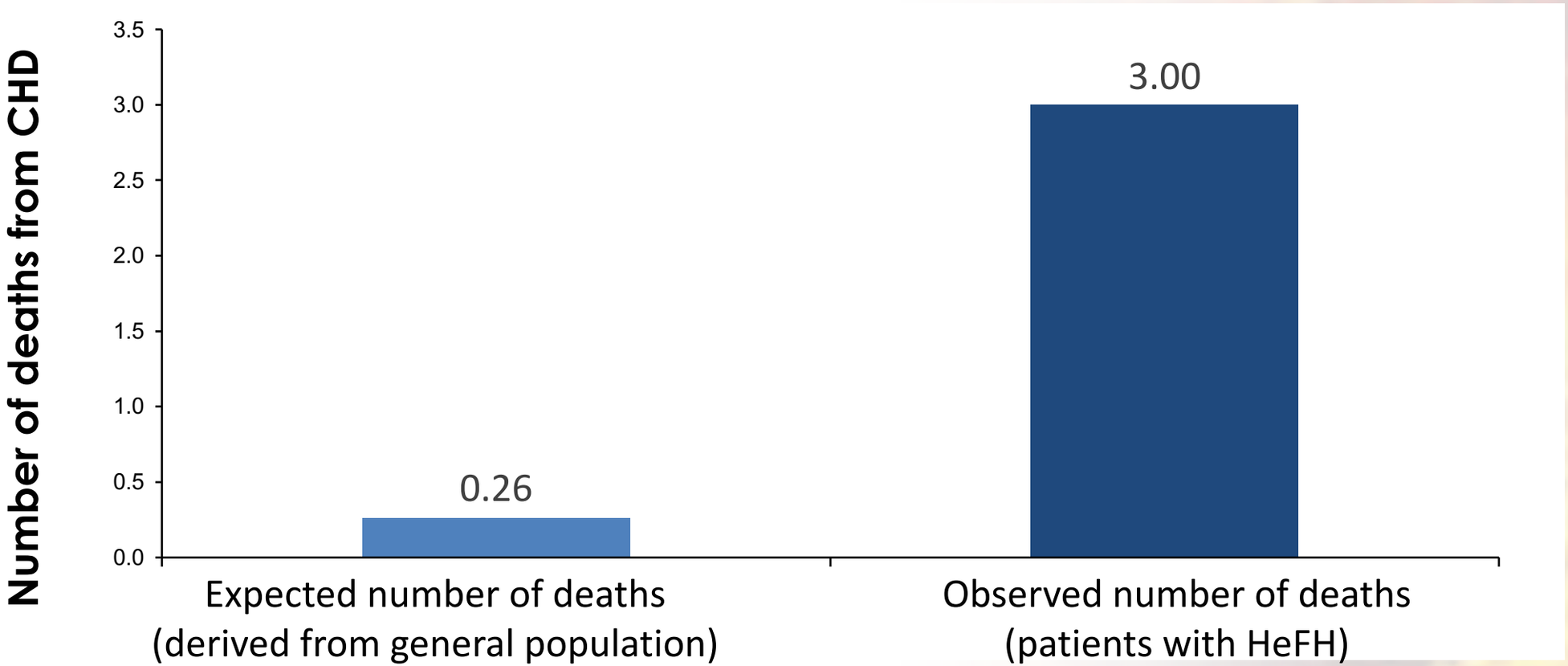


Adults with FH (LDL-C > 190 mg/dL) were associated with 5-fold increased risk for long-term CHD and ASCVD compared with LDL-C levels < 130 mg/dL

Perak AM, et al. *Circulation*. 2016;134:9-19.

Young Adult Patients with FH Have 11.5x Higher Risk of Death from CHD Compared to the General Population

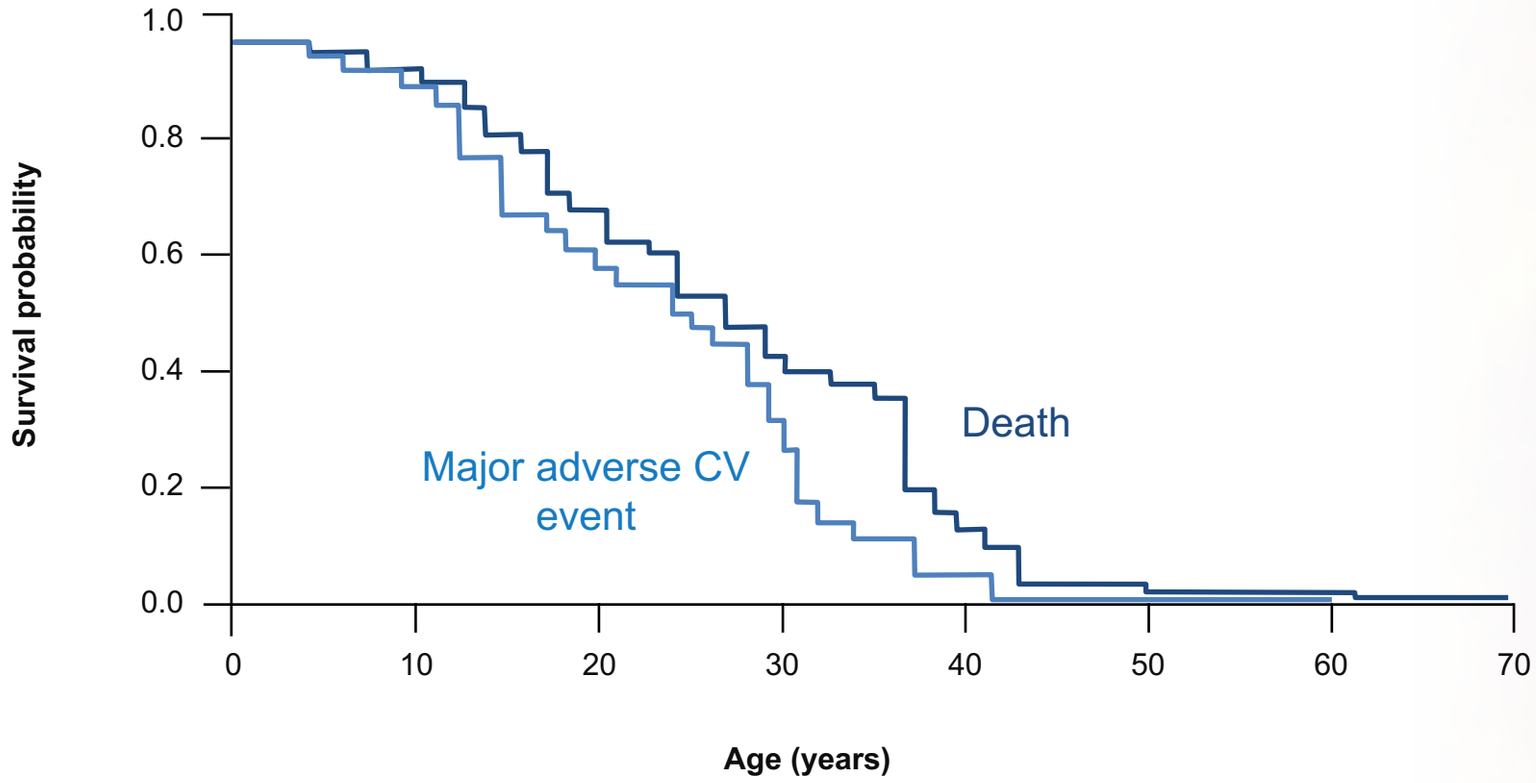
Long-Term Prospective Registry Study of 3,382 Patients With HeFH Evaluated Coronary Mortality After Widespread Use of Statins



Neil A, et al. *Eur Heart J.* 2008;29;2625-2633.

Patients With HoFH Experience Very Premature CV Events and Death

Age at First Major Adverse CV Event and at Death

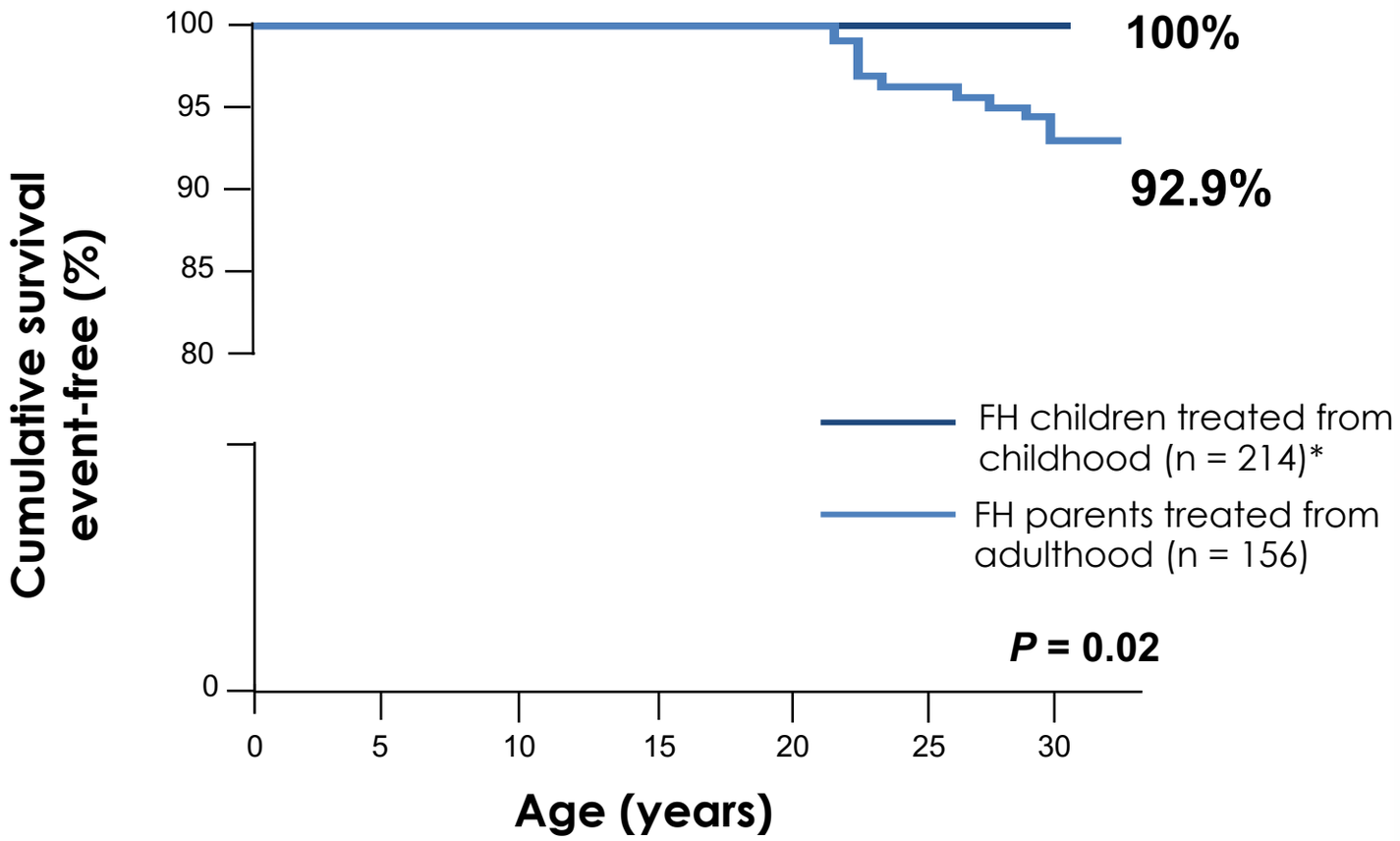


- Children with HoFH who died from acute MI as young as 4 years old have been reported
- These patients require early diagnosis and intensive therapeutic intervention from an early age
- If untreated, patients with HoFH are likely to develop CHD as teenagers and die from an acute Mi before reaching 20 years of age

1. Cuchel M, et al. *Eur Heart J.* 2014;35:2146-2157. 2. Raal FJ, et al. *Circulation.* 2011;124:2202-2207. 3. Reiner Z. *Nat Rev Cardiol*. 2015;12:565–575.

Early Identification and Initiation of Appropriate Treatment for FH Is Needed to Delay Mortality

Impact of Start of Statin Treatment on Coronary Outcomes



- Early treatment of FH can reduce LDL-C burden, improve endothelial function and attenuate the progression of atherosclerosis and improve coronary outcomes
- The greater long-term benefit underscores the need for the initiation of treatment earlier rather than later in life
- Initiation of statin therapy on diagnosis is effective in prevention of premature CVD and CV mortality

1. Wiegman A, et al. *Eur Heart J*. 2015;36:2425-2437. 2. Braamskamp MJAM, et al. *J Am Coll Cardiol*. 2016;67(4):455-461.

Summary

- LDL-C is a proatherogenic particle that triggers the atherosclerotic pathway
- Genetic mutations in LDL-R, ApoB and PCSK9 are the common causes of FH
- FH results in increased exposure time to LDL-C translating to higher CV risk
- Early detection of FH with effective treatment significantly impacts CV risk reduction

THE CHOLESTEROL DILEMMA

Cholesterol Metabolism and Plaque Formation

Focus on FH Individuals

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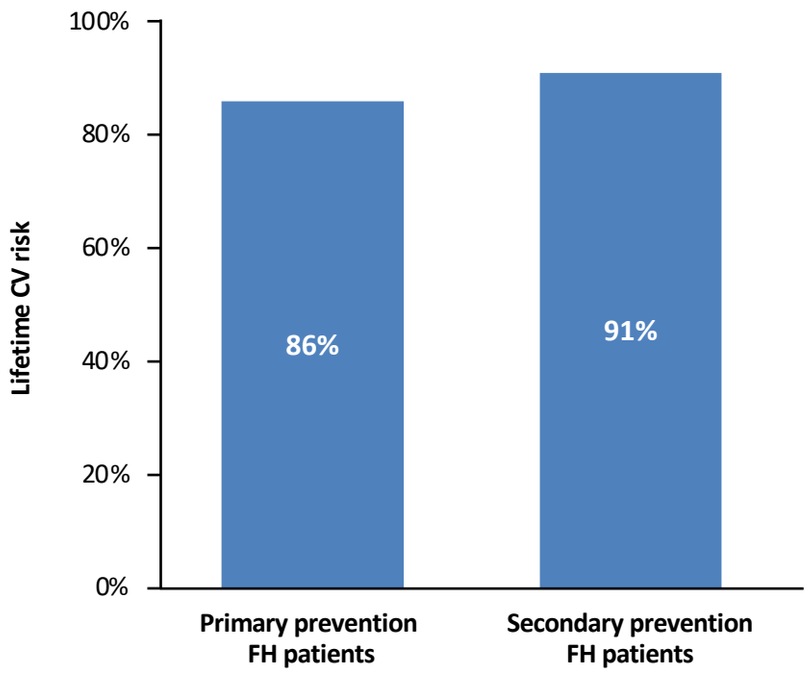
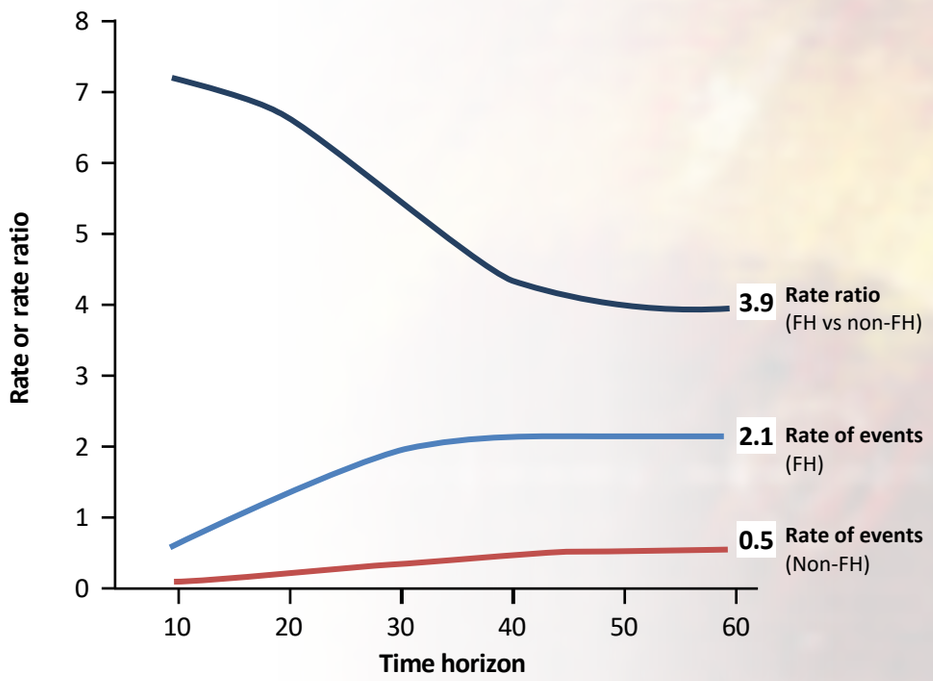
Preventive Cardiology, Clinical Lipidology and Hypertension

Patients With FH Experience a Markedly Increased CV Event Rate

Prediction of Lifetime CV Risk* in FH Patients†



Prediction of Lifetime Event Rates in FH and Non-FH Patients



Primary prevention FH patients have almost the same risk of CV events as patients with FH who have already had an event[1]

*Risk of one or more CV events.

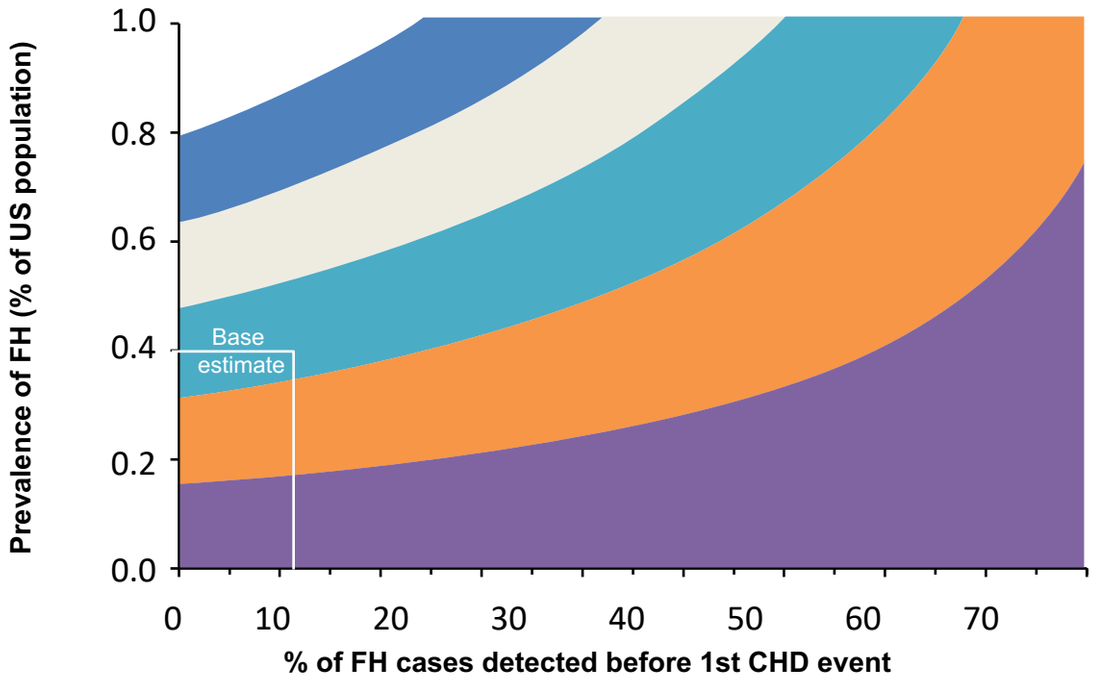
†CV risk calculations based on Benn et al.[2] were used on patient characteristics from RUTHERFORD-2 clinical trial population.

CV, cardiovascular; FH, familial hypercholesterolemia.

1. Villa G. et al, *Eur Heart J Qual Care Clin Outcomes.* 2017;3:274-280. 2. Benn M. et al, *J Clin Endocrinol Metab*. 2012;97:3956-3964.

Undetected FH Contributes to Premature CHD Mortality in the US

Proportion of Premature CHD Mortality Attributable to Undetected FH in the US Across a Spectrum of FH Prevalence and Detection Estimates



Percentage of premature CHD mortality in the US attributable to undetected FH:

- 4–5%
- 3–4%
- 2–3%
- 1–2%
- < 1%

- For the base estimate* the model projected that:
  - Undetected FH led to > 44,000 CHD deaths
  - > 132,000 years of lost life for a 10-year period

Missed diagnosis of FH accounts for 2.4% of premature CHD deaths and 0.6% of all CHD deaths in the US

An FH prevalence of 1 in 250 (0.4%) to account for genotypic FH and US population census data were used, and assuming 90% undetected and untreated, a calibrated and validated Markov model of the natural history of FH in the US population, including fatal and nonfatal CHD, was developed.

CHD, coronary heart disease; FH, familial hypercholesterolemia.

Mendelson MM, et al. abstract 15395: Estimating Coronary Heart Disease Morbidity and Mortality From Heterozygous Familial Hypercholesterolemia in the United States. Circulation. 2015;132:A15395.