Laboratory Implications of the 2013 American College of Cardiology / American Heart Association Lipid Guidelines

Case: A 45 y/o man is seeking counseling about the prevention of arteriosclerotic cardiovascular disease (ASCVD). *How do you counsel him?*

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4-27-2015; web

Learning objectives:

1. List and explain the causes of elevations in LDL-C.

2. Describe the scientific basis for the 2013 ACC/AHA guidelines concerning the treatment of hypercholesterolemia.

3. Identify patients that can benefit from statin therapy.

4. Plan and interpret the laboratory evaluation of patients with hypercholesterolemia.

*W*hat is the composition and function of the major lipoproteins in the circulation?

Density / Name	Abbrev-iation	Major lipid(s) carried	Notes
Chylomicron	(Chylo)	Tg	Post-prandial Tg carrier
Very low	VLDL	Tg	Major nl Tg carrier
Intermediate	IDL	Chol & Tg	Nl concentration: low
Low	LDL	Chol	Major nl chol. carrier
High	HDL	Chol	Reverse-chol. transport

*W*hat is the apoprotein composition of the clinically important lipoproteins in the circulation?

Lipoprotein	Major apolipoproteins	Pathway
Chylomicron	Apo CII, Apo E, Apo B_{48}	Exogenous
VLDL	Apo CII, Apo E, Apo B_{100}	Endogenous
IDL	Apo E, Apo B_{100}	Endogenous
LDL	Apo B_{100}	Endogenous
HDL	Apo A1	Reverse chol. transport

*W*here are lipoproteins produced and how are they cleared from the circulation?

Dietary fat (Tg)
v
Lipase + colipase + bile
v
Glycerol, FFA's, monoglycerides
v
Absorption
v
Resynthesis into Tg

Exogenous pathway

FFA, MG

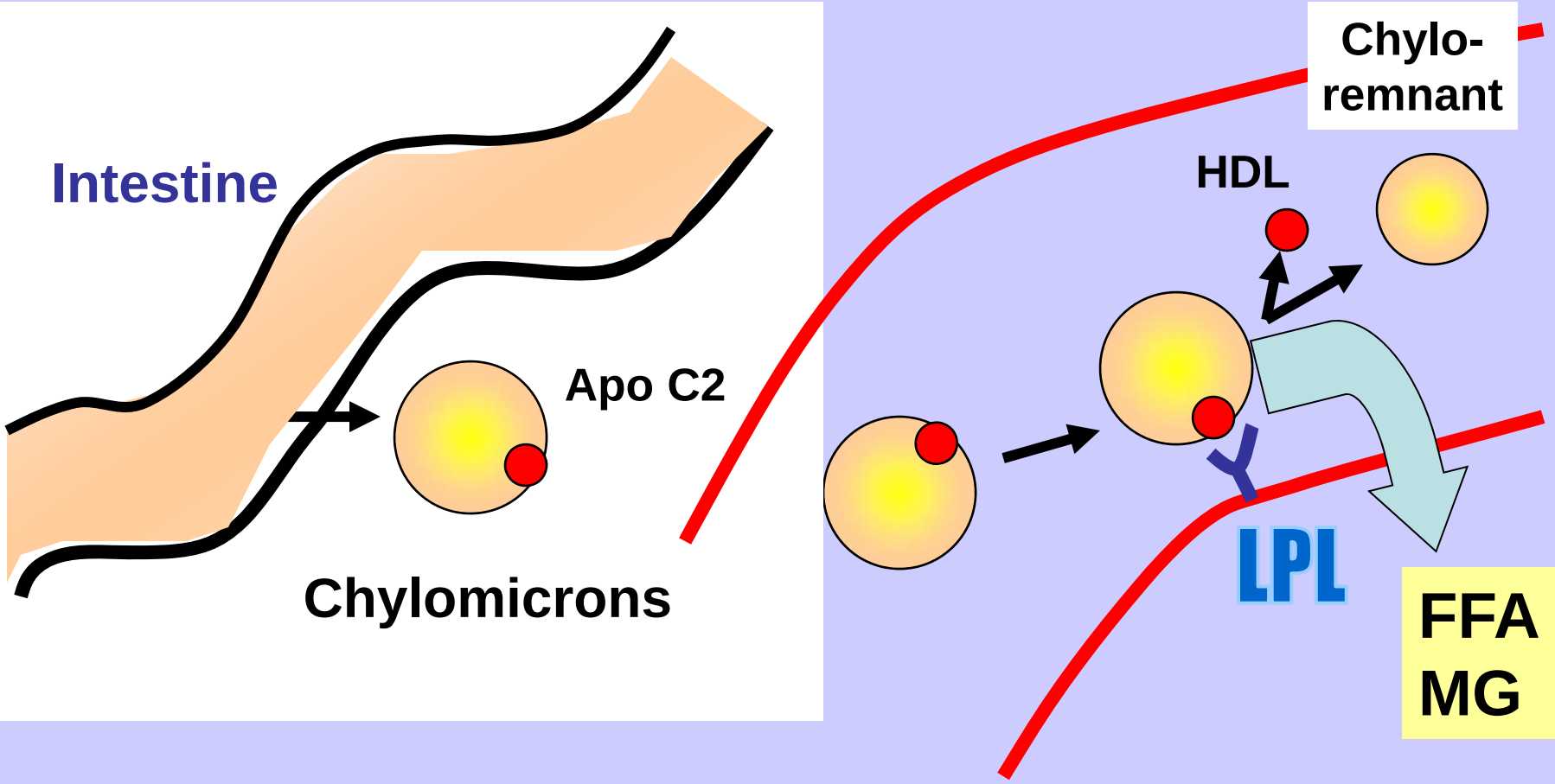
--- > Chylo — **Lymphatics**

--- LPL--- > Chylomicron remnants --- > LDL-R
(Apo CII) — **Circulation**

Liver
(Apo E)
Apo B48 (structural)

LPL = lipoprotein lipase

NORMAL PHYSIOLOGY



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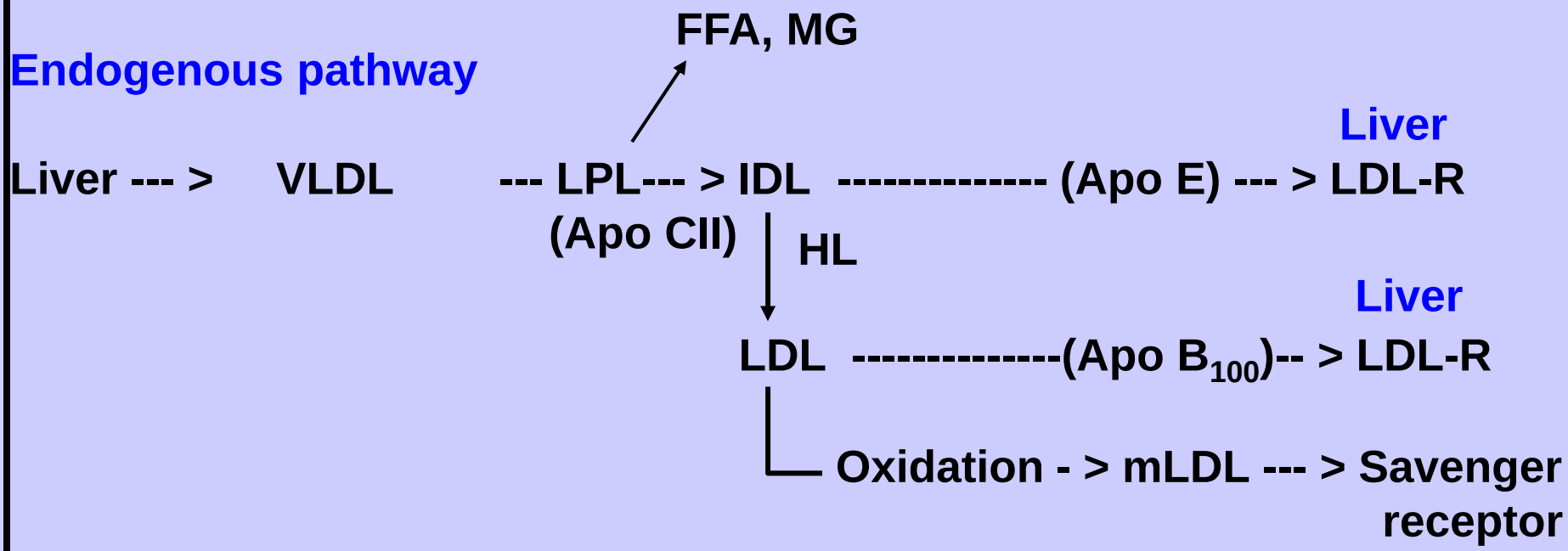

LPL = lipoprotein lipase

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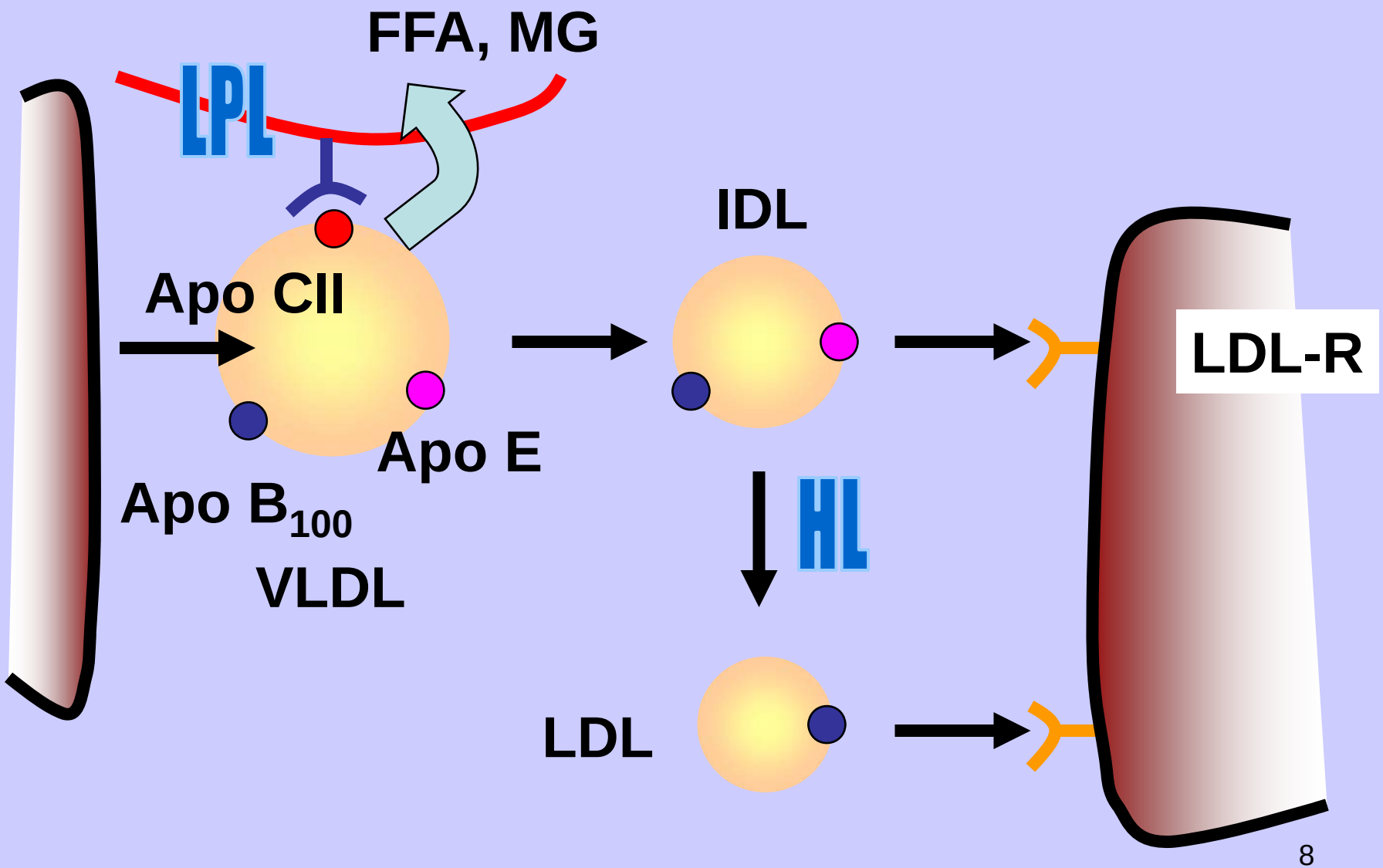
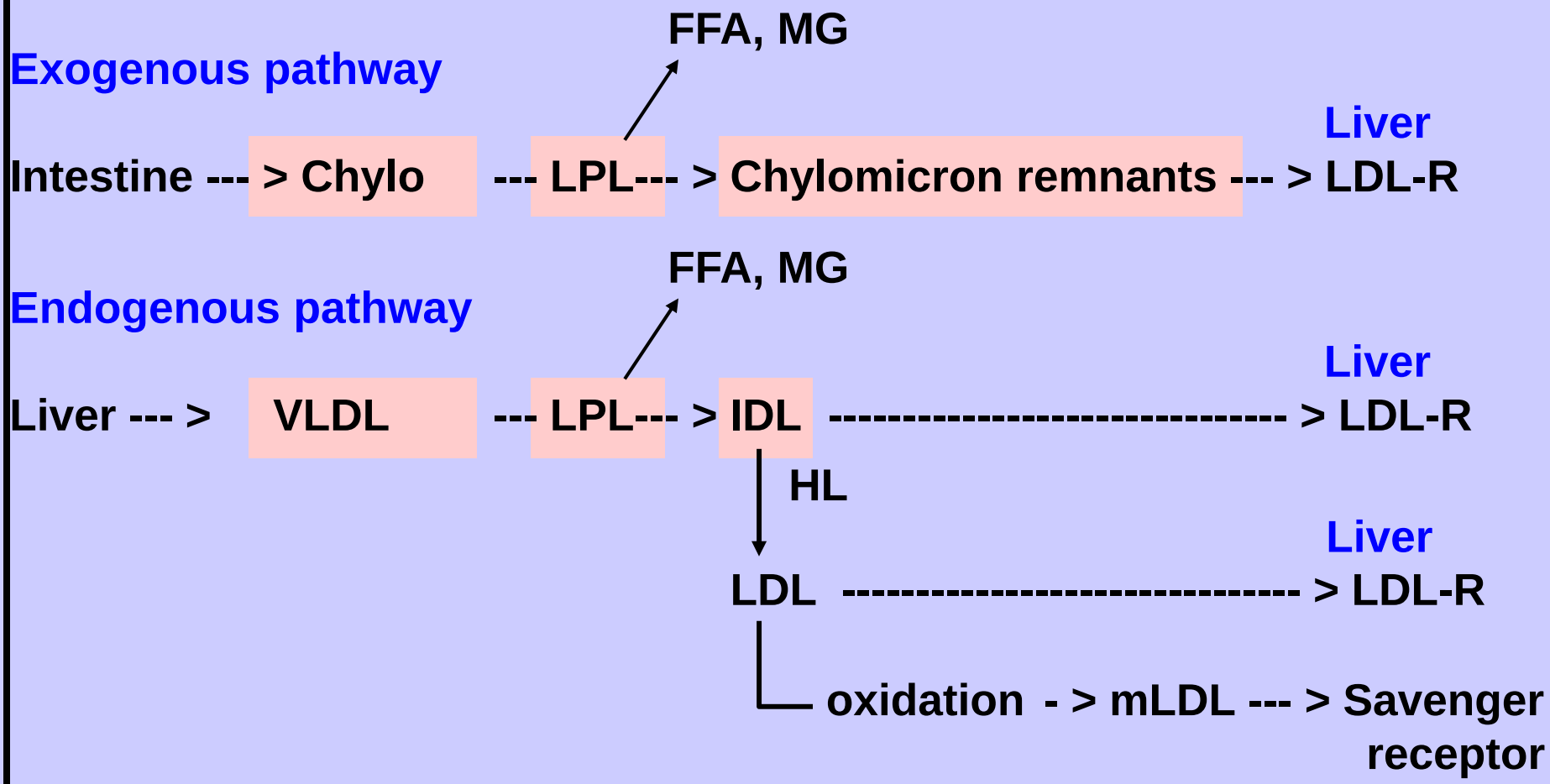


*H*ow do the exogenous and the endogenous pathways compare?



LPL = lipoprotein lipase

*W*hat is the significance of increased concentrations of each of the various lipoproteins?

Lipoprotein	Consequence(s) of elevated levels
Chylomicron	Pancreatitis (>1,000 - 2,000 mg/dL)*
VLDL	Incr. risk of atherosclerosis*
IDL	Incr. risk of atherosclerosis (esp. PVD)
LDL	Incr. risk of atherosclerosis
HDL	Decr. risk of atherosclerosis

*** Tg - HDL-C: inverse relationship**

*W*hat is the significance of decreased concentrations of each of the various lipoproteins?

Lipoprotein	Significance of decreased levels
Chylomicron	[normally absent in fasting plasma]
VLDL	Decr. risk of atherosclerosis*
IDL	[normally very low levels in fasting plasma]
LDL	Decr. risk of atherosclerosis*
HDL	Incr. risk of atherosclerosis

* r/o: liver disease, malnutrition or abetalipoproteinemia

Cardiovascular disease is multifactorial

Risk factors

Not-modifiable

- Age
- Men > Women
- Past medical history
- Family history

Modifiable

- Hypertension
- Dyslipidemia
- Diabetes
- Smoking
- Obesity
- Hypercoaguability

What is the classification of dyslipidemia according to Frederickson?


Donald S. Fredrickson in 1961

HLP	Elevation(s)		Lipoproteins
I	Tg		Chylomicrons
IIA	LDL-C		LDL
IIB	LDL-C & Tg		LDL & VLDL
III	Total chol. & Tg	IDL	
IV	Tg		VLDL
V	Tg		Chylomicrons & VLDL

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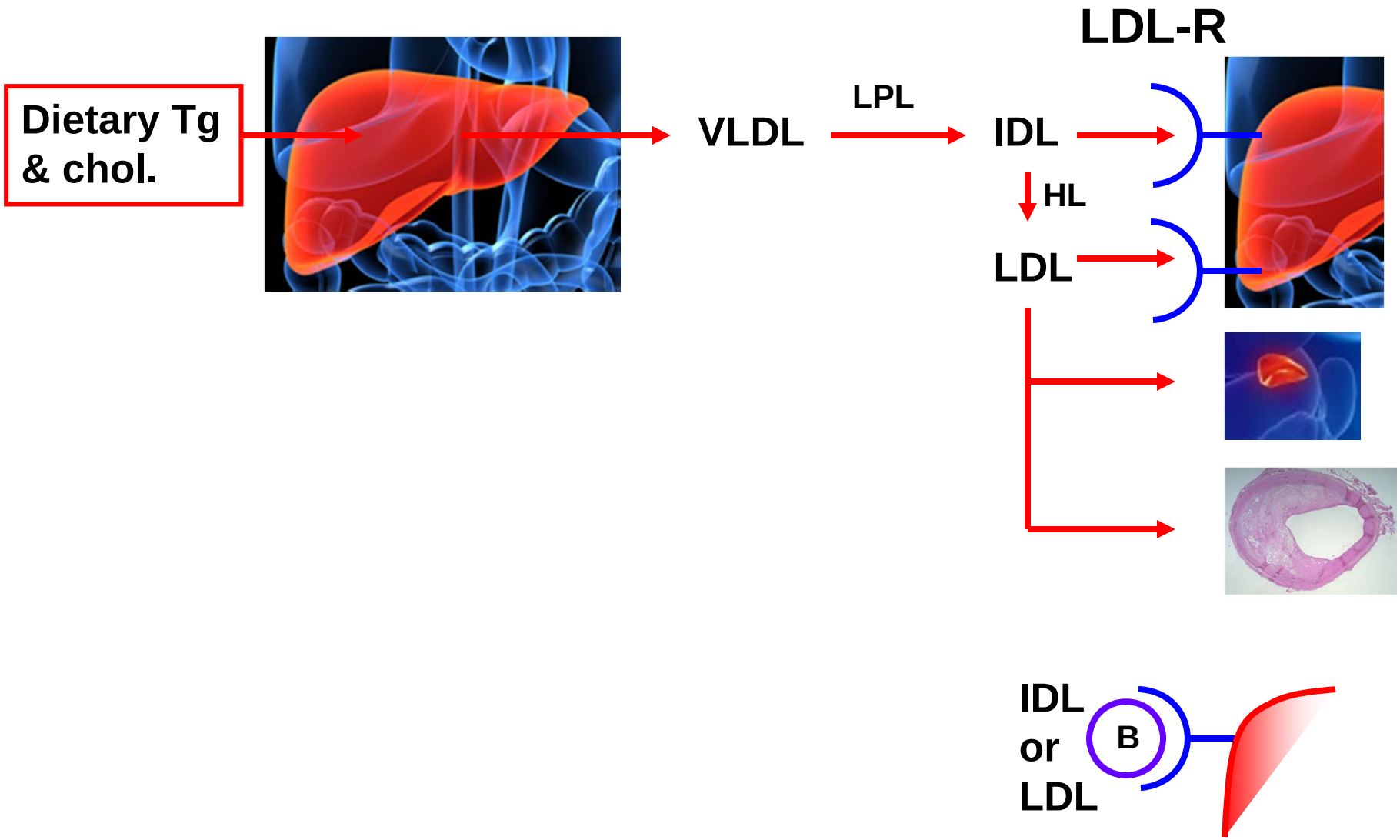
What regulates LDL levels?



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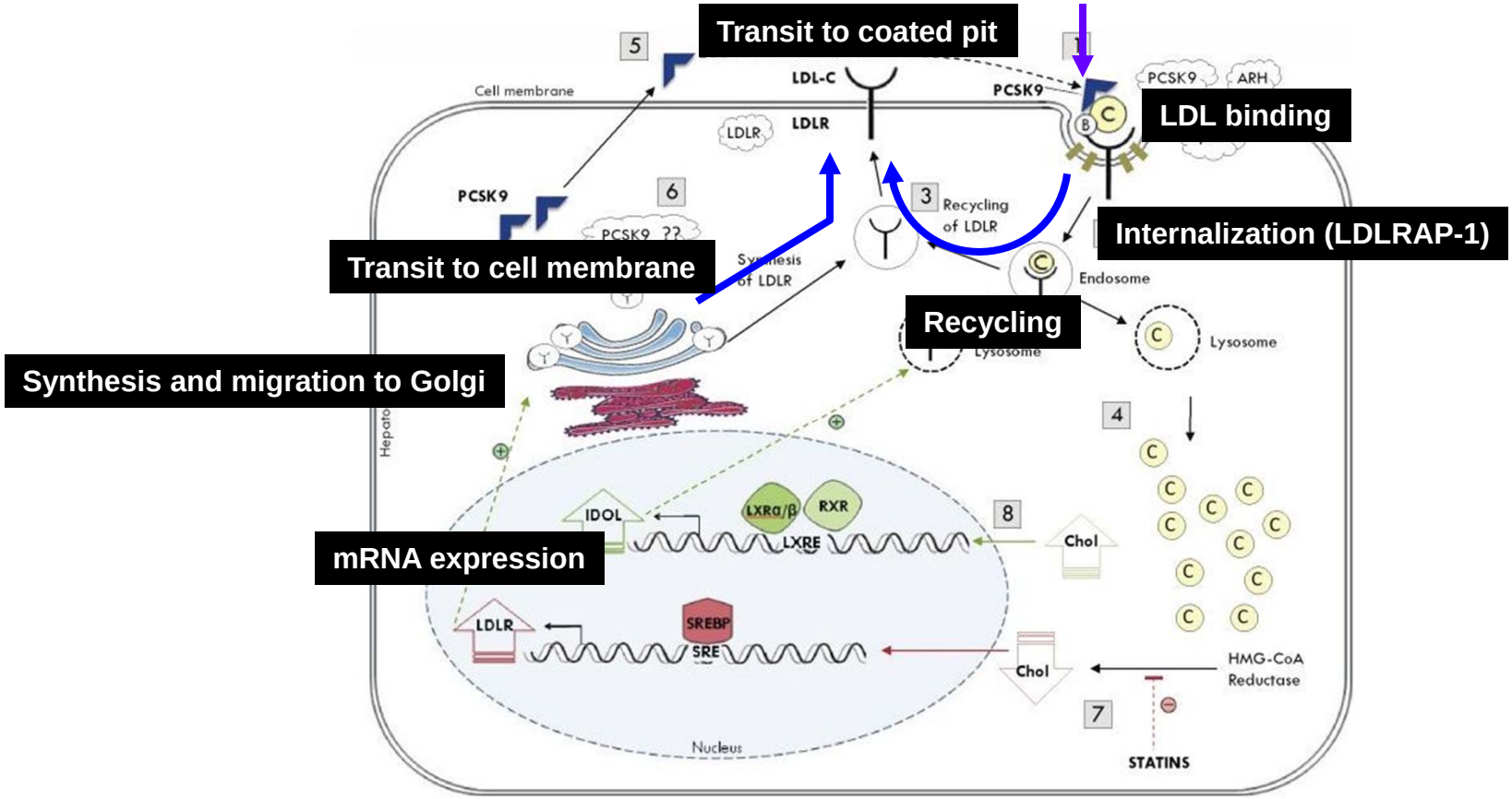
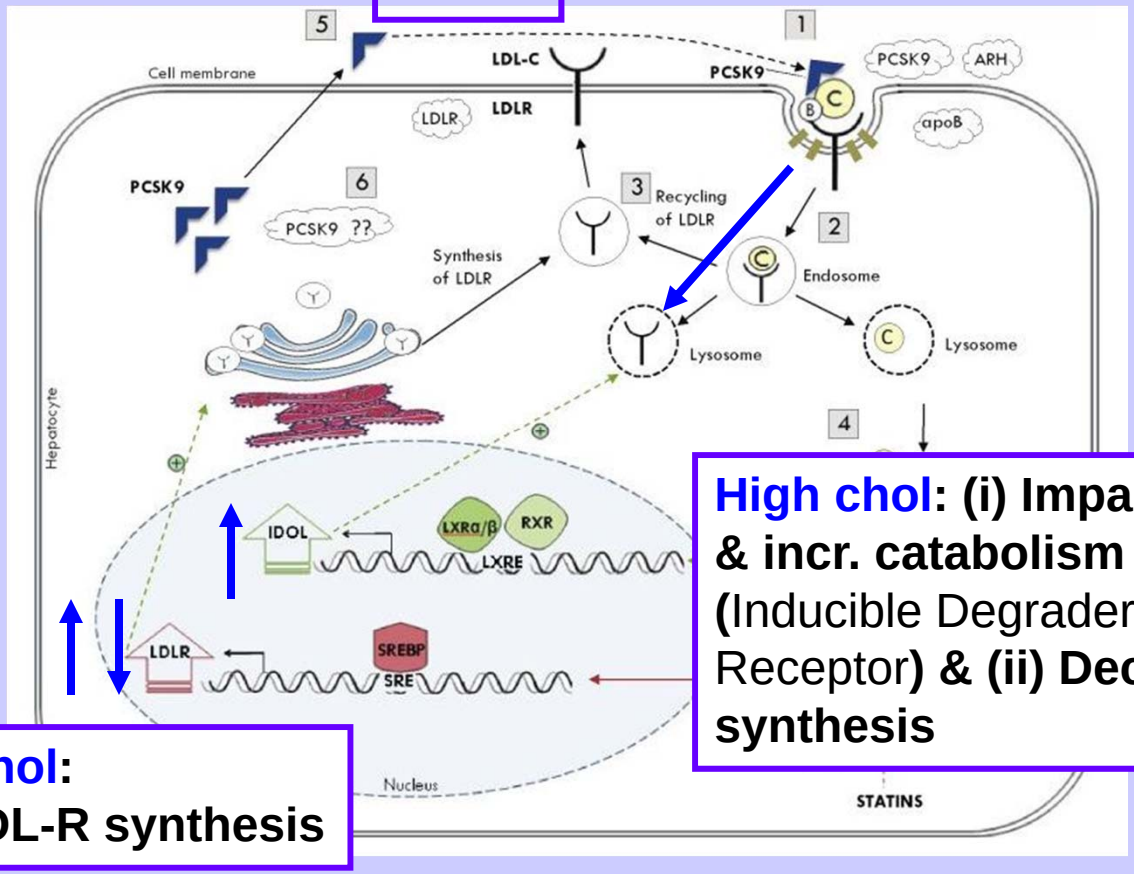
How does the LDL receptor *function* to remove LDL from the circulation? LDL-R expression

PCSK9 Proprotein Convertase Subtilisin/Kexin Type 9



Molecular Pathways of Disease in Familial Hypercholesterolemia (1) The LDL receptor on the surface of hepatocytes binds ApoB-100 of the LDL particle forming a complex. (2) A clathrin-coated pit is formed and the ligand-receptor complex is endocytosed via interactions involving **the** **LDLR Adaptor Protein 1** (LDLRAP1). (3) Inside the hepatocyte, the complex dissociates, the LDLR recycles to the cell membrane, (4) and free cholesterol is used inside the cell. (5) PCSK9 (**Proprotein Convertase Subtilisin/Kexin Type 9**) serves as a post-transcriptional inhibitor of LDLR. It is secreted and inhibits LDLR through cell-surface interactions. (6) The presence of an intracellular pathway for PCSK9-mediated LDLR inhibition is still a subject of controversy. (7) In response to decreased cholesterol such as during treatment with statins, Steroid Response Element Binding Protein (SREBP) binds to the Steroid Response Element (SRE) on the DNA and induces the transcription of the LDLR. (8) The sterol-responsive nuclear receptor LXR on the other hand responds to increased intracellular cholesterol inducing the transcription of IDOL, a recently discovered molecule that induces the ubiquitin-mediated degradation of the LDLR. Clouds in the figure refer to genes in which mutations have been associated with increased LDL-C levels.

How does is LDL receptor expression *regulated*?



High chol: (i) Impaired recycling & incr. catabolism via IDOL (Inducible Degrader Of the LDL-Receptor**) & (ii) Decr. LDL-R synthesis**

Low chol:
Inc. LDL-R synthesis

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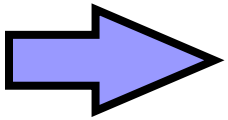
What are the causes of elevated LDL-C?

Pathophysiology: Increased LDL production and/or decreased LDL clearance

Acquired causes 

Genetic causes

What are the acquired causes of elevated LDL-C?

Diet-induced	**(incr. FFA subtrate for cholesterol synthesis)**
Hypothyroidism	**(decr. LDL-R expression)**
Diabetes mellitus	**(overproduction; apo B glycation; many possible HLP phenotypes)**
Nephrotic syn.	**(overproduction; many possible HLP phenotypes)**
Obstructive liver dis.	**(decr. bile salt excretion; decr. LDL-R expression)**

What are the genetic causes of elevated LDL-C?

Familial hypercholesterolemia (FH)

Defects in the LDL-R (apo B_{100}- apo E receptor)

Familial combined hyperlipidemia (FCH)

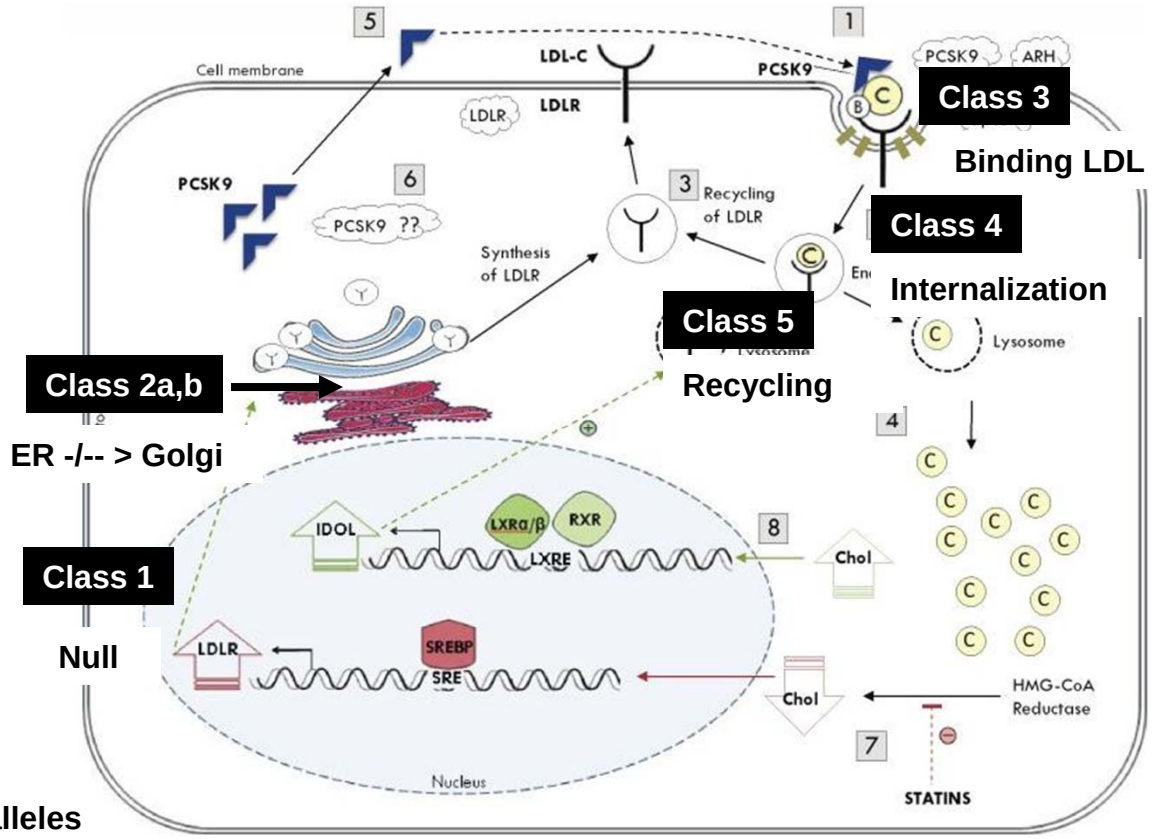
Hyperapo-B-lipoproteinemia

Autosomal recessive hypercholesterolemia (ARH)

PCSK9 gain-of-function mutations causing ADH (autosomal dominant hypercholesterolemia)

Polygenic hypercholesterolemia

*W*hat LDL-R mutations *cause* familial hypercholesterolemia (FH)?



Class 1 **Null alleles**
Class 2a **Complete blockade of receptor movement from ER -- > Golgi**
Class 2b **Partial blockade of receptor movement from ER -- > Golgi**
Class 3 **Defective binding alleles**
Class 4 **Defective internalization alleles**
Class 5 **Defective recycling alleles**

Class 1 includes null alleles that result in complete absence of the LDL receptor.
Class 2 includes defective transport alleles, which disrupt normal folding of the receptor and cause either failure in transport to the cell surface or successful transport of truncated, mutated receptors.
Class 2a mutations completely block the transport of the receptor from the endoplasmic reticulum to the Golgi apparatus.
Class 2b mutations result in a partial blockade of transport of the receptor from the endoplasmic reticulum to the Golgi apparatus.
Class 3 includes defective binding alleles that affect binding of LDL and, in some cases, binding of VLDL as well.
Class 4 includes defective internalization alleles that affect the concentration of normal receptors in clathrin-coated pits for internalization by the hepatocyte.
Class 5 includes defective recycling alleles that prevent dissociation of the receptor and the ligand and thereby interrupt recycling of the receptor.

What would suggest the diagnosis of familial hyper-cholesterolemia (FH)?

AD inheritance of HLP IIA or IIB

Signs and symptoms of heterozygous FH in adults include:

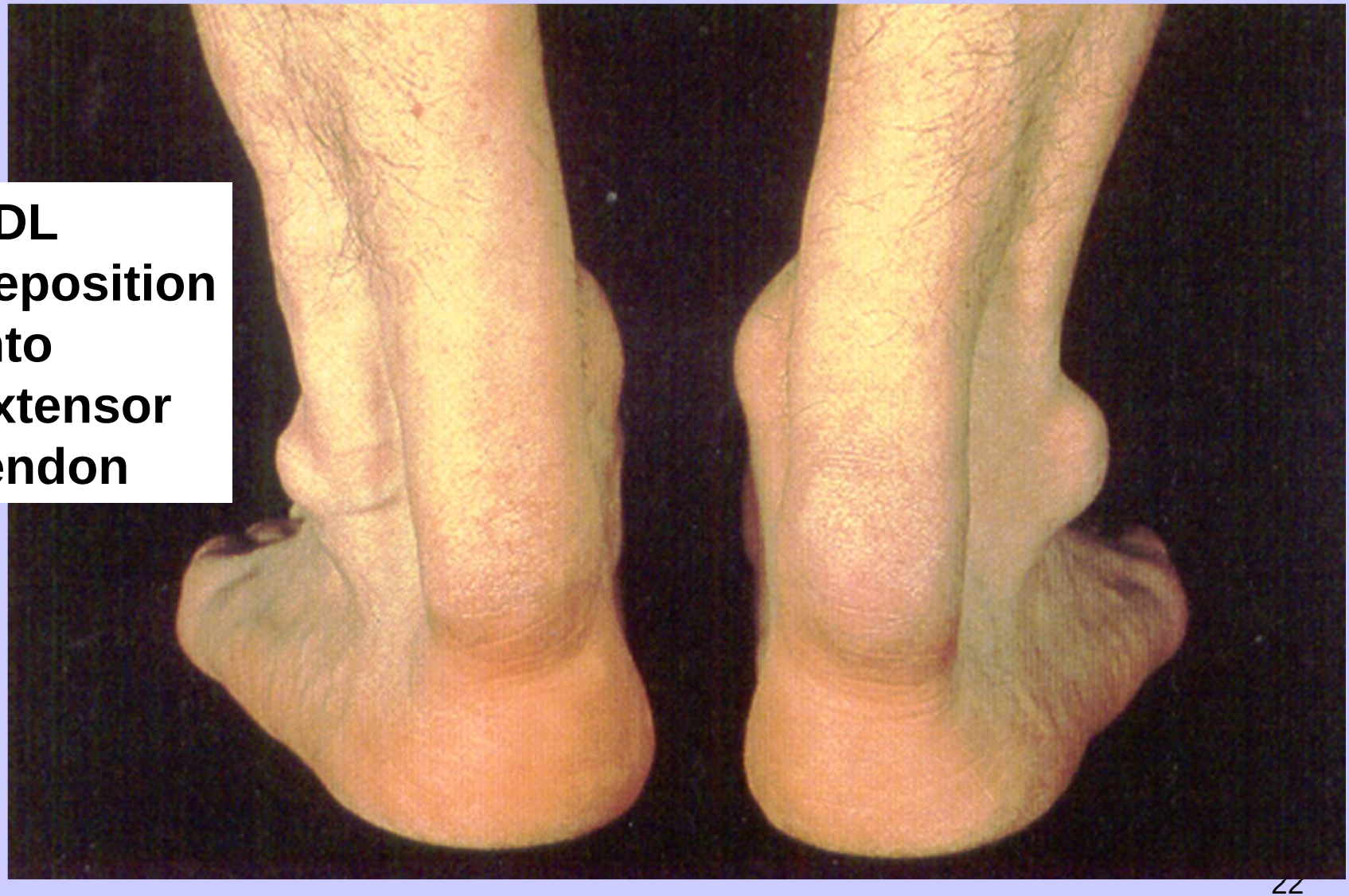
- Severe hypercholesterolemia since childhood (incr. LDL-C in cord blood)
- Symptoms of ASCVD w/o other CV risk factors
- Symptoms of recurrent Achilles tendonitis or arthritic complaints

Untx'ed: Tendon xanthomas (Achilles tendons, metacarpo-phalangeal [MCP] extensor tendons)
- by third decade of life: >60% affected

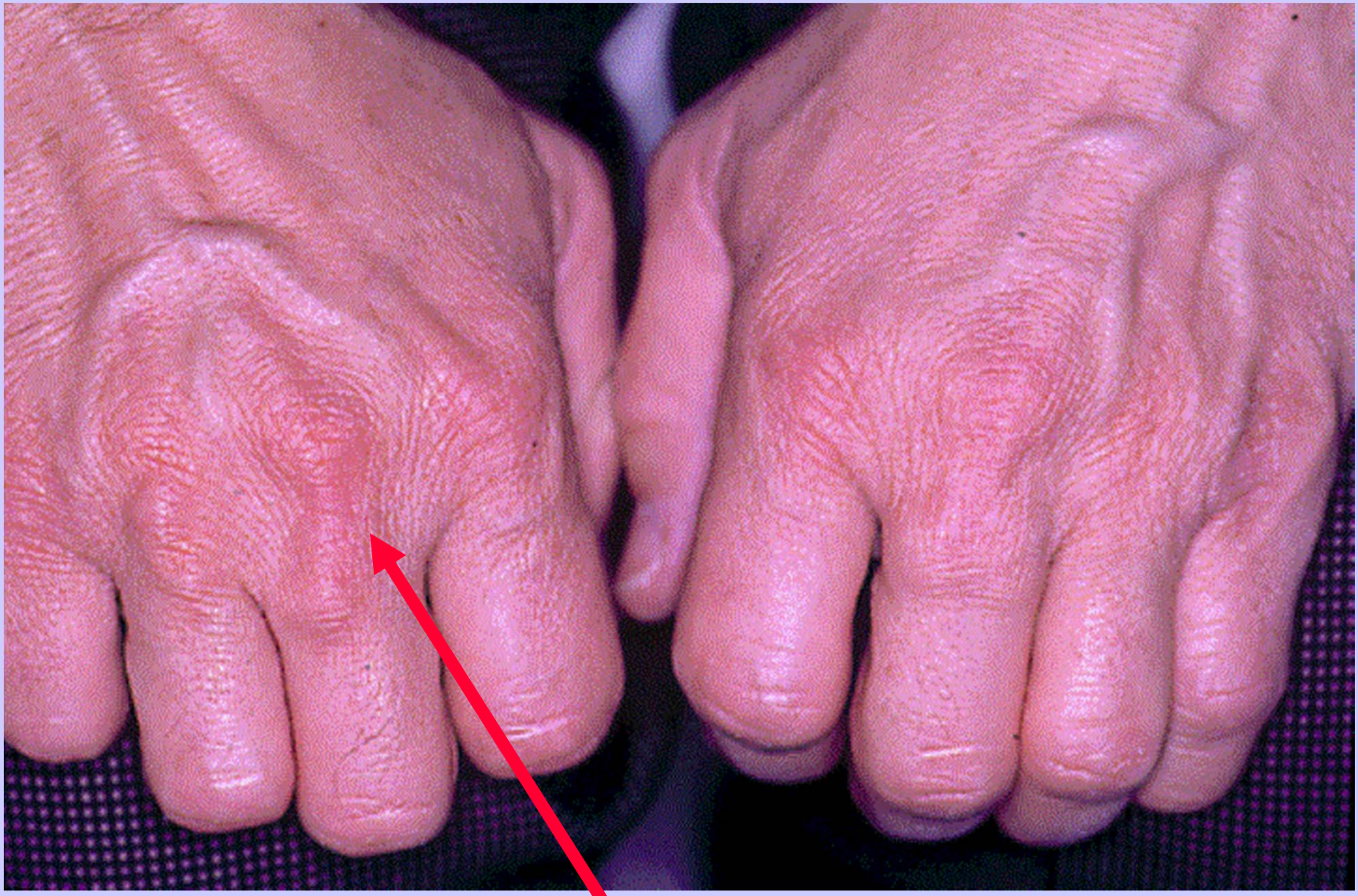
Xanthelasmas (xanthomas around the eyes)

Frequency: 1 in 500

Tendous xanthomas of the Achilles tendon

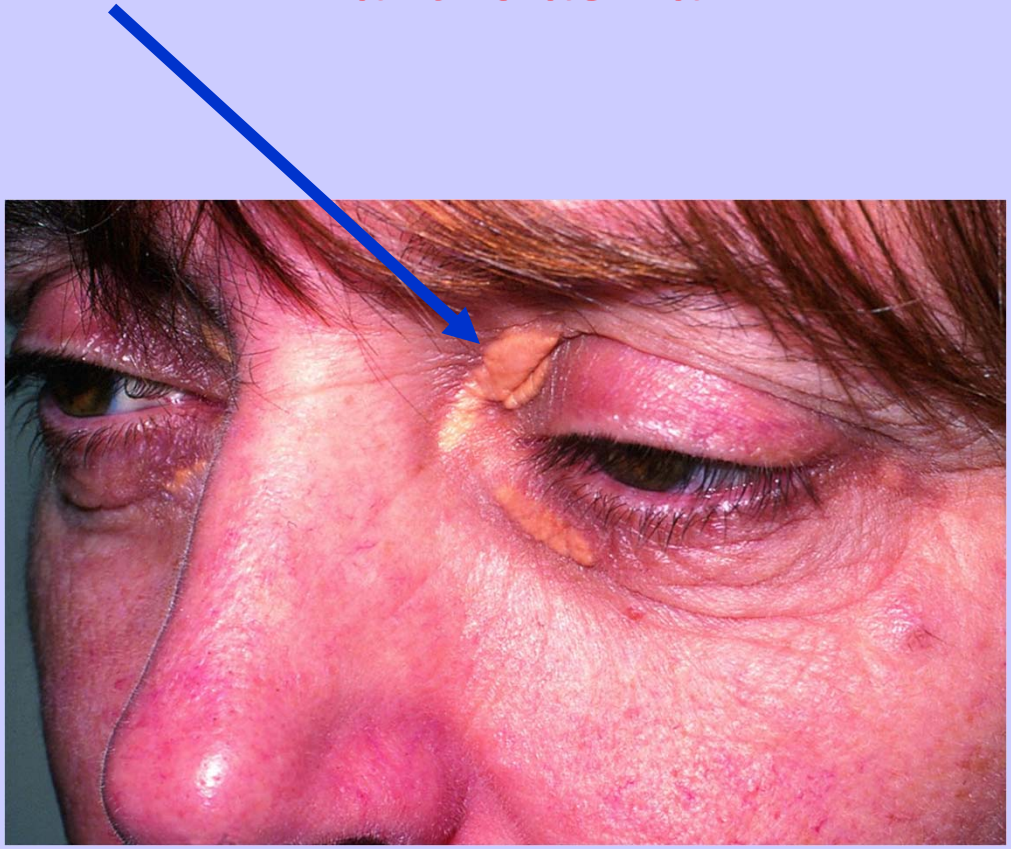


LDL deposition into extensor tendon



Tendenous thickening

Xanthelasma



Xanthelasma are yellow plaques that occur most commonly near the inner canthus of the eyelid, more often on the upper lid than the lower lid. Xanthelasma palpebrarum is the most common cutaneous xanthoma.

Xanthelasma can be soft, semisolid, or calcareous. Frequently, they are symmetrical; often, 4 lids are involved. Xanthelasma have a tendency to progress, coalesce, and become permanent.

The term xanthelasma is derived from the Greek xanthos (yellow) and elasma (beaten metal plate).One half of these lesions are associated with elevated plasma lipid levels. Some occur with altered lipoprotein composition or structure, such as lowered high-density lipoprotein (HDL) levels. They frequently occur in patients with type II hyperlipidemia and in the type IV phenotype. Source: http://emedicine.medscape.com/article/1213423-overview#a0101

What is the consequence of homozygous FH?

Early-onset ASCVD

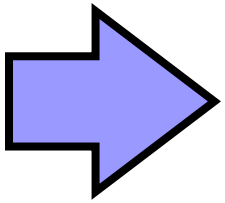
Aortic valve disease

Premature death

What are the genetic causes of HLP type IIA?

Familial hypercholesterolemia (FH)

Familial combined hyperlipidemia (FCH)



Hyperapo-B-lipoproteinemia

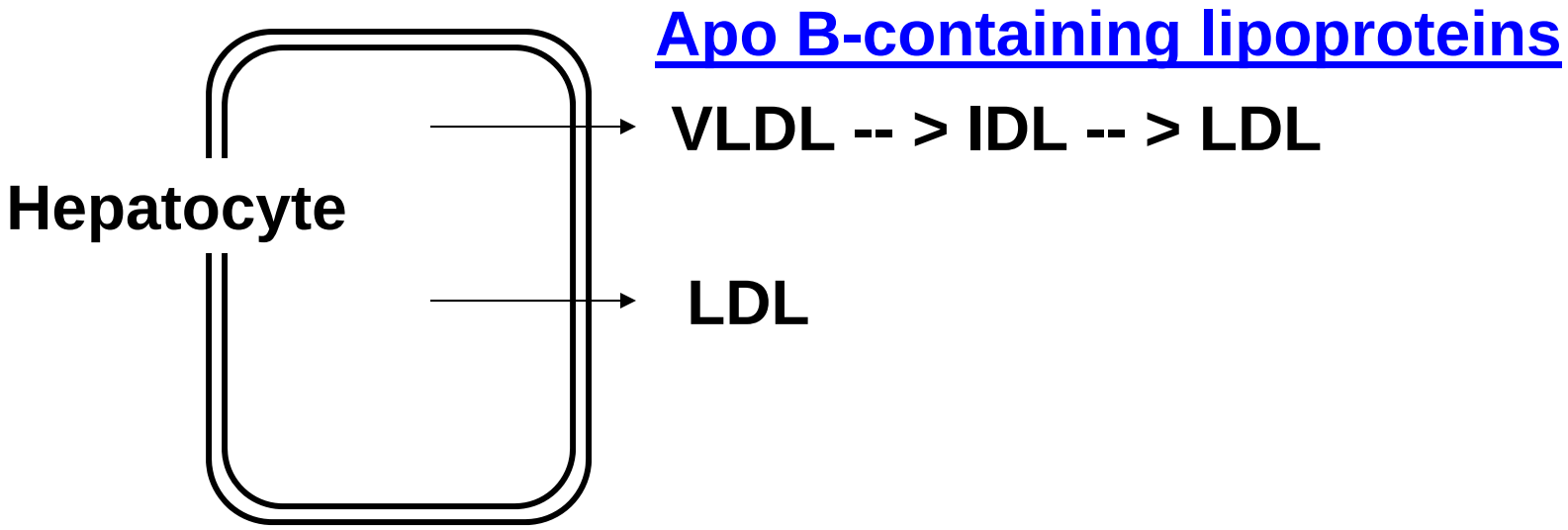
Autosomal recessive hypercholesterolemia (ARH)

PCSK9 gain-of-function mutations causing ADH (autosomal dominant hypercholesterolemia)

Polygenic hypercholesterolemia

What causes familial combined hyperlipidemia?

Overproduction of apo B leading to increases in LDL (IIA), VLDL (IV) or both LDL & VLDL (IIB)



Frequency: ~ 1 in 170

What would suggest the diagnosis of familial combined hyperlipidemia?

Autosomal dominant inheritance of:

HLP IIA

HLP IIB or

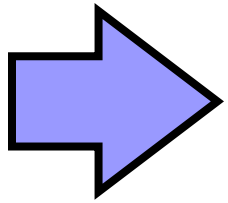
HLP IV . . . . in various family members

What are the genetic causes of HLP type IIA?

Familial hypercholesterolemia (FH)

Familial combined hyperlipidemia (FCH)

Hyperapo-B-lipoproteinemia



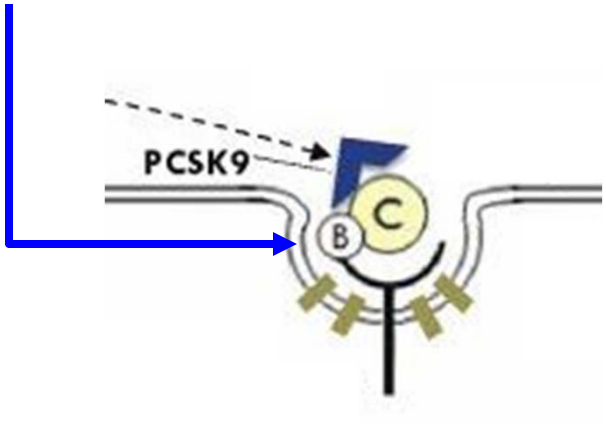
Autosomal recessive hypercholesterolemia (ARH)

PCSK9 gain-of-function mutations causing ADH (autosomal dominant hypercholesterolemia)

Polygenic hypercholesterolemia

What causes hyperapo-B-lipoproteinemia?

Defective apo B w/ reduced apo B binding to LDL-R



What would suggest the diagnosis of hyperapo-B-lipoproteinemia?

Similar clinical presentation as FH but w/o hypertriglyceridemia (IIA-only phenotype)

Usually cannot be distinguished from FH

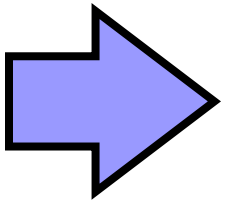
What are the genetic causes of HLP type IIA?

Familial hypercholesterolemia (FH)

Familial combined hyperlipidemia (FCH)

Hyperapo-B-lipoproteinemia

Autosomal recessive hypercholesterolemia (ARH)



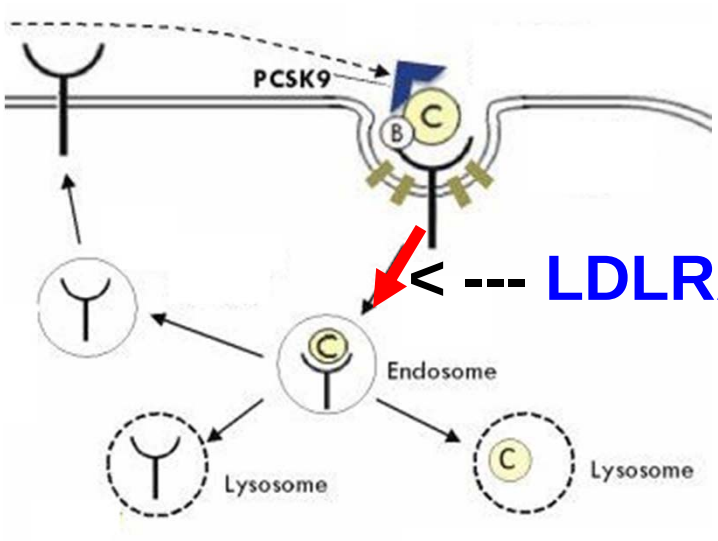
PCSK9 gain-of-function mutations causing ADH (autosomal dominant hypercholesterolemia)

Polygenic hypercholesterolemia

What causes autosomal recessive hypercholesterolemia?

Mutation in: low density lipoprotein receptor adaptor protein 1 (LDLRAP-1)

- necessary for proper internalization of:
LDL-R- LDL particle complex



Plasma membrane

< --- LDLRAP-1

Semin Vasc Med. 2004 Aug;4(3):241-8.
Autosomal recessive hypercholesterolemia.
Soutar AK1, Naoumova RP.

Autosomal recessive hypercholesterolemia (ARH) presents with a clinical phenotype similar to that of classical homozygous familial hypercholesterolemia (FH) caused by defects in the low-density lipoprotein (LDL) receptor gene but is more variable, generally less severe, and more responsive to lipid-lowering therapy than homozygous FH; furthermore, FH is inherited with a dominant pattern. The approximately 50 known affected ARH individuals are mostly of Sardinian or Middle Eastern origin, but rare cases of ARH have occurred worldwide. The physiological defect in ARH is a failure of some, but not all, cell types to mediate LDL receptor-dependent internalization of LDL and is caused by mutations in the gene for a putative adaptor protein called ARH. In affected cells, the LDL receptor gene is normal but LDL receptor protein accumulates at the cell surface; this also occurs in livers of recombinant mice lacking ARH, providing an explanation for the failure of clearance of LDL from plasma in ARH patients. The structural features of the ARH protein and its capacity to interact with the internalization sequence of the LDL receptor, plasma membrane phospholipids, and the clathrin endocytic machinery suggest that it plays a key role in the LDL receptor pathway.

What would suggest the diagnosis of autosomal recessive hypercholesterolemia?

Difficult to differentiate from FH

Lacks FHx (AR)

Less severe than FH

Semin Vasc Med. 2004 Aug;4(3):241-8.
Autosomal recessive hypercholesterolemia.
Soutar AK1, Naoumova RP.

Author information
Abstract

Autosomal recessive hypercholesterolemia (ARH) presents with a clinical phenotype similar to that of classical homozygous familial hypercholesterolemia (FH) caused by defects in the low-density lipoprotein (LDL) receptor gene but is more variable, generally less severe, and more responsive to lipid-lowering therapy than homozygous FH; furthermore, FH is inherited with a dominant pattern. The approximately 50 known affected ARH individuals are mostly of Sardinian or Middle Eastern origin, but rare cases of ARH have occurred worldwide. The physiological defect in ARH is a failure of some, but not all, cell types to mediate LDL receptor-dependent internalization of LDL and is caused by mutations in the gene for a putative adaptor protein called ARH. In affected cells, the LDL receptor gene is normal but LDL receptor protein accumulates at the cell surface; this also occurs in livers of recombinant mice lacking ARH, providing an explanation for the failure of clearance of LDL from plasma in ARH patients. The structural features of the ARH protein and its capacity to interact with the internalization sequence of the LDL receptor, plasma membrane phospholipids, and the clathrin endocytic machinery suggest that it plays a key role in the LDL receptor pathway.

What are the genetic causes of HLP type IIA?

Familial hypercholesterolemia (FH)

Familial combined hyperlipidemia (FCH)

Hyperapo-B-lipoproteinemia

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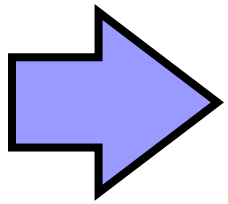
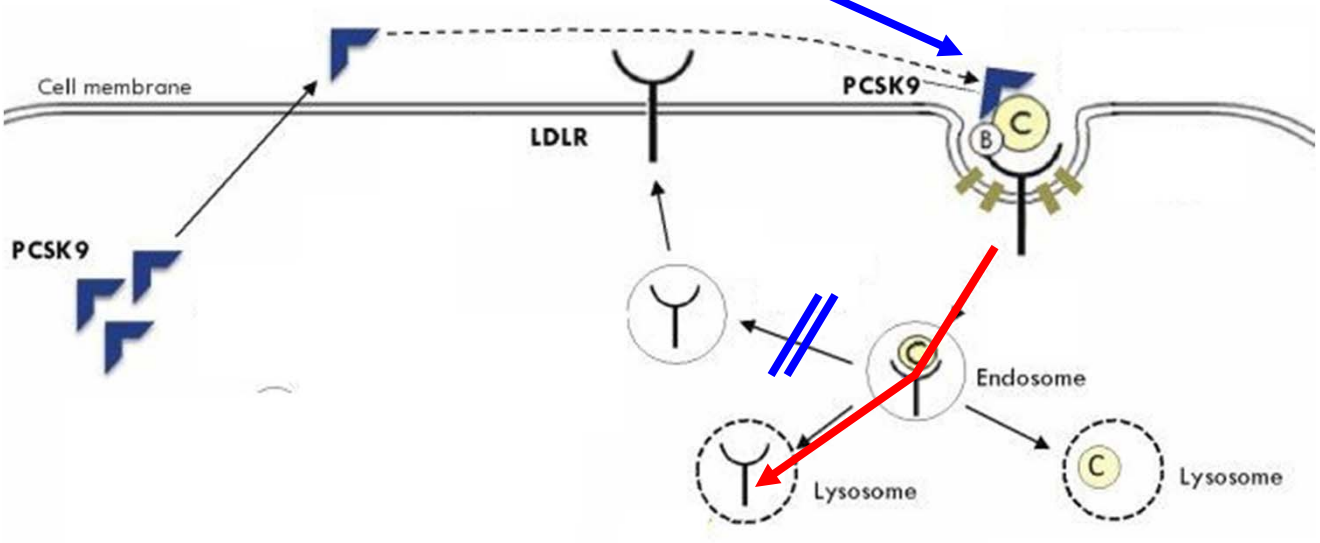
PCSK9 gain-of-function mutations causing ADH (autosomal dominant hypercholesterolemia)



Polygenic hypercholesterolemia

What causes hypercholesterolemia in patients with PCSK9 gain-of-function mutations?

Incr. degradation of LDL-R by PCSK9 (proprotein convertase subtilisin/kexin type 9) binding to the LDL-R.



What would suggest the diagnosis of PCSK9 gain-of-function mutations causing ADH (autosomal dominant FH)?

Difficult to differentiate from FH

Large numbers of PCSK9 polymorphisms are associated with cholesterol levels in population studies

Potential target for inhibitors of PSCK9 to lower LDL

LOF mutation in PCSK9 --- > decreased LDL-cholesterol

Expert Opin Investig Drugs. 2014 May 26:1-11. [Epub ahead of print]
Investigational therapies for the treatment of atherosclerosis.
Tomkin GH1, Owens D.
Author information
Abstract

Introduction: There is great need for new drugs to reduce cholesterol in those patients who have not achieved target levels on statins as well as those who are statin intolerant. Areas covered: In this review, the authors discuss the new antisense oligotide inhibitor of apo B synthesis, mipomersen; pro-protein convertase subtilisin/kexin type 9 (PCSK9) inhibitors and cholesterol ester transport protein (CETP) inhibitors. Furthermore, the authors discuss cholesterol absorption and chylomicron synthesis with an emphasis on microsomal triglyceride transfer protein (MTP) inhibitors, which inhibit very-low-density lipoprotein production in the liver and chylomicron inhibition in the intestine. Finally, the authors also discuss Apo A1- and adenosine triphosphate-binding cassette transporter A1 (ABCA1)-promoting drugs. A literature review was performed through PubMed using the terms atherosclerosis, hypercholesterolemia, Apo B inhibition, PSCK9, CETP inhibitors, MTP inhibitors, apo A1 mimetics and ABCA1. Expert opinion: So far, research suggests that PCSK9 inhibitors will be successful with mipomersen being used for those patients who do not respond well or who are still not at target. However, it is difficult to see where CETP inhibitors will fit in except with patients who have very low high-density lipoprotein. The MTP inhibitor lomitapide is currently only licensed for familial homozygous hypercholesterolemia but the intestinal inhibitors may have a future, particularly in familial combined hyperlipidemia. The future will be most exciting.

Protein Sci. Mar 1997; 6(3): 501–523.
Subtilases: the superfamily of subtilisin-like serine proteases.
R. J. Siezen and J. A. Leunissen

Subtilases are members of the clan (or superfamily) of subtilisin-like serine proteases. Over 200 subtilases are presently known, more than 170 of which with their complete amino acid sequence. In this update of our previous overview (Siezen RJ, de Vos WM, Leunissen JAM, Dijkstra BW, 1991, Protein Eng 4:719-731), details of more than 100 new subtilases discovered in the past five years are summarized, and amino acid sequences of their catalytic domains are compared in a multiple sequence alignment. Based on sequence homology, a subdivision into six families is proposed. Highly conserved residues of the catalytic domain are identified, as are large or unusual deletions and insertions. Predictions have been updated for Ca(2+)-binding sites, disulfide bonds, and substrate specificity, based on both sequence alignment and three-dimensional homology modeling.

SUBTILISIN: a protease secreted by a soil bacillus (Bacillus amyloliquefaciens)
Source: http://www.merriam-webster.com/dictionary/subtilisin

Proprotein Convertase Subtilisin/Kexin Type 9

Entrez Gene summary for PCSK9 Gene: This gene encodes a member of the subtilisin-like proprotein convertase family, which includes proteases that process protein and peptide precursors trafficking through regulated or constitutive branches of the secretory pathway. The encoded protein undergoes an autocatalytic processing event with its prosegment in the ER and is constitutively secreted as an inactive protease into the extracellular matrix and trans-Golgi network. It is expressed in liver, intestine and kidney tissues and escorts specific receptors for lysosomal degradation. It plays a role in cholesterol and fatty acid metabolism. Mutations in this gene have been associated with autosomal dominant familial hypercholesterolemia. Alternative splicing results in multiple transcript variants. (provided by RefSeq, Feb 2014)

UniProtKB/Swiss-Prot: PCSK9_HUMAN, Q8NBP7; Function: Crucial player in the regulation of plasma cholesterol homeostasis. Binds to low-density lipid receptor family members: low density lipoprotein receptor (LDLR), very low density lipoprotein receptor (VLDLR), apolipoprotein E receptor (LRP1/APOER) and apolipoprotein receptor 2 (LRP8/APOER2), and promotes their degradation in intracellular acidic compartments. Acts via a non-proteolytic mechanism to enhance the degradation of the hepatic LDLR through a clathrin LDLRAP1/ARH-mediated pathway. May prevent the recycling of LDLR from endosomes to the cell surface or direct it to lysosomes for degradation. Can induce ubiquitination of LDLR leading to its subsequent degradation. Inhibits intracellular degradation of APOB via the autophagosome/lysosome pathway in a LDLR-independent manner. Involved in the disposal of non-acetylated intermediates of BACE1 in the early secretory pathway. Inhibits epithelial Na(+) channel (ENaC)-mediated Na(+) absorption by reducing ENaC surface expression primarily by increasing its proteasomal degradation. Regulates neuronal apoptosis via modulation of LRP8/APOER2 levels and related anti-apoptotic signaling pathways

Source: http://www.genecards.org/cgi-bin/carddisp.pl?gene=PCSK9&search=47d076e180ade31f7985c0914d943f8b

Kexin is a prohormone processing protease found in the budding yeast that shares structural similarities with the bacterial protease subtilisin.

N Engl J Med. 2015 Apr 16;372(16):1489-99. doi: 10.1056/NEJMoa1501031. Epub 2015 Mar 15.

Efficacy and safety of alirocumab in reducing lipids and cardiovascular events.

Robinson JG, Farnier M, Krempf M, Bergeron J, Luc G, Averna M, Stroes ES, Langslet G, Raal FJ, El Shahawy M, Koren MJ, Lepor NE, Lorenzato C, Pordy R, Chaudhari U, Kastelein JJ; ODYSSEY LONG TERM Investigators. Collaborators (343)

Abstract

BACKGROUND:

Alirocumab, a monoclonal antibody that inhibits proprotein convertase subtilisin-kexin type 9 (PCSK9), has been shown to reduce low-density lipoprotein (LDL) cholesterol levels in patients who are receiving statin therapy. Larger and longer-term studies are needed to establish safety and efficacy.

METHODS:

We conducted a randomized trial involving 2341 patients at high risk for cardiovascular events who had LDL cholesterol levels of 70 mg per deciliter (1.8 mmol per liter) or more and were receiving treatment with statins at the maximum tolerated dose (the highest dose associated with an acceptable side-effect profile), with or without other lipid-lowering therapy. Patients were randomly assigned in a 2:1 ratio to receive alirocumab (150 mg) or placebo as a 1-ml subcutaneous injection every 2 weeks for 78 weeks. The primary efficacy end point was the percentage change in calculated LDL cholesterol level from baseline to week 24.

RESULTS:

At week 24, the difference between the alirocumab and placebo groups in the mean percentage change from baseline in calculated LDL cholesterol level was -62 percentage points (P<0.001); the treatment effect remained consistent over a period of 78 weeks. The alirocumab group, as compared with the placebo group, had higher rates of injection-site reactions (5.9% vs. 4.2%), myalgia (5.4% vs. 2.9%), neurocognitive events (1.2% vs. 0.5%), and ophthalmologic events (2.9% vs. 1.9%). In a post hoc analysis, the rate of major adverse cardiovascular events (death from coronary heart disease, nonfatal myocardial infarction, fatal or nonfatal ischemic stroke, or unstable angina requiring hospitalization) was lower with alirocumab than with placebo (1.7% vs. 3.3%; hazard ratio, 0.52; 95% confidence interval, 0.31 to 0.90; nominal P=0.02).

CONCLUSIONS:

Over a period of 78 weeks, alirocumab, when added to statin therapy at the maximum tolerated dose, significantly reduced LDL cholesterol levels. In a post hoc analysis, there was evidence of a reduction in the rate of cardiovascular events with alirocumab. (Funded by Sanofi and Regeneron Pharmaceuticals; ODYSSEY LONG TERM ClinicalTrials.gov number, NCT01507831.).

What are the genetic causes of HLP type IIA?

Familial hypercholesterolemia (FH)

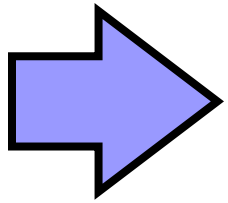
Familial combined hyperlipidemia (FCH)

Hyperapo-B-lipoproteinemia

Autosomal recessive hypercholesterolemia (ARH)

PCSK9 gain-of-function mutations causing ADH (autosomal dominant hypercholesterolemia)

Polygenic hypercholesterolemia



What causes polygenic hypercholesterolemia?

Undetermined

J Med Genet. 2014 Jul 1. pii: jmedgenet-2014-102405. Whole exome sequencing of familial hypercholesterolaemia patients negative for LDLR/APOB/PCSK9 mutations. Futema M1, Plagnol V2, Li K1, Whittall RA1, Neil HA3, Seed M4; on behalf of the Simon Broome Consortium, Bertolini S5, Calandra S6, Descamps OS7, Graham CA8, Hegele RA9, Karpe F10, Durst R11, Leitersdorf E12, Lench N13, Nair DR14, Soran H15, Van Bockxmeer FM16; UK10K Consortium, Humphries SE1.

BACKGROUND: Familial hypercholesterolaemia (FH) is an autosomal dominant disease of lipid metabolism, which leads to early coronary heart disease. Mutations in LDLR, APOB and PCSK9 can be detected in 80% of definite FH (DFH) patients. **This study aimed to identify novel FH-causing genetic variants in patients with no detectable mutation.** METHODS AND RESULTS: Exomes of 125 unrelated DFH patients were sequenced, as part of the UK10K project. First, analysis of known FH genes identified 23 LDLR and two APOB mutations, and patients with explained causes of FH were excluded from further analysis. Second, common and rare variants in genes associated with low-density lipoprotein cholesterol (LDL-C) levels in genome-wide association study (GWAS) meta-analysis were examined. There was no clear rare variant association in LDL-C GWAS hits; however, there were 29 patients with a high LDL-C SNP score suggestive of polygenic hypercholesterolaemia. Finally, a gene-based burden test for an excess of rare (frequency <0.005) or novel variants in cases versus 1926 controls was performed, with variants with an unlikely functional effect (intronic, synonymous) filtered out. CONCLUSIONS: No major novel locus for FH was detected, with no gene having a functional variant in more than three patients; however, an excess of novel variants was found in 18 genes, of which the strongest candidates included CH25H and INSIG2 ($p<4.3\times10^{-4}$ and $p<3.7\times10^{-3}$ respectively). This suggests that **the genetic cause of FH in these unexplained cases is likely to be very heterogeneous**, which complicates the diagnostic and novel gene discovery process.

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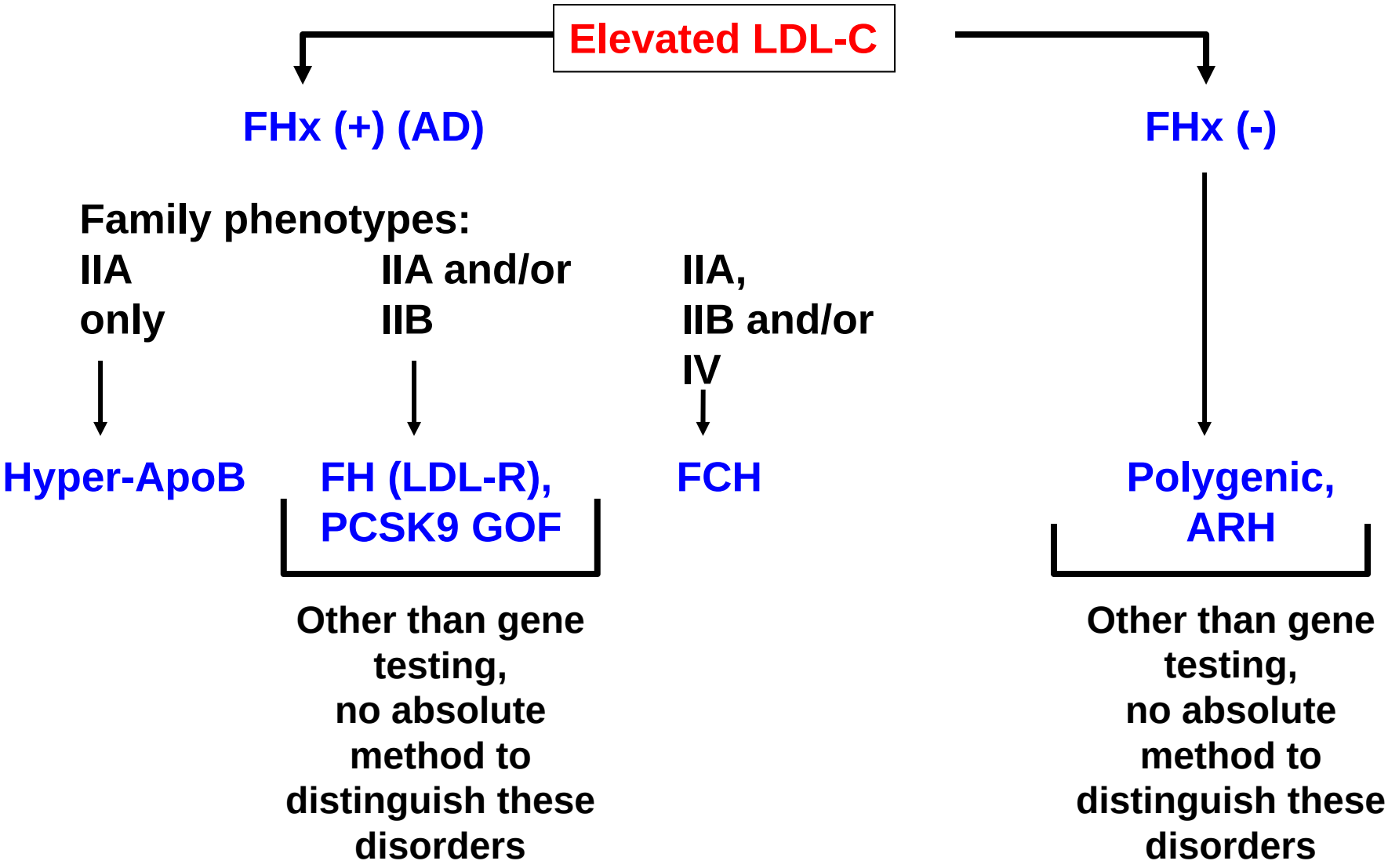
What would suggest the diagnosis of polygenic hyperlipidemia?

Modest hypercholesterolemia with or without a FHx of hypercholesterolemia

May be diet responsive

Incr. fat and cholesterol in diet -- > incr. liver chol. -- > decr. LDL-R expression -- > decr. LDL clearance



Familial hypercholesterolemia (FH)
Familial combined hypercholesterolemia (FCH)
Hyperapo-B-lipoproteinemia
Autosomal recessive hypercholesterolemia (ARH)
PCSK9 gain-of-function mutations causing ADH (autosomal dominant hypercholesterolemia)
Polygenic hypercholesterolemia

Is genetic testing required?

No!

J Am Coll Cardiol. 2014 May 20;63(19):1935-47. doi: 10.1016/j.jacc.2014.01.060. Epub 2014 Mar 12.
The severe hypercholesterolemia phenotype: clinical diagnosis, management, and emerging therapies.
Sniderman AD1, Tsimikas S2, Fazio S3.

The severe hypercholesterolemia phenotype includes all patients with marked elevation of low-density lipoprotein cholesterol (LDL-C) levels. The most common cause is autosomal dominant hypercholesterolemia, an inherited disorder caused by mutations either in LDL receptor, apolipoprotein B (APOB), or proprotein convertase subtilisin kexin type 9 (PCSK9) genes. However, it is now known that many subjects with severe inherited hypercholesterolemia have no defects in these genes. These cases are caused either by mutations in genes yet to be identified or are consequences of polygenic, epigenetic, or acquired defects. Because the clinical consequences of extreme hypercholesterolemia are the same no matter the cause, the focus should be on the identification of subjects with severe hypercholesterolemia, followed by phenotypic screening of family members. Genetic screening is not necessary to diagnose or initiate treatment for the severe hypercholesterolemia phenotype.

Management of severe hypercholesterolemia is based on risk factor modification and use of multiple lipid-lowering medications. Lipoprotein apheresis is indicated for coronary artery disease (CAD) patients taking maximally tolerated therapy and with LDL-C levels >200 mg/dl (>300 mg/dl if without CAD). A microsomal triglyceride transfer protein inhibitor and an antisense oligonucleotide against APOB have recently been approved for use in subjects with clinically diagnosed homozygous familial hypercholesterolemia. PCSK9 inhibitors, currently in phase II and III trials, lower LDL-C up to an additional 70% in the setting of maximally tolerated medical therapy and have the potential to reduce LDL-C to <70 mg/dl in most patients. Early identification of affected individuals and aggressive treatment should significantly reduce the burden of cardiovascular disease in society.

See: http://www.ncbi.nlm.nih.gov/books/NBK174884/

Disease characteristics. Familial hypercholesterolemia (FH) is characterized by severely elevated LDL cholesterol (LDL-C) levels that cause atherosclerotic plaque deposition in arteries and a markedly increased risk of coronary artery disease at an early age. Cholesterol deposits are also sometimes found in the tendons (xanthomas) and/or around the eyes (xanthelasmas). In FH, the more common cardiovascular disease is coronary heart disease (CHD), which may manifest as angina and myocardial infarction; stroke occurs more rarely.

Heterozygous FH (HeFH) can often be directly attributed to a heterozygous pathogenic variant in one of three genes (LDLR, APOB, PCSK9) known to account for 60%-80% of FH. FH is relatively common (prevalence 1:200-500). Persons with untreated FH are at an approximately 20-fold increased risk for CHD. Untreated men are at a 50% risk for a fatal or non-fatal coronary event by age 50 years; untreated women are at a 30% risk by age 60 years.

In contrast, homozygous FH (HoFH) results from either biallelic (i.e., 2) mutations in one of these known genes or one mutation in each of two different genes. HoFH is much rarer (prevalence 1:160,000 to 1:1,000,000). Most individuals with HoFH experience severe CHD by their mid-20s. The rate of either death or coronary bypass surgery by the teenage years is high. Severe aortic stenosis is also common.

Diagnosis/testing. Several formal diagnostic criteria exist for FH. The likelihood of FH is increased in individuals with high levels of low density lipoprotein cholesterol (LDL-C) (in untreated adults: >190 mg/dL [>4.9 mmol/L] or total cholesterol levels >310 mg/dL [>8 mmol/L]; in untreated children or adolescents: LDL-C levels >160 mg/dL [4.1 mmol/L] or total cholesterol levels >230 mg/dL [>6 mmol/L]); history of premature coronary heart disease (CHD); xanthomas, xanthelasmas, and/or corneal arcus; and a family history of FH. The diagnosis of HeFH can be confirmed by the presence of a pathogenic variant in one of the three genes (LDLR, APOB, and PCSK9) in which mutation is known to account for 60%-80% of FH.

See: http://www.ncbi.nlm.nih.gov/books/NBK174884/

Management. Treatment of manifestations: Guidelines for the management of adults and children with HeFH and HoFH have been published by multiple national/international organizations. All individuals with HeFH are at high risk for CVD and should be treated actively with diet/lifestyle changes and pharmacotherapy to lower their lipid levels. Pharmacotherapy should initially be statin-based, followed by addition of other drugs if the targeted LDL-C level is not achieved.

Children and adults with HoFH usually require LDL apheresis. Liver transplantation is also being used in rare circumstances at some centers.

Prevention of primary manifestations: Statin therapy in combination with a heart-healthy diet (including reduced intake of saturated fat and increased intake of soluble fiber to 10-20 g/day), and increased physical activity

Surveillance: Guidelines have been published by multiple national and international organizations.

A child who has a family history of FH, who is heterozygous for the FH pathogenic variant in his or her family, who has a family history of premature CVD, or who has an elevated serum cholesterol concentration should have lipid levels checked before age ten years; some guidelines advise checking cholesterol as early as age two to five years.

During treatment, individuals of any age diagnosed with:

HeFH should have lipid levels monitored as recommended;
HoFH should be monitored with various imaging modalities (including echocardiograms, CT angiograms and cardiac catheterization) as recommended.

Agents/circumstances to avoid: Smoking, high intake of saturated and transunsaturated fat, excessive intake of cholesterol, sedentary lifestyle, obesity, hypertension, and diabetes mellitus.

Evaluation of relatives at risk: Early diagnosis and treatment of first-degree and second-degree relatives at risk for FH can reduce morbidity and mortality. The genetic status of at-risk family members can be clarified by either: (1) molecular genetic testing if the pathogenic variant has been identified in an affected family member; or (2) measurement of LDL-C concentration.

Pregnancy management: Pregnant women should incorporate all the recommended lifestyle changes including low-saturated fat intake, no smoking, and high dietary soluble fiber. Statins are contraindicated in pregnancy due to concerns for teratogenicity and should be discontinued prior to conception. Bile acid binding resins (colesevelam) are generally considered safe (Class B for pregnancy), and LDL apheresis is also occasionally used if there is evidence of established CHD.

See: http://www.ncbi.nlm.nih.gov/books/NBK174884/

Genetic counseling. HeFH and HoFH are inherited in an autosomal co-dominant manner.

Almost all individuals diagnosed with HeFH have an affected parent; the proportion of HeFH caused by de novo mutation is unknown but appears to be extremely low. Each child of an individual with HeFH has a 50% chance of inheriting the pathogenic variant.

If both parents have HeFH, each child has a 75% chance of having FH (i.e., 50% chance of having HeFH and 25% chance of having HoFH).

If the pathogenic variant has been identified in a family member with HeFH (or if both pathogenic variants have been identified in a family member with HoFH), prenatal testing for pregnancies at increased risk is possible. Requests for prenatal testing for conditions which (like FH) do not affect intellect and have some treatment available are not common.

See: http://www.ncbi.nlm.nih.gov/books/NBK174884/

Diagnosis

In this GeneReview:

Familial hypercholesterolemia (FH) refers to hypercholesterolemia resulting from a heterozygous pathogenic variant in one of several genes (LDLR, APOB, and PCSK9); it is also referred to as heterozygous FH (HeFH). FH is relatively common disorder (prevalence 1:200-1:500).

Homozygous FH (HoFH) refers to familial hypercholesterolemia resulting from biallelic mutations in one of these same genes (LDLR, APOB, and PCSK9). HoFH is much rarer than HeFH (prevalence 1:160,000 to 1:1,000,000) [Nordestgaard et al 2013].

Currently three formal diagnostic criteria for FH are widely used in Western countries [Civeira 2004, Haase & Goldberg 2012]. (See Harada-Shiba et al [2012] for criteria used in non-Western countries.)

- **US MEDPED Program**
- **UK Simon Broome Familial Hypercholesterolaemia Registry**
- **Dutch Lipid Clinic Network**

All three rely on a combination of the following [World Health Organization Human Genetics Programme 1998, Rader et al 2003, Nordestgaard et al 2013]:

- **Extreme hypercholesterolemia**
- **Clinical history of premature coronary heart disease (CHD) caused by plaque build-up and subsequent plaque rupture in the coronary arteries [Rosamond et al 2007, Reiner et al 2011].**
- **Findings on physical examination (xanthomas, corneal arcus)**
- **Family medical history**
- **Presence of a pathogenic variant in a gene known to be associated with FH**

See: http://www.ncbi.nlm.nih.gov/books/NBK174884/

Suggestive Findings

Familial hypercholesterolemia (FH) is suspected in individuals with the following findings.

Extreme hypercholesterolemia

Heterozygous FH

Untreated adults: low-density lipoprotein cholesterol (LDL-C) levels >190 mg/dL (>4.9 mmol/L) or total cholesterol levels >310 mg/dL (>8 mmol/L).

Untreated children or adolescents: LDL-C levels >160 mg/dL (>4 mmol/L) or total cholesterol levels >230 mg/dL (>6 mmol/L) [Goldberg et al 2011, Nordestgaard et al 2013]. Note that in the initial evaluation of children, a non-fasting lipid panel can be obtained first and, if abnormal or borderline, a fasting LDL-C level should be obtained [Martin et al 2013]. Elevation of two consecutive LDL-C levels is often recommended to confirm the diagnosis.

Note: (1) More extreme elevations of LDL-C or total cholesterol are common. (2) Age-specific LDL-C or total cholesterol levels are more specific in determining the likelihood of FH; for instance LDL-C or total cholesterol levels >95% percentile for age, gender, and country [Starr et al 2008, Nordestgaard et al 2013]. (3) Computer (including mobile-based) applications (kkitcreations.com) can assist with the determination of the likelihood of FH based on the formal diagnostic criteria.
HoFH. Total cholesterol levels are generally, but not always, >500 mg/dL (>13 mmol/L).

Clinical history of premature coronary heart disease (CHD) and cardiovascular disease (CVD) (i.e., CHD and stroke). Presentation may include:

- **Angina pectoris**
- **Myocardial infarction**
- **Peripheral vascular diseases**

Note: Although stroke is possible, it is less common in FH than in premature CHD [Huxley et al 2003].

HeFH. Untreated men are at a 50% risk for CHD by age 50 years. Untreated women are at a 30% risk by age 60 years [Slack 1969, Stone et al 1974, Civeira 2004, Hopkins et al 2011].
HoFH. Untreated individuals often die in their 20s or earlier. Most treated individuals experience severe vascular disease by their mid-20s. Aortic stenosis is common [Raal & Santos 2012].

Physical examination findings

Xanthomas (patches of yellowish cholesterol buildup in particular areas of the body as a result of extremely high levels of LDL-C). Common locations include:
- **Around the eyelids (xanthelasma palpebrarum or more commonly just xanthelasma) in FH and HoFH;**
- **Tendons of the elbows, hands, knees, and feet, particularly the Achilles tendon (tendonous xanthomas) [Rader et al 2003, Tsouli et al 2005, Elis et al 2011]; seen in 30%-50% of persons with FH and a higher percentage of persons with HoFH;**
- **Interdigital xanthomas (between the fingers) in HoFH.**

Corneal arcus (white, gray, or blue opaque ring in the corneal margin): because this becomes increasingly common in the general population with age, it is only diagnostic in younger individuals, particularly before age 45 years.

Of note: It is common for individuals with FH to have no visible signs of the disease.

Family medical history. The likelihood of FH is increased in individuals with a family history of familial hypercholesterolemia, high levels of LDL cholesterol, early-onset (i.e., age <50 years) coronary heart disease (CHD) (especially premature myocardial infarction), and xanthomas.

See: http://www.ncbi.nlm.nih.gov/books/NBK174884/

Confirmatory Finding

The gold standard for diagnosis of FH used in many countries is presence of a pathogenic variant in a gene known to be associated with FH [Nordestgaard et al 2013]. Genetic testing most commonly involves the three genes LDLR, APOB, and PCSK9, as mutation of one of these genes accounts for approximately 60%-80% of FH (Table 1).

In the United States, genetic testing is recommended when other laboratory tests have not definitively established the diagnosis of FH.

Table 1. Summary of Molecular Genetic Testing Used in Familial Hypercholesterolemia (FH)

Gene [1]	Proportion of FH Attributed to Pathogenic Variants in This Gene [2]	Test Method
LDLR	60%-80%	Sequence analysis [3, 4]
		Deletion/duplication analysis [4, 5]
APOB	1%-5%	Targeted mutation analysis [6]
		Sequence analysis [3,4]
		Deletion/duplication analysis [5, 7]
PCSK9	0%-3%	Targeted mutation analysis [6]
		Sequence analysis
		Deletion/duplication analysis [5, 7]
Unknown [8, 9]	20%-40%	NA

See: http://www.ncbi.nlm.nih.gov/books/NBK174884/

1. See Table A. Genes and Databases for chromosome locus and protein name. See Molecular Genetics for information on allelic variants.

2. The yield for genetic testing varies by the pre-test probability of the disease as determined by the clinical diagnostic criteria. In "definite" FH the yield of genetic testing for identification of a pathogenic variant approaches 80%; in "probable" or "possible" FH the yield is lower (~35%-60%) [DeMott et al 2008].

3. Sequence analysis detects variants that are benign, likely benign, of unknown significance, likely pathogenic, or pathogenic. Pathogenic variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exonic or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here

4. Some laboratories may use massively parallel sequence analysis (i.e., next-generation sequencing). Depending on test design, this method may detect both sequence variants and deletions/duplications [Vandrovcova et al 2013].

5. Testing that identifies exonic or whole-gene deletions/duplications not detectable by sequence analysis of the coding and flanking intronic regions of genomic DNA. Included in the variety of methods that may be used are: quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and chromosomal microarray (CMA) that includes this gene/chromosome segment.

6. Targeted mutation analysis refers to testing for one or more specific variants. See Molecular Genetics for information on common variants that may be included in such testing. Note that variants tested may vary by laboratory.

7. No deletions or duplications involving APOBI or PCSK9 have been reported to cause familial hypercholesterolemia. (Note: By definition, deletion/duplication analysis identifies rearrangements that are not identifiable by sequence analysis of genomic DNA.)

8. De Castro-Orós et al [2010]

9. It has been suggested that a polygenic etiology is most likely in the majority of individuals with a clinical diagnosis of FH in whom no pathogenic variant in one of the three known genes can be identified. This suggestion is based on the presence in these individuals of a greater than average number of common LDL-C-raising variants (i.e., a high "LDL-SNP score") [Talmud et al 2013].

See: http://www.ncbi.nlm.nih.gov/books/NBK174884/

Genetically Related (Allelic) Disorders

LDLR. No phenotypes other than those discussed in this GeneReview are known to be associated with pathogenic variants in LDLR.

APOB. Pathogenic variants in APOB cause homozygous or heterozygous hypobetalipoproteinemia (which is characterized by extremely low levels of LDL-C) or apolipoprotein B [Burnett et al 2012].

PCSK9. Heterozygous or homozygous loss-of-function pathogenic variants in PCSK9 cause hypocholesterolemia (reduced blood cholesterol levels). Loss-of-function pathogenic variants lead to an increase in the number of low density lipoprotein receptors on the surface of liver cells, resulting in quicker than usual removal of LDL-C from the blood and, hence, a reduced risk for coronary heart disease [Cohen et al 2006, Pandit et al 2008].

Genotype-Phenotype Correlations

In FH the phenotype is largely a function of whether the pathogenic variant is (1) heterozygous (i.e., heterozygous FH) or (2) biallelic (i.e., two pathogenic variants in the same gene (i.e., homozygous FH).

In FH caused by a heterozygous LDLR pathogenic variant, the phenotype is largely a function of the variant type (and thereby the LDL-C levels):

- **Complete loss of function variants generally leads to more severe disease due to higher LDL-C levels.**
- **Partial loss of function variants results in less severe disease due to lower LDL-C levels.**

Heterozygous FH caused by an APOB pathogenic variant is reported to be less severe than HeFH caused by a pathogenic variant in LDLR or PCSK9 [Hopkins et al 2011].

See: http://www.ncbi.nlm.nih.gov/books/NBK174884/

Penetrance

LDLR

Penetrance for FH approaches 90% in persons with a heterozygous LDLR pathogenic variant [Pimstone et al 1998].

Penetrance for FH can be incomplete in persons with a heterozygous APOB pathogenic variant [Fahed & Nemer 2011].

PCSK9

Penetrance is around 90% in persons heterozygous for the c.381T>A (p.Ser127Arg) pathogenic variant.

Penetrance in persons heterozygous for the p.Asp374Tyr pathogenic variant is high, with FH manifesting at a young age [Naoumova et al 2005].

Penetrance for other heterozygous PCSK9 pathogenic variants remains largely unknown [Cariou et al 2011].

Prevalence

The prevalence of FH in the general population has traditionally been cited as 1:500. However, emerging data suggest that the prevalence of FH is higher than this in white/European populations, perhaps as common as 1:200 [Nordestgaard et al 2013].

FH is more common (due to founder effects) in several populations (Table 2). Of note, data are limited on prevalence of FH in most African and South Asian/Indian populations.

Table 2. Prevalence of FH in Select Populations

Population	Prevalence
General population	1:200-500
French Canadian	1:270
Christian Lebanese	1:85
Tunisia	1:165
South African Afrikaners	1:72 to 1:100
South African Ashkenazi Jews	1:67

Austin et al [2004]

See: http://www.ncbi.nlm.nih.gov/books/NBK174884/

Differential Diagnosis

Conditions with clinical findings similar to those of familial hypercholesterolemia (FH) include the following:

27-hydroxylase deficiency (cerebrotendonous xanthomatosis), which is characterized by xanthomas. Distinguishing features are normal LDL cholesterol (LDL-C) levels and the presence of dementia, ataxia, and cataracts. Inheritance is autosomal recessive.

Dysbetahyperlipoproteinemia (type III hyperlipidemia) which may include xanthomas; caused by biallelic pathogenic variants (E2/E2) in APOE, the gene encoding apolipoprotein E. Mode of inheritance is autosomal recessive [Fung et al 2011].

Sitosterolemia (phytosterolemia), which is distinguished by normal or only mildly elevated LDL-C levels. Inheritance is autosomal recessive.

Familial combined hyperlipidemia (see APOE p.Leu167del-Related Lipid Disorders)

Conditions with laboratory findings similar to those of FH include the following [Goldberg et al 2011]:

Hypercholesterolemia secondary to obesity, diabetes mellitus, hypothyroidism, drugs (e.g., steroids), or kidney disease. Inheritance follows a non-Mendelian pattern.

Autosomal recessive hypercholesterolemia caused by biallelic pathogenic variants in LDLRAP1. Persons with biallelic pathogenic variants have LDL-C >400 mg/dL (>10 mmol/L), whereas heterozygotes have normal LDL-C levels.

Familial combined hyperlipidemia (FCHL) which includes elevated LDL-C and triglycerides. While FCHL is a complex polygenic disorder, heterozygous pathogenic variants in APOB and USF1 (associated with autosomal dominant inheritance) are causative in a minority of families [Naukkarinen et al 2006, Hegele et al 2009].

See: http://www.ncbi.nlm.nih.gov/books/NBK174884/

Table A. Familial Hypercholesterolemia: Genes and Databases

Gene Symbol	Chromosomal Locus	Protein Name	Locus Specific	HGMD
APOB	2p24.1	Apolipoprotein B-100	APOB database	APOB
LDLR	19p13.2	Low-density lipoprotein receptor	LDLR @ LOVD The low density lipoprotein receptor (LDLR) gene	LDLR
PCSK9	1p32.3	Proprotein convertase subtilisin/kexin type 9	The PCSK9 gene mutation database PCSK9 @ LOVD	PCSK9

Data are compiled from the following standard references: gene symbol from HGNC; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from UniProt. For a description of databases (Locus Specific, HGMD) to which links are provided, click here.

See web site for more details and references

In 2013, new guidelines for the management of hypercholesterolemia were issued by the American College of Cardiology and the American Heart Association and the (ACC/AHA).

Stone NJ, et al.
2013 ACC/AHA Blood Cholesterol Guideline

2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults

A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines

Endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation, American Pharmacists Association, American Society for Preventive Cardiology, Association of Black Cardiologists, Preventive Cardiovascular Nurses Association, and WomenHeart: The National Coalition for Women with Heart Disease

While these guidelines updated NCEP ATP III, the new guidelines are NOT termed "ATP IV."

Circulation. 2014 Jun 24;129(25 Suppl 2):S1-45.

How do the ACC/AHA 2013 guidelines* differ from the NCEP ATPIII guidelines?

*** Goff DC Jr, Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB, Gibbons R, Greenland P, Lackland DT, Levy D, O'Donnell CJ, Robinson JG, Schwartz JS, Shero ST, Smith SC Jr, Sorlie P, Stone NJ, Wilson PW. 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014 Jun 24;129(25 Suppl 2):S49-73.**

These guidelines are based on studies that were adequately powered to determine if lowering LDL-C improved outcome.

Outcome based!

None of the previous studies treated "to target" as recommended by NCEP ATP III guidelines.

What 4 categories of patients benefit from statin therapy?

1. **Clinical ASCVD.**
2. **LDL-C =>190 mg/dL.**
3. **Diabetes (40 - 75 y/o) & LDL-C 70-189 mg/dL (w/o ASCVD).**
4. **LDL-C 70 - 189 mg/dL & 10-year ASCVD risk of =>7.5% (w/o ASCVD, w/o DM)**

Note: Moderate evidence supports the use of statins for primary prevention:

Age:	**40 - 75**
LDL-C:	**70 – 189 mg/dL**
10-y ASCVD risk:	**5 – <7.5%**

Selected individuals may also benefit from statin tx:

Age:	**<40 - >75**
10-y ASCVD risk:	**<5%**

How is CV risk assessed using the 2013 ACC/AHA guidelines?

2013 Prevention Guidelines Tools

CV RISK CALCULATOR

http://my.americanheart.org/professional/StatementsGuidelines/Prevention-Guidelines_UCM_457698_SubHomePage.jsp

Variables: **Age; sex; race; systolic BP; treatment for hypertension: yes/no; total cholesterol; HDL-C; diabetes: present/absent; and smoking: yes/no.**

Calculates:

10 year risk	**for ASCVD.**
10 year risk	**for ASCVD w/ optimal risk factors**
Lifetime risk	**for ASCVD (ages 20-59 y/o)**

Decision tree:

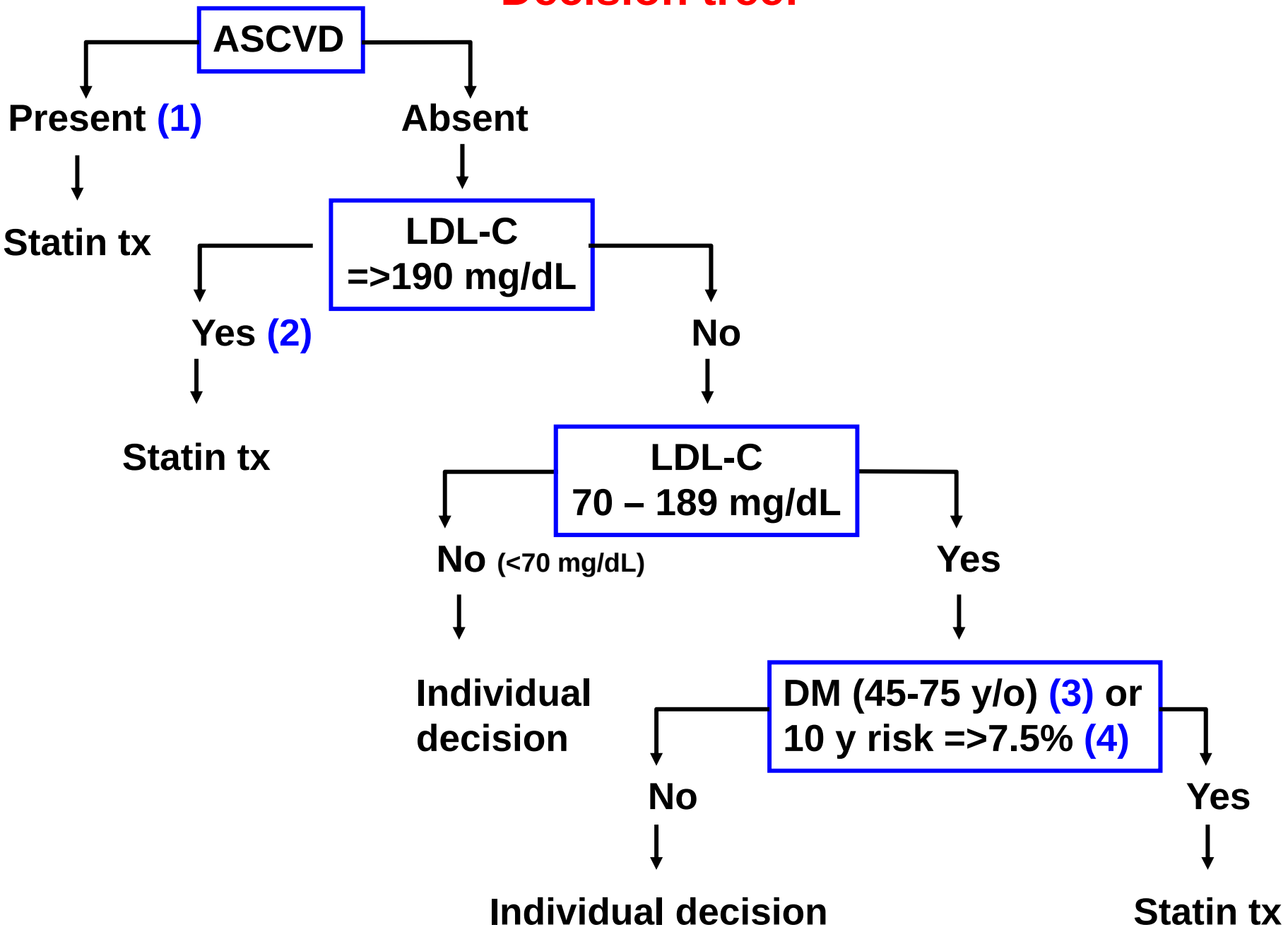


Table 6. Expert Opinion Thresholds for Use of Optional Screening Tests When Risk-Based Decisions About Initiation of Pharmacological Therapy Are Uncertain After Quantitative Risk Assessment

Measure	Support Revising Risk Assessment Upward	Do Not Support Revising Risk Assessment
Family history of premature CVD	Male <55 years of age Female <65 years of age (first-degree relative)	Occurrences at older ages only (if any)
hs-CRP	≥2 mg/L	<2 mg/L
CAC score	≥300 Agatston units or ≥75th percentile for age, sex, and ethnicity*	<300 Agatston units and <75th percentile for age, sex, and ethnicity*
ABI	<0.9	≥0.9

*For additional information, see http://www.mesa-nhlbi.org/CACReference.aspx.

ABI indicates ankle-brachial index; CAC, coronary artery calcium; CVD, cardiovascular disease; and hs-CRP, high-sensitivity C-reactive protein.

Have the risk estimates for CVD as determined by the ACC/AHA 2013 guidelines been challenged?

Yes!

There are a number of studies that suggest risk is overstated by 78%*

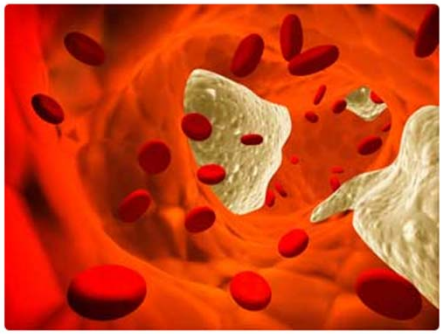
Recent source:
http://www.medscape.com/viewarticle/839912?nlid=76748_2825&src=wnl_edit_medn_imed&uac=65959EZ&spon=18

REGARDS investigators respond to criticism of new AHA/ACC cholesterol treatment guidelines

by Nicole Wyatt

December 11, 2013 | Print | Email

New cholesterol treatment guidelines from the **American Heart Association** and the **American College of Cardiology** have drawn concern since their release on Nov. 13.



The main issue, initially raised in a commentary published in The Lancet in November, is with a formula developed and published with the guidelines to assess the risk of having a heart attack or stroke.

The commentary in The Lancet suggested that the new formula predicted that too many people would have a heart attack or stroke. This concern was raised when the chance of having a heart attack or stroke predicted in the new guidelines was evaluated in several "validation studies" that were not used in developing the formula.

In one example, the formula was tested against data from the **Reasons for Geographic And Racial Differences in Stroke (REGARDS)** study. REGARDS is based at the School of Public Health at the **University of Alabama at Birmingham**.

http://www.uab.edu/news/innovation/item/4444-regards-investigators-respond-to-criticism-of-new-aha-acc-cholesterol-treatment-guidelines

What laboratory testing is required to exclude secondary causes of hypercholesterolemia?

R/o secondary causes	Evaluation
Diet-induced hypercholesterolemia	Evaluate his diet, body wt.
Drug-induced hypercholesterolemia	Drug hx: diuretics, CyA, glucocorticoids, amiodarone
Obstructive liver disease	ALT, ALP, bilirubin
Nephrosis	Cr, BUN, urinalysis
Diabetes	FPG, 2 hr glu (OGTT), A1c
Hypothyroidism	TSH

Table 6. Secondary Causes of Hyperlipidemia Most Commonly Encountered in Clinical Practice

Secondary Cause	Elevated LDL-C	Elevated Triglycerides
Diet	Saturated or *trans* fats, weight gain, anorexia nervosa	Weight gain, very-low-fat diets, high intake of refined carbohydrates, excessive alcohol intake
Drugs	Diuretics, cyclosporine, glucocorticoids, amiodarone	Oral estrogens, glucocorticoids, bile acid sequestrants, protease inhibitors, retinoic acid, anabolic steroids, sirolimus, raloxifene, tamoxifen, beta blockers (not carvedilol), thiazides
Diseases	Biliary obstruction, nephrotic syndrome	Nephrotic syndrome, chronic renal failure, lipodystrophies
Disorders and altered states of metabolism	Hypothyroidism, obesity, pregnancy*	Diabetes (poorly controlled), hypothyroidism, obesity; pregnancy*

Adapted with permission from Stone et al (80).

*Cholesterol and triglycerides rise progressively throughout pregnancy (80); treatment with statins, niacin, and ezetimibe are contraindicated during pregnancy and lactation.

LDL-C indicates low-density lipoprotein cholesterol.

How is the “aggressiveness” of therapy classified?

High-Intensity Statin Therapy

Definition: Daily dose lowers LDL-C, on average, by approximately =>50%

Atorvastatin	(40)–80 mg
Rosuvastatin	20 (40) mg

Moderate-Intensity Statin Therapy

Definition: Daily dose lowers LDL-C, on average, by approximately 30% to <50%

Atorvastatin	10 (20) mg
Rosuvastatin	(5) 10 mg
Simvastatin	20–40 mg
Pravastatin	40 (80) mg
Lovastatin	40 mg
Fluvastatin	XL 80 mg
Fluvastatin	40 mg BID
Pitavastatin	2–4 mg

Low-Intensity Statin

Definition: Therapy Daily dose lowers LDL-C, on average, by <30%

Simvastatin	10 mg
Pravastatin	10–20 mg
Lovastatin	20 mg
Fluvastatin	20–40 mg
Pitavastatin	1 mg

How intensely should hypercholesterolemia be treated? (1)

Four categories of patients that benefit from statin therapy and the intensity of tx:

	High-intensity		Moderate-intensity
Clinical ASCVD.	**<75 y/o:**		**=>75 y/o**
1^0 incr.: LDL-C =>190 mg/dL.	**=>21 y/o (1)**		
Diabetes (40-75 y/o) & LDL-C 70-189 mg/dL w/o ASCVD.	**10 y risk =>7.5%**		**10 y risk <7.5%**
LDL-C 70 - 189 mg/dL & 10-year ASCVD risk of =>7.5% (40-75 y/o; w/o ASCVD, w/o DM) (2)	**Yes**	**(or)**	**Yes**

(1) High-intensity (other drugs may be required to attain a decr. in LDL-C of at least 50%).

(2) Decision w/ pt regarding intensity of tx; factors to consider: *LDL-C =>160 mg/dL, family history of premature ASCVD, hs-CRP =>2.0 mg/L, CAC score =>300 Agaston units, ABI <0.9, or lifetime ASCVD risk*

	High-intensity	Moderate-intensity
LDL-C 70 - 189 mg/dL & 10-year ASCVD risk of =>7.5% (40-75 y/o; w/o ASCVD, w/o DM) (1)	Yes	Yes

(1) Decision w/ pt regarding intensity of tx; factors to consider: LDL-C =>160 mg/dL, family history of premature ASCVD, hs-CRP =>2.0 mg/L, CAC score =>300 Agaston units, ABI <0.9, or lifetime ASCVD risk

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ABI indicates ankle-brachial index; CAC, coronary artery calcium; CVD, cardiovascular disease; and hs-CRP, high-sensitivity C-reactive protein.

Ankle-Brachial Index Test

This test is done by measuring blood pressure at the ankle and in the arm while a person is at rest. Measurements are usually repeated at both sites after 5 minutes of walking on a treadmill.

The ankle-brachial index (ABI) result is used to predict the severity of peripheral arterial disease (PAD). A slight drop in your ABI with exercise means that you probably have PAD. This drop may be important, because PAD can be linked to a higher risk of heart attack or stroke.

Why It Is Done

This test is done to screen for peripheral arterial disease of the legs. It is also used to see how well a treatment is working (such as medical treatment, an exercise program, angioplasty, or surgery).

Results

The ABI result can help diagnose peripheral arterial disease (PAD). A lower ABI means you might have PAD. A slight drop in the ABI with exercise, even if you have a normal ABI at rest, means that you probably have PAD.

Normal

A normal resting ankle-brachial index is 1.0 to 1.4. This means that your blood pressure at your ankle is the same or greater than the pressure at your arm, and suggests that you do not have significant narrowing or blockage of blood flow.1

Abnormal

An abnormal resting ankle-brachial index is 0.9 or lower. If the ABI is 0.91 to 0.99, it is considered borderline abnormal.1

http://www.webmd.com/heart-disease/ankle-brachial-index-test

6.1.2. Recommendations for CQ1: Use of Newer Risk Markers After Quantitative Risk Assessment

Recommendation 1. If, after quantitative risk assessment, a risk-based treatment decision is uncertain, assessment of 1 or more of the following—family history, hs-CRP, CAC score, or ABI—may be considered to inform treatment decision making.

NHLBI Grade: E (Expert Opinion); ACC/AHA COR: IIb†, LOE: B†

Recommendation 2. Routine measurement of CIMT is not recommended in clinical practice for risk assessment for a first ASCVD event.

NHLBI Grade: N (No recommendation for or against); ACC/AHA COR III: No Benefit†, LOE: B

Recommendation 3. The contribution of ApoB, chronic kidney disease, albuminuria, and cardiorespiratory fitness to risk assessment for a first ASCVD event is uncertain at present.

NHLBI Grade: N (No recommendation for or against)

How should patients be monitored while being treated for hypercholesterolemia? (1)

Regularly monitor adherence to lifestyle and drug therapy with *lipid* and safety assessments

Assess adherence, response to therapy, and adverse effects within 4–12 wk following statin initiation or change in therapy

- Measure a fasting lipid panel

How should patients be monitored while being treated for hypercholesterolemia? (2)

If on high-intensity statin:

=>50% decr. in LDL-C -- > goal achieved
<50% decr. in LDL-C -- > goal not achieved

If on moderate-intensity statin:

=>30% decr. in LDL-C -- > goal achieved
<30% decr. in LDL-C -- > goal not achieved

If goal not achieved:

Action: review lifestyle, compliance
r/o 2^0 causes of incr. LDL-C (if not previously evaluated)
Incr. statin dose
If at max dose, change statin, add non-statin*

*** add non-statin if high-risk: High-risk individuals include those with clinical ASCVD, an untreated LDL-C =>190 mg/dL suggesting genetic hypercholesterolemia, or individuals with diabetes 40 to 75 years of age and LDL-C 70 to 189 mg/dL.**

Should CK and ALT be routinely monitored while on statins?

No*

Unless there is a previous history of disease or present symptoms; ALT should be measured before beginning therapy

What are the major conclusions of the ACC/AHA 2013 guidelines that supersede NCAP ATP III?

The Pearls . . .

Recommendations: based on randomized controlled trials (RCT)

Statins: reduce the risk of ASCVD in 1^0 & 2^0 prevention trials

What are the major conclusions of the ACC/AHA 2013 guidelines that supersede NCAP ATP III?

The Pearls . . .

No benefit for: NYHA class II - IV heart failure
Hemodialysis patients

Do not treat to pre-specified LDL-C

Treat to target % reduction in LDL-C

For patients achieving the target % reduction in LDL-C, addition of non-statin (e.g., niacin) showed no benefit in RCT trials

The RCTs identified in the systematic evidence review indicated a consistent reduction in ASCVD events from 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitor (statin) therapy in secondary- and primary-prevention populations, with the exception of no ASCVD event reduction when statin therapy was initiated in those with New York Heart Association class II to IV heart failure or those receiving maintenance hemodialysis. The RCTs either compared fixed doses of statins with placebo or untreated controls, or compared fixed doses of higherintensity statins with moderate-intensity statins. These trials were not designed to evaluate the effect of titrated (dose-adjusted) statin treatment to achieve prespecified LDL-C or non–HDL-C goals. Therefore, the Expert Panel was unable to find RCT

evidence to support titrating cholesterol-lowering drug therapy to achieve target LDL-C or non–HDL-C levels, as recommended by Adult Treatment Panel III (6–8). Notably, the Expert Panel did find RCT evidence that use of therapy (e.g., niacin) to additionally lower non–HDLC, once an LDL-C target was achieved, did not further reduce ASCVD outcomes (9). The Expert Panel also found extensive RCT evidence that the appropriate intensity of statin therapy should be used to reduce ASCVD risk in those most likely to benefit. The work of the Expert Panel was informed by the reports of the Lifestyle Management (10) and Risk Assessment Work Groups (11) (Figure 1). A summary of the major recommendations for the treatment of cholesterol to reduce ASCVD risk is provided in Table 3.

Thank you for your attention.

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