Update on the Management of Hyperlipidemia

Carolyn Finocchiaro, ARNP

22nd Annual Northeast Regional Nurse Practitioner Conference – May 6-8, 2015

DISCLOSURES

- Speakers' Bureau for Boehringer Ingelheim.
- There has been no commercial support or sponsorship for this program.
- The program co-sponsors do not endorse any products in conjunction with any educational activity.

ACCREDITATION

Boston College Connell School of Nursing Continuing Education Program is accredited as a provider of continuing nursing education by the American Nurses Association Massachusetts, an accredited approver by the American Nurses Credentialing Center's Commission on Accreditation.

SESSION OBJECTIVES

- Summarize the current ACC/AHA prevention guidelines and the rationale for the recommendations.
- Discuss risk calculation and how this will guide lipid management.
- Discuss the importance of lifestyle management in association with medication in order to help prevent cardiovascular events.

Dyslipidemia and CV Risk: A Clinical Overview

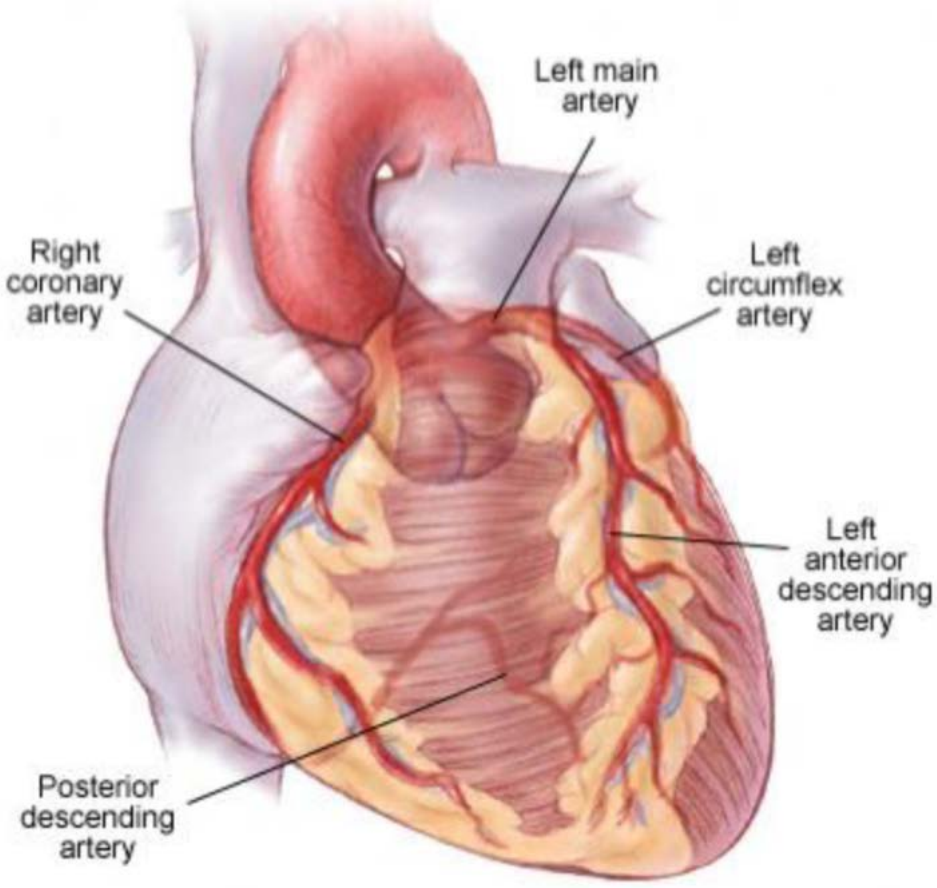
Carolyn Finocchiaro, APRN, CLS

Objectives

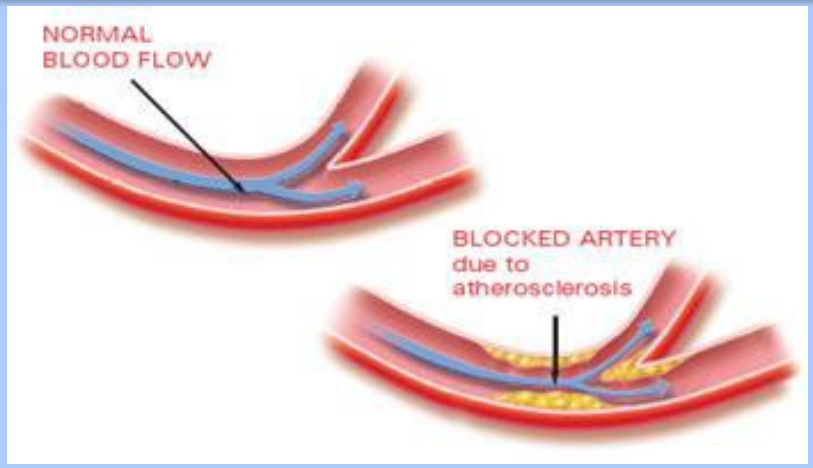
Review and Discuss

- Cholesterol metabolism and pathophysiology of atherogenic dyslipidemia
  - Role of lipids (cholesterol) and lipoproteins (e.g., LDL)
  - Lipid values and testing
- Predictors of cardiovascular risk
- Application of current guidelines
- Overview of current therapies for dyslipidemia

Major Arteries of the Heart and Atherosclerosis Formation



The role of these arteries is to bring oxygenated blood to the heart (which is a giant muscle).



Atherosclerosis: Buildup of cholesterol and other material, called plaque, on the arterial walls.

Risk Factors Associated with CHD

Major Risk Factors for CHD

- High blood pressure
- High blood cholesterol
- Tobacco use
- Unhealthy diet
- Physical inactivity
- Diabetes
- Advancing age
- Inherited (genetic) disposition

FO

Other Risk Factors

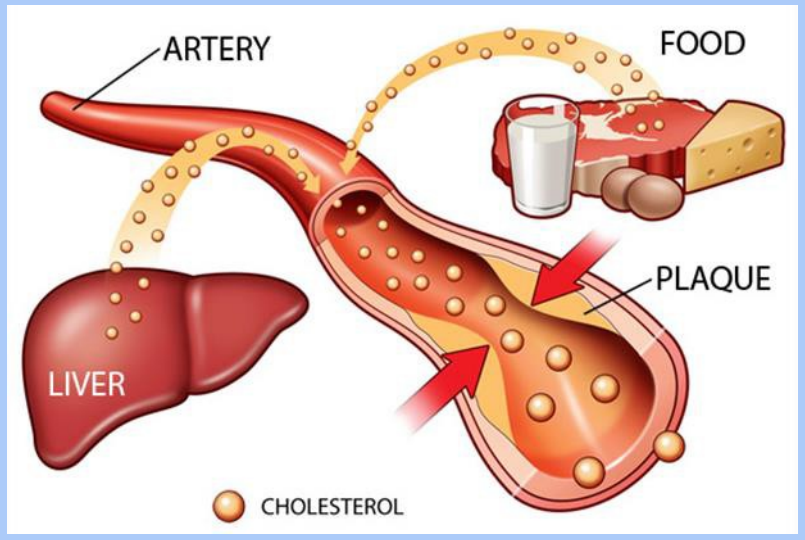
- Poverty
- Low educational status
- Poor mental health (depression)
- Inflammation and blood clotting disorders

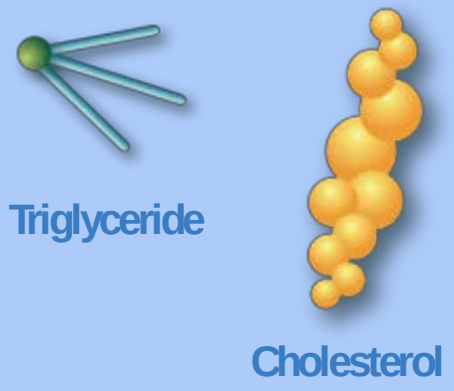
World Health Organization. Types of cardiovascular disease. http://www.who.int/cardiovascular_diseases/en/cvd_atlas_01_types.pdf. Accessed September 9, 2011.

Lipid/Cholesterol Metabolism and Dyslipidemia

Lipids

- Cholesterol: fat (lipid) found in many food sources and produced naturally in the body
- Triglycerides: type of fat (lipid) in the bloodstream and adipose tissue. Consists of three fatty acids on 1 glycerol backbone

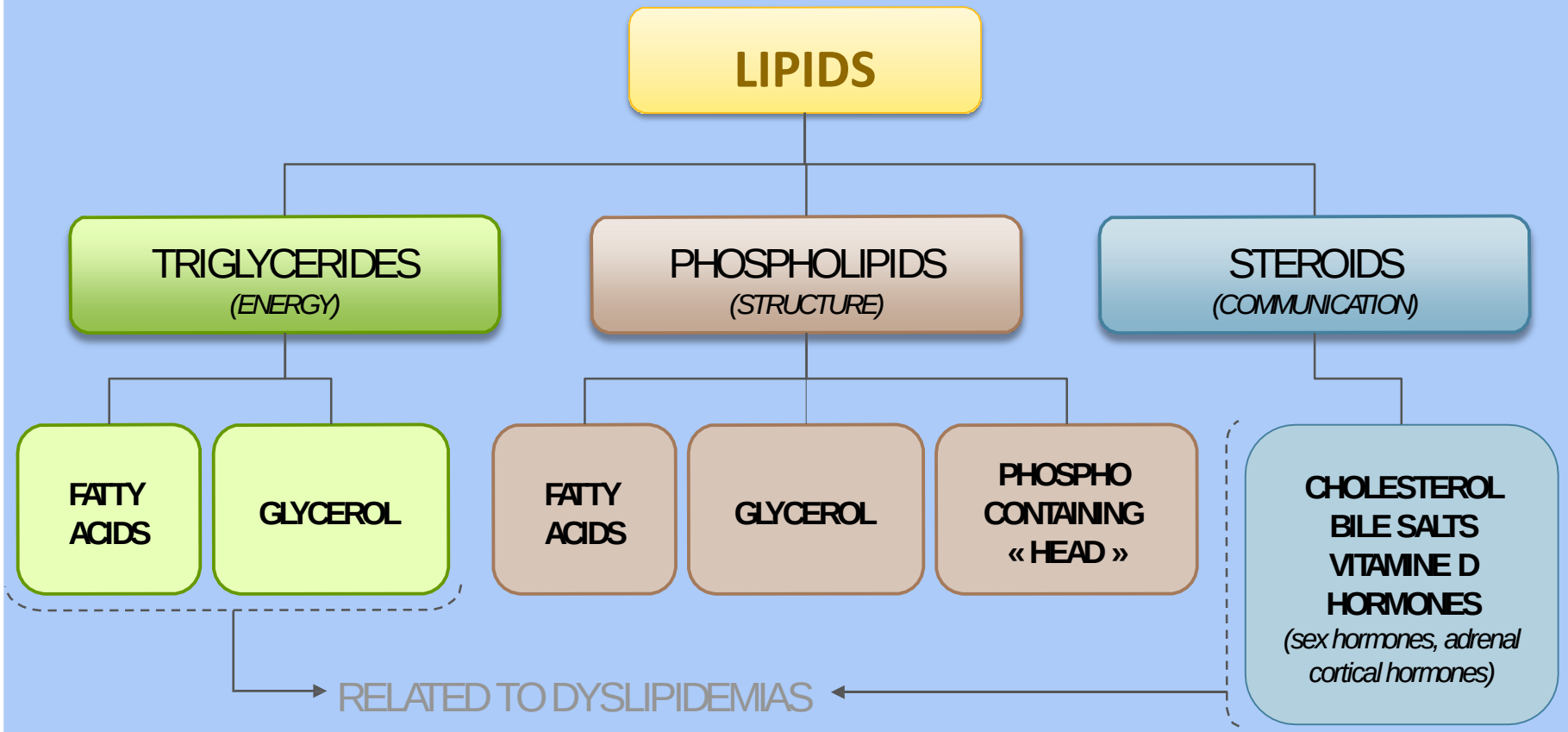




*apo(a) = apolipoprotein (a).

Rader DJ, Hobbs HH. *Disorders of Lipoprotein Metabolism.* In Harrison's Online. The McGraw-Hill Companies. Available at www.accessmedicine.com. Accessed on Jan 4, 2013.

There Are Three Major Lipid Classes



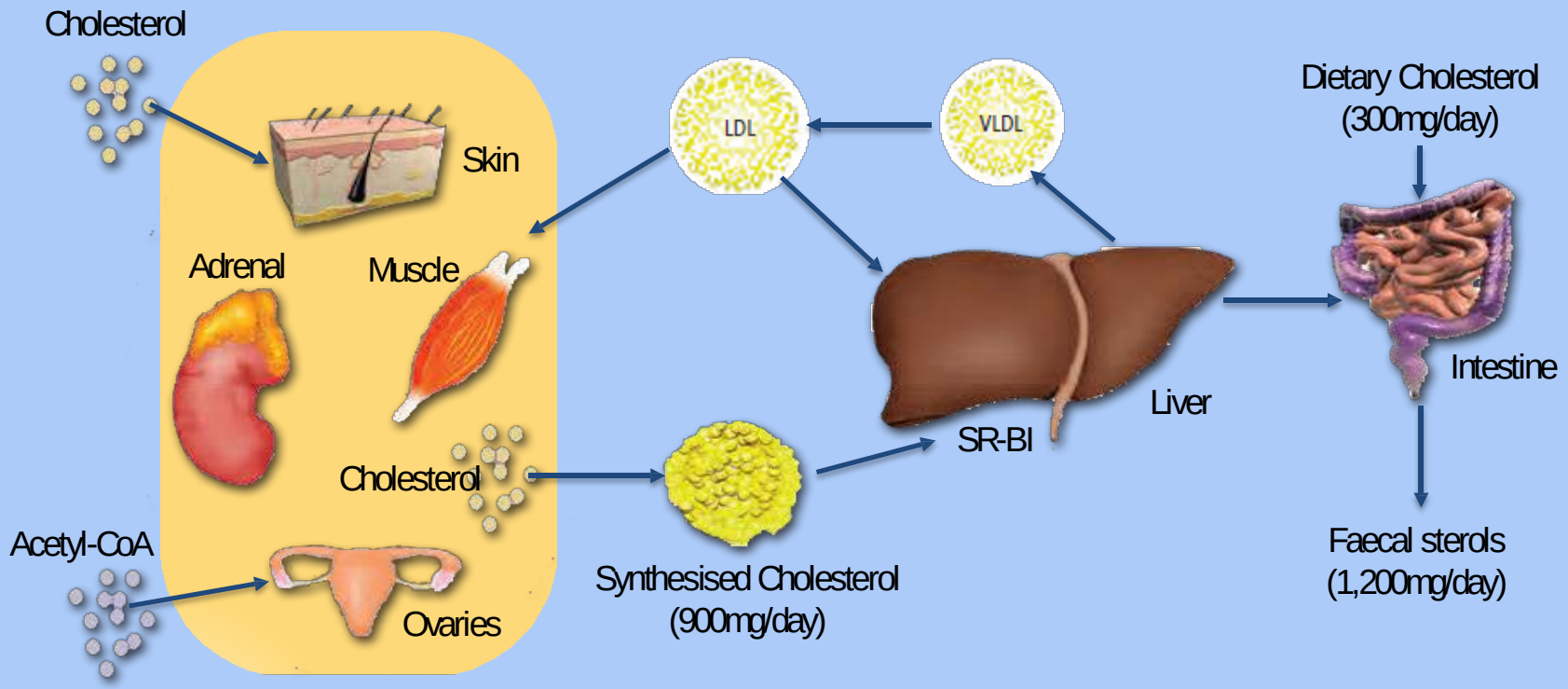
Cholesterol Has an Important Function in the Body

- Cholesterol is a type of fat (lipid) found in many food sources and produced naturally in the body[1]
- It has 3 main functions within the body[2]
  - Necessary part of cell walls
  - Precursor chemical for steroid compounds
  - Formation of bile acids for digestion

The liver is the main organ for the regulation of cholesterol.[3]

1. AHA. About cholesterol. http://www.heart.org/HEARTORG/Conditions/Cholesterol/AboutCholesterol/About-Cholesterol_UCM_001220_Article.jsp. Accessed September 14, 2011.
2. Cox RA, et al. In: Walker HK, et al, eds. *Clinical Methods: The History, Physical, and Laboratory Examinations*. 3rd ed. 1990. 153-160.
3. Havel RJ, et al. In: Scriver CR, et al, eds. *The Metabolic & Molecular Bases of Inherited Disease*. Vol 2. 8th ed. 2001:2705-2716.

Cholesterol Balance



Synthesis
Mainly in the liver, endocrine organs, muscle and skin

Absorption
From the diet and excretion into bile

Of the cholesterol absorbed in the intestines: 25% is from dietary sources (exogenous) 75% is from biliary sources undergoing enterohepatic circulation (endogenous).

Kostner K. www.touchcardiology.com/files/article_pdfs/kostner.pdf. Accessed September 9, 2011. Reprinted by permission.

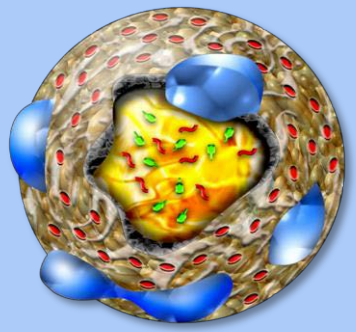
Lipoproteins

Lipoproteins:

- Particles that transport cholesterol and triglycerides and are comprised of proteins (apolipoproteins), phospholipids, triglycerides, and cholesterol
- Range in density, depending on amount of triglycerides
- Names reflect density:
  - VLDL (Very Low Density Lipoproteins)
  - IDL (Intermediate Density Lipoproteins)
  - LDL (Low Density Lipoproteins)
  - HDL (High Density Lipoprotein)
  - Lp(a) stands for lipoprotein(a); the abbreviation reflects its structure as an LDL particle (lipoprotein) attached to the protein, apo(a)*
- Most made in liver and have large proteins (called apolipoproteins) as their structural core
  - VLDL has Apo B 100, Apo CI, Apo CII, Apo C III and Apo E.
  - IDL has Apo E and Apo B 100
  - LDL and Lp(a), has Apo B
  - HDL has Apo AI and Apo A II

Why Lipoproteins?

Oil and water don't mix



Lipids (triglycerides, phospholipids, sterols) need vehicles (lipoproteins) to travel through aqueous media[1,2]:

- Lymph
- Plasma

Lipoproteins help transport lipids[1,3]:

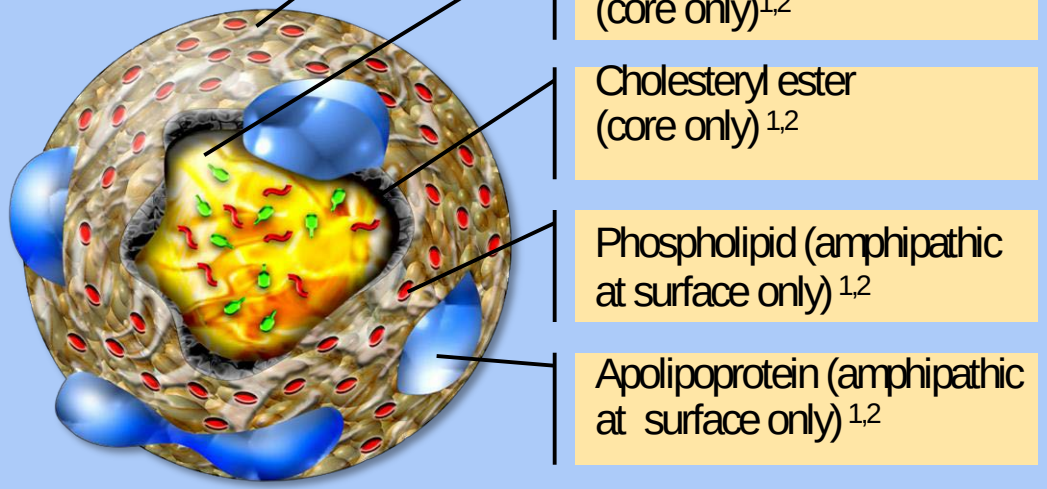
- Absorb/distribute dietary/intestinal lipids
- Re-distribute endogenous lipids
- Energy use/storage
- Cell structure

1. Cox RA, et al. In: Walker HK, et al, eds. *Clinical Methods: The History, Physical, and Laboratory Examinations*. 3rd ed. 1990. 153-160.
2. Rader DJ, Hobbs HH, "*Chapter 356. Disorders of Lipoprotein Metabolism*" (Chapter). Fauci AS, et al: *Harrison's Principles of Internal Medicine*, 18e: http://www.accessmedicine.com/content.aspx?aID=9143689.

- *Hyperlipidaemia.* Eds Durrington P, Sniderman A. Health Press Ltd, Oxford, 2000:1-17

Structure of a Lipoprotein

- Lipoproteins are a grouping of different lipid molecules and proteins that vary in size[1]
- There are 4 major elements: cholesterol, TGs, phospholipids, and specific proteins called apolipoproteins[1]



Artwork used with permission from the National Lipid Association.

1. Havel RJ, et al. In: Scriver CR, et al, eds. *The Metabolic & Molecular Bases of Inherited Disease*. Vol 2. 8th ed. 2001:2705-2716.
2. In: *Fast Fact - Hyperlipidaemia*. Eds Durrington P, Sniderman A. Health Press Ltd, Oxford, 2000:1-17.

3 Major Classes of Lipoproteins

- The 3 major classes of lipoproteins are LDL, HDL, and VLDL[1]

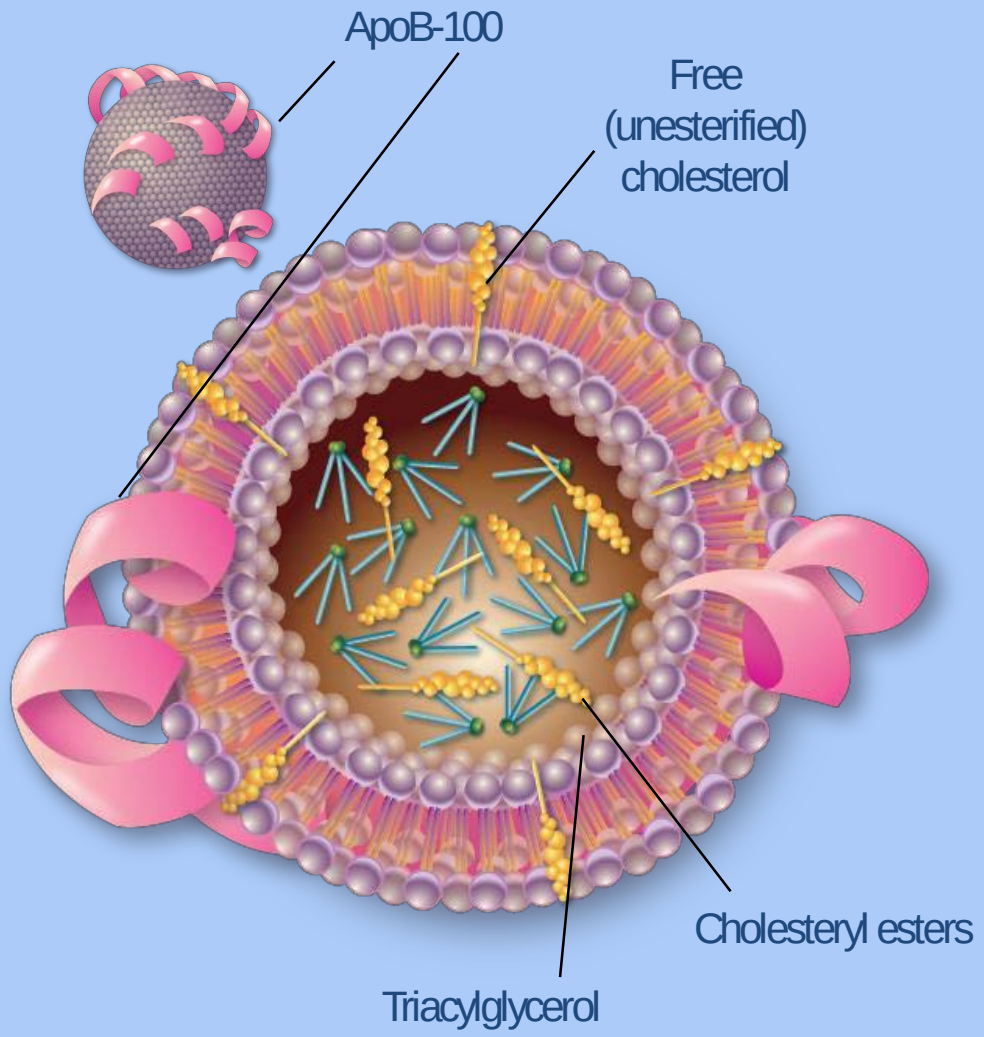
Lipoproteins[1]	Percent of Total Serum Cholesterol[1]	Major Apolipoproteins[1]	Function[2,3]
LDL[a]	60% to 70%	Apo B-100 (Apo B)	Delivers cholesterol
HDL[a]	20% to 30%	Apo AI and Apo AII	Reverse cholesterol transport
VLDL[a]	10% to 15%	Apo B, Apo Cs, and Apo E	Transports endogenous triglycerides, phospholipids, cholesterol, and cholesteryl esters

[a]More commonly measured as cholesterol concentration [–C]: LDL-C, HDL-C, and VLDL-C.

LDL = High-density lipoprotein; HDL = High-density lipoprotein; VLDL = very low-density lipoprotein.

1. NCEP ATP III Final Report. *Circulation.* 2002;106(25):3143-342; 2. Rader DJ, Hobbs HH, "*Chapter 356. Disorders of Lipoprotein Metabolism*" (Chapter). Fauci AS, et al: *Harrison's Principles of Internal Medicine*, 18e: http://www.accessmedicine.com/content.aspx?aID=9143689; 3. Havel RJ, et al. In: Scriver CR, et al, eds. *The Metabolic & Molecular Bases of Inherited Disease.* Vol 2. 8th ed. 2001:2705-2716.

Atherogenic, Apo B-Containing Lipoproteins, Deposit Cholesterol, Initiating CVD



- Cholesterol is carried through the arteries by atherogenic lipoproteins
  - 70% of cholesterol is carried by LDL (low density lipoprotein) particles
  - Other lipoproteins include VLDL, IDL, and Lp(a)
- Each atherogenic lipoprotein has one Apo B molecule, a single large protein as its structural core

Elevated Plasma Levels of LDL, HDL, and Triglycerides

Low-density lipoprotein (LDL)[1,2]

- 60-70% of the total cholesterol in the bloodstream
- LDL-C is commonly quoted as 'bad' cholesterol
- Major cause of atherosclerosis and cardiovascular diseases

High-density lipoprotein (HDL)[1,2]

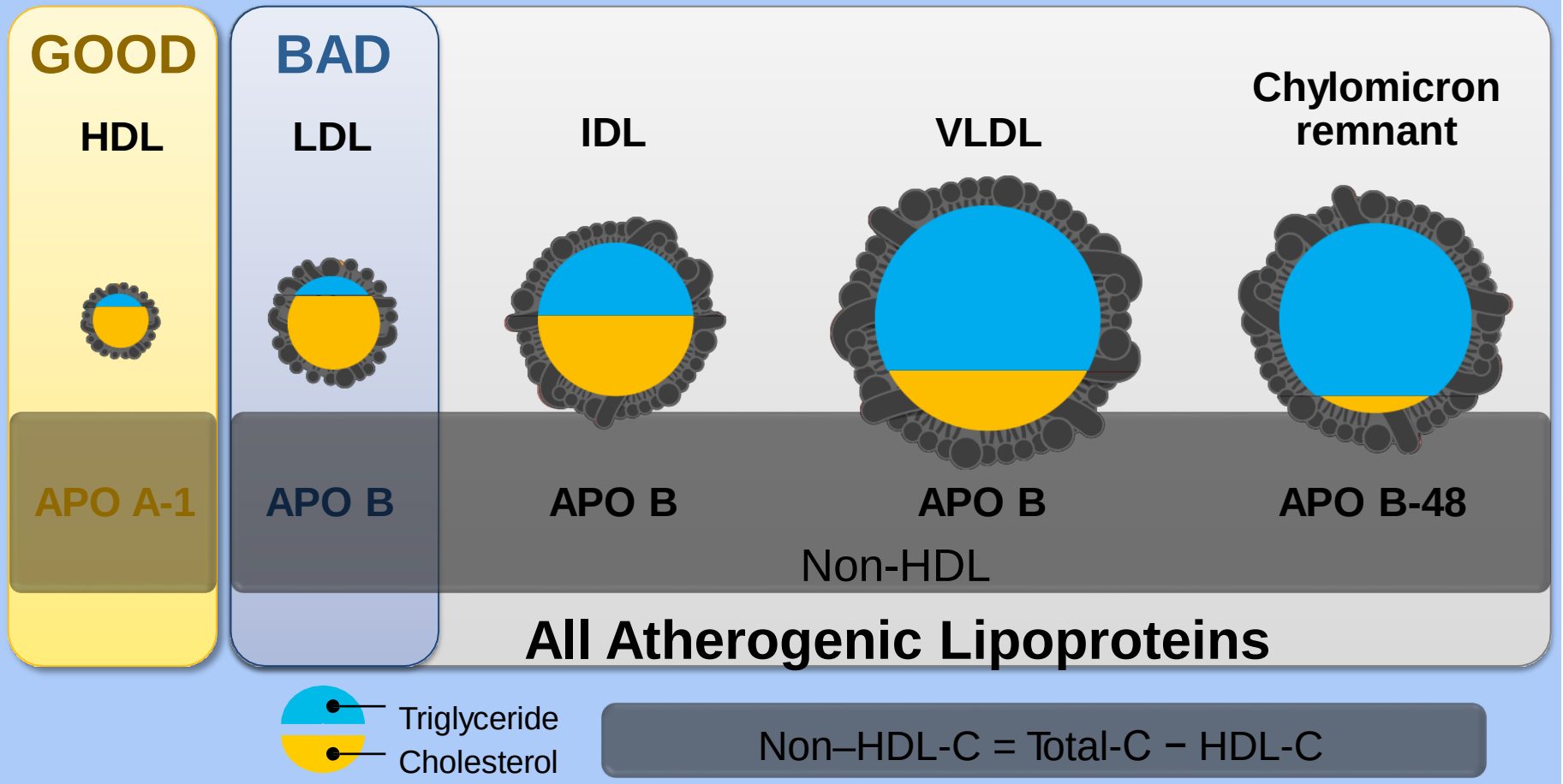
- HDL-C is commonly quoted as 'good' cholesterol
- High HDL-C levels are anti-atherogenic
- Higher risk for atherosclerosis when low HDL-C levels

Triglycerides (TG)[1,2]

- High levels of TG may contribute to the stiffening of the arteries and increase in plaque buildup

1. NCEP ATP III Final Report. *Circulation*. 2002;106(25):3143–342.
2. AHA. What your cholesterol level means. http://www.heart.org/HEARTORG/Conditions/What-Your-Cholesterol-Levels-Mean_UCM_305562_Article.jsp. Accessed September 14, 20

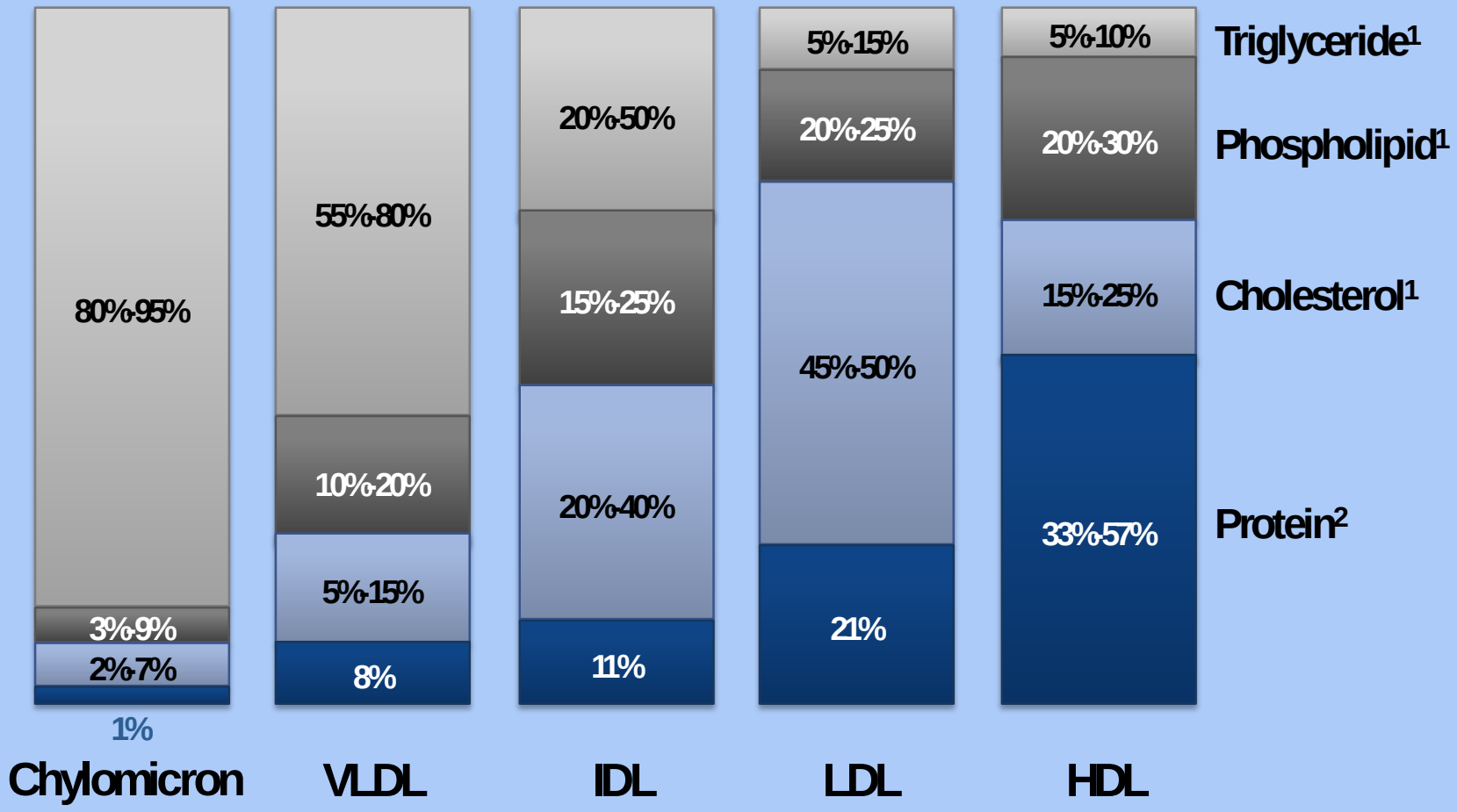
What Is Non–HDL-C?



Artwork used with permission from the National Lipid Association; NCEP ATP III Final Report. *Circulation*. 2002;106(25):3143–342.

NP-WW-CL-1113

Composition of Lipoproteins

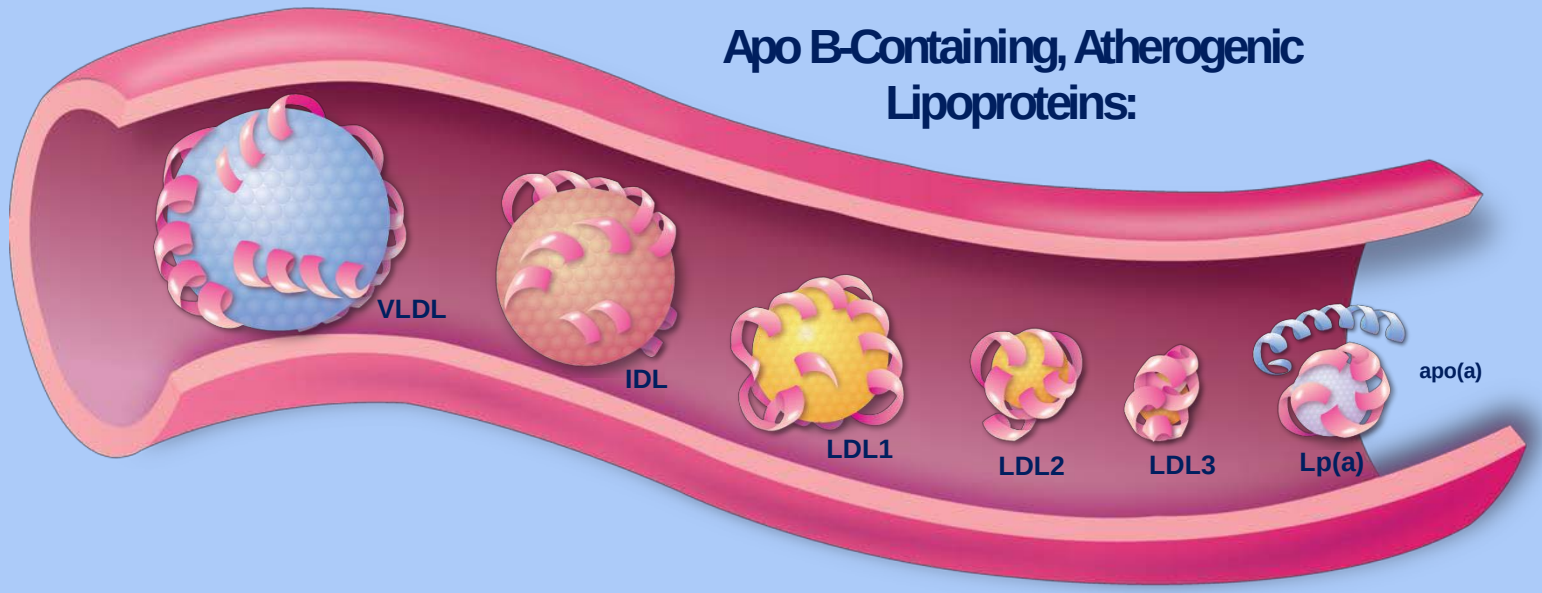


IDL= intermediate-density lipoprotein.

1. Smith CM, et al. *Marks' Basic Medical Biochemistry: A Clinical Approach*, Image Bank. 3rd ed. Lippincott Williams & Wilkins, a Wolters Kluwer business; 2009: 649.

Role of Apolipoproteins in Lipid Metabolism

- Apolipoproteins (apo) coat lipoprotein particles and serve a number of functions including the transport of lipids in the blood and recognition of lipoprotein particles by enzymes which process or remove lipids from the lipoprotein particles[1]
- Apo B occurs as 1 molecule per LDL particle, either Apo B-48 (chylomicron) or Apo B-100 (VLDL, IDL or LDL), is present on each lipoprotein particle[1,2]

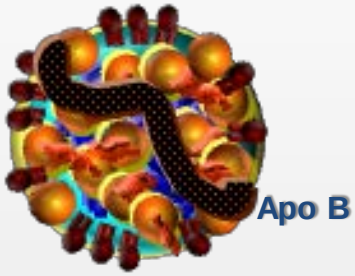


1. Rader DJ, Hobbs HH, "*Chapter 356. Disorders of Lipoprotein Metabolism*" (Chapter). Fauci AS, et al: *Harrison's Principles of Internal Medicine*, 18e: http://www.accessmedicine.com/content.aspx?aID=9143689.
2. The Center for Cholesterol Management. Dayspring T: Apolipoprotein B 100 and 48 . http://www.lipidcenter.com/pdf/apoB_100_vs_apoB48.pdf.

Apolipoprotein B (Apo B) as a Measure of Circulating LDL Particle Number (LDL-P) Concentration

Position Statement from the AACC Lipoproteins and Vascular Diseases Division Working Group on Best Practices:

- LDL cholesterol (LDL-C) has been the cornerstone measurement for the assessment of cardiovascular disease (CVD) risk
- Awareness gradually developed that Apo B, occurring as 1 molecule per LDL particle, was a more representative indicator of the concentration of LDL



LDL

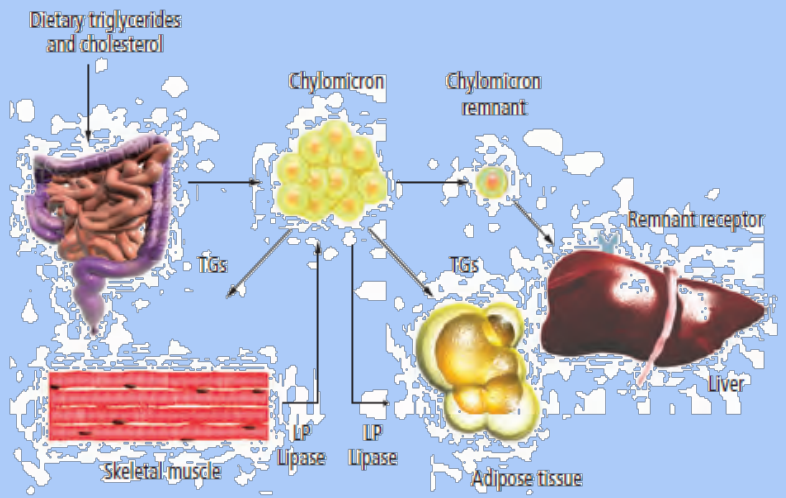
Results from prospective studies generally demonstrate the superiority of Apo B or LDL-P over LDL-C measurement for the assessment of risk.

Artwork used with permission from T. Dayspring, MD; Contois JH, et al. *Clin Chem.* 2009;55(3):407–419.

The Lipid Transport System in Plasma Involves 2 Pathways: Lipid Metabolism

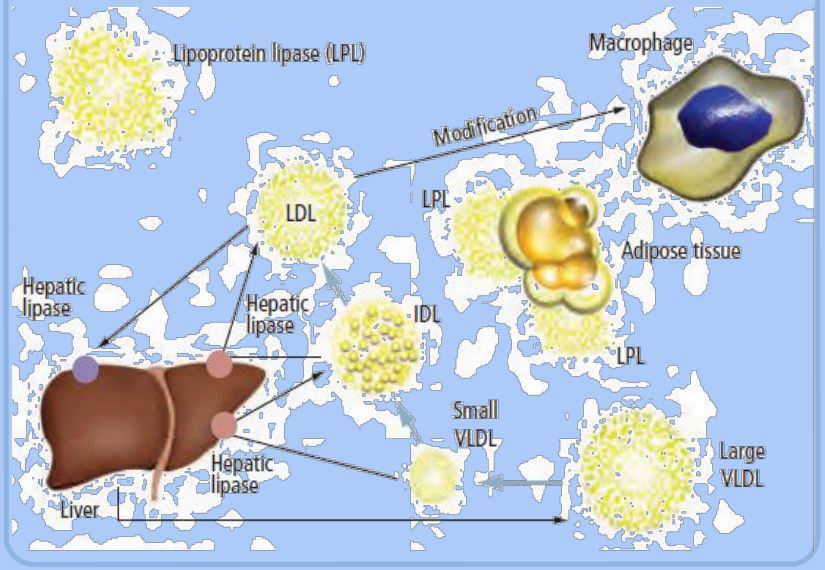
Exogenous Pathway

Route for the transport of cholesterol and TGs absorbed from dietary fat in the intestine



Endogenous Pathway

Route for cholesterol and TGs to reach the plasma from the liver and other nonintestinal tissues



Kostner K. www.touchcardiology.com/files/article_pdfs/kostner.pdf. Accessed September 9, 2011. Reprinted by permission.

Predictors of Cardiovascular Risk

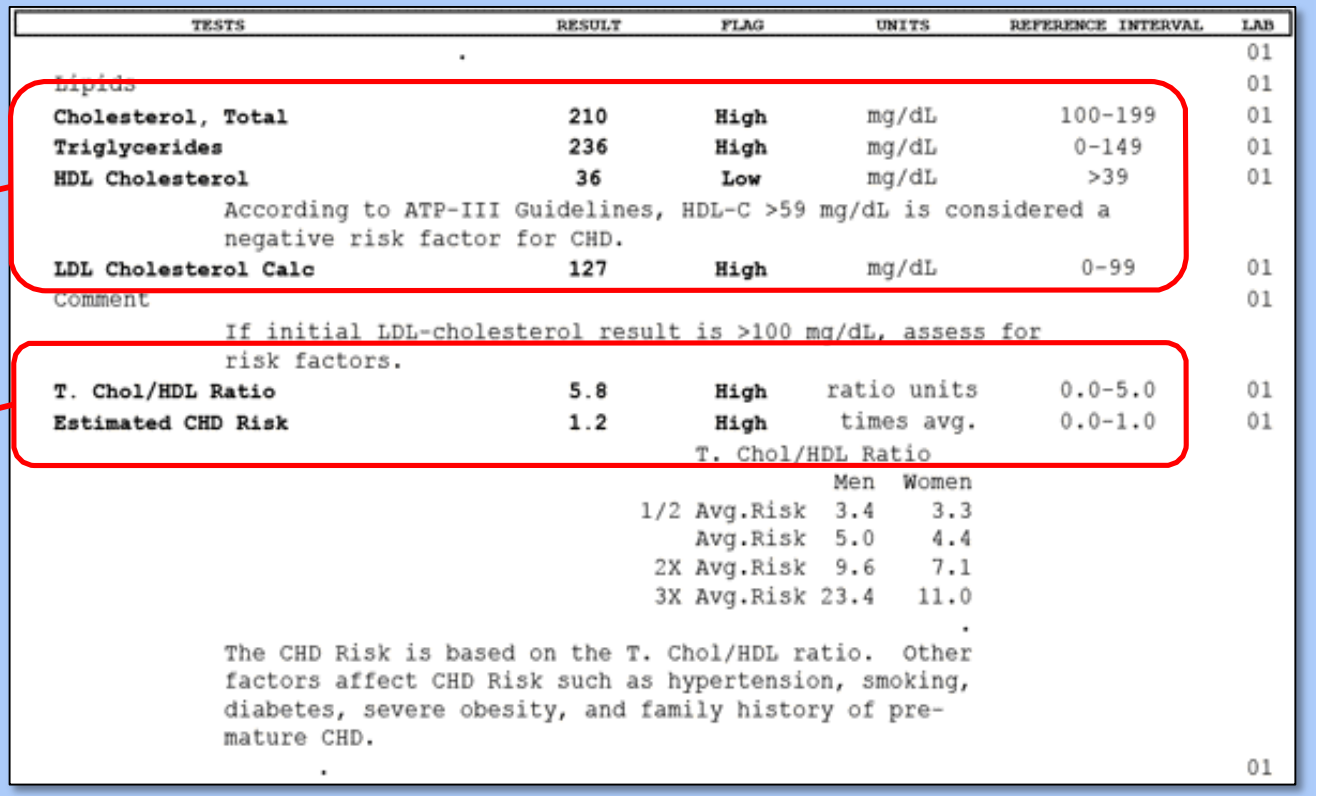
Coronary Risk Profile (Lipid Panels)

- Measure the cholesterol or triglyceride content of lipoproteins, expressed as mg/dL (or mmol/L) of cholesterol or triglyceride.
- A standard lipid panel includes:
  - Total cholesterol (TC)
  - Low-density lipoprotein (LDL) cholesterol
  - High-density lipoprotein (HDL) cholesterol
  - Triglycerides

Example of Standard Lipid Panel

Identifies basic lipid parameters (LDL-C, TGs, and HDL-C)…

….TC/HDL ratio and estimated CHD risk



TESTS	RESULT	FLAG	UNITS	REFERENCE INTERVAL	LAB
					01
Lipids					01
Cholesterol, Total	**210**	**High**	mg/dL	100-199	01
Triglycerides	**236**	**High**	mg/dL	0-149	01
HDL Cholesterol	**36**	**Low**	mg/dL	>39	01
According to ATP-III Guidelines, HDL-C >59 mg/dL is considered a negative risk factor for CHD.					
LDL Cholesterol Calc	**127**	**High**	mg/dL	0-99	01
Comment					01
If initial LDL-cholesterol result is >100 mg/dL, assess for risk factors.					
T. Chol/HDL Ratio	**5.8**	**High**	ratio units	0.0-5.0	01
Estimated CHD Risk	**1.2**	**High**	times avg.	0.0-1.0	01

T. Chol/HDL Ratio

	Men	Women
1/2 Avg.Risk	3.4	3.3
Avg.Risk	5.0	4.4
2X Avg.Risk	9.6	7.1
3X Avg.Risk	23.4	11.0

The CHD Risk is based on the T. Chol/HDL ratio. Other factors affect CHD Risk such as hypertension, smoking, diabetes, severe obesity, and family history of pre-mature CHD.

01

Advanced Lipid Panels

Advanced Lipid Panels

- Used to enhance CVD risk assessment, especially in individuals with low or normal LDL cholesterol, by detecting the:
  - Presence of higher concentrations of atherogenic lipoprotein particle concentrations (e.g., apoB) or,
  - Presence of small dense LDL particles

Lipid Parameters	Description
Apo B	Direct measurement of the number of lipoprotein particles, including LDL, IDL, and VLDL
Lp(a)	LDL particle with an inherited apoprotein (a) variant attached
Apo A1	Major protein component of HDL
LDL-P	Direct measure of LDL particle number
LDL particle size	Smaller LDL particles appear to be more atherogenic
Lp-PLA_2	Marker for vascular-specific inflammation
hsCRP	One of a number of acute phase reactant proteins that increases in response to inflammatory stimuli

Advanced Lipid Panels

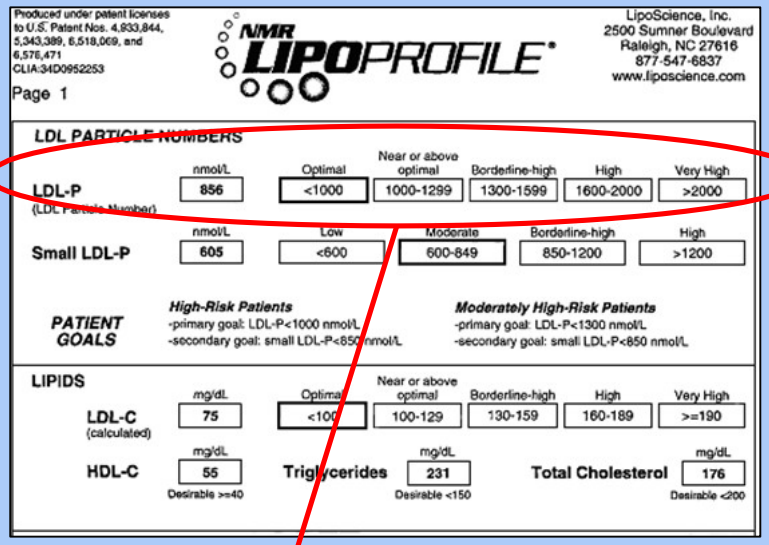
Examples of Advanced Lipid Panels

- **"NMR Lipoprofile" (LipoScience):** FDA approved technology that gives a direct measure of LDL particle number (LDL-P) along with standard cholesterol results.
- **"VAP Test" (Atherotech):** Directly measures LDL –C, measurement of LDL pattern density (Pattern B), and lipoprotein subclasses such as HDL2 and HDL3.
- **"Berkeley" (Berkeley Heart Lab):** Lipoprotein subfractionation by ion mobility that captures the size and subclasses of the entire lipoprotein particle range, including VLDL, IDL, LDL, and HDL.

.

Examples of Advanced Lipid Panels

NMR Lipoprofile®



Produced under patent licenses to U.S. Patent Nos. 4,933,844, 5,343,389, 6,518,069, and 6,576,471
CLIA:34D0952253

NMR LIPOPROFILE®

LipoScience, Inc.
2500 Sumner Boulevard
Raleigh, NC 27616
877-547-6837
www.liposcience.com

Page 1

LDL PARTICLE NUMBERS

	nmol/L	Optimal	Near or above optimal	Borderline-high	High	Very High
LDL-P (LDL Particle Number)	856	<1000	1000-1299	1300-1599	1600-2000	>2000

	nmol/L	Low	Moderate	Borderline-high	High
Small LDL-P	605	<600	600-849	850-1200	>1200

PATIENT GOALS

High-Risk Patients
-primary goal: LDL-P<1000 nmol/L
-secondary goal: small LDL-P<850 nmol/L

Moderately High-Risk Patients
-primary goal: LDL-P<1300 nmol/L
-secondary goal: small LDL-P<850 nmol/L

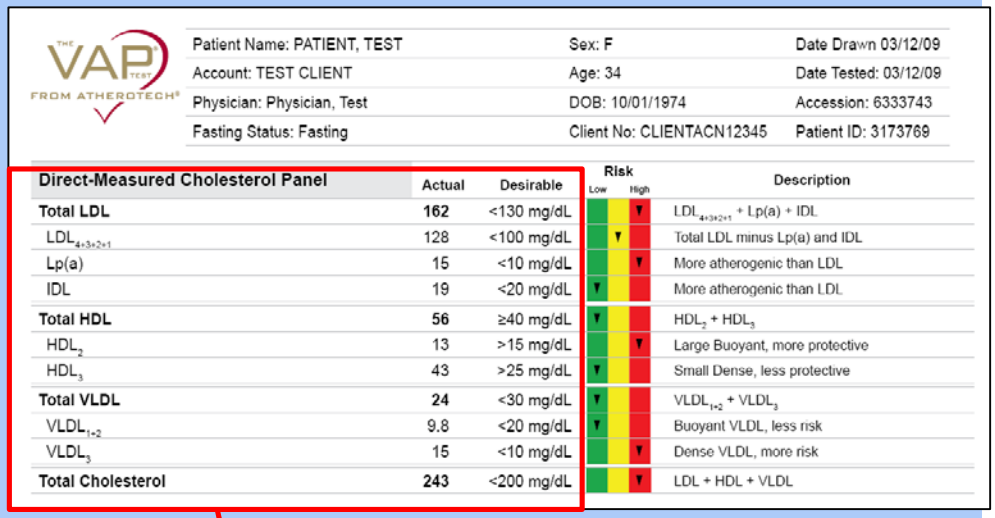
LIPIDS

	mg/dL	Optimal	Near or above optimal	Borderline-high	High	Very High
LDL-C (calculated)	75	<100	100-129	130-159	160-189	>=190

	mg/dL		mg/dL		mg/dL
HDL-C	55	Triglycerides	231	Total Cholesterol	176
	Desirable >=40		Desirable <150		Desirable <200

LDL particle number (LDL-P) and optimal levels

The VAP® Test



THE VAP TEST FROM ATHEROTECH®

Patient Name: PATIENT, TEST	Sex: F	Date Drawn 03/12/09
Account: TEST CLIENT	Age: 34	Date Tested: 03/12/09
Physician: Physician, Test	DOB: 10/01/1974	Accession: 6333743
Fasting Status: Fasting	Client No: CLIENTACN12345	Patient ID: 3173769

Direct-Measured Cholesterol Panel	Actual	Desirable	Risk (Low / High)	Description
Total LDL	**162**	<130 mg/dL	▼	$LDL_{4+3+2+1}$ + Lp(a) + IDL
$LDL_{4+3+2+1}$	128	<100 mg/dL	▼	Total LDL minus Lp(a) and IDL
Lp(a)	15	<10 mg/dL	▼	More atherogenic than LDL
IDL	19	<20 mg/dL	▼	More atherogenic than LDL
Total HDL	**56**	≥40 mg/dL	▼	HDL_2 + HDL_3
HDL_2	13	>15 mg/dL	▼	Large Buoyant, more protective
HDL_3	43	>25 mg/dL	▼	Small Dense, less protective
Total VLDL	**24**	<30 mg/dL	▼	$VLDL_{1+2}$ + $VLDL_3$
$VLDL_{1+2}$	9.8	<20 mg/dL	▼	Buoyant VLDL, less risk
$VLDL_3$	15	<10 mg/dL	▼	Dense VLDL, more risk
Total Cholesterol	**243**	<200 mg/dL	▼	LDL + HDL + VLDL

Lipoproteins, subclasses, and desired amounts

Classification of Lipid Disorders: Dyslipidemia

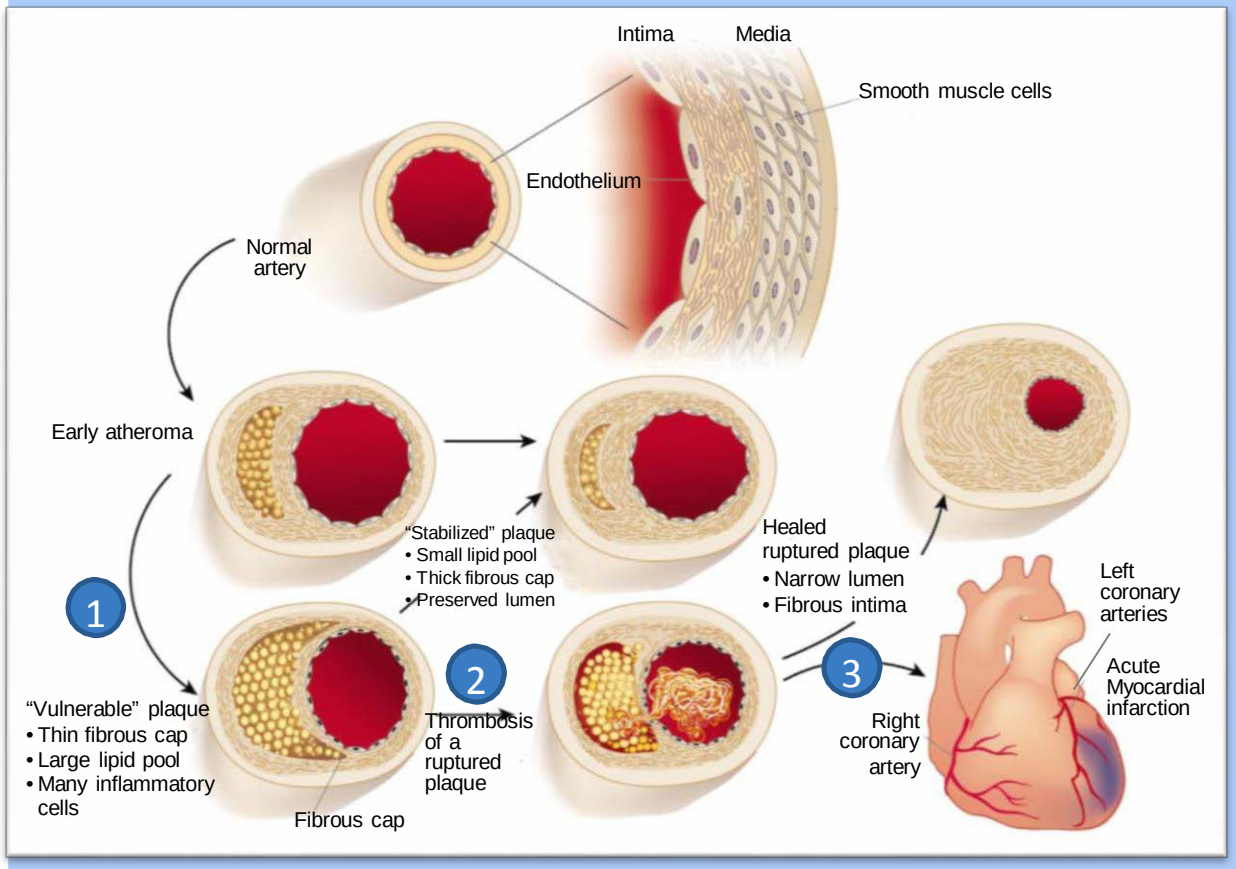
- Dyslipidemia is defined as **abnormal levels of lipids in the blood**

Frederickson Classification of Lipid Disorders

Type	Elevated Particles	Associated-clinical Disorders	Serum TC	Serum TG
Type I	Chylomicrons	LPL deficiency, Apo C-II deficiency	→	↓↓
Type IIa	LDL	Familial hypercholesterolemia (FH), polygenic hypercholesterolemia, nephrosis, hypothyroidism, familial combined hyperlipidemia	↑↑	→
Type IIb	LDL, VLDL	Familial combined hyperlipidemia	↑↑	↑
Type III	IDL	Dysbetalipoproteinemia	↑	↑
Type IV	VLDL	Familial hypertriglyceridemia, familial combined hyperlipidemia, sporadic hypertriglyceridemia, diabetes	→↑	↑↑
Type V	Chylomicrons, VLDL	Diabetes	↑	↑↑

↑= increased; ↑↑= greatly increased; →= normal; →↑= normal or increased

Too Much Cholesterol in the Blood, Along With Other Substances, Can Lead to Atherosclerosis



Cholesterol (lipid) is transported to and deposited in artery walls by lipoproteins[1]

1. Atherosclerosis (or hardening of the arteries) is a progressive disease caused when fat, cholesterol, and other substances, build up in the inner walls of arteries and form hard structures called plaques[2,3]
2. Sometimes this plaque can break open[2]
3. When this happens, a blood clot forms and blocks the artery causing heart attacks and strokes[2]

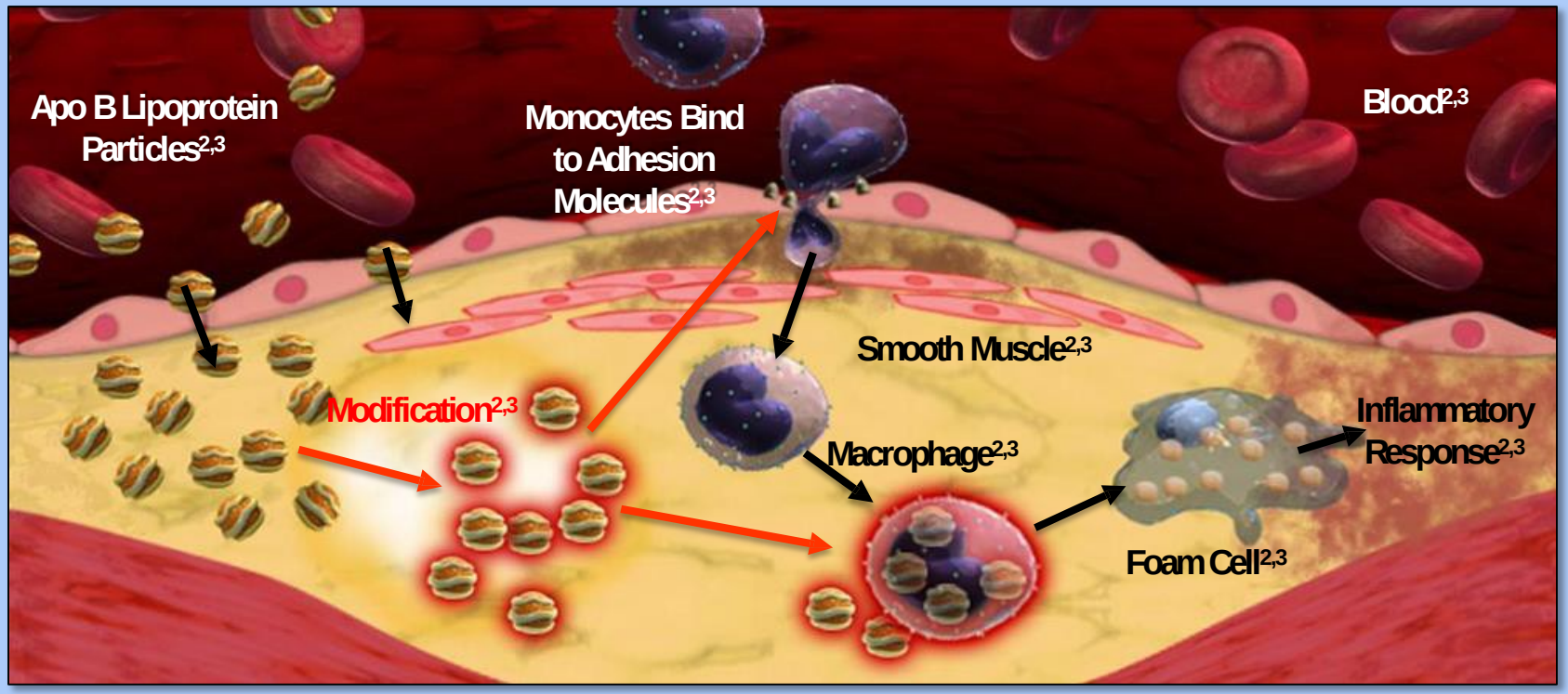
Reprinted by permission from Macmillan Publishers Ltd. from *Nature*. 2002;420(6917):868-874, @2002.
http://www.nature.com/nature/journal/v420/n6917/full/nature01323.html

1.Cox RA, et al. In: Walker HK, et al, eds.. *Clinical Methods: The History, Physical, and Laboratory Examinations*. 3rd ed. 1990. 153-160; 2. Libby P. *Nature*. 2002;420(6917):868–874; 3. AHA. What are heart disease and stroke? http://www.heart.org/idc/groups/heart-public/@wcm/@hcm/documents/downloadable/ucm_300313.pdf. Accessed September 9, 2011.

MAT-US-1113

Early Stages of Atherogenesis Involve Apo B

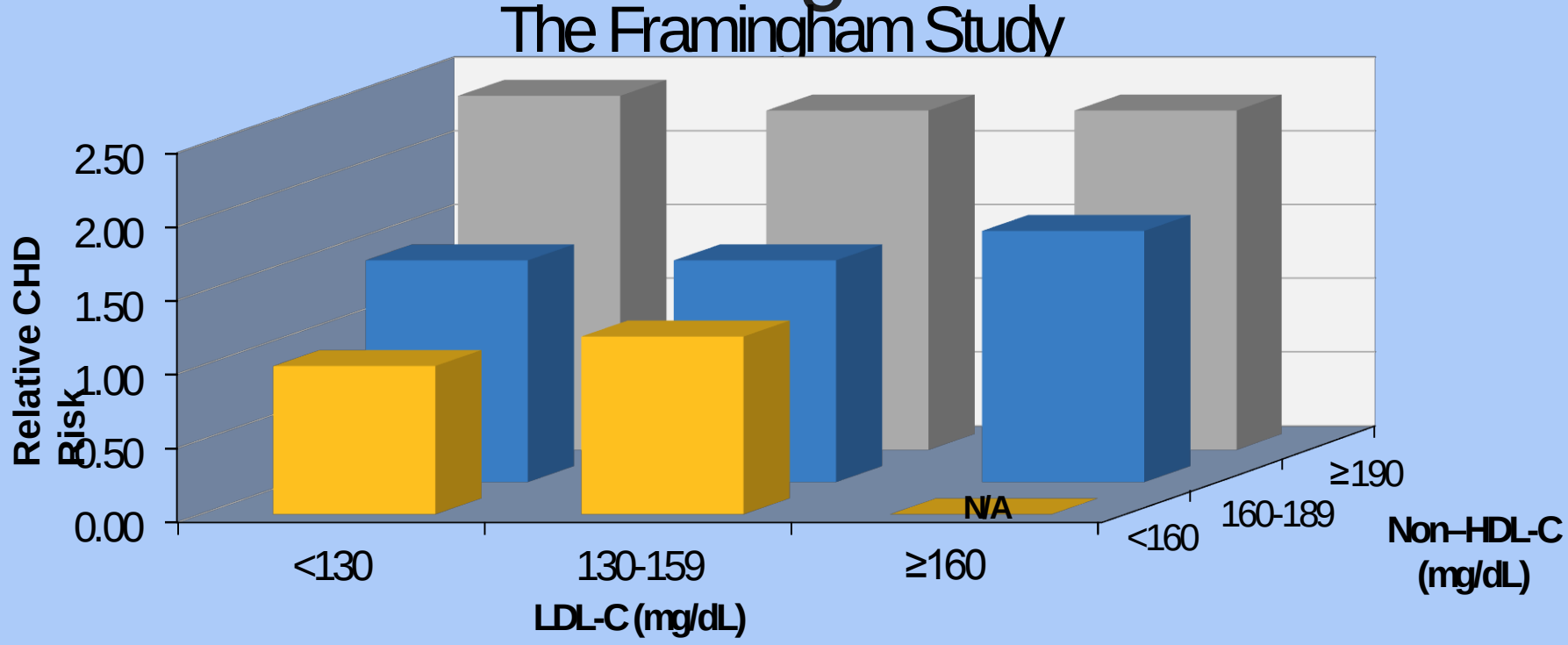
- Serum total Apo B has been shown to have a strong predictive power for severity of coronary atherosclerosis and CHD events[1]



Artwork used with permission from the National Lipid Association.

1. NCEP ATP III Final Report. *Circulation*. 2002;106(25):3143–342.
2. Williams KJ, et al. *Arterioscler Thromb Vasc Biol*. 2005;25(8):1536–1540.
3. Steinberg D et, al. *N Engl J Med*. 1989;320(14):915–924.

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



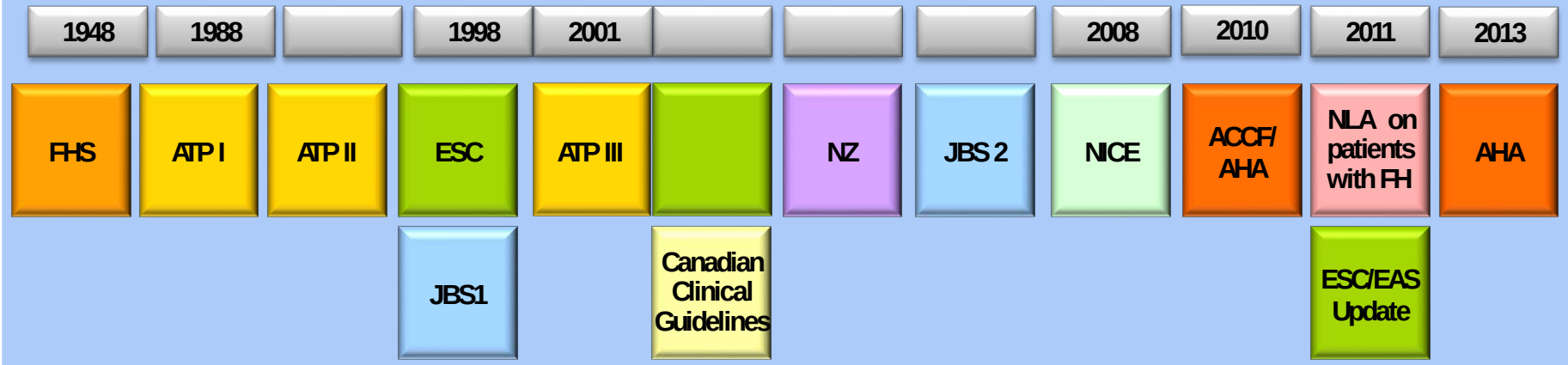
- Within Non–HDL-C levels, no association was found between LDL-C and the risk for CHD
- Strong, positive, graded association of Non–HDL-C with CHD seen at every LDL-C level

Liu J, et al. *Am J Cardiol.* 2006;98:1363–1368. Reprinted by permission.

Dyslipidemia Management Guidelines

Management of Dyslipidemia Guidelines

- Several national and international associations have issued guidelines to recommend therapeutic levels of lipoproteins



NCEP ATP III Guidelines: CV Risk Assessment

Major Risk Factors Other Than LDL-C Used In Risk Factor Counting

- Age (men ≥45 years; women ≥55 years)
- Current cigarette smoking
- Hypertension (blood pressure
  - ≥140/90 mm Hg or on antihypertensive medication)
- Low HDL-C (<40 mg/dL)
- Family history of premature CHD (Myocardial infarction or sudden death in male first-degree relative <55 years
  - of age and in female first-degree relative
  - <65 years of age)

Assessment tool: Framingham Risk Score

- Determines an individual's 10-year absolute CHD risk and is based on 5 major independent risk factors
  - High systolic blood pressure
  - Cigarette smoking
  - High TC
  - Low HDL-C
  - Age
- It's recommended for patients with 2 or more risk factors

NCEP ATP III = The NCEP Adult Treatment Panel III (ATP III).

NCEP ATP III Final Report. *Circulation*. 2002;106(25):3143–342.

MPH031118

NCEP ATP III Guidelines: Dyslipidemia Risk Stratification

- The initial step in dyslipidemia management is to stratify a patient based on his/her level of risk for an acute cardiovascular event

Risk Factors	Risk Category
Very High Risk	CHD or CHD risk equivalents and a 10-year risk of >20%[a]
High Risk	≥2 risk factors and a 10-year risk of 10 to 20%
Moderate Risk	≥2 risk factors and a 10-year risk of <10%
Low Risk	0 to 1 risk factor

[a]CHD=history of MI, unstable or stable angina, coronary artery procedure, or evidence of clinically significant myocardial ischemia; CHD risk equivalents = manifestations of non coronary forms of atherosclerotic disease, diabetes, and 2 risk factors with 10-year risk od CHD>20%.

Grundy SM, et al. *Circulation*. 2004;110(2):227–239.

NCEP ATP III Guidelines: Goals for Lipid-lowering Therapy

Risk Category		Treatment Goals[1,2]	
		LDL-C (mg/dL)	Non–HDL-C (mg/dL)
Very High Risk	CHD or CHD risk equivalents (10-year risk >20%)	<100 (optional goal: <70)	<130 (optional goal: <100)
High Risk	≥2 risk factors (10-year risk 10%-20%)	<130 (optional goal: <100)	<160 (optional goal: <130)
Moderate Risk	≥2 risk factors (10-year risk <10%)	<130	<160
Low Risk	0-1 risk factors	<160	<190

1. NCEP ATP III Final Report. *Circulation.* 2002;106(25):3143–3421
2. Grundy SM, et al. *Circulation.* 2004;110(2):227–239.

Committee on Cardiovascular and Metabolic Diseases
CCMD
CCMDweb.org
©2013
KnowledgePoint360 Group, LLC

ASCVD Risk Reduction Is Goal

Update to 2004 ATP III cholesterol guidelines update

Then:	*Now:*
Statin therapy to achieve LDL-C & non–HDL-C targets	Statin therapy for all individuals at increased ASCVD risk who are likely to benefit from risk reduction → *"Statin benefit" groups*

Lifestyle modification is the cornerstone before and during cholesterol-lowering therapy

ASCVD=atherosclerotic cardiovascular disease

CCMDweb.org

Stone NJ, et al. *J Am Coll Cardiol*. 2013. doi:10.1016/j.jacc.2013.11.002

Committee on Cardiovascular and Metabolic Diseases

CCMD

CCMDweb.org

©2013 KnowledgePoint360 Group, LLC

Statin Benefit Groups for ASCVD Prevention

Recommendation:

- High- or moderate-intensity statin therapy for all who will benefit from ASCVD risk reduction
- Lifestyle modification before, during statin therapy

4 statin benefit groups:

1. Clinical ASCVD
2. Primary elevations of LDL-C ≥190 mg/dL
3. Age 40-75 yrs with diabetes and LDL-C 70-189 mg/dL
4. Age 40-75 with LDL-C 70-189 mg/dL and estimated 10-yr ASCVD risk ≥7.5%

ASCVD risk reduction benefit outweighs risk of adverse effects

ASCVD=atherosclerotic cardiovascular disease: history of myocardial infarction, stable or unstable angina, coronary revascularization, stroke, or transient ischemic attack of atherosclerotic origin; and peripheral arterial disease or revascularization

Stone NJ, et al. *J Am Coll Cardiol*. 2013. doi:10.1016/j.jacc.2013.11.002.

Committee on Cardiovascular and Metabolic Diseases
CCMD
CCMDweb.org
©2013
KnowledgePoint360 Group, LLC

ASCVD Statin Benefit Group 1: Secondary Prevention

Secondary prevention

Adults with clinical ASCVD (candidates for statin therapy)

Age ≤75 yrs	*High-intensity statin*
Age >75 yrs <u>or</u> Not candidate for high-intensity statin	*Moderate-intensity statin*

High-intensity statin	Moderate-intensity statin
↓ LDL-C by ≥50%	↓ LDL-C by 30%-50%

ASCVD=atherosclerotic cardiovascular disease: history of myocardial infarction, stable or unstable angina, coronary revascularization, stroke, or transient ischemic attack of atherosclerotic origin; and peripheral arterial disease or revascularization

Stone NJ, et al. *J Am Coll Cardiol*. 2013. doi:10.1016/j.jacc.2013.11.002.

Committee on Cardiovascular and Metabolic Diseases
CCMD
CCMDweb.org
©2013
KnowledgePoint360 Group, LLC

ASCVD Statin Benefit Group 2: Primary Prevention LDL-C ≥190

Primary prevention

Adults with primary LDL-C ≥190 mg/dL—
familial hypercholesterolemia (candidates for statin therapy)

High-intensity statin

If not candidate for high-intensity statin:
Moderate-tolerated statin

High-intensity statin	Moderate-intensity statin
↓ LDL-C by ≥50%	↓ LDL-C by 30%-50%

ASCVD=atherosclerotic cardiovascular disease: history of myocardial infarction, stable or unstable angina, coronary revascularization, stroke, or transient ischemic attack of atherosclerotic origin; and peripheral arterial disease or revascularization

Stone NJ, et al. *J Am Coll Cardiol*. 2013. doi:10.1016/j.jacc.2013.11.002.

Committee on Cardiovascular and Metabolic Diseases
CCMD
CCMDweb.org
©2013
KnowledgePoint360 Group, LLC

ASCVD Statin Benefit Group 3: Primary Prevention Diabetes

Primary prevention—diabetes

Adults aged 40-75 yrs with diabetes and LDL-C 70-189 mg/dL (candidates for statin therapy)

Moderate-intensity statin If estimated 10-yr ASCVD risk ≥7.5%: *High-intensity statin*

High-intensity statin	Moderate-intensity statin
↓ LDL-C by ≥50%	↓ LDL-C by 30%-50%

ASCVD=atherosclerotic cardiovascular disease: history of myocardial infarction, stable or unstable angina, coronary revascularization, stroke, or transient ischemic attack of atherosclerotic origin; and peripheral arterial disease or revascularization

Stone NJ, et al. *J Am Coll Cardiol*. 2013. doi:10.1016/j.jacc.2013.11.002.

Committee on Cardiovascular and Metabolic Diseases
CCMD
CCMDweb.org
©2013 KnowledgePoint360 Group, LLC

ASCVD Statin Benefit Group 4: Primary Prevention ≥7.5% 10-Yr Risk, No Diabetes

Primary prevention—no diabetes

Adults aged 40-75 yrs with LDL-C 70-189 mg/dL and estimated 10-yr ASCVD risk ≥7.5%*

Moderate- to high-intensity statin

High-intensity statin	Moderate-intensity statin
↓ LDL-C by ≥50%	↓ LDL-C by 30%-50%

ASCVD=atherosclerotic cardiovascular disease: history of myocardial infarction, stable or unstable angina, coronary revascularization, stroke, or transient ischemic attack of atherosclerotic origin; and peripheral arterial disease or revascularization

Stone NJ, et al. *J Am Coll Cardiol*. 2013. doi:10.1016/j.jacc.2013.11.002.

Committee on Cardiovascular and Metabolic Diseases
CCMD
CCMDweb.org
©2013 KnowledgePoint360 Group, LLC

Estimated 10-Yr ASCVD Risk Guides Statin Therapy

- For primary prevention of ASCVD in individuals with LDL-C 70-189 mg/dL

→ Estimated absolute *10-yr ASCVD risk* guides statin initiation

- For primary prevention of ASCVD in individuals with diabetes

→ Estimated absolute *10-yr ASCVD risk* guides statin intensity

- For individuals with clinical ASCVD or LDL-C ≥190 mg/dL already in a statin benefit group

→ Not appropriate to estimate 10-yr ASCVD risk

ASCVD=atherosclerotic cardiovascular disease: history of myocardial infarction, stable or unstable angina, coronary revascularization, stroke, or transient ischemic attack of atherosclerotic origin; and peripheral arterial disease or revascularization

Stone NJ, et al. *J Am Coll Cardiol*. 2013. doi:10.1016/j.jacc.2013.11.002.

Committee on Cardiovascular and Metabolic Diseases
CCMD
CCMDweb.org
©2013 KnowledgePoint360 Group, LLC

High- and Moderate-Intensity Statin Therapy

High-Intensity Statin Therapy	Moderate-Intensity Statin Therapy
Lowers LDL-C by ~≥50%	Lowers LDL-C by ~30% to <50%
Atorvastatin 40*-80 mg Rosuvastatin 20 mg (*40 mg*)	Atorvastatin 10 mg (*20 mg*) Rosuvastatin (*5 mg*) 10 mg Simvastatin 20-40 mg† Pravastatin 40 mg (*80 mg*) Lovastatin 40 mg *Fluvastatin XL 80 mg* Fluvastatin 40 mg bid *Pitavastatin 2-4 mg*

*Down titrate if unable to tolerate atorvastatin 80 mg;
†Initiation of or titration to simvastatin is not recommended by the FDA due to increased myopathy risk
Italics denotes FDA-approved doses that were not tested in trials reviewed for guideline development
Once-daily doses unless otherwise specified. Avg LDL-C–lowering potential listed expected to vary in clinical practice.

Stone NJ, et al. *J Am Coll Cardiol*. 2013. doi:10.1016/j.jacc.2013.11.002.

Committee on Cardiovascular and Metabolic Diseases
CCMD
CCMDweb.org

©2013 KnowledgePoint360 Group, LLC

The Argument Against LDL-C, Non–HDL-C Targets

- No RCTs demonstrating
  - Titrated drug therapy to achieve targets reduces ASCVD risk
  - What targets should be
- Unknown magnitude of incremental ASCVD risk reduction with one target compared to another
- Unknown rate of adverse events from multidrug therapy to attain targets
- Use of LDL targets may result in under-treatment with statin therapy
  - Suboptimal dose used when target achieved
- …Or overtreatment with nonstatin drugs
  - Adding nonstatin therapy to achieve target results in down-titration of statin for safety reasons
  - Nonstatin drugs have not been shown to reduce ASCVD risk

ASCVD=atherosclerotic cardiovascular disease: history of myocardial infarction, stable or unstable angina, coronary revascularization, stroke, or transient ischemic attack of atherosclerotic origin; and peripheral arterial disease or revascularization

Stone NJ, et al. *J Am Coll Cardiol*. 2013. doi:10.1016/j.jacc.2013.11.002.

Committee on Cardiovascular and Metabolic Diseases
CCMD
CCMDweb.org
©2013 KnowledgePoint360 Group, LLC

Role of Biomarkers & Imaging Tests

Select individuals *not* in 1 of 4 statin benefit groups — Decision to initiate statin unclear

May consider other factors influencing ASCVD risk:

- Primary LDL-C ≥160 mg/dL or other evidence of genetic hyperlipidemias
- Family history of premature ASCVD with onset <55 yrs in first-degree male relative, <65 yrs female
- hs-CRP ≥2 mg/L
- CAC score ≥300 Agatston units (or ≥75th percentile for age, sex, ethnicity)
- ABI <0.9
- Elevated lifetime ASCVD risk

Also consider:

- Potential ASCVD risk benefits, adverse effects
- Drug-drug interactions
- Patient preferences for statin treatment

ASCVD=atherosclerotic cardiovascular disease: history of myocardial infarction, stable or unstable angina, coronary revascularization, stroke, or transient ischemic attack of atherosclerotic origin; and peripheral arterial disease or revascularization
ABI=ankle-brachial index; CAC=coronary artery calcium; hs-CRP=high-sensitivity C-reactive protein

Stone NJ, et al. *J Am Coll Cardiol*. 2013. doi:10.1016/j.jacc.2013.11.002.

Committee on Cardiovascular and Metabolic Diseases
CCMD
CCMDweb.org
©2013
KnowledgePoint360 Group, LLC

LDL-C, Non–HDL-C Targets

Recommendations	NHLBI Grade	ACC/AHA COR | LOE
1. No recommendations for or against specific LDL-C or non–HDL-C targets for primary or secondary ASCVD prevention	N/A	N/A

No evidence supporting titration of cholesterol-lowering drug therapy to achieve optimal LDL-C or non–HDL-C levels

ASCVD=atherosclerotic cardiovascular disease: acute coronary syndrome, history of myocardial infarction, stable or unstable angina, coronary revascularization, stroke, or transient ischemic attack of atherosclerotic origin; and peripheral arterial disease or revascularization
COR=class of recommendation; LOE=level of evidence

Stone NJ, et al. *J Am Coll Cardiol*. 2013. doi:10.1016/j.jacc.2013.11.002.

Committee on Cardiovascular and Metabolic Diseases
CCMD
CCMDweb.org
©2013 KnowledgePoint360 Group, LLC

Statin Therapy for Secondary Prevention

Recommendations	NHLBI Grade	ACC/AHA COR | LOE
Secondary Prevention: Clinical ASCVD		
1. Adults aged ≤75 yrs: Initiate or continue high-intensity statin therapy as first-line therapy unless contraindicated	A (Strong)	I | A
2. Moderate-intensity statin therapy: If high-intensity contraindicated or statin intolerant	A (Strong)	I | A
3. Age >75 yrs: Evaluate potential for ASCVD risk-reduction benefits, adverse effects, DDIs; and consider patient preferences when initiating high- or moderate-intensity statin Continue statin therapy if tolerant	E (Expert Opinion)	IIa | B

ASCVD=atherosclerotic cardiovascular disease: history of myocardial infarction, stable or unstable angina, coronary revascularization, stroke, or transient ischemic attack of atherosclerotic origin; and peripheral arterial disease or revascularization
COR=class of recommendation; DDIs=drug-drug interactions; LOE=level of evidence

Stone NJ, et al. *J Am Coll Cardiol*. 2013. doi:10.1016/j.jacc.2013.11.002.

Committee on Cardiovascular and Metabolic Diseases
CCMD
CCMDweb.org

©2013 KnowledgePoint360 Group, LLC

Statin Therapy for Primary Prevention—LDL-C ≥190

Recommendations	NHLBI Grade	ACC/AHA COR | LOE
Primary Prevention: LDL-C ≥190 mg/dL		
1. LDL-C ≥190 mg/dL or TG ≥500 mg/dL: Evaluate for secondary causes of hyperlipidemia	B (Moderate)	I | B
2. High-intensity statin therapy for primary LDL-C ≥190 mg/dL unless contraindicated *10-yr ASCVD risk estimation not required* If high-intensity statin intolerant: use maximum-tolerated statin	B (Moderate)	I | B
3. Untreated primary LDL-C ≥190 mg/dL: Intensify statin therapy to achieve ≥50% LDL ↓	E (Expert Opinion)	IIa | B
4. Untreated primary LDL-C ≥190 mg/dL after maximum intensity of statin therapy achieved: May consider adding nonstatin drug to further lower LDL-C*	E (Expert Opinion)	IIb | C

ASCVD=atherosclerotic cardiovascular disease: history of myocardial infarction, stable or unstable angina, coronary revascularization, stroke, or transient ischemic attack of atherosclerotic origin; and peripheral arterial disease or revascularization
*Evaluate potential for ASCVD risk reduction benefits, adverse effects, drug-drug interactions; consider patient preferences
COR=class of recommendation; LOE=level of evidence

Stone NJ, et al. *J Am Coll Cardiol*. 2013. doi:10.1016/j.jacc.2013.11.002.

Committee on Cardiovascular and Metabolic Diseases
CCMD
CCMDweb.org
©2013
KnowledgePoint360 Group, LLC

Statin Therapy for Primary Prevention—Diabetes & LDL-C 70-189

Recommendations	NHLBI Grade	ACC/AHA COR | LOE
Primary Prevention: Diabetes & LDL-C 70-189 mg/dL—no clinical ASCVD		
1. Age 40-75 yrs with diabetes: Moderate-intensity statin therapy	A (Strong)	I | A
2. Age 40-75 yrs with diabetes and estimated 10-yr ASCVD risk* ≥7.5% : High-intensity statin therapy unless contraindicated	E (Expert Opinion)	IIa | B
3. Age <40 or >75 yrs with diabetes: Evaluate potential for ASCVD benefits, adverse effects, DDIs; consider patient preferences when initiating, continuing, or intensifying statin therapy	E (Expert Opinion)	IIa | C

*Estimated 10-yr ASCVD risk includes first occurrence of nonfatal MI, CHD death, and nonfatal and fatal stroke

ASCVD=atherosclerotic cardiovascular disease: history of myocardial infarction, stable or unstable angina, coronary revascularization, stroke, or transient ischemic attack of atherosclerotic origin; and peripheral arterial disease or revascularization
COR=class of recommendation; DDIs=drug-drug interactions; LOE=level of evidence

Stone NJ, et al. *J Am Coll Cardiol*. 2013. doi:10.1016/j.jacc.2013.11.002.

Committee on Cardiovascular and Metabolic Diseases
CCMD
CCMDweb.org
©2013
KnowledgePoint360 Group, LLC

Statin Therapy for Primary Prevention—LDL-C 70-189, No Diabetes

2013 ACC/AHA Guideline: Cholesterol Treatment to Reduce ASCVD Risk in Adults

Recommendations	NHLBI Grade	ACC/AHA COR | LOE
Primary Prevention: LDL-C 70-189 mg/dL—no diabetes or clinical ASCVD		
1. Estimate 10-yr ASCVD risk* to guide statin therapy initiation for primary prevention	E (Expert Opinion)	I | B
2. Age 40-75 yrs with LDL-C 70-189 mg/dL and estimated 10-yr ASCVD risk* ≥7.5%: Moderate-to-high–intensity statin therapy	A (Strong)	I | A
3. Age 40-75 with LDL-C 70-189 mg/dL and estimated 10-yr ASCVD* risk 5% to <7.5%: Moderate-intensity statin therapy	C (Weak)	IIa | B
4. Before initiating statin: HCP and patient to discuss potential for ASCVD risk reduction benefits, adverse effects, DDIs, patient preferences	E (Expert Opinion)	IIa | C
5. LDL-C <190 and not in a statin benefit group or risk assessment unclear, consider: LDL-C ≥160, family hx premature ASCVD, hs-CRP >2, CAC score ≥300, ABI <0.9, lifetime ASCVD risk Eval risk reduction benefits, AEs, DDIs, patient prefs	E (Expert Opinion)	IIb | C

*Estimated 10-yr ASCVD risk includes first occurrence of nonfatal MI, CHD death, and nonfatal and fatal stroke
ASCVD=atherosclerotic cardiovascular disease: history of myocardial infarction, stable or unstable angina, coronary revascularization, stroke, or transient ischemic attack of atherosclerotic origin; and peripheral arterial disease or revascularization
AEs=adverse effects; COR=class of recommendation; DDIs=drug-drug interactions; LOE=level of evidence

Stone NJ, et al. *J Am Coll Cardiol.* 2013. doi:10.1016/j.jacc.2013.11.002.

Committee on Cardiovascular and Metabolic Diseases
CCMD
CCMDweb.org

Heart Failure and Hemodialysis

©2013
KnowledgePoint360 Group, LLC

Recommendations	NHLBI Grade	ACC/AHA COR | LOE
1. No recommendations regarding initiation or discontinuation of statins in patients with NYHA class II-IV ischemic systolic heart failure or those on maintenance hemodialysis	N/A	N/A

- Treating clinician to consider *before* prescribing statin for these patients:
  - Potential ASCVD risk reduction benefit, adverse effects, DDIs, cautions, contraindications
  - Choice of statin dose

ASCVD=atherosclerotic cardiovascular disease: history of myocardial infarction, stable or unstable angina, coronary revascularization, stroke, or transient ischemic attack of atherosclerotic origin; and peripheral arterial disease or revascularization
COR=class of recommendation; DDIs=drug-drug interactions; LOE=level of evidence; NYHA=New York Heart Association

Stone NJ, et al. *J Am Coll Cardiol*. 2013. doi:10.1016/j.jacc.2013.11.002.

Committee on Cardiovascular and Metabolic Diseases
CCMD
CCMDweb.org
©2013 KnowledgePoint360 Group, LLC

High-Intensity Statin for Secondary ASCVD Prevention

- Individuals with clinical ASCVD at increased risk for
  - Recurrent ASCVD
  - ASCVD death
- High-intensity statin therapy reduces ASCVD events more than moderate-intensity statin therapy in adults aged ≤75 yrs

Initiate high-intensity statin for adults ≤75 yrs with clinical ASCVD
If on low or moderate statin therapy, increase intensity — unless history of intolerance to higher dose, other factors influencing safety
If high-intensity contraindicated or potential for adverse effects: moderate-intensity as second option if tolerated

ASCVD=atherosclerotic cardiovascular disease: history of myocardial infarction, stable or unstable angina, coronary revascularization, stroke, or transient ischemic attack of atherosclerotic origin; and peripheral arterial disease or revascularization

Stone NJ, et al. *J Am Coll Cardiol*. 2013. doi:10.1016/j.jacc.2013.11.002.

Committee on Cardiovascular and Metabolic Diseases
CCMD
CCMDweb.org
©2013 KnowledgePoint360 Group, LLC

Secondary ASCVD Prevention for Age >75 Yrs

- Moderate-intensity statin therapy shown to reduce ASCVD events in adults aged >75 yrs

Moderate-intensity statin therapy
Consider for individuals aged >75 yrs with clinical ASCVD
Individualize therapy based on potential for ASCVD risk reduction benefits, adverse effects, DDIs, patient preferences
Continue statin therapy if no tolerance issues

ASCVD=atherosclerotic cardiovascular disease: history of myocardial infarction, stable or unstable angina, coronary revascularization, stroke, or transient ischemic attack of atherosclerotic origin; and peripheral arterial disease or revascularization

Stone NJ, et al. *J Am Coll Cardiol*. 2013. doi:10.1016/j.jacc.2013.11.002.

Committee on Cardiovascular and Metabolic Diseases

CCMD

CCMDweb.org

©2013 KnowledgePoint360 Group, LLC

Statin Initiation for Secondary Prevention: Age ≤75 Yrs

Age ≤75 yrs with clinical ASCVD: not on statin therapy

1

Initial evaluation before initiating statin therapy:

- Fasting lipid panel
- ALT
- CK
- Consider eval for secondary causes or conditions influencing statin safety

2

No contraindications, comorbidities, DDIs influencing statin safety, or history of statin intolerance

3

- Initiate *high-intensity* statin therapy
- Counsel on lifestyle

4

Monitor statin therapy

Evaluate and treat lab abnormalities

1. TG ≥500 mg/dL
2. LDL-C ≥190 mg/dL
   - Secondary causes
   - If primary, screen for FH
3. Unexplained ALT >3X ULN

ASCVD=atherosclerotic cardiovascular disease: history of myocardial infarction, stable or unstable angina, coronary revascularization, stroke, or transient ischemic attack of atherosclerotic origin; and peripheral arterial disease or revascularization; ALT=alanine aminotransferase; CK=creatinine kinase; DDIs=drug-drug interactions; FH=familial hypercholesterolemia; ULN=upper limit of normal

Stone NJ, et al. *J Am Coll Cardiol*. 2013. doi:10.1016/j.jacc.2013.11.002.

Committee on Cardiovascular and Metabolic Diseases

CCMD

CCMDweb.org

©2013 KnowledgePoint360 Group, LLC

Statin Initiation for Secondary Prevention: Age >75 Yrs

Age >75 yrs* with clinical ASCVD *or* with conditions or DDIs influencing statin safety, or history of statin intolerance: not on statin therapy

1

Initial evaluation before initiating statin therapy:

- Fasting lipid panel
- ALT
- CK
- Consider eval for secondary causes or conditions influencing statin safety

2

- Initiate *moderate-intensity* statin therapy
- Counsel on lifestyle

3

Monitor statin therapy

Evaluate and treat lab abnormalities

1. TG ≥500 mg/dL
2. LDL-C ≥190 mg/dL
   - Secondary causes
   - If primary, screen for FH
3. Unexplained ALT >3X ULN

*Reasonable to evaluate for ASCVD potential benefits and adverse effects, and to consider patient preferences in initiating or continuing a moderate- or high-intensity statin

ASCVD=atherosclerotic cardiovascular disease: history of myocardial infarction, stable or unstable angina, coronary revascularization, stroke, or transient ischemic attack of atherosclerotic origin; and peripheral arterial disease or revascularization; ALT=alanine aminotransferase; CK=creatinine kinase; DDIs=drug-drug interactions; FH=familial hypercholesterolemia; ULN=upper limit of normal

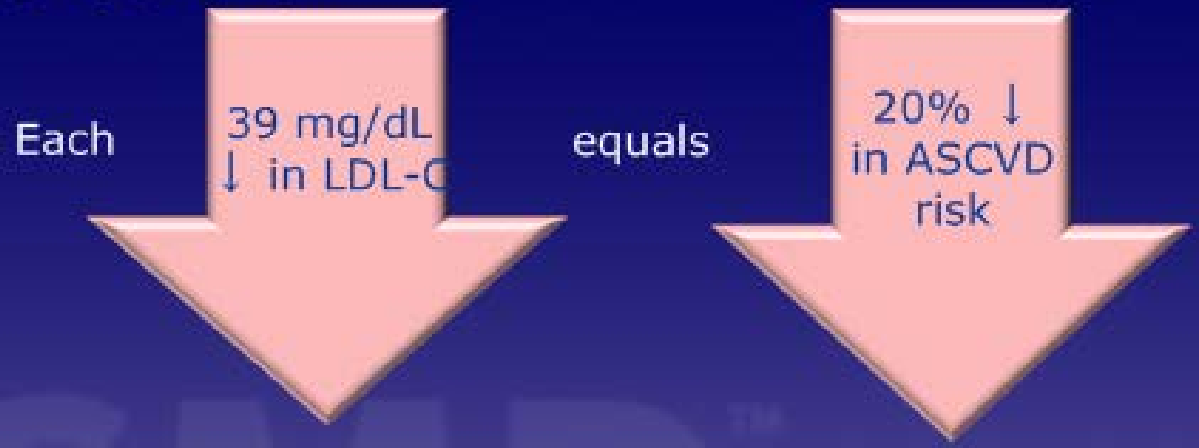
Stone NJ, et al. *J Am Coll Cardiol.* 2013. doi:10.1016/j.jacc.2013.11.002.

Committee on Cardiovascular and Metabolic Diseases
CCMD
CCMDweb.org

©2013 KnowledgePoint360 Group, LLC

Primary ASCVD Prevention for LDL-C ≥190 mg/dL

- Primary, severe LDL-C elevations (≥190 mg/dL) confer a high lifetime risk for ASCVD events
  - Lifetime exposure to markedly high LDL-C from genetic causes
- *High-intensity* statin therapy for all adults aged ≥21 yrs with LDL-C ≥190
  - If not already diagnosed and treated before age 21
- Substantial LDL-C reductions, intensive risk factor management needed to reduce ASCVD risk



- *High-intensity* statin therapy to achieve ≥50% LDL-C reduction
- *But*—maximal statin therapy may not be adequate for sufficient LDL reduction to blunt ASCVD risk: nonstatin medications often needed

ASCVD=atherosclerotic cardiovascular disease

Stone NJ, et al. *J Am Coll Cardiol*. 2013. doi:10.1016/j.jacc.2013.11.002.

Committee on Cardiovascular and Metabolic Diseases

CCMD

CCMDweb.org

Statin Initiation for Primary ASCVD Prevention: *Age 40-75 With Diabetes or LDL ≥190*

©2013 KnowledgePoint360 Group, LLC

No clinical ASCVD, not on lipid-lowering treatment

1

Initial evaluation before initiating statin therapy:

- Fasting lipid panel
- ALT
- A1C (if diabetes status unknown)
- CK
- Consider eval for secondary causes or conditions influencing statin safety

2

- Assign to statin benefit group: *Diabetes & age 40-75 or LDL ≥190*
- Counsel on lifestyle

3

Discuss with patient

- ASCVD risk reduction benefits
- Adverse effects
- DDIs
- Patient preferences

4

- Initiate statin therapy based on statin benefit group assignment
- Reinforce need for healthy lifestyle

Eval & treat lab abnormalities

1. TG ≥500 mg/dL
2. LDL-C ≥190 mg/dL
   - Secondary causes
   - If primary, screen for FH
3. Unexplained ALT >3X ULN

5

Monitor statin therapy

ASCVD=atherosclerotic cardiovascular disease: history of myocardial infarction, stable or unstable angina, coronary revascularization, stroke, or transient ischemic attack of atherosclerotic origin; and peripheral arterial disease or revascularization; ALT=alanine aminotransferase; CK=creatinine kinase; DDIs=drug-drug interactions; ULN=upper limit of normal

Stone NJ, et al. *J Am Coll Cardiol*. 2013. doi:10.1016/j.jacc.2013.11.002.

Committee on Cardiovascular and Metabolic Diseases
CCMD
CCMDweb.org

Statin Initiation for Primary ASCVD Prevention: *Age 40-75, LDL 70-189, No Diabetes*

©2013 KnowledgePoint360 Group, LLC

No clinical ASCVD or diabetes, not on lipid-lowering treatment

1

Initial evaluation before initiating statin therapy:

- Fasting lipid panel
- ALT
- CK
- Consider eval for secondary causes or conditions influencing statin safety

Evaluate and treat lab abnormalities: TG ≥500, LDL ≥190 (secondary causes; if primary, screen for FH), unexplained ALT >3X ULN

2

- Assign to statin benefit group: *No diabetes, age 40-75, LDL 70-189*
- Counsel on lifestyle

3

Estimate 10-yr ASCVD risk with Pooled Cohort Equations

≥7.5% | 5% to <7.5% | <5%

Discuss with patient

- ASCVD risk reduction benefits
- Adverse effects
- DDIs
- Patient preferences

Select patients*: Consider add'l factors† to inform treatment decision

4

- Initiate statin therapy based on statin benefit group assignment
- Reinforce need for healthy lifestyle

5

Monitor statin therapy

ASCVD=atherosclerotic cardiovascular disease: history of myocardial infarction, stable or unstable angina, coronary revascularization, stroke, or transient ischemic attack of atherosclerotic origin; and peripheral arterial disease or revascularization; *Includes age <40 or >75 and LDL<190; †Incl primary LDL ≥160 or other evidence of genetic hyperlipidemias, family history early ASCVD, hs-CRP ≥2, CAC score ≥300, ABI <0.9, elevated lifetime ASCVD risk
ALT=alanine aminotransferase; CK=creatinine kinase; ULN=upper limit of normal

Stone NJ, et al. *J Am Coll Cardiol*. 2013. doi:10.1016/j.jacc.2013.11.002.

Committee on Cardiovascular and Metabolic Diseases
CCMD
CCMDweb.org
©2013 KnowledgePoint360 Group, LLC

Primary ASCVD Prevention in Individuals With Diabetes

- *Moderate-intensity* statin therapy for individuals with diabetes aged 40-75
- *High-intensity* statin therapy if diabetes, age 40-75, and 10-yr ASCVD risk ≥7.5%

Diabetes aged 40-75 yrs
➢ Substantially increased lifetime risk for ASCVD events and death
➢ Greater morbidity and worse survival after ASCVD onset

- Individualize statin therapy based on ASCVD risk reduction benefits, potential for adverse effects and DDIs, patient preferences

ASCVD=atherosclerotic cardiovascular disease: history of myocardial infarction, stable or unstable angina, coronary revascularization, stroke, or transient ischemic attack of atherosclerotic origin; and peripheral arterial disease or revascularization

Stone NJ, et al. *J Am Coll Cardiol*. 2013. doi:10.1016/j.jacc.2013.11.002.

Committee on Cardiovascular and Metabolic Diseases
CCMD
CCMDweb.org
©2013 KnowledgePoint360 Group, LLC

Primary ASCVD Prevention in Individuals With LDL 70-189—No Diabetes

- Estimated 10-yr ASCVD risk guides initiation of statin therapy
- *Moderate-* or *high-intensity* statin therapy to reduce ASCVD risk if age 40-75 with 10-yr ASCVD risk ≥7.5%
  - Reduction in ASCVD risk outweighs potential for adverse effects

LDL-C 70-189—No clinical ASCVD or diabetes Age 40-75
➢ Initiate statin therapy if 10-yr ASCVD risk ≥7.5*

ASCVD=atherosclerotic cardiovascular disease: history of myocardial infarction, stable or unstable angina, coronary revascularization, stroke, or transient ischemic attack of atherosclerotic origin; and peripheral arterial disease or revascularization

*If not already candidates for statin therapy based on the presence of ASCVD, diabetes or LDL-C ≥190 mg/dL

Stone NJ, et al. *J Am Coll Cardiol*. 2013. doi:10.1016/j.jacc.2013.11.002.

Primary ASCVD Prevention for Individuals Not in A Statin Benefit Group

Committee on Cardiovascular and Metabolic Diseases
CCMD
CCMDweb.org
©2013 KnowledgePoint360 Group, LLC

- Adults with LDL-C <190 who are not identified in statin benefit group *or*
- Adults for whom risk-based treatment is uncertain after risk assessment

Factors influencing decision to initiate statin therapy	
➢ Clinician knowledge, experience, and skill ➢ Patient preferences	
Before initiating statin therapy, clinician and patient to discuss	
➢ Potential for ASCVD risk reduction benefits, adverse effects, DDIs	
Additional factors to consider for select individuals	
➢ LDL-C ≥160 mg/dL*	➢ Family history of premature ASCVD
➢ hs-CRP ≥2 mg/dL	➢ CAC score ≥300 Agatston units
➢ ABI <0.9	➢ Elevated lifetime ASCVD risk

ASCVD=atherosclerotic cardiovascular disease: history of myocardial infarction, stable or unstable angina, coronary revascularization, stroke, or transient ischemic attack of atherosclerotic origin; and peripheral arterial disease or revascularization
*Or other evidence of genetic dyslipidemias
CAC=coronary artery calcium; DDIs=drug-drug interactions; hs-CRP=high-sensitivity C-reactive protein

Stone NJ, et al. *J Am Coll Cardiol.* 2013. doi:10.1016/j.jacc.2013.11.002.

10-Yr ASCVD Risk Assessment Calculator—Primary Prevention

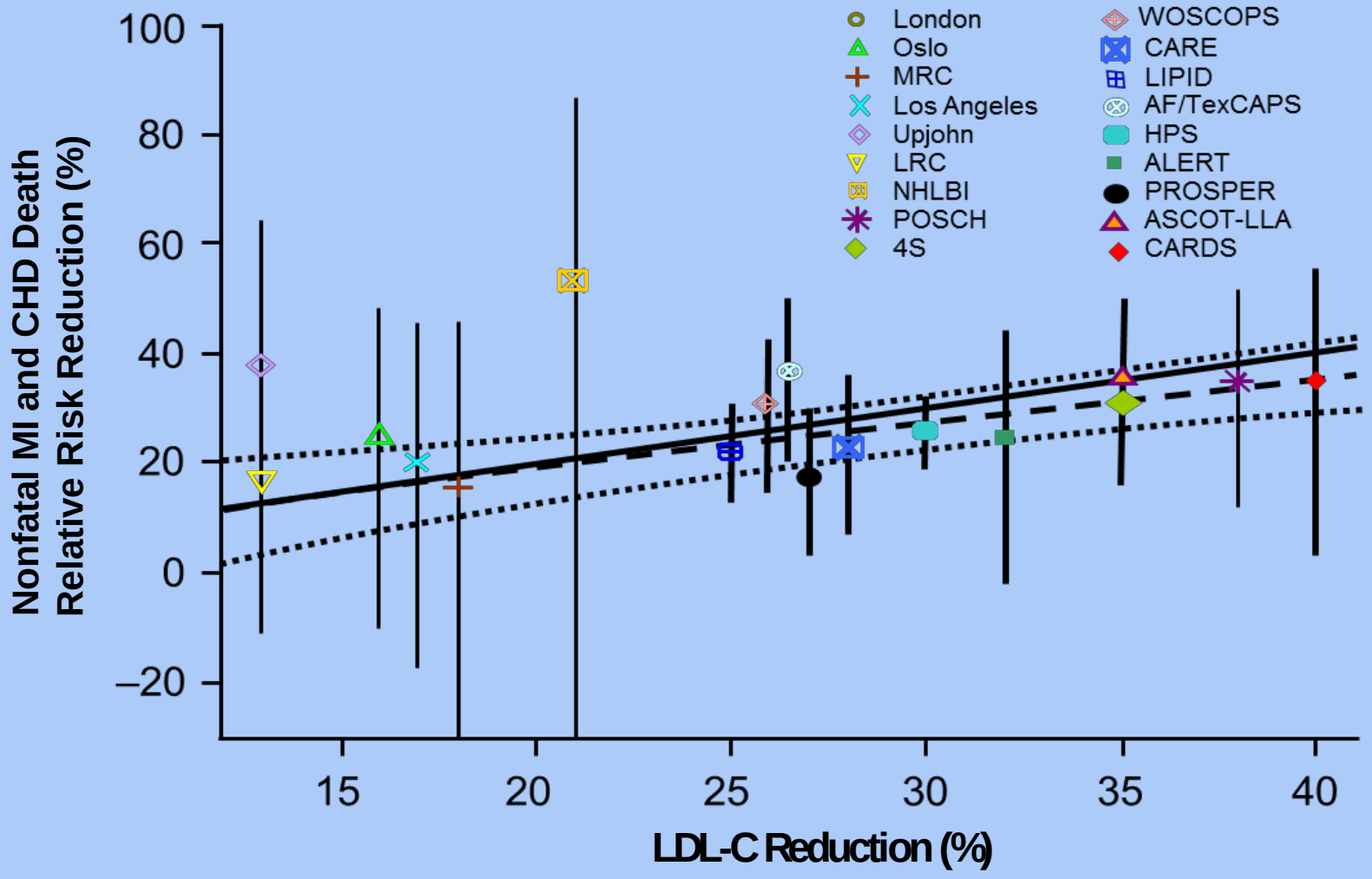
©2013 KnowledgePoint360 Group, LLC

- Comprehensive assessment of 10-yr risk for ASCVD event
  - Includes CHD and stroke
- Use Pooled Cohort Risk Assessment Equations
  - http://my.americanheart.org/cvriskcalculator
- Predicts stroke and CHD events in non-Hispanic Caucasian and African American men and women aged 40-79 years with or without diabetes and LDL-C 70-189 mg/dL

ASCVD=atherosclerotic cardiovascular disease; history of myocardial infarction, stable or unstable angina, coronary revascularization, stroke, or transient ischemic attack of atherosclerotic origin; and peripheral arterial disease or revascularization
CHD=coronary heart disease

Stone NJ, et al. *J Am Coll Cardiol*. 2013. doi:10.1016/j.jacc.2013.11.002.

Multiple Studies Showed a Relationship Between LDL-C Reduction and CHD Relative Risk



MI = Myocardial Infarction

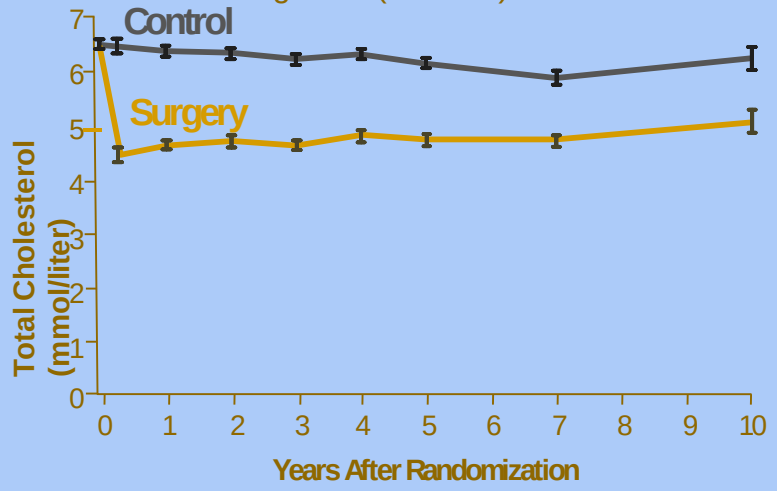
Adapted with permission from Robinson JG, et al. *J Am Coll Cardiol.* 2005;46:1855–1862. Reprinted by permission.

Effect of Partial Ileal Bypass Surgery on Mortality and Morbidity from Coronary Heart Disease in Patients with Hypercholesterolemia

POSCH Trial

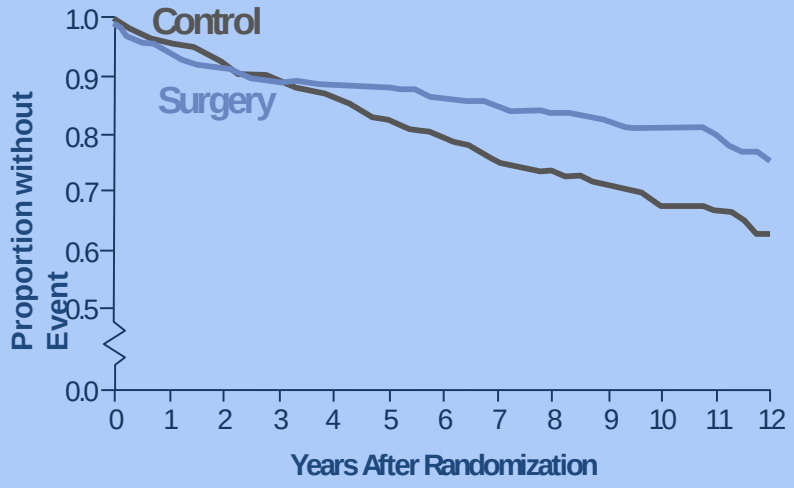
Total Plasma Cholesterol Levels in the Control and Surgery Groups

Values are means with 95 percent confidence intervals. The difference between the groups at each follow-up interval was significant (P<0.0001).



Confirmed Myocardial Infarction and Death Due to Atherosclerotic Coronary Heart Disease as a Combined End Point ("Event") in the Study Groups

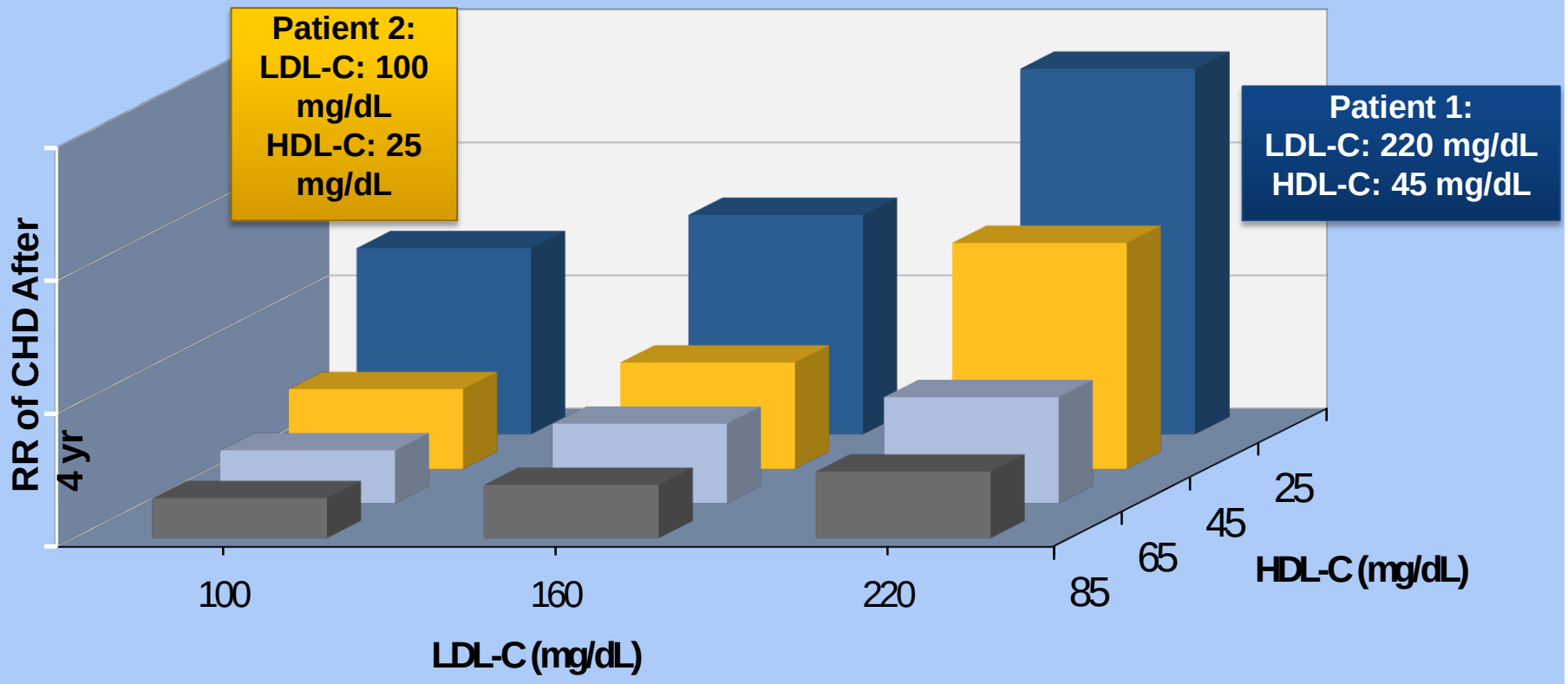
The difference between the groups was significant (P<0.001). The numbers of patients at risk for an event are shown at two-year intervals.



Control	417	384	352	320	213	92	36
Surgery	421	383	368	357	247	116	49

Buchwald H, et al. *N Engl J Med.* 1990;323:946–955. Reprinted by permission.

Low HDL-C Greatly Increases CHD Risk



*Data represent men age 50–70 yr from the Framingham Study.
Adapted from and reprinted with permission from Castelli WP. *Can J Cardiol.* 1988;4(suppl A):5A. Reprinted by permission.

Lipid Lowering Therapy

Objectives

- Understand importance of treating serum cholesterol
- Understand current and future therapies for dyslipidemia
- Understand primary and secondary outcomes data with available treatments for dyslipidemia
- Understand important information regarding commonly used lipid lowering therapies

Primary and secondary outcomes data

Outcomes Data by Class

- Primary Prevention of Cardiovascular Disease (CVD)[1]:
  - Preventing CVD before it occurs
- Secondary Prevention of Cardiovascular Disease (CVD)[1]:
  - Preventing additional attacks of CVD after the first attack has occurred

Intervention	No. Trials	No. Treated	Mean Cholesterol Reduction (%)	Non-fatal MI	CHD Incidence (% Change)	CHD Mortality (% Change)
Statins[2*]	12	17,405	20	NA	-30	-29
Nicotinic Acid (Niacin)[3]	7	5,137	NA	NA	NA	-16
Fibric Acid Derivatives (Fibrates)[4]	6	11,590	NA	-21	NA	NA
Bile Acid Sequestrants[2]	3	1,992	9	NA	-21	-32

1. American College of Chest Physicians. *Patient's Guide to Primary and Secondary Prevention of Cardiovascular Disease Using Blood-Thinning (Anticoagulant) Drugs.* 2012.; 2. The Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). NIH Publication No. 02-5215; September 2002.; 3. Duggal JK, et al. *J Cardiovasc Pharmacol Ther.* 2010;15(2):158-166.; 4. Saha SA, et al. *Int J Cardiol.* 2010;141(2):157-166.

MRFIT showed strong correlation between serum cholesterol and CVD mortality

Objective

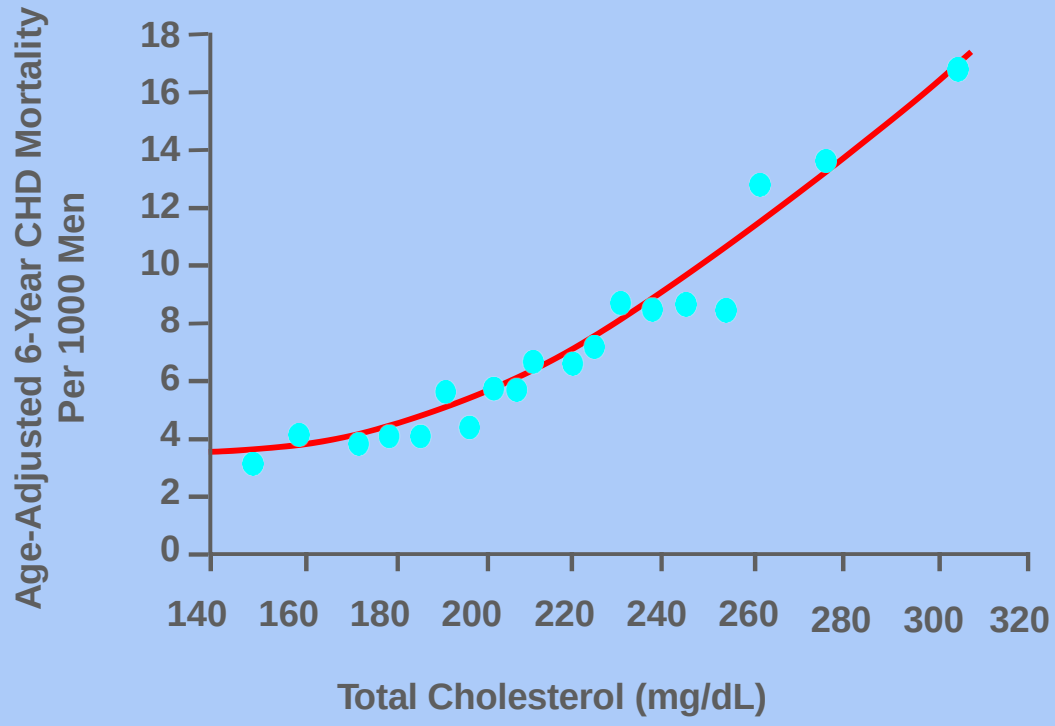
- To test the effect of a multifactor intervention program on mortality from coronary heart disease (CHD)

Design

- Randomized, primary prevention trial; N=361,662

Results

- Each 1% reduction in total cholesterol level resulted in a 2% decrease in CHD risk



MRFIT: Multiple Risk Factor Intervention Trial
Martin MJ et al. Lancet. 1986;2:933-936.

Current and Future Management Options for Dyslipidemia

Current Therapies

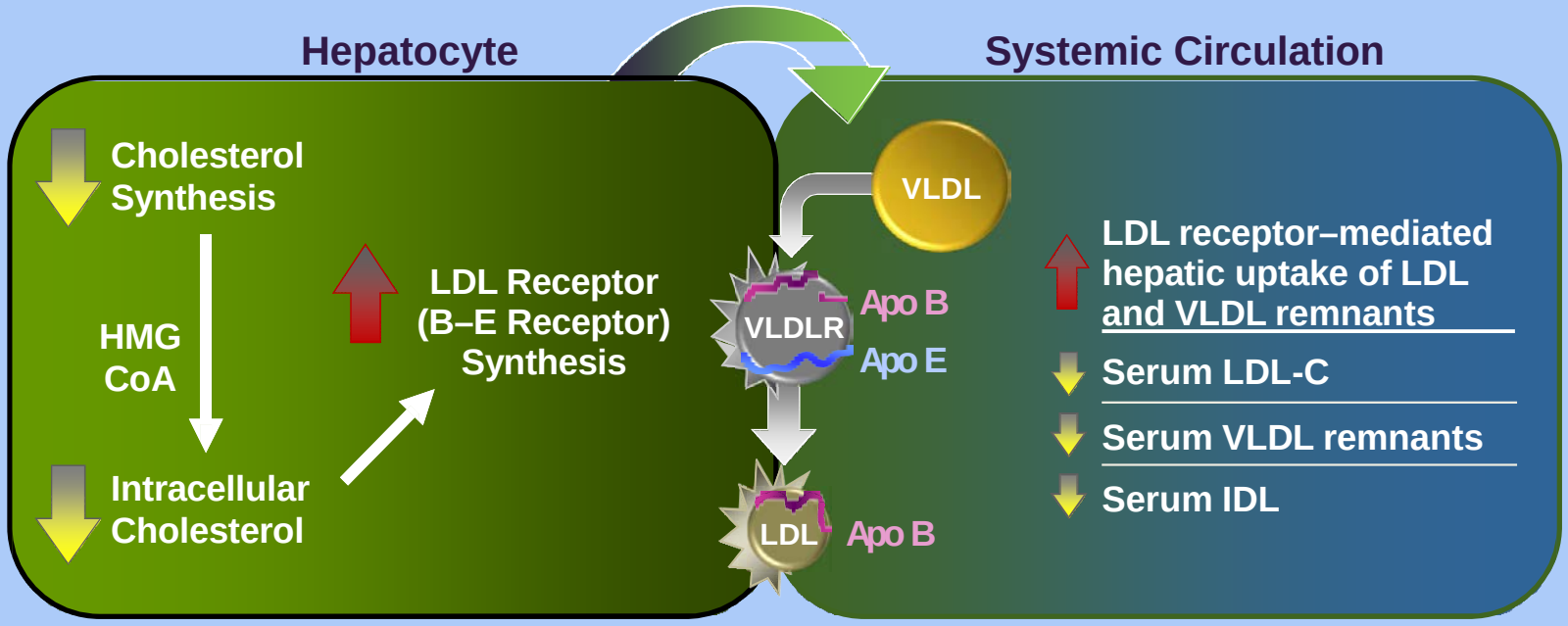
- Statins (HMG-CoA Reductase Inhibitors)
- Cholesterol Absorption Inhibitor (CAI)
- Bile Acid Sequestrants (BAS)
- Nicotinic Acid (Niacin)
- Omega-3 Fatty Acids (FAs)
- Fibric Acid Derivatives (Fibrates)
- Microsomal Triglyceride Transfer Protein (MTP) Inhibitor
- LDL Apheresis

Future Therapies

- PCSK9 Monoclonal Antibody (mAB)
- Cholesterol Ester Transfer Protein (CETP)

Statins
(HMG-CoA Reductase Inhibitors)

Statin Mechanism of Action



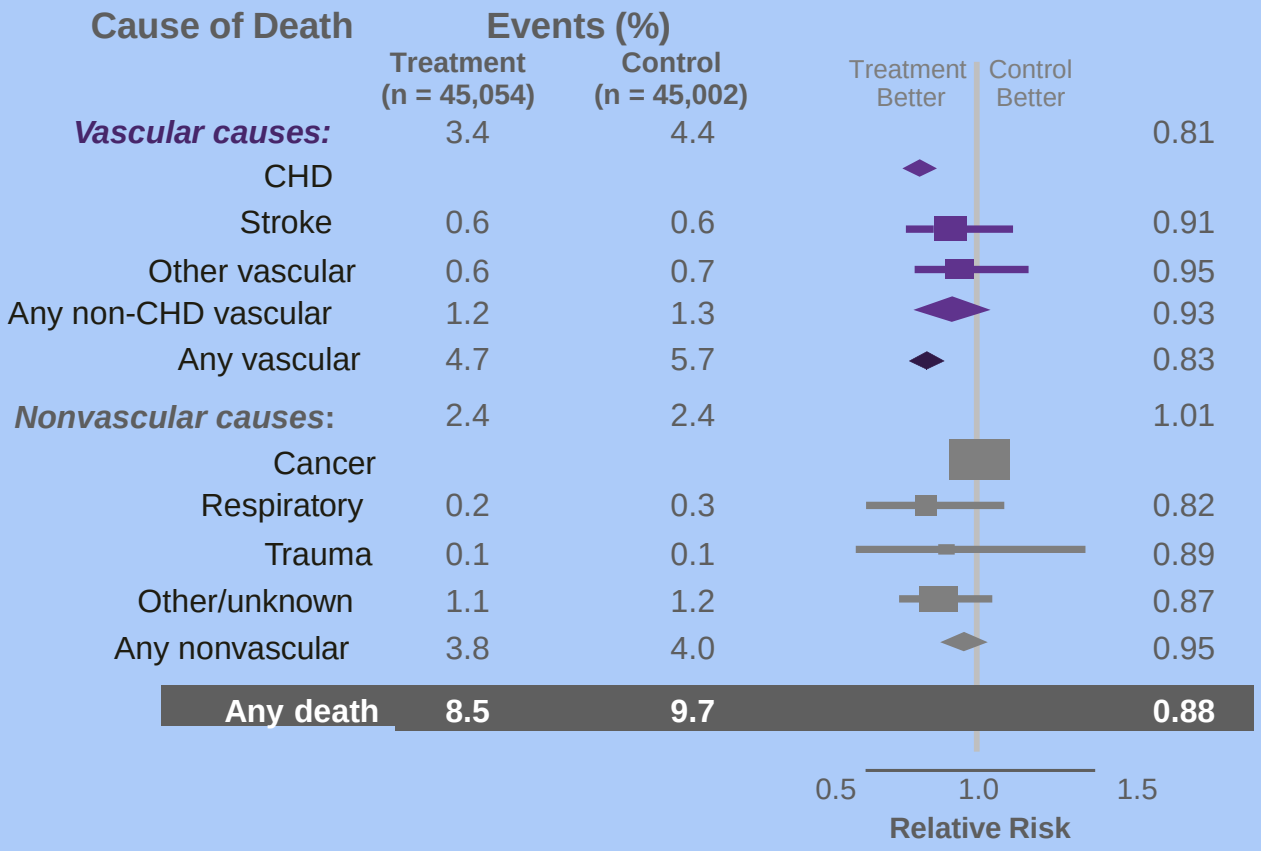
Statin Mechanism of Action:

- Inhibit HMG CoA reductase (rate-limiting step in cholesterol biosynthesis)
- Reduce hepatic cholesterol content
- Increase expression of LDL receptors

The Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). NIH Publication No. 02-5215; September 2002.

In a Meta-analysis of 14 Primary and Secondary Prevention Trials with Statins

Statins Reduced All-cause Death by 12%



A reduction in LDL-C of 39 mg/dL sustained for 5 years would result in a reduction in risk of major vascular events of approximately 20%, regardless of the baseline LDL-C.

Baigent C, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomized trials of statins. *Lancet.* 2005. 8;366(9493):1267-1278.

Statin Therapy

Indication[1,2]	As adjunctive to diet to reduce elevated Total-C, LDL-C, Apo B, non-HDL-C, and triglycerides and to increase HDL-C in adult patients with primary hyperlipidemia or mixed dyslipidemia. As adjunctive therapy to diet to slow the progression of atherosclerosis in adult patients as part of a treatment strategy to lower Total-C, and LDL-C to target levels (Crestor); reduce risk of stroke, myocardial infarction, and arterial revascularization procedures. To reduce risk of non-fatal myocardial infarction, fatal and non-fatal stroke, hospitalization for CHF, and angina To reduce Total-C and LDL-C in adult patients with homozygous familial hypercholesterolemia (HoFH) (ZOCOR®); To reduce Total-C and LDL-C in adult patients with HoFH, as an adjunct to other lipid lowering treatments (e.g., LDL apheresis) (LIPITOR®); To reduce Total-C, LDL-C, and Apo B in patients with HoFH (CRESTOR®)
Available Drugs (Generics)[3]	MEVACOR® (lovastatin), PRAVACHOL® (pravastatin), ZOCOR® (simvastatin), LESCOL® (fluvastatin), LIPITOR® (atorvastatin), LIVALO® (pitavastatin), CRESTOR® (rosuvastatin)
Lipid/lipoprotein Effects[3,4]	LDL-C: ↓ 18-55%
	HDL-C: ↑ 5-15%
	TGs: ↓ 14-28%
	Apo B: ↓ 33%
Effectiveness in Persons with HoFH[5-7]	LDL-C: ↓ 14-28%

1. LIPITOR® (atorvastatin) Prescribing Information. 2. CRESTOR® (rosuvastatin) Prescribing Information. 3. The Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). NIH Publication No. 02-5215; September 2002. 4. Harper R, Jacobson T. Using Apolipoprotein B to Manage Dyslipidemic Patients: Time for a Change? *Mayo Clin Proc*.2010;85(5):440-445. 5. Raal et al. *Atherosclerosis*. 1997;135:249. 6. Raal et al. *Atherosclerosis.* 2000;150:421. 7. Marais et al. *Atherosclerosis.* 2008;197:400-406.

Statin Therapy (cont.)

Major Side/Adverse Effect	Myopathy, increased liver transaminases
Pregnancy Category	X
Contraindications	Active or chronic liver disease, concomitant use of cyclosporine, macrolide antibiotics, various anti-fungal agents and cytochrome P-450 inhibitors
Dosage Range and Available Preparations	Lovastatin: 10, 20, 40 mg tablets Pravastatin: 10, 20, 40 mg tablets Simvastatin: 5, 10, 20, 40, 80 mg tablets Fluvastatin: 20, 40 mg capsules, 80 mg XL tablets Atorvastatin: 10, 20, 40, 80 mg tablets Rosuvastatin: 5, 10, 20, 40 mg tablets Pitavastatin: 1, 2, 4 mg tablets
Outcomes Data	Statin therapy reduces risk for acute coronary syndrome (ACS), coronary procedures, and other coronary outcomes in both primary and secondary prevention. They also reduce risk for stroke in secondary prevention. Primary prevention: WOSCOPS, AFCAPS/TexCAPS, CARDS, ASCOT-LLA, JUPITER Secondary Prevention: 4S, CARE LIPID, HPS, TNT
Recommendation(s)	Statins should be considered as first-line drugs when LDL-lowering drugs are indicated to achieve LDL treatment goals.

The Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). NIH Publication No. 02-5215; September 2002.

Statin Therapy: Primary Prevention Outcomes Data in Key Studies

Study	Drug evaluated	No. patients, demographics	Study length	Outcomes
WOSCOPS[1,2]	Pravachol (pravastatin)	6595 men, 45-64 years; elevated LDL-C	Median follow-up, 4.8 years	First coronary event (CHD death, nonfatal MI)
AFCAPS/TexCAPS[3]	Mevacor (lovastatin)	5608 men, 997 women; average TC, LDL-C, below average HDL-C	Median follow-up, 5.2 years	First acute major coronary event (fatal/nonfatal MI, unstable angina, sudden cardiac death)
CARDS[4,5]	Lipitor (atorvastatin)	2838 patients with type 2 diabetes, 40-75 years; normal LDL-C	Median follow-up, 3.9 years	First acute CHD event, coronary revascularization, stroke
ASCOT-LLA[4,6]	Lipitor	10,305 patients with hypertension, 40-79 years; normal TC	Median follow-up, 3.3 years	First nonfatal MI, fatal CHD
JUPITER[7,8]	Crestor (rosuvastatin)	17,802 patients; LDL<130 mg/dL, hsCRP≥2.0 mg/L	Median follow-up, 1.9 years	MI, stroke, arterial revascularization, hospitalization for unstable angina, CV death

1.Pravachol PI® (pravastatin) Prescribing Information. 2. Shepherd J, et al. *N Engl J Med*. 1995;333:1301-1307. 3. Downs JR, et al. *JAMA*. 1998;279(20):1615-22. 4. LIPITOR® (atorvastatin) Prescribing Information. 5. Colhoun HM, et al. *Lancet.* 2004;364(9435):685-96. 6. Sever PS, et al. *Lancet.* 2003;361(9364):1149-58. 7. CRESTOR® (rosuvastatin) Prescribing Information. 8. Ridker PM, et al. *N Engl J Med*. 2008;359(21):2195-207.

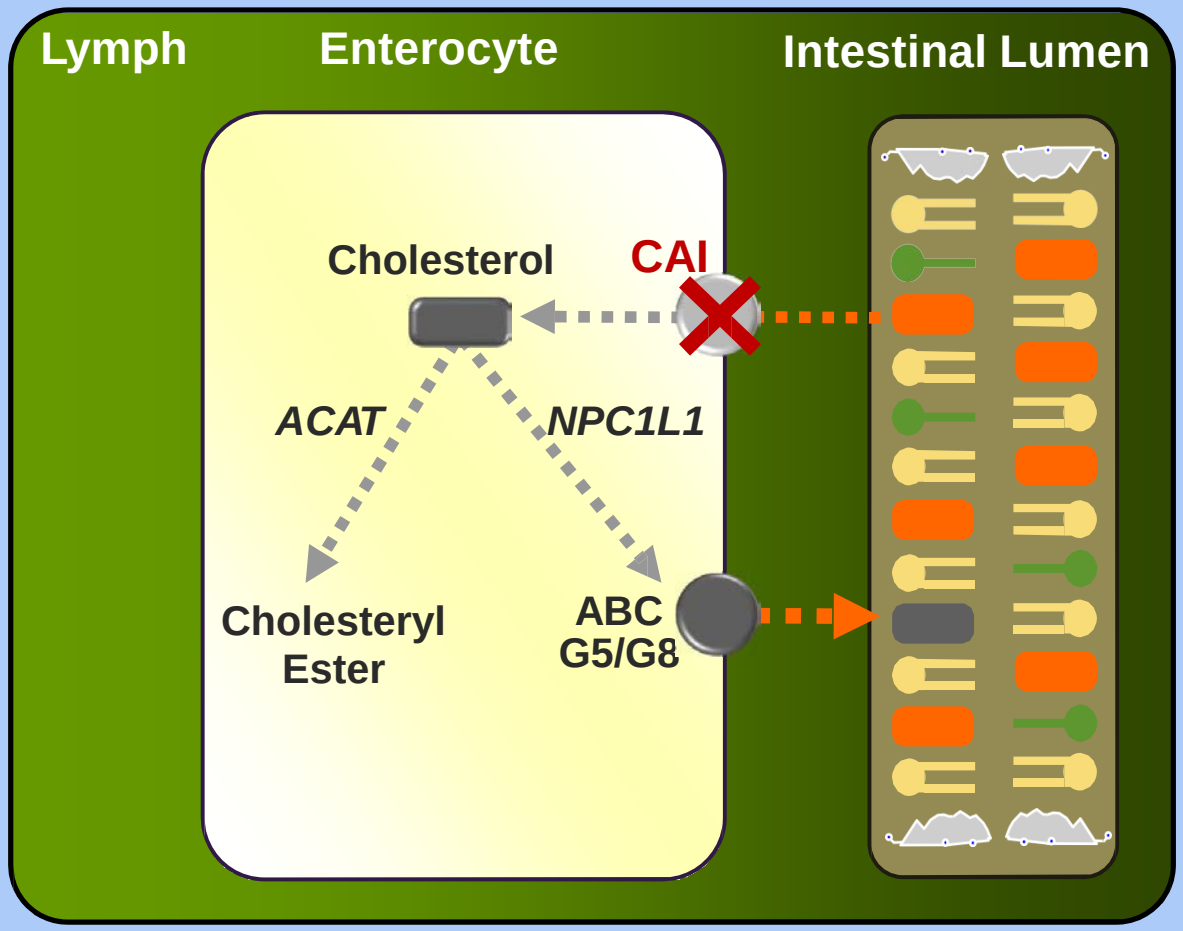
Statin Therapy: Secondary Prevention Outcomes Data in Key Studies

Study	Drug evaluated	No. patients, demographics	Study length	Outcomes
4S[1,2]	Zocor (simvastatin)	4,444 patients, 35-71 years; baseline CHD	Median follow-up, 5.4 years	All-cause mortality, CHD mortality, nonfatal MI, revascularization, fatal/nonfatal stroke
CARE LIPID[3]	Pravachol (pravastatin)	3583 men, 576 women; MI in previous 3-20 months, normal TC	Median follow-up, 4.9 years	First recurrent coronary events (CHD death, nonfatal MI), revascularization procedure, stroke/TIA
HPS[1,4]	Zocor	20,536 patients, 40-80 years; CHD, history of CHD, diabetes, stroke, peripheral vessel disease, hypertension (in males ≥65 years)	Mean follow-up, 11.0 years	All-cause, CHD mortality
TNT[5,6]	Lipitor (atorvastatin)	10,001 patients, ≥65 years; clinical evident CHD, initially achieved LDL-C target of <130 mg/dL	Median follow-up, 4.9 years	Death due to CHD, nonfatal MI, resuscitated cardiac arrest, fatal/nonfatal stroke

Cholesterol Absorption Inhibitor (CAI)

Cholesterol Absorption Inhibitor (CAI)

Mechanism of Action



CAI Mechanism of Action:

- Inhibits intestinal and biliary cholesterol absorption by blocking NPC1L1 protein in the jejunal brush border
- Increases expression of LDL receptors
- Lowers LDL-C
- Lowers Non-HDL-C

Phan BA, et al. *Vasc Health Risk Manag*. 2012;8:415-427.

Cholesterol Absorption Inhibitor

Indication[1]	Administered alone: As adjunctive therapy to diet for the reduction of elevated total cholesterol (total-C), low density lipoprotein cholesterol (LDL-C), apolipoprotein B (ApoB), and non-high density lipoprotein cholesterol (non-HDL-C) in patients with primary hyperlipidemia. In combination with statins: As adjunctive therapy to diet for the reduction of elevated total-C, LDL-C, ApoB, and non-HDL-C in patients with primary hyperlipidemia. In combination with atorvastatin or simvastatin: To reduce elevated Total-C and LDL-C in patients with homozygous familial hypercholesterolemia (HoFH).
Available Drugs (Generics)	ZETIA® (Ezetimibe)
Lipid/lipoprotein Effects (Monotherapy)[1]	LDL-C: ↓ 18%
	HDL-C: ↑ 1%
	TGs: ↓ 8%
	Apo B: ↓ 16%
Effectiveness in Persons with HoFH[2]	LDL-C: ↓ 21%
Major Side/Adverse Effect[2]	Similar elevations in transaminases (three times the upper limit of normal with alanine transaminase or aspartate transaminase) as compared to placebo when given as monotherapy.
Pregnancy Category[1]	C
Contraindications[1]	In patients with active liver disease or unexplained persistent elevations in hepatic transaminase levels; nursing mothers, patients with known hypersensitivity to any component of ezetimibe.

1. Zetia® (ezetimibe) Prescribing Information. 2. Phan BA, et al. *Vasc Health Risk Manag.* 2012;8:415-427.

Cholesterol Absorption Inhibitor (cont.)

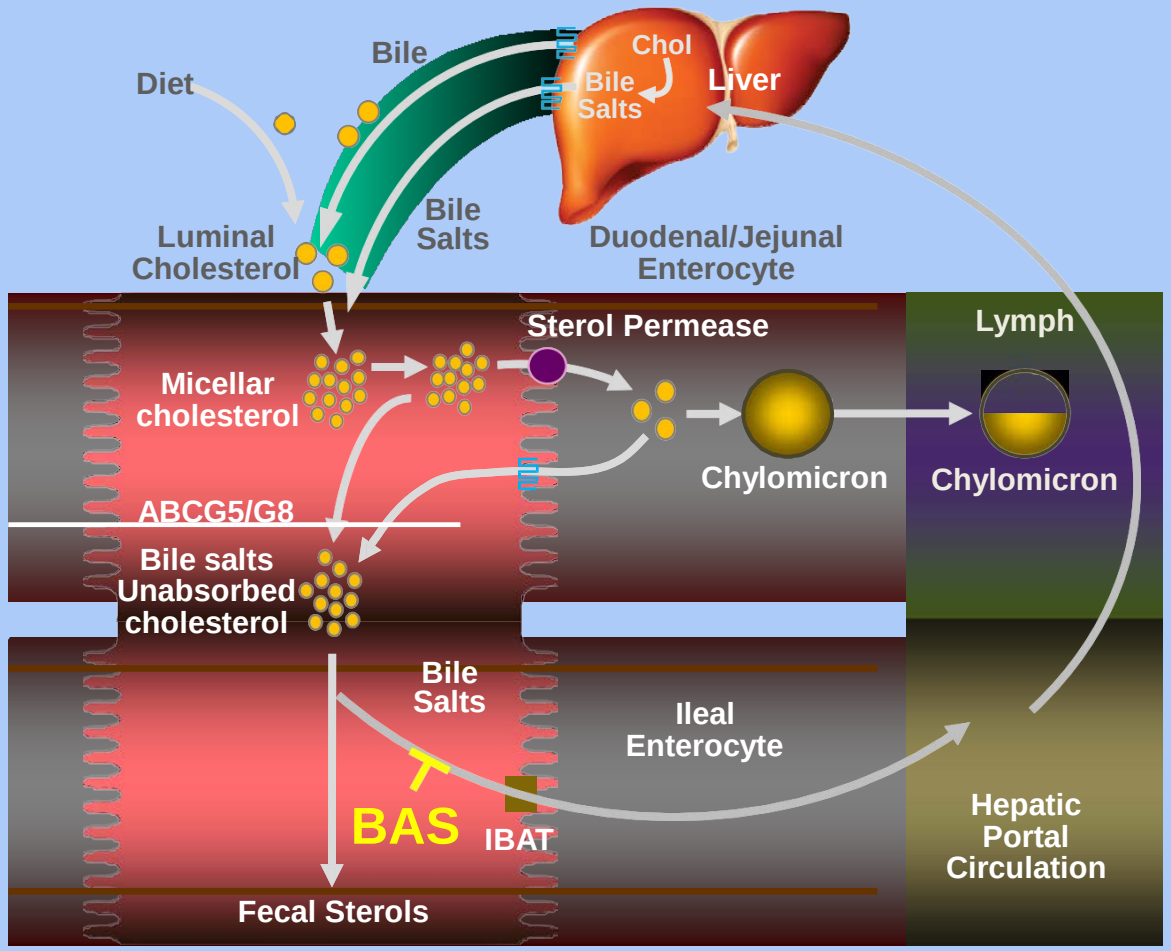
Available Preparations[1]	10 mg tablets
Outcomes Data[2]	Secondary Prevention: IMPROVE-IT (IMProved Reduction of Outcomes: Vytorin Efficacy International Trial) in combination with simvastatin (Expected completion: November 2014)
Recommendation(s)[1]	Ezetimibe should remain a viable adjunct to statin therapy in the treatment of hypercholesterolemia

1. Zetia® (ezetimibe) Prescribing Information. 2. Phan BA, et al. *Vasc Health Risk Manag.* 2012;8:415-427.

Bile Acid Sequestrants (BAS)

Bile Acid Sequestrants (BAS)

Mechanism of Action



BAS Mechanism of Action:

- Bind bile acids in the intestine reducing the enterohepatic recirculation of bile acids, which releases feedback regulation on conversion of cholesterol to bile acids in the liver
- The resulting decrease in hepatocyte cholesterol content enhances LDL-receptor expression, which in turn lowers serum LDL-cholesterol concentration

The Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). NIH Publication No. 02-5215; September 2002.

Bile Acid Sequestrants (BAS)

Indication[1]	As an adjunct to diet and exercise to reduce elevated LDL-C in adults with primary hyperlipidemia as monotherapy or in combination with a statin. (WELCHOL PI) Not indicated in HoFH.
Available Drugs (Generics)	WELCHOL® (colesevelam), QUESTRAN® (cholestyramine), COLESTID® (colestipol)
Lipid/lipoprotein Effects[1,2]	LDL-C: ↓ 15-30%
	HDL-C: ↑ 3-5%
	TGs: no effect or increase
	Apo B: ↓ 12% (Monotherapy)
Effectiveness in Persons with HoFH[3]	↓ 21%
Major Side/Adverse Effect[2]	Upper and lower gastrointestinal complaints common; decrease absorption of other drugs
Pregnancy Category[1]	B
Contraindications[2]	Familial dysbetalipoproteinemia (Triglycerides > 400 mg/dL), triglycerides > 200 mg/dL
Dosage Range and Preparations[2]	Cholestyramine: 4-24g Colestipol: 5-30 (5g packets, 1g tablets) Colesevelam: 625–4.4g (625 mg tablets)

1. WELCHOL® (colesevelam) Prescribing Information. 2. The Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). NIH Publication No. 02-5215; September 2002. 3. Gagne et al. *Circulation.*

Bile Acid Sequestrants (BAS)

Outcomes Data	Sequestrant therapy reduces risk for CHD. CHD risk reduction trial(s): Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT)
Recommendation(s)	Bile acid sequestrants should be considered as LDL-lowering therapy for persons with moderate elevations in LDL cholesterol, for younger persons with elevated LDL cholesterol, for women with elevated LDL cholesterol who are considering pregnancy, for persons needing only modest reductions in LDL cholesterol to achieve target goals, and for combination therapy with statins in persons with very high LDL-cholesterol levels

The Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). NIH Publication No. 02-5215; September 2002.

Nicotinic Acid (Niacin)

Nicotinic Acid (Niacin)

Indication[1]	To reduce elevated TC, LDL-C, Apo B and TG levels, and to increase HDL-C in patients with primary hyperlipidemia and mixed dyslipidemia. Not indicated in HoFH.
Available Drugs (Generics)[2]	Crystalline nicotinic acid Sustained-release (or timed-release) nicotinic acid NIASPAN® (Extended-release nicotinic acid)
Lipid/lipoprotein Effects[1,2]	LDL-C: ↓ 5-25%
	HDL-C: ↑ 15-35%
	TGs: ↓ 20-50%
	Apo B: ↓ 12% (1500 mg)
	Lipoprotein A: ↓ 8-32%
Effectiveness in Persons with HoFH	Not studied
Major Side/Adverse Effect[2]	Flushing, hyperglycemia, hyperuricemia or gout, upper gastrointestinal distress, hepatotoxicity, especially for sustained-release form.
Pregnancy Category[1]	C
Contraindications[2]	Chronic liver disease, severe gout, hyperuricemia; high doses in type 2 diabetes
Dosage Range[2]	Crystalline nicotinic acid: 1.5–4.5g Sustained-release nicotinic acid: 1–2g Extended-release nicotinic acid (Niaspan®): 1–2g
Available Preparations[2]	Many OTC preparations by various manufacturers for both crystalline and sustained- release nicotinic acid. The extended-release preparation (Niaspan®) is a prescription drug.

1. Niaspan® (extended-release nicotinic acid) Prescribing Information. 2. The Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). NIH Publication No. 02-5215; September 2002.

Nicotinic Acid (Niacin) (cont.)

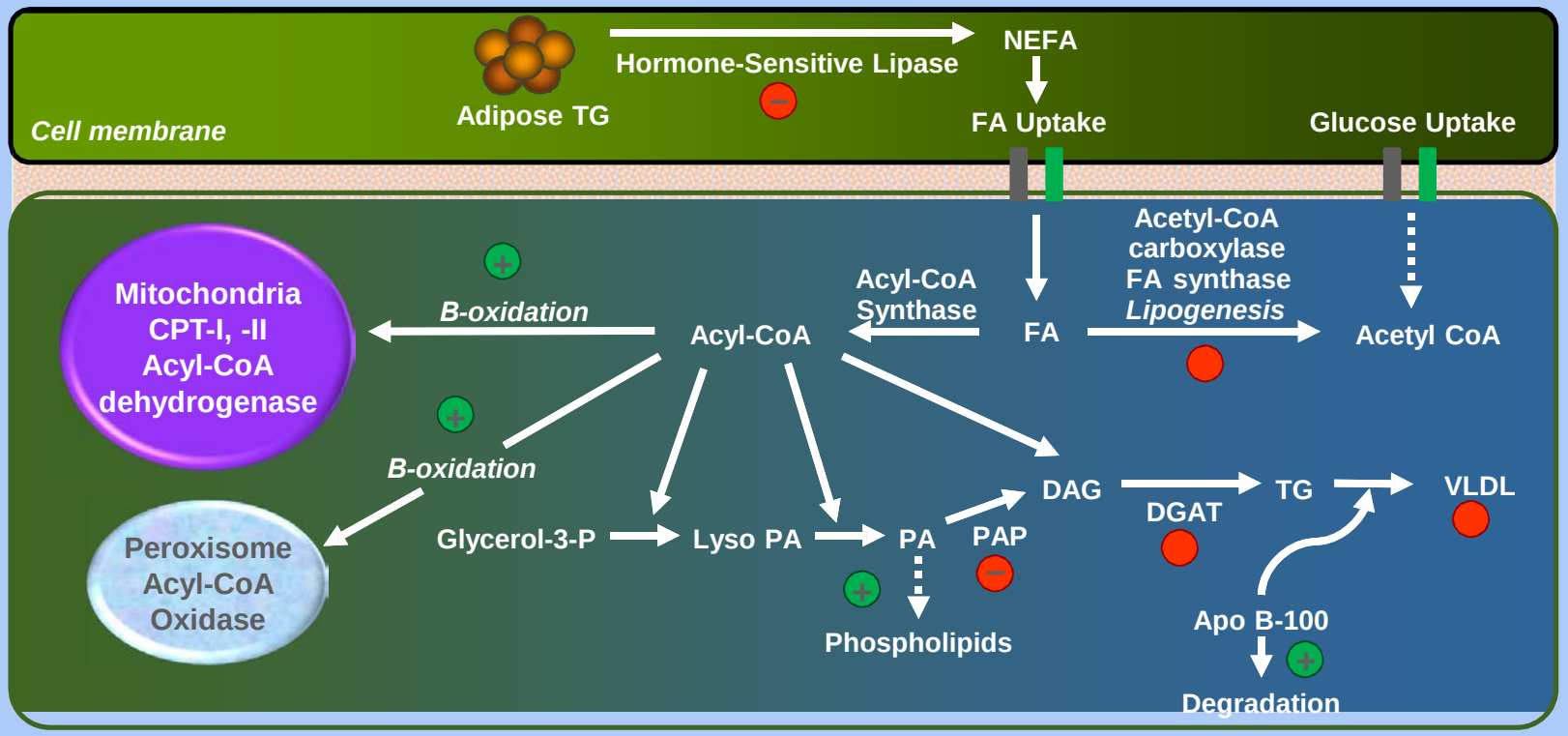
Outcomes Data	Nicotinic acid therapy produces a moderate reduction in CHD risk, either when used alone or in combination with other lipid-lowering drugs. CV prevention trials: Coronary Drug Project (CDP)
Recommendation(s)	Nicotinic acid should be considered as a therapeutic option for higher-risk persons with atherogenic dyslipidemia. It should be considered as a single agent in higher-risk persons with atherogenic dyslipidemia who do not have a substantial increase in LDL-cholesterol levels, and in combination therapy with other cholesterol-lowering drugs in higher-risk persons with atherogenic dyslipidemia combined with elevated LDL-cholesterol levels.

The Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). NIH Publication No. 02-5215; September 2002.

Omega-3 Fatty Acids (FAs)

Omega-3 Fatty Acid

Mechanism of Action



Omega-3 Fatty Acid Mechanism of Action:

- Modulating very-low-density lipoprotein (VLDL) and chylomicron metabolism. There is a consistent finding in the literature that the end effect of fish oil is decreased hepatic secretion of VLDL
- Promotion of apoB degradation in the liver through the stimulation of an autophagic process

Weitz D, et al. Fish oil for the treatment of cardiovascular disease. *Cardiol Rev*. 2010;18(5):258-263.

Omega-3 Fatty Acid

Indication[1]	As an adjunct to diet to reduce TG levels in patients with severe hypertriglyceridemia (TG ≥ 500 mg/dl)
Available Drugs (Generics)	LOVAZA® (omega-3-Acid Ethyl Esters), VASCEPA® (icosapent ethyl), EPANOVA® (omega-3-carboxylic acids)
Lipid/lipoprotein Effects[2]	LDL-C: Increase/no change
	HDL-C: Increase/no change
	TGs: ↓ 20-50%
	Apo B: NA
Effectiveness in Persons with HoFH	Not sufficiently studied
Major Side/Adverse Effect[3]	Potential bleeding complications with the co-administration of anticoagulants
Pregnancy Category[1]	C
Contraindications[1]	Patients with known hypersensitivity to O3s or any of their components
Dosage Range and Preparations	Omega-3-Acid Ethyl esters: 4 g qd capsules Icosapent ethyl: 4 g qd capsules Omega-3-carboxylic acids: 2-4g capsules

1. EPANOVA® (omega-3-carboxylic acids) Prescribing Information. 2. Bays H, et al. Bays HA, Tighe AP, Sadovsky R, et al. Prescription omega-3 fatty acids and their lipid effects: physiological mechanisms of action and clinical implications. *Expert Rev Cardiovasc Ther.* 2008;6(3):391-409. 3. Weitz D, et al. *Cardiol Rev.* 2010;18(5):258-263.

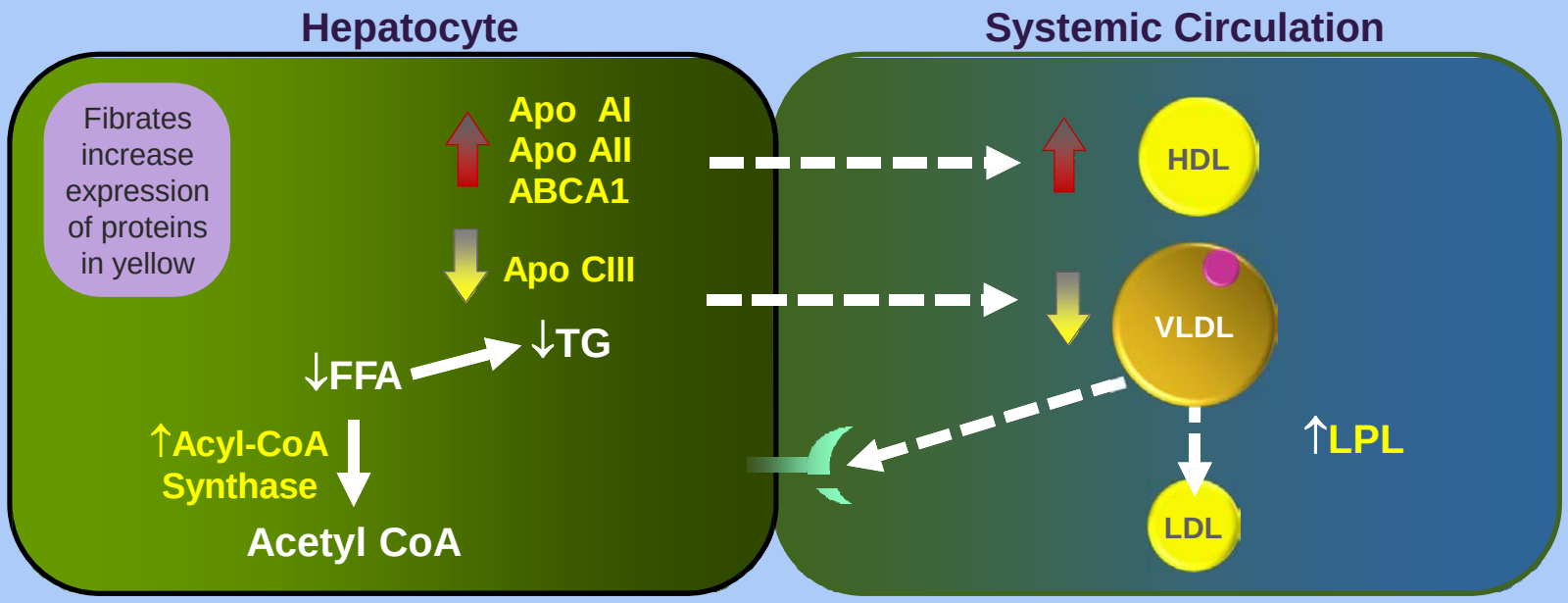
Omega-3 Fatty Acid (cont.)

Outcomes Data[1,2]	DART Study; Lyon Diet Heart Study; GISSI-Prevenzione trial The ATP III panel recognizes that n-3 fatty acids can be a therapeutic option in secondary prevention.
Recommendation(s)[1]	Higher dietary intakes of n-3 fatty acids in the form of fatty fish or vegetable oils are an option for reducing risk for CHD. This recommendation is optional because of the strength of the evidence is only moderate at present.

1. Weitz D, et al. *Cardiol Rev.* 2010;18(5):258-263. 2. The Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). NIH Publication No. 02-5215; September 2002.

Fibric Acid Derivatives (Fibrates)

Fibric Acid Derivatives (Fibrates)
Mechanism of Action



Fibric Acid Mechanism of Action:

- Down regulate the apo C-III gene
- Up regulate genes for apo A-I, fatty acid transport protein, fatty acid oxidation, and possibly lipoprotein lipase
- Enhance the catabolism of TGRLP, whereas increased fatty acid oxidation reduces formation of VLDL triglycerides

The Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). NIH Publication No. 02-5215; September 2002.

\

Fibric Acid Derivatives

Indication[1,2]	As an adjunct to diet in combination with a statin to reduce TG and increase HDL-C in patients with mixed dyslipidemia and CHD or a CHD risk equivalent who are on optimal statin therapy to achieve their LDL-C goal. As adjunctive therapy to diet to reduce elevated low-density lipoprotein cholesterol (LDL-C), total cholesterol (Total-C), Triglycerides and apolipoprotein B (Apo B), and to increase high-density lipoprotein cholesterol (HDL-C) in adult patients with primary hypercholesterolemia or mixed dyslipidemia.
Available Drugs (Generics)	LOPID® (gemfibrozil), TRICOR® (fenofibrate), LIPOFEN®, TRILIPIX® (fenofibric acid)
Lipid/lipoprotein Effects[1,3,4]	LDL-C: ↓ 5-20%
	HDL-C: ↑ 10-35%
	TGs: ↓ 20-50%
	Apo B: ↓ 5%
Effectiveness in Persons with HoFH	Not sufficiently studied
Major Side/Adverse Effect[3]	Dyspepsia, various upper gastrointestinal complaints, cholesterol gallstones, myopathy
Pregnancy Category[2]	C

1. TRILIPIX® (fenofibric acid) Prescribing Information. 2. TRICOR® (fenofibrate) Prescribing Information. 3. The Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). NIH Publication No. 02-5215; September 2002.

Fibric Acid Derivatives

Contraindications	Severe hepatic or renal insufficiency
Dosage Range and Preparations	Gemfibrozil: 600–1200 mg tablets Fenofibrate: 67 and 200 mg tablets Fenofibric acid: 145 mg tablets
Outcomes Data	Primary Prevention Trial(s): Helsinki Heart Study (HHS); WHO Clofibrate Study Secondary Prevention Trial(s): Veterans Administration HDL Intervention Trial (VA-HIT)
Recommendation(s)	Fibrates can be recommended for persons with very high triglycerides to reduce acute pancreatitis. Fibrate therapy should be considered as option for treatment if persons with established CHD who have low levels of LDL cholesterol and atherogenic dyslipidemia

The Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). NIH Publication No. 02-5215; September 2002.

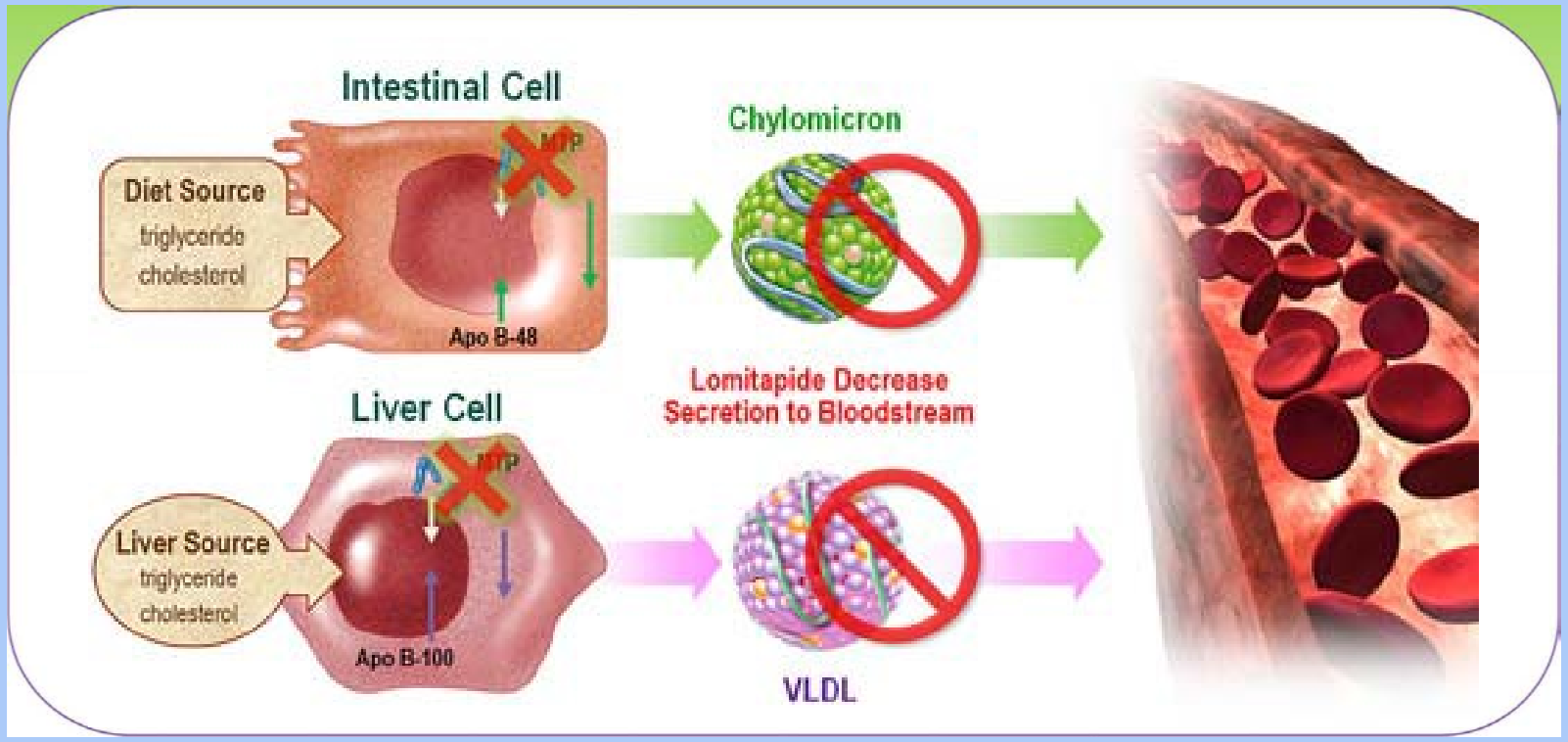
Anti-Sense Apo B Inhibitor

Microsomal Triglyceride Transfer Protein (MTP) Inhibitor

Microsomal Triglyceride Transfer Protein (MTP) Inhibitor

Mechanism of Action

- Small-molecule MTP inhibitor designed as oral, once-daily treatment for homozygous FH



- MOA: MTP (microsomal triglyceride transfer protein) is responsible for transferring lipid (triglyceride) onto Apo B48 in the intestine and on to Apo B100 in the liver
- MTP inhibition limits secretion of cholesterol and triglycerides from intestine and liver

Microsomal Triglyceride Transfer Protein (MTP) Inhibition

Indication	As an adjunct to a low-fat diet and other lipid-lowering treatments, including LDL apheresis where available, to reduce low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), apolipoprotein B (apo B), and non-high-density lipoprotein cholesterol (non-HDL-C) in patients with homozygous familial hypercholesterolemia (HoFH).
Available Drugs (Generics)	JUXTAPID® (lomitapide) capsules
Lipid/lipoprotein Effects	LDL-C: ↓ 40%
	HDL-C: ↓ 7%
	TGs: ↓ 45%
	Apo B: ↓ 39%
Effectiveness in Persons with HoFH	↓ 40%
Major Side/Adverse Effect	Gastrointestinal; diarrhea, vomiting, increased ALT or hepatotoxicity and abdominal pain
Pregnancy Category	X
Contraindications	Pregnancy, with moderate or strong CYP3A4 inhibitors, and patients with moderate or severe hepatic impairment (based on Child-Pugh category B or C) and patients with active liver disease, including unexplained persistent elevations of serum transaminases
Dosage Range and Preparations	Lomitapide: 5–20mg capsules

JUXTAPID® (lomitapide) Prescribing Information.

Microsomal Triglyceride Transfer Protein (MTP) Inhibition (cont.)

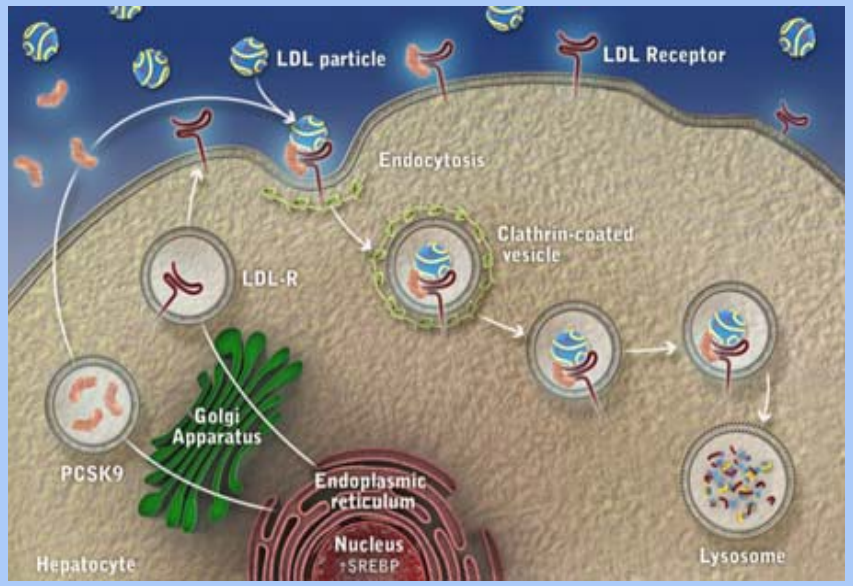
Outcomes Data	Not available
Recommendation(s)	JUXTAPID is a microsomal triglyceride transfer protein inhibitor indicated as an adjunct to a low-fat diet and other lipid-lowering treatments, including LDL apheresis where available. It is indicated to reduce low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), apolipoprotein B (apo B), and non-high-density lipoprotein cholesterol (non-HDL-C) in patients with homozygous familial hypercholesterolemia (HoFH)
REMS Information	Because of the risk of hepatotoxicity associated with JUXTAPID therapy, JUXTAPID is available through a restricted program under the REMS. Under the JUXTAPID REMS, only certified healthcare providers and pharmacies may prescribe and distribute JUXTAPID

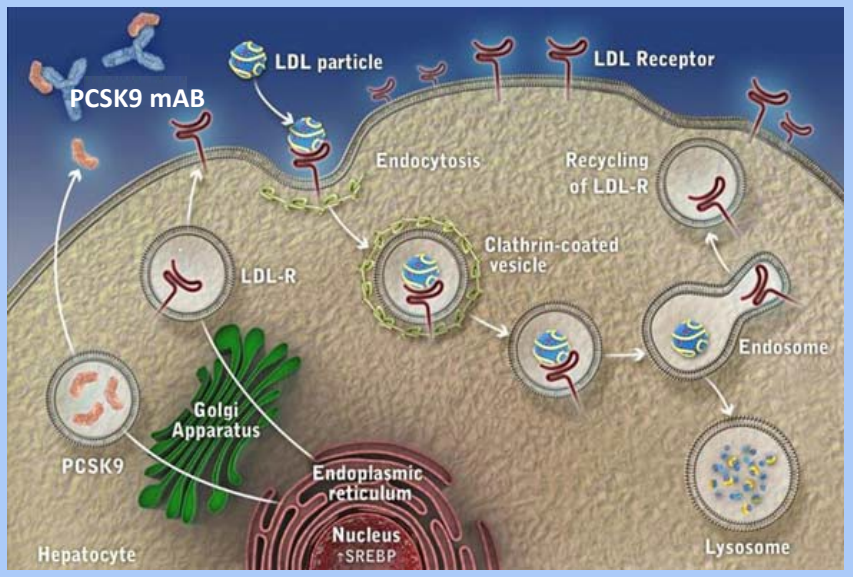
JUXTAPID® (lomitapide) Prescribing Information.

PCSK9 Monoclonal Antibody (mAB)

PCSK9 Monoclonal Antibody

Mechanism of Action





Proprotein convertase subtilisin/kexin type (PCSK9) is a protein secreted by the hepatocytes which "chaperones" the LDL receptor from the cell surface and into the cell for lysosomal degradation.

mAB MOA: An antibody to PCSK9 binds to the PCSK9 protein, thereby inhibiting its effect on the LDL receptor.

Maki KC. *Lipid Luminations: Emerging Therapies for Familial Hypercholesterolemia.* National Lipid Association Publication.

PCSK9 Monoclonal

Indication	Pending FDA approval
Available Drugs (Generics)	AMG 145 (evolocumab), SAR236553/REGN727 (alirocumab)*, RN316 (bococizumab)
Lipid/lipoprotein Effects[1]	LDL-C: ↓ 28-65%
	HDL-C: Not reported
	TGs: Not reported
	Apo B: Not reported
Effectiveness in Persons with HoFH[2]	↓ 31% (Range: +10.3% to -55.7%)
Major Side/Adverse Effect	In clinical trials: Infusion reactions, upper respiratory tract, influenza
Pregnancy Category	Pending FDA approval
Contraindications	Pending FDA approval
Dosage Range and Preparations	AMG 145 (evolocumab): 140 mg or 420 mg injection SAR236553/REGN727 (alirocumab): 150 mg or 300 mg injection RN316 (bococizumab): 50 mg, 100 mg or 150 mg injection

*Clinical trials have been in HeFH.

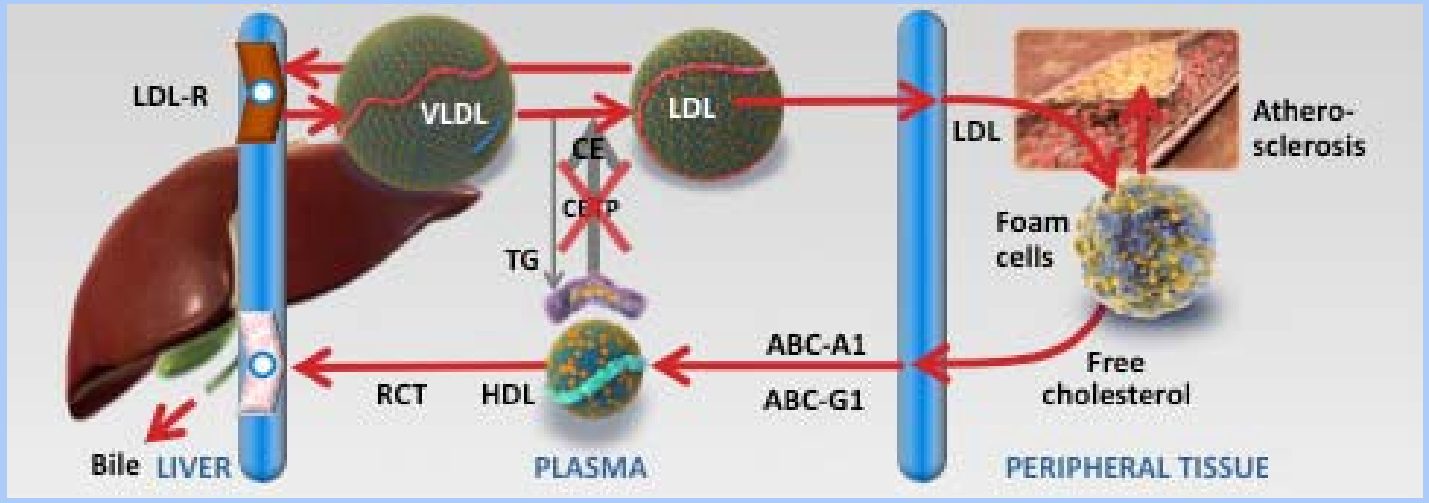
1. Maxwell, KN. Antibodies to PCSK9: A Superior Way to Lower LDL Cholesterol? *Circ Res.* 2012;111:274-277. 2. EAS Madrid abstract 1177. Raal F, Honarpour N, Blom DJ et al. Trial evaluating evolocumab, a PCSK9 antibody in patients with homozygous FH (TESLA): Results of the randomised, double-blind placebo-controlled trial.

PCSK9 Monoclonal Antibodies (cont.)

Outcomes Data	Not available
Recommendation(s)	AMG 145 (evolocumab) is a fully human monoclonal antibody that inhibits proprotein convertase subtilisin/kexin type 9 (PCSK9). SAR236553/REGN727 (alirocumab) is s a potential first-in-class, subcutaneously administered, fully-human antibody that lowers low- density lipoprotein (LDL) cholesterol by targeting PCSK9. A PCSK9 with a late stage development with the broad global 22,000 patient ODYSSEY clinical trial program.

Cholesterol Ester Transfer Protein (CETP)

Cholesterol Ester Transfer Protein
Mechanism of Action



- CETP, a lipid transfer protein secreted by the liver and mainly bound to HDL, facilitates the transfer of cholesteryl esters from HDL particles to apo B–containing VLDL, LDL, and chylomicron particles in exchange for triglyceride
- MOA: inhibition of CETP through antisense oligodeoxynucleotides, HDL-C levels are markedly increased with substantial reduction in atherosclerotic lesions

Barter P, et al. Cholesteryl Ester Transfer Protein (CETP) Inhibition as a Strategy to Reduce Cardiovascular Risk. *Jour Lipid Res.* 2012;53(9):1755-1766.

Cholesterol Ester Transfer

Indication	Pending FDA approval
Available Drugs (Generics)	MK-0859 (anacetrapib), LY2484595 (evacetrapib)
Lipid/lipoprotein Effects	LDL-C: ↓ 7-40%
	HDL-C: ↑ 34-138%
	TGs: None reported
	Apo B: None reported
Effectiveness in Persons with HoFH	(A Phase III trial examining the usefulness, of adding anacetrapib to maximum tolerated statin treatment in patients with HoFH, is due to report in 2015)
Major Side/Adverse Effect	Potential increases in cardiovascular events and total mortality due to aldosterone increases and blood pressure
Pregnancy Category	Pending FDA approval
Contraindications	Pending FDA approval
Dosage Range and Preparations	MK-0859 (anacetrapib): 10, 40, 150, 300 mg injection LY2484595 (evacetrapib): 30, 100, 500 mg injection

Barter P, et al. Cholesteryl Ester Transfer Protein (CETP) Inhibition as a Strategy to Reduce Cardiovascular Risk. *Jour Lipid Res.* 2012;53(9):1755-1766.

Cholesterol Ester Transfer

Outcomes Data	REVEAL: Randomized Evaluation of the Effects of Anacetrapib through Lipid Modification DEFINE: Determining the Efficacy and Tolerability of CETP Inhibition with Anacetrapib
Recommendation(s)	MK-0859 (anacetrapib) is an orally active, potent, and selective CETP inhibitor in Phase III development (MERCK) LY2484595 (evacetrapib) is a novel benzazepine compound, is a potent and selective inhibitor of CETP (ELI LILLY)

Barter P, et al. Cholesteryl Ester Transfer Protein (CETP) Inhibition as a Strategy to Reduce Cardiovascular Risk. *Jour Lipid Res.* 2012;53(9):1755-1766.

LDL Apheresis

LDL Apheresis

Indication[1]	For use in performing low density lipoprotein cholesterol (LDL-C) apheresis to acutely remove LDL-C from the plasma of the following high risk patient populations for whom diet has been ineffective and maximum drug therapy has either been ineffective or not tolerated: • Group A. Functional Hypercholesterolemic Homozygotes with LDL-C > 500 mg/dl; • Group B. Functional Hypercholesterolemic Heterozygotes with LDL-C > 300 mg/dl; and • Group C. Functional Hypercholesterolemic Heterozygotes with LDL-C > 200 mg/dl and documented coronary heart disease.
Available Drugs (Generics)[2]	Cascade filtration, Immunoadsorption, Heparin Induced LDL Precipitation (HELP), LDL adsoprtion, LDL hemoperfusion (DALI), LDL hemoperfusion (liposorber)
Lipid/lipoprotein Effects[2]	LDL-C: ↓ 35-75%
	HDL-C: ↑ 5-50%
	TGs: ↓ 40-70%
	Apo B: None reported
Effectiveness in Persons with HoFH	See above for effectiveness

1. LIPOSORBER® LA-15 System Prescribing Information. 2. Bombauer R, et al. LDL-Apheresis: Technical and Clinical Aspects. *ScientificWorldJourna*l. 2012;2012:314283. 3. American Society for Apheresis. Procedure: LDL-apheresis. Available at: http://www.apheresis.org/~ASSETS/DOCUMENT/Fact%20Sheets/LDL%20Apheresis.pdf. Accessed on 01/15/13. 4. Sułowicz W, Stompór T. LDL-apheresis and immunoadsorption: novel methods in the treatment of renal diseases refractory to conventional therapy. *Nephrol Dial Transplant*. 2003;18(S5):v59-62.

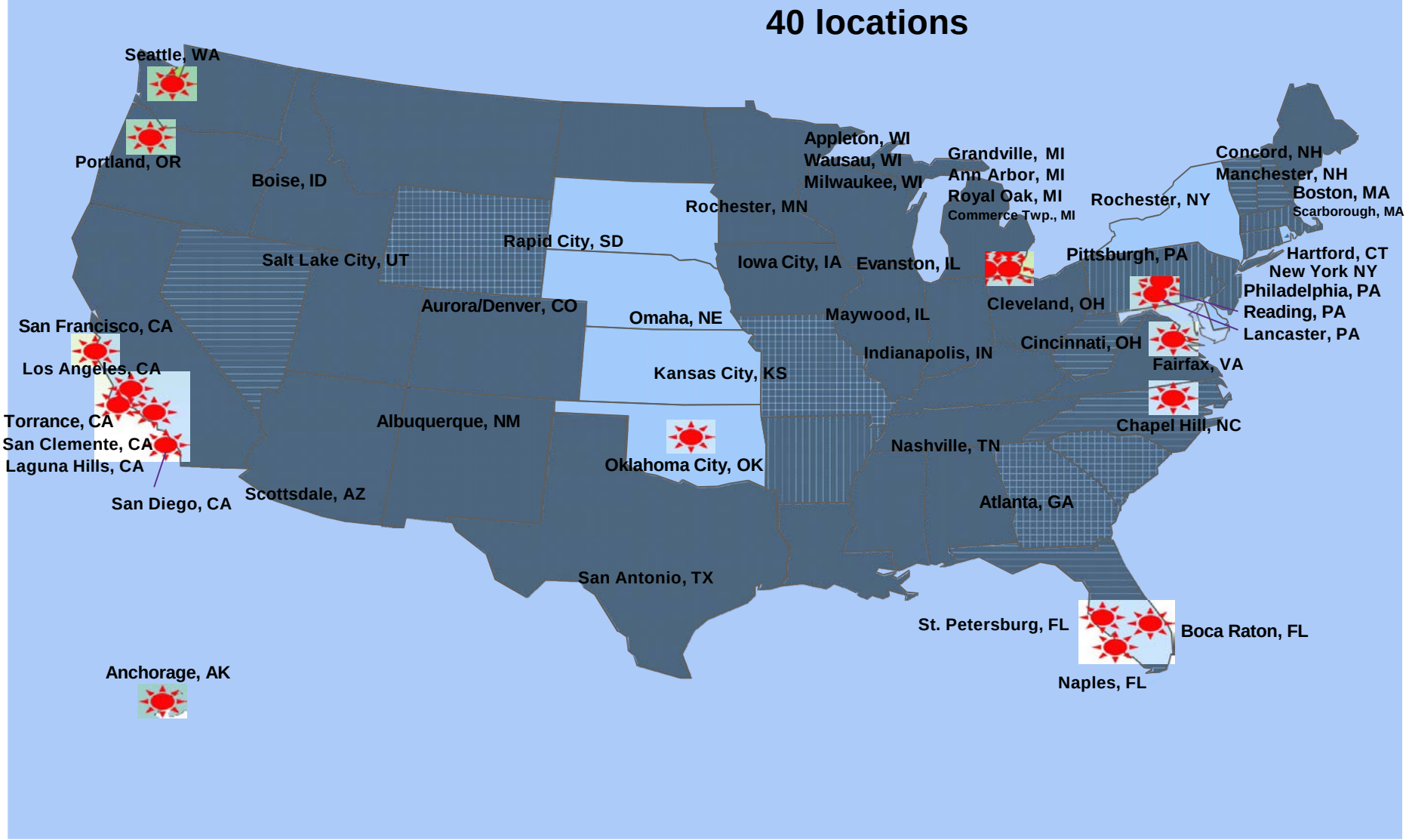
LDL Apheresis (cont.)

Major Side/Adverse Effect[3,4]	Allergic reactions, fatigue, nausea, chest pain, dizziness, hypotension
Pregnancy Category	B
Contraindications	None reported
Dosage Range and Preparations[1]	Cascade filtration: (2,500–3,000 mL plasma) Immunoadsorption: (4,000–5,000 mL) Heparin Induced LDL Precipation (HELP): (2,500–3,000 mL) LDL adsoprtion: (2,500–3,000 mL) LDL hemoperfusion (DALI): 1.6 blood volume LDL hemoperfusion (liposrober): 1.5 blood volume
Outcomes Data	None reported
Recommendation(s)[2]	Healthcare practitioners should refer candidates for LDL apheresis to qualified sites. Self-referrals are also possible. A listing of sites qualified to perform LDL apheresis is in development and will be posted on the National Lipid Association website (www.lipid.org).

1. Bombauer R, et al. LDL-Apheresis: Technical and Clinical Aspects. *ScientificWorldJournal.* 2012;2012:314283. 2. Ito MK, McGowan MP, Moriarty PM; National Lipid Association Expert Panel on Familial Hypercholesterolemia. Management of familial hypercholesterolemias in adult patients: recommendations from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. Clin Lipidol. 2011;5(3 Suppl):S38-45.

Current Liposorber® Treatment Sites:

40 sites



Homozygous Familial Hypercholesterolemia (HoFH)

HoFH: A Rare, Genetic Lipid Disorder

- Characterized by extreme hypercholesterolemia and early and/or progressive atherosclerosis[1]
- Believed to occur in only 6.25 out of every one million persons[2]
  - Estimated that HoFH affects about 42,880 people globally
  - True prevalence of HoFH may be underestimated because of inadequate data and under-diagnosis[3]
- People with HoFH have inherited mutations that prevent their body from clearing cholesterol properly, leading to very high levels of LDL-C, even after taking standard cholesterol medications

1. Mahley RW, et al. In: Kronenberg: Williams Textbook of Endocrinology; 2008.
2. Cuchel M, et al. Eur Heart J (2014) 35 (32): 2146-2157
3. Goldberg A, et al. *J Clin Lipidol.* 2011;5:S1-S8.

HoFH: Clinical Profiles From Multiple Phase 3 Trials

	Baseline Mean Age, y	Baseline CHD Status	Baseline LDL-C, mg/dL* [LLT status]
Simvastatin (N=12)[1]	26 (range 15-39)	• 42% had previous CABG • 17% had coronary angioplasty • 8% had aortic valve replacement	552 [Untreated] (range 363-764)
(N=35)[2]	(range 2-39)	surgery, or CABG	(range 374-980)
Ezetimibe (N=50)[3]	32 (±4)	• 44% had premature CHD	≈322 [Treated] (not specified)
Rosuvastatin (N=44)[4]	28 (range 8-63)	• Not specified	513 [Untreated] (range 293-791)
KYNAMRO (N=51)[5,6]	32 (range 12-53)	• ≈60% had atherosclerotic disease • ≈50% had aortic valve stenosis • ≈25% had revascularization	≈426 [Treated] (range 172-704)
Lomitapide (N=29)[7,8]	31 (range 18-55)	• 93% had CV disease • 72% had valvular disease • 72% had CAD	336 [Treated] (range 152-564)
Evolocumab (N=49)[9]	31 (range 13-57)	• 43% had CAD • 25% had previous CABG • 14% had previous aortic valve replacement	348 [Treated] (not provided)

*Represents values in all patients at baseline, including control group.

CABG = coronary artery bypass graft; CAD = coronary artery disease; LLT = lipid-lowering therapy.

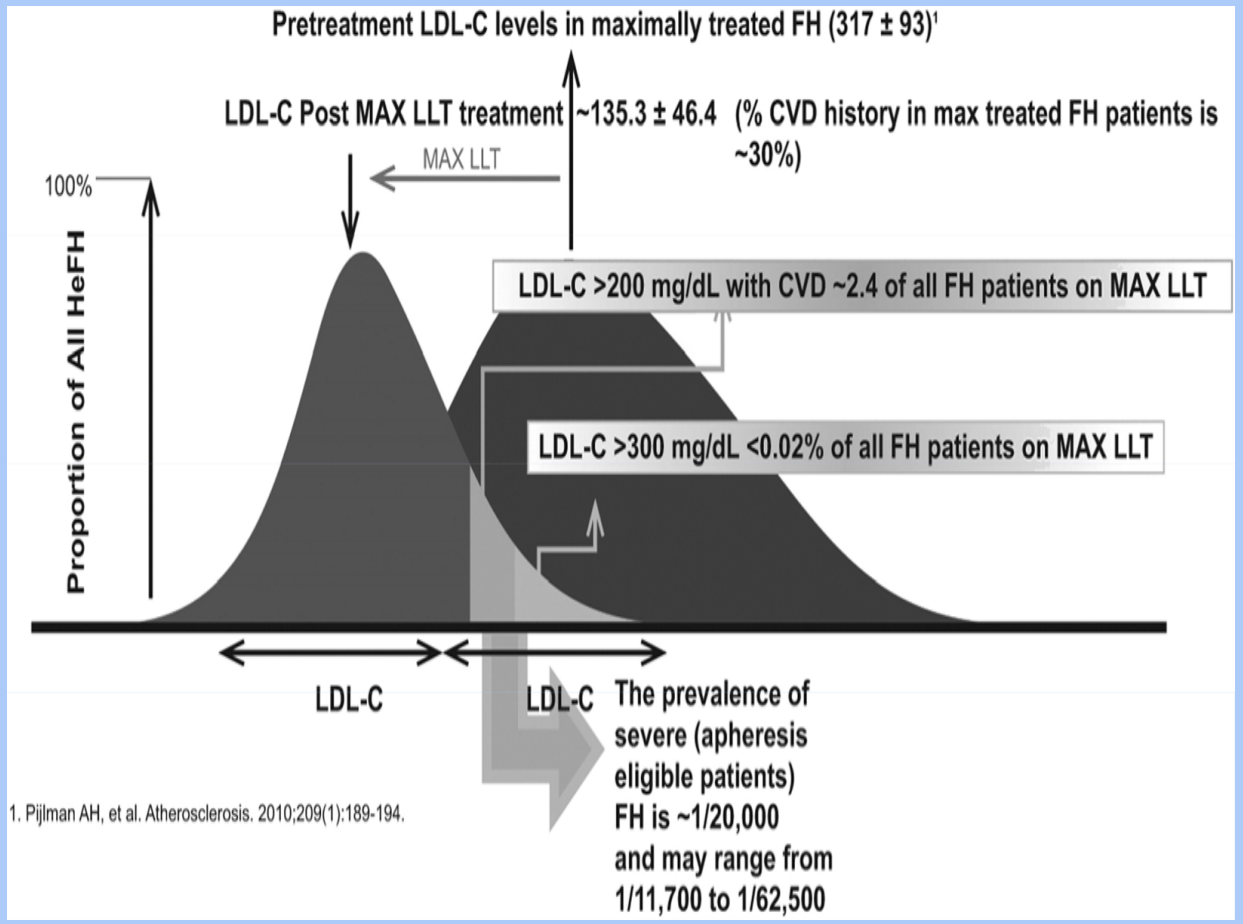
1. Raal FJ, et al. *Atherosclerosis*. 1997;135:249-256; 2. Raal FJ, et al. *Atherosclerosis*. 2000;150:421-428;
3. Gagné C, et al. *Circulation*. 2002;105:2469-2475; 4. Marais AD, et al. *Atherosclerosis.* 2008;197:400-406;
5. Raal FJ, et al. *Lancet*. 2010;375:998-1006; 6. KYNAMRO® (mipomersen sodium) injection full Prescribing Information. January 2013;
7. Cuchel M, et al. *Lancet*. 2013;381:40-46; 8. Supplement to: Cuchel M, et al. *Lancet*. 2013;381:40-46;
9. Raal F, et al. EAS 2014 Madrid abstract 1177.

HoFH: Comparable in Prevalence to Other Rare, Genetic Disorders

Disorder	Estimated US Pop.	Clinical Sequelae
HoFH[1,2,3]	2032	Premature, occlusive CAD
MPS-II (Hunter syndrome)[4]	500	Severe mental impairment
Paroxysmal nocturnal hemoglobinuria[5,6]	5,000	Vascular thrombosis
MPS-IV (Morquio syndrome)[7]	8,750	Extreme skeletal abnormalities
Hereditary angioedema[8]	6,800-34,000	Swelling of SC tissue

1.Nemati MH, et al. *Gen Thorac Cardiovasc Surg*. 2009;57(2):94-97.
2.Ersoy U and Güvener M. *Acta Paediatr*. 2000;89(12)1501-1502.
3. Cuchel M, et al. Eur Heart J (2014) 35 (32): 2146-2157.
4.Wraith JE, et al. *Eur J Pediatr*. 2008;167(3):267-277.
5. Risitano AM and Rotoli B. *Biologics*. 2008;2(2):205-222.
6.Mayo Clinical Website http://www.mayomedicallaboratories.com/articles/hottopics/transcripts/2010/2010-pnh/03.html. Accessed April 13, 2012.
7. Onçağ G, et al. *Angle Orthod*. 2006;76(2):335-340.
8. HAEA: US Hereditary Angioedema Association. What is HAE? http://hereditaryangioedema.com. Accessed April 13, 2012.

Estimated US Prevalence of apheresis eligible patients with or without CHD[1]

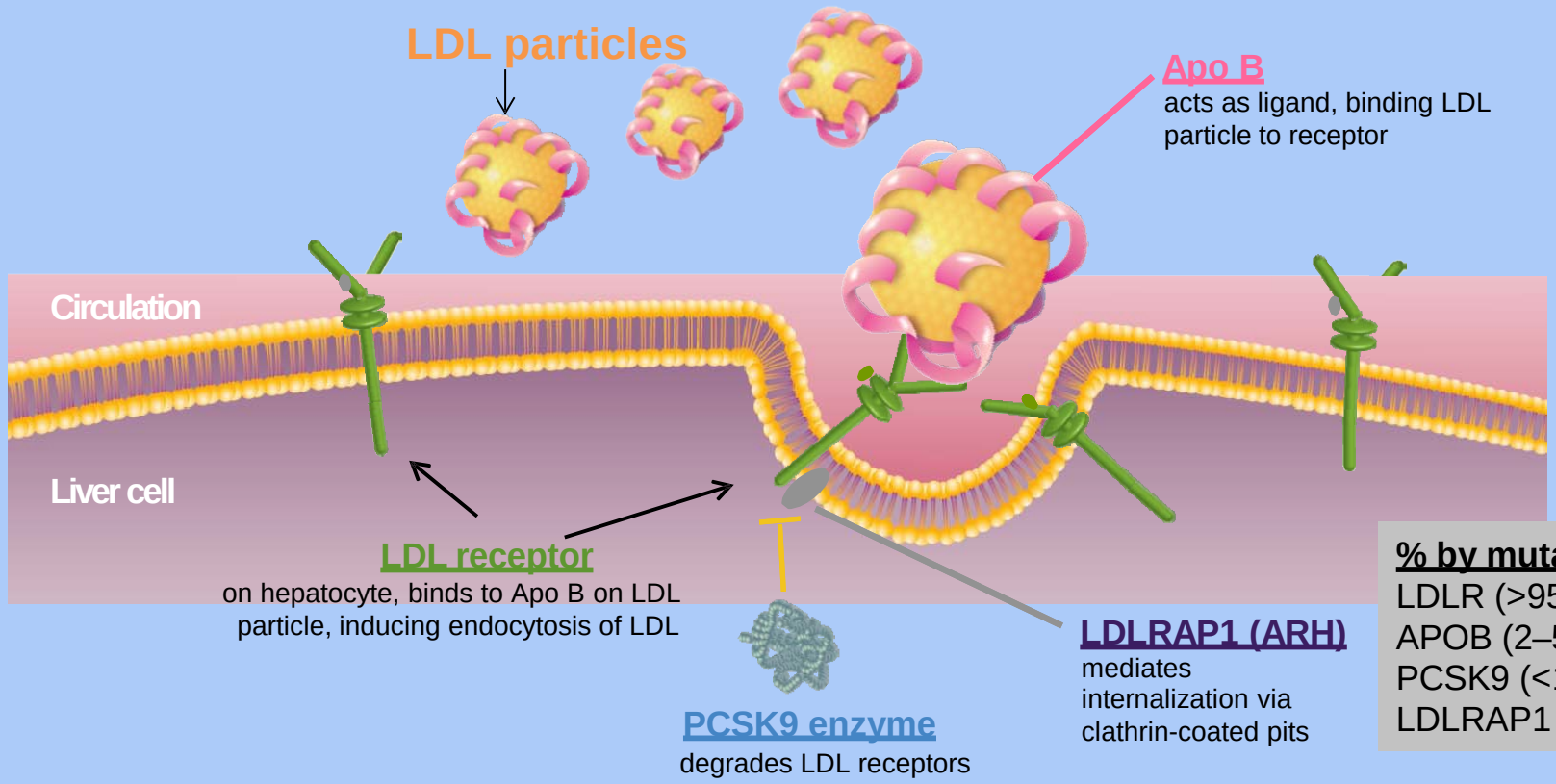


On the basis of this prevalence calculation and on post treatment LDL-C levels, these patients with severe FH and LDL-C levels .300 mg/dL (.7.76 mmol/L) bear phenotypic resemblance to patients with HoFH and may be considered the functional equivalents of homozygous patients.

1.Vishwanath J Clin Lipidol. 2014:8:18-28

HoFH is Caused by Genetic Mutations that Affect the Clearance of Atherogenic Lipoproteins

HoFH is typically caused by mutations in LDLR, Apo B, PCSK9, LDLRAP1, or other as-yet-unidentified genes[1]



% by mutation
LDLR (>95%)
APOB (2–5%)
PCSK9 (<1%)
LDLRAP1 (<1%)

PCSK9 = proprotein convertase subtilisin/kexin type 9; LDLR = LDL receptor; LDLRAP1 = LDL receptor adapter protein 1.
Image reproduced from http://www.dls.ym.edu.tw/ol_biology2/ultranet/Endocytosis.html.

1. De Castro-Oros I, et al. *Appl Clin Genet.* 2010;3:53-64.
2. Cuchel M, et al. EHJ 2014; 35: 2

HoFH & Inheritance of Mutations

- HoFH may be caused by ~1, 700 mutations[1]
- HoFH includes both “pure” HoFH & Compound HeFH[2]
  - **Pure HoFH[2]:** Inherited the same mutation from both parents
  - **Compound HeFH[2]:** Inherited different mutations from each parent

HoFH Mutation Inheritance: An Illustration

Individual		Mother	Father
Unaffected		• No FH Mutation	• No FH Mutation
HeFH (1 FH Mutation)		• FH Mutation 1	• No FH Mutation
		• No FH Mutation	• FH Mutation 1
HoFH (2 FH Mutations)	**2 different FH mutations** (Compound HeFH)	• FH Mutation 1	• FH Mutation 2
	2 of the same FH mutations (“Pure” HoFH)	• FH Mutation 1	• FH Mutation 1

1. LDLR Locus - Mutation List. Available at: http://www.ucl.ac.uk/fhold/mutta
2. Raal FJ, Santos RD. *Atherosclerosis*. 2012;223:262-268.

HoFH: Rare, but Potentially Under-recognized

- HoFH is extremely rare. It is believed to occur in only 6.25 out of every one million persons - or 42,880 people globally.[1]
- **As with other rare diseases, the true prevalence of HoFH may be underestimated because of inadequate data and under-diagnosis.[2]**
- Although it may be diagnosed in childhood, **HoFH may also go undiagnosed into adulthood3**

1. Cuchel M, et al. Eur Heart J (2014) 35 (32): 2146-2157.
2. Raal FJ, Santos RD. *Atherosclerosis*. 2012;223:262-268.
3. Hoeg, JM et al. *Arterioscler Thromb.* 1994 ;14(7):1066-1074.

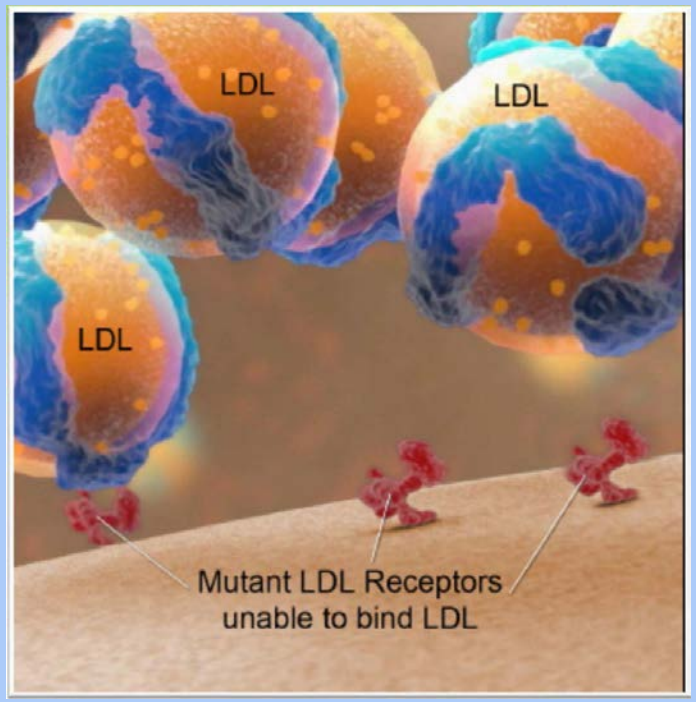
HoFH & Genetic Analysis

- **There are ~1,700 mutations recognized to cause HoFH[1]**

- **However, genetic testing is generally not needed for diagnosis**

  - Genetic analysis does not generally affect management or treatment decisions[2]

  - Additional mutations remain unknown, making results non-definitive[3]



1. LDLR Locus - Mutation List. Available at: http://www.ucl.ac.uk/fhold/muttab.html. Accessed May 30, 2014.
2. Raal FJ, Santos RD. *Atherosclerosis*. 2012;223:262-268.
3. Goldberg A et al. *J Clin Lipidol*. 2011;5:S1-S8.

Genetic Screening Recommendations from the NLA Expert Panel on Familial Hypercholesterolemia

- Genetic screening for FH is generally not needed for diagnosis or clinical management but may be useful when the diagnosis is uncertain.
- Identification of a causal mutation may provide additional motivation for some patients to implement appropriate treatment.
- Importantly, a negative genetic test does not exclude FH, since approximately 20% of clinically *definite* FH patients will not be found to have a mutation despite an exhaustive search using current methods.

NLA = National Lipid Association.

Hopkins PN et al. *J Clin Lipidol*. 2011;5(suppl 3):S9-S19.

HoFH May be Recognized Clinically

- Multiple clinical definitions exist for HoFH
- Diagnostic criteria may include one or more of the following factors:
  - **Lipid parameters**, e.g. elevations measured by
    - Total-C and/or LDL-C
    - Levels may be untreated and/or treated
  - Presence of **premature** CHD (age <55 for men, age <65 for women)
  - **Family history** of premature CHD or hypercholesterolemia
  - **Physical findings** if present (e.g. planar xanthomas)

1. Raal FJ, Santos RD. *Atherosclerosis*. 2012;223:262-268.
2. Hoeg, JM et al. *Arterioscler Thromb.* 1994 ;14(7):1066-1074.

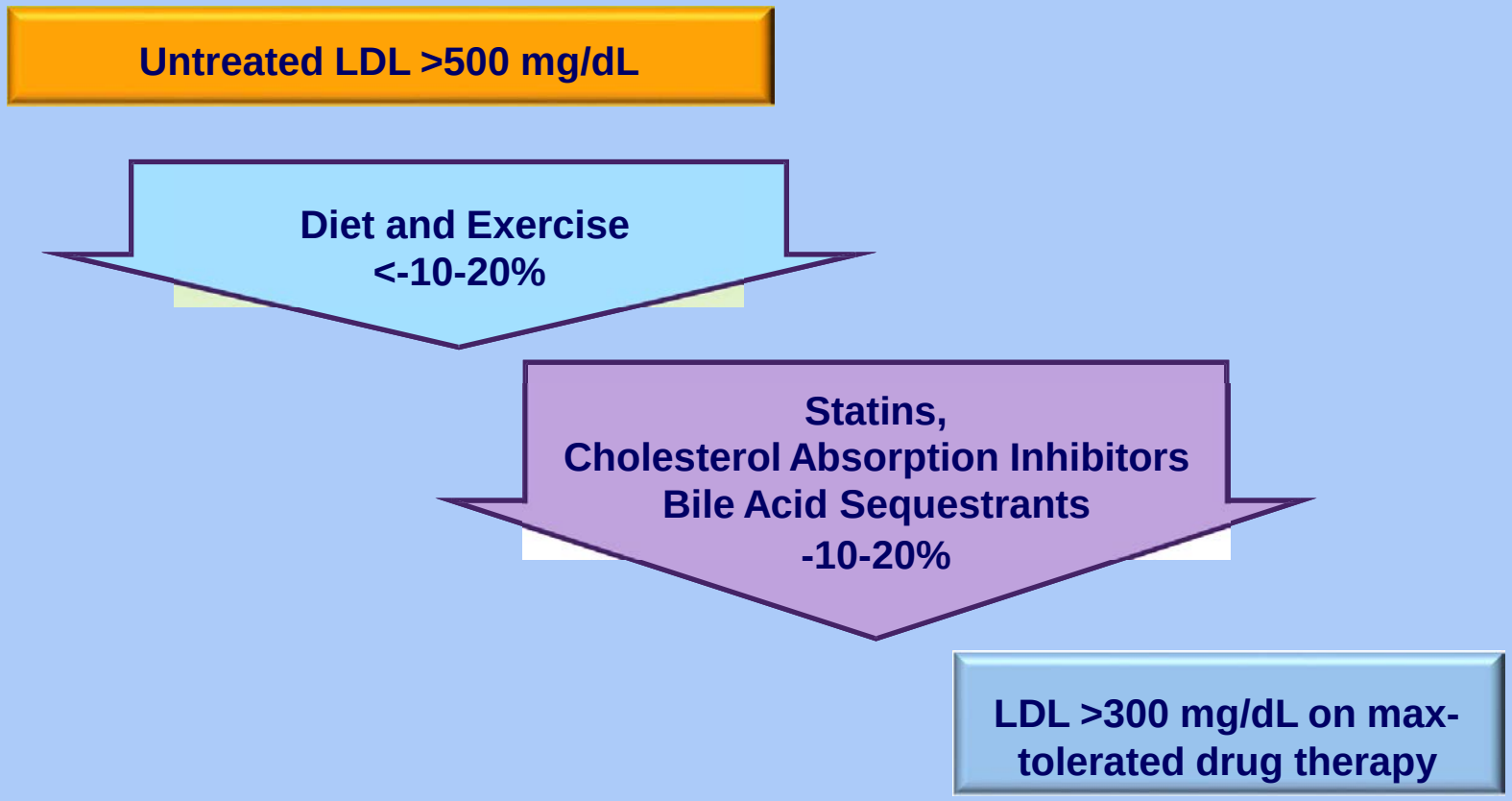
Multiple Diagnostic Criteria, Lack of Consensus in Medical Literature for HoFH:

Publication	Diagnostic criteria for HoFH
Seftel et al. [4]	• Serum cholesterol concentration >14.3 mmol/L (550 mg/dL) • Appearance of xanthomas during first decade of life • Hypercholesterolemia or clinical signs of hypercholesterolemia in both parents
Moorjani et al. [5]	• Plasma cholesterol levels >550 mg/dL • Appearance of xanthomas at an early age • Detection of hypercholesterolemia in both parents
Haitas et al. [8]	• Hypercholesterolemia in both parents (when available) • Total serum cholesterol >13 mmol/L (500 mg/dL) + presence of xanthomas in first decade of life
Raal et al. [9,10]	• Untreated serum LDL consistently >12 mmol/L (463 mg/dL) • Appearance of xanthomas in first decade of life • Hypercholesterolemia, or its clinical features, documented in both parents • Confirmation by DNA analysis for LDLR mutations
Goldstein [2]	• Unique yellow-orange cutaneous xanthomas (frequently present at birth) • Tendon xanthomas, corneal arcus, generalized atherosclerosis during childhood • Plasma cholesterol >650 mg/dL in non-jaundiced child
Gagne et al. [11]	Two mutant alleles at LDLR confirmed by genetic testing or • LDL-C ≥ 220 mg/dL (5.69 mmol/L) while receiving lipid-lowering therapy at the highest tolerated dose (<15% response) • LDL-C > 90th percentile in ≥ 2 first-degree relatives • Presence of tendonous xanthomas and/or manifestations of premature coronary heart disease or corneal arcus

Publication	Diagnostic criteria for HoFH
Marais et al. [12]	• Childhood cutaneous or tendonous xanthomata • Total cholesterol >15 mmol/L (600 mg/dL) • Both parents should have severe hypercholesterolemia (>7.5 mmol/L or 300 mg/dL) or tendonous xanthomas • Family history of premature ischemic heart disease
Kolansky et al. [13]	Total cholesterol >500 mg/dL Xanthomas at an early age Presence of hypercholesterolemia in proband's parents or other first-degree relative
Marais et al. [14]	Clinical criteria: Fasting LDL >500 mg/dL (12.9 mmol/L), triglycerides < 600 mg/dL (6.8 mmol/L) Either xanthomata before age 10 years or FH in both parents Genetic criteria: identification of 2 LDLR gene mutations Functional criteria: <30% uptake compared to normal of LDL and up-regulated fibroblasts
Santos et al. [15]	Untreated LDL >500 mg/dL Plus at least one: • Genetic testing confirmation of 2 mutated LDL-R alleles • Tendonous and/or tuberous xanthoma prior to age 10 years • Documented elevated LDL and both parents consistent with HeFH (LDL >200 mg/dL). If parent unavailable, history of CAD in first-degree relative (male <55 years or female <60 years of age)
Raal et al. [16]	• Untreated LDL cholesterol >13 mmol/L • And either appearance of xanthomas before age 10 years or familial hypercholesterolemia in both parents
Mabuchi et al. [7]	• Juvenile xanthomatosis with plasma cholesterol about 2 times that of parents or other family members with HeFH • Genetic diagnostic criteria: true homozygosity, compound heterozygosity, or double heterozygosity for FH genes

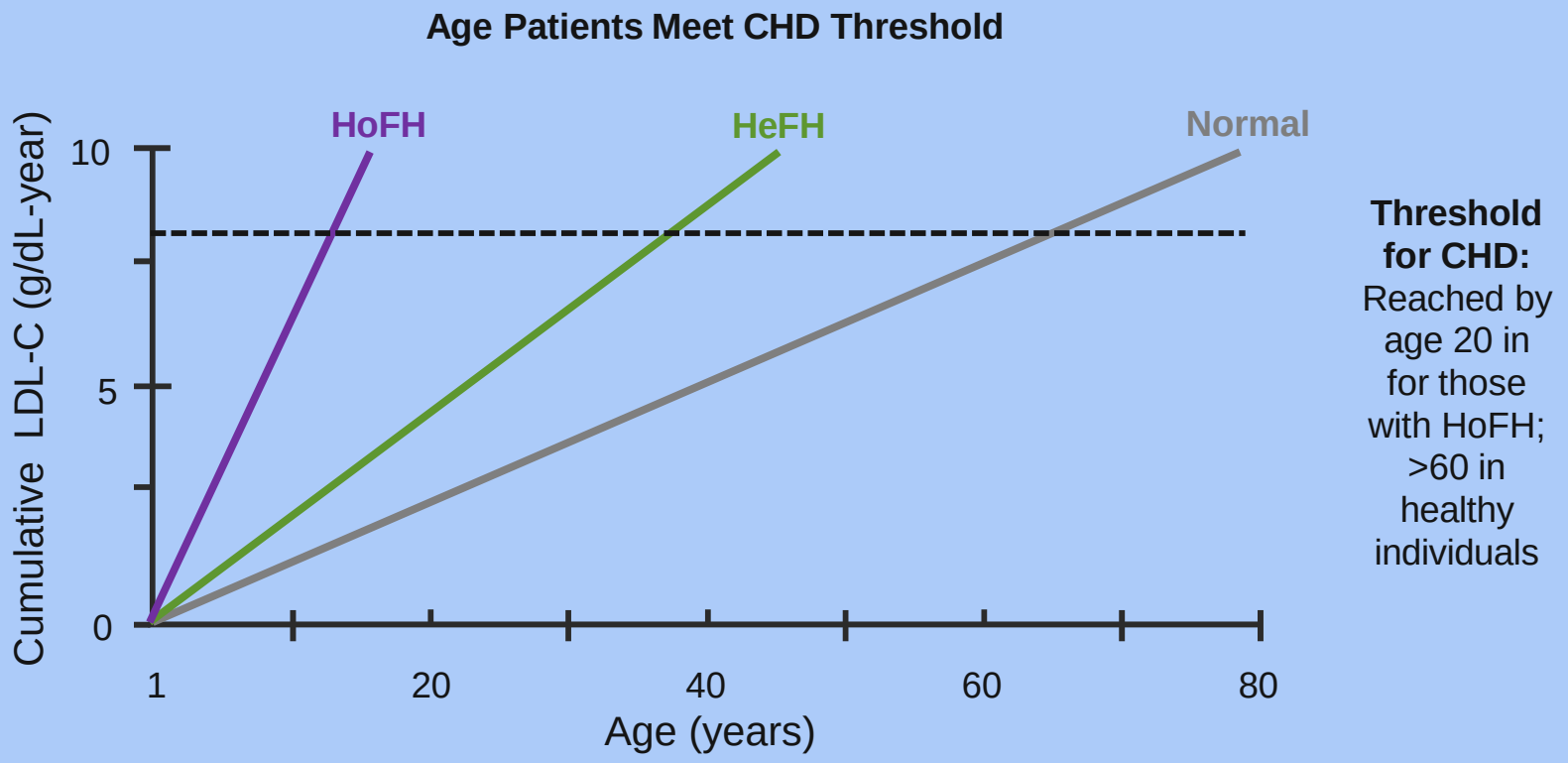
1. Adapted from Raal FJ, Santos RD. Atherosclerosis. 2012;223:262-268

Illustration of LDL-C Levels in HoFH



1. Goldberg A, et al. *J Clin Lipidol.* 2011;5:S1-S8.
2. Raal FJ, et al. *Lancet*. 2010;375:998-1006.

In HoFH, Lifelong Exposure to Extreme Levels of LDL-C Leads to Early CHD



The safety and effectiveness of KYNAMRO® (mipomersen sodium) injection have not been established in pediatric patients.

HeFH = heterozygous familial hypercholesterolemia; HoFH = homozygous familial hypercholesterolemia; CHD = coronary heart disease

Adapted from Horton JD, et al. *J Lipid Res*. 2009;50(suppl):S172-S177.

In HoFH, Atherosclerosis May Often Present as Aortic Stenoses

- Coronary arteries and the aortic root, including the valve, are known to be the affected site of atherosclerosis in HoFH[1]

- HoFH patients are more likely to present with severe aortic valvular and supravalvular stenosis of the ascending aorta[2]

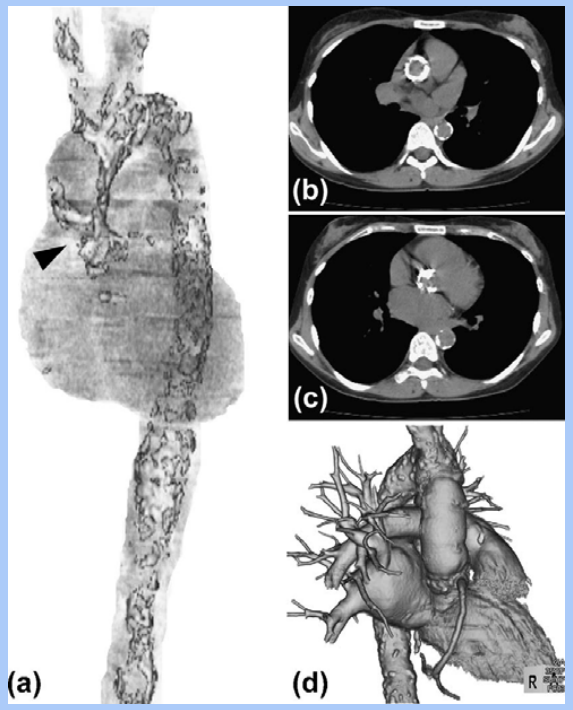
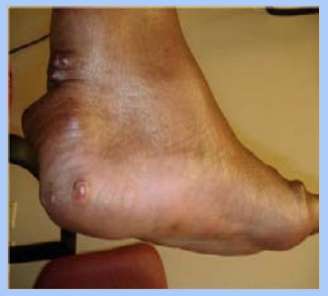


Fig (a) Unenhanced 3-dimensional computed tomography (CT) showed supravalvular stenosis (arrow), funneling of ascending aorta and calcification of the entire aorta. (b and c) Preoperative 2-dimensional CT. (d) Postoperative enhanced CT.[1]

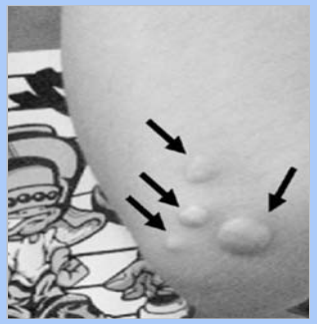
1. Saito S, et al. *Eur J Cardiothorac Surg.* 2006;29(1):114-116.

In some cases, HoFH patients may present with xanthomas or Corneal Arcus

- Xanthomas of the Achilles tendon occur with the more severe forms of FH and are associated with pain[1]



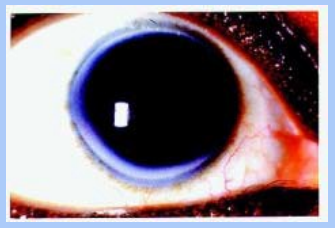
24-year-old female[3]



11-year-old male[2]

- Studies have demonstrated skin disorders can greatly affect QoL, and are strongly linked to emotional stress

- Corneal Arcus



1. Scheel AK et al., Atherosclerosis. 2004;174(1):133-139.
2. Ohshiro T, et al. *J Atheroscler Thromb.* 2009;16(5):698-701.
3. East He, et al. Familial hypercholesterolemia in African Americans. Poster presented at ENDO 2011

Genetic Disorders, Premature CHD, and HoFH are Associated with Emotional Impact on QOL

- Genetic diseases have a recognized emotional impact
- HoFH patients have been associated with emotional impact on QoL:
  - Even when treated effectively, significant anxiety about developing CHD[4]
  - Increased anxiety about the anticipated CHD in a loved one
  - Worry about passing on 'bad genes'[2]
    - 80% of parents of children with FH report suffering distress because of the child's illness[3]
    - 38% of parents state that the disorder was an emotional burden on the family[3]

Please Note: KYNAMRO® (mipomersen sodium) injection is not indicated to reduce anxiety or improve quality of life in patients with HoFH

1. McAllister M, et al. *Am J Med Genet A*. 2007;143A(22):2651-2661.
2. Ågård A, Bolmsjö IÅ, Hermerén G, Wahlstöm J. *Patient Educ Couns*. 2005;57(2):162-167.
3. deJongh S, et al. *Acta Paediatr.* 2003;92(9):1096-1101.
4. Hollman G et al. *Prev Med* 2003;36:569-574.

Summary

- HoFH is a rare, genetic lipid disorder characterized by extreme hypercholesterolemia and early and/or progressive atherosclerosis
- True prevalence of HoFH may be **underestimated** because of inadequate data and under-diagnosis
- Although HoFH may be **diagnosed in childhood, it may also go undiagnosed**
- into adulthood
- Genetic testing is generally **not needed** for diagnosis
- **Multiple clinical diagnostic criteria exist for HoFH: There is a lack of consensus in medical literature**
- Clinical diagnostic criteria may include factors such as: very high lipid levels, presence of premature CHD, family history of premature CHD or hypercholesterolemia,physical findings if present (e.g. planar xanthomas)

Understanding The Liver

The Liver and Its Functions

- Largest organ in the body
  - Weighs approximately 3 lbs.
- Functions:
  - Filters blood coming from the digestive tract, before passing it to the rest of the body
  - Detoxifies chemicals and metabolizes drugs
  - Secretes bile that ends up back in the intestines
  - Makes proteins important for blood clotting and other functions

http://www.webmd.com/digestive-disorders/picture-of-the-liver. Accessed June 16, 2014.

Image purchased from canstockphoto.com

Liver Function Panel and Tests (LFTs): Why and How They Are Done

- Liver function tests check the levels of certain enzymes and proteins in your blood[1]
- Liver function tests can be used to:
  - Screen for liver infections[1], gallbladder[2], and biliary tract[2] abnormalities
  - Monitor the progression of a disease, such as viral or alcoholic hepatitis, and determine how well a treatment is working[1]
  - Measure the severity of a disease, particularly scarring of the liver (cirrhosis)[1]
  - Monitor possible side effects of medications[1]
- LFTs are performed via a blood draw. Blood samples are sent to a laboratory for testing.[3]

1. http://www.mayoclinic.org/tests-procedures/liver-function-tests/basics/why-its-done/prc-20012602. Accessed July 1, 2014.
2. http://www.merckmanuals.com/home/liver_and_gallbladder_disorders/diagnosis_of_liver_gallbladder_and_biliary_disorders/tests_for_liver_gallbladder_and_biliary_disorders.html. Accessed August 28, 214.
3. http://www.healthline.com/health/liver-function-tests#Procedure. Accessed July 1, 2014.

Common Liver Function Panel and Tests (LFTs)

- Liver function panel checks how well the liver is working and consists of many different blood tests[1]

Liver Test	What Test Is Reporting[1]	Normal Range[2]
Alanine aminotransferase (ALT)	Measures the amount of this enzyme in the blood; measured to see if the liver is damaged or diseased. Low levels of ALT are normally found in the blood. When the liver is damaged or diseased, it releases ALT into the bloodstream.	0 -40 (IU/L)
Aspartate aminotransferase (AST)	Measures the amount of this enzyme in the blood; when body tissue or an organ such as the heart or liver is diseased or damaged, additional AST is released into the bloodstream. The amount of AST in the blood is directly related to the extent of the tissue damage.	10 -34 (IU/L)
Alkaline phosphatase (ALP)	Measures the amount of the enzyme ALP in the blood; made mostly in the liver and in bone; the amounts of different types of ALP in the blood may be measured and used to determine whether a high level is from the liver or bones.	44 -147 IU/L
Bilirubin	Measures the amount of bilirubin in a blood sample; Produced when the liver breaks down old red blood cells; When bilirubin levels are high, the skin and whites of the eyes may appear yellow (jaundice).	Direct: 0 -0.3 mg/dL

1. http://www.webmd.com/digestive-disorders/picture-of-the-liver. Accessed June 16, 2014.
2. http://www.nlm.nih.gov/medlineplus/ency/article/003436.htm. Accessed June 16, 2014.

Common Causes of Elevated Liver Enzymes

- Certain prescription medications, including statins
- Drinking alcohol
- Heart failure
- Hepatitis A, B, C
- Biliary system abnormalities
- Nonalcoholic fatty liver disease - dysmetabolic syndrome (which includes diabetes mellitus, hypertension, hyperuricemia, hypertriglyceridemia, in women PCOS)
- Obesity
- Over-the-counter pain medications, including acetaminophen

http://www.mayoclinic.org/symptoms/elevated-liver-enzymes/basics/causes/sym-20050830. Access August 16, 2014.

Important Terminology

Terminology	Definition
Prothrombin time (PT)	A test of the time it takes for a blood sample to clot, under specific conditions in a lab. If low levels of clotting factors are present, the prothrombin time is longer. PTT is partial thromboplastin time.[1] A PT test evaluates the coagulation factors VII, X, V, II, and I (fibrinogen).[2]
Partial Thromboplastin Time (PTT)	May be ordered along with a PT test to evaluate hemostasis, the process that the body uses to form blood clots to help stop bleeding. The PTT evaluates the coagulation factors XII, XI, IX, VIII, X, V, II (prothrombin), and I (fibrinogen) as well as prekallikrein (PK) and high molecular weight kininogen (HK).[2]
International normalized ratio (INR)[1]	A standardized way for all labs to report PT, so their results can be compared accurately with each other.
Childs Pugh[3]	A score that is used with the Model for End-Stage Liver Disease (MELD) to determine priority for liver transplantation.

- PT and INR rise in people with **severe** liver disease because the liver fails to make normal amounts of certain clotting factors.[1]

1. http://www.webmd.com/a-to-z-guides/liver-function-test-lft?page=2. Accessed August 16, 2014.
2. http://labtestsonline.org/understanding/analytes/aptt/tab/test/. Accessed August 16, 2014.
3. http://www.2minutemedicine.com/the-child-pugh-score-prognosis-in-chronic-liver-disease-and-cirrhosis-classics-series/. Accessed September, 12, 2014.

Hy's Law

- Based on Hy Zimmerman's inductive reasoning, term coined by Robert Temple in 1980s as a "biomarker" of drug hepatotoxicity, a signal for potential serious risk. Applied only to hepatocellular toxicity, not to cholestatic reactions or other liver diseases. Adapted from Hy's conclusions.

Hepatocellular Injury

- Elevated aminotransferases (ATs), but at what level?
  - 2x Upper Limit of Normal (ULN), but too common and benign
  - 3x ULN
  - 8x ULN, 10x or greater ULN; what is signal: noise threshold?

Plus Jaundice

- Implies injury that impairs bilirubin excretion, for which there is high capacity before accumulation occurs.
  - Bilirubin threshold 3 mg/dL for seeing jaundice but imprecise
  - Bilirubin 2 mg/dL, 2x ULN, still implies impaired liver function

http://www.fda.gov/downloads/Drugs/ScienceResearch/ResearchAreas/ucm076783.pdf. Access August 16, 2014.

Common Liver Diseases: A Brief Overview

Liver Disease and Potential Causes

- Any disturbance of liver function that causes illness (also referred to as hepatic disease)
- A broad term that covers all the potential problems that cause the liver to fail to perform its designated functions
  - Usually, more than 75% or three quarters of liver tissue needs to be affected before decrease in function occurs

Potential Causes of Liver Disease

- Cells can become inflamed
- Bile flow can be obstructed
- Cholesterol or triglycerides can accumulate
- Blood flow to the liver may be compromised
- Liver tissue can be damaged by chemicals and minerals, or infiltrated by abnormal cells

http://www.medicinenet.com/liver_disease/article.htm. Accessed July 25, 2014.

Common Types of Liver Disease

- Cirrhosis
- Hepatic steatosis (fatty liver)
- Non-alcoholic fatty liver disease (NAFLD)
- Non-alcoholic steatohepatitis (NASH)

Hepatic Steatosis (Fatty Liver)[1]

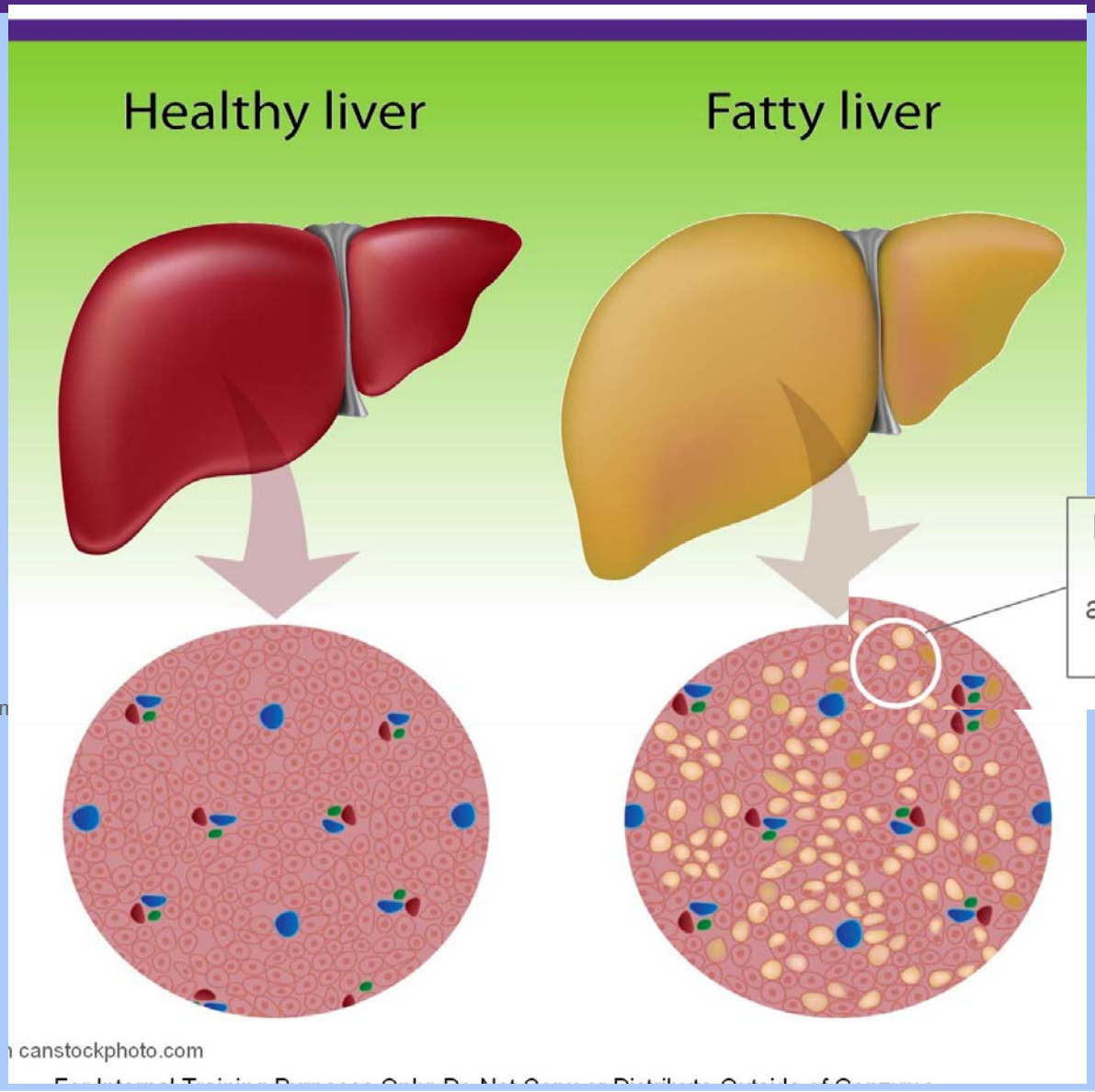
- Characterized by the excessive accumulation of triglycerides in the form of lipid droplets in the liver
- Can be caused by chronic excessive alcohol intake (alcoholic steatosis) or obesity, excessive lipids in the diet (nonalcoholic steatohepatitis, NASH)
- Increases risk of developing hepatocellular carcinoma

Potential Causes of Fatty Liver Disease

Nutritional	Drugs	Metabolic or Genetic	Other
Protein-calorie Malnutrition	Glucocorticoids	Lipodystrophy	Inflammatory bowel disease
Starvation		Dysbetalipoproteinemia and familial hypobetalipoproteinemia[2]	Small bowel overgrowth with bacterial overgrowth
Total Parenteral Nutrition (TPN)		Cholesterol ester storage	HIV infection
Rapid Weight Loss		Webe-Christian disease	Environmental hepatotoxins
GI Surgery for Obesity	Antiviral agents	Wolman's disease	Bacillus cereus toxins

1. National Health and Nutrition Examination Survey (NHANES) III. Hepatic Steatosis Ultrasound Images Assessment Procedures Manual. November 2010.
2. http://ghr.nlm.nih.gov/condition/familial-hypobetalipoproteinemia. Accessed September 2, 2014.

Hepatic Steatosis (Fatty Liver)



from

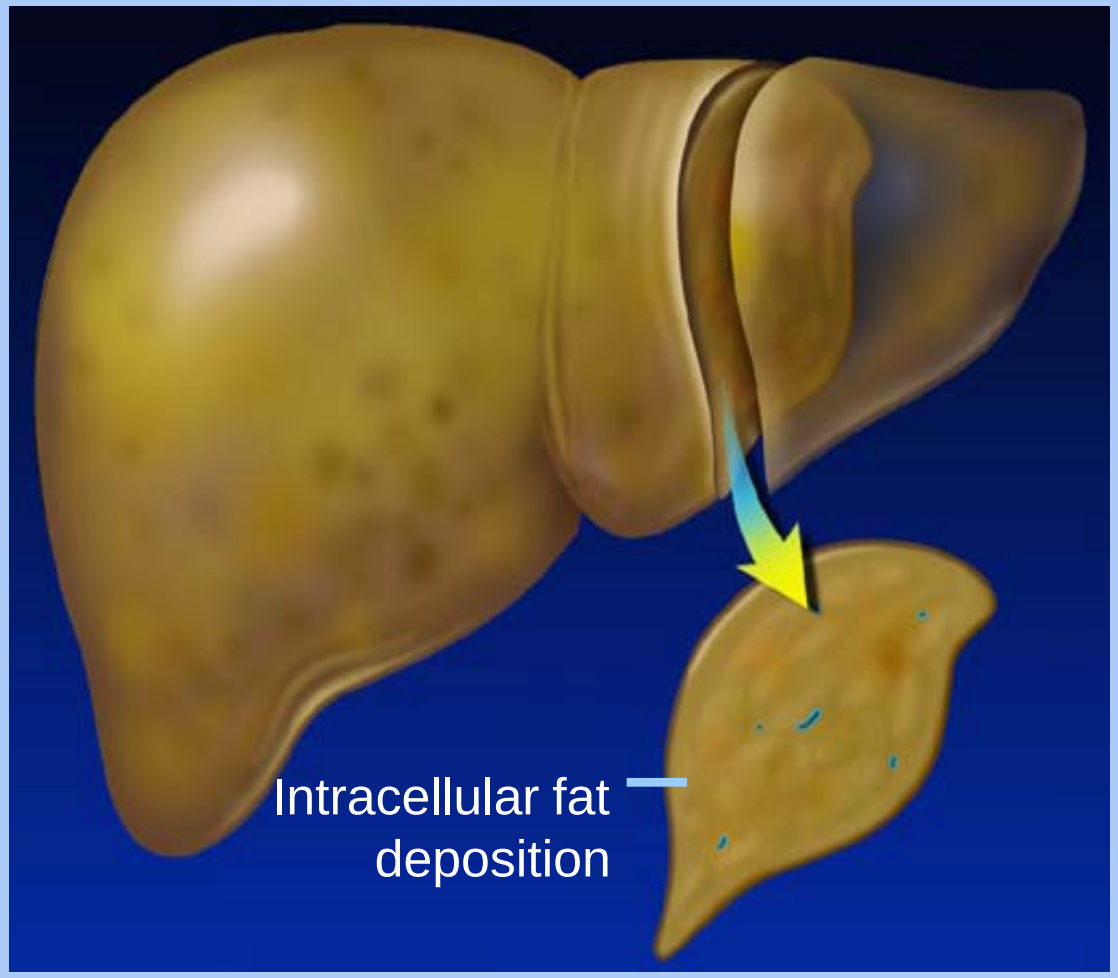
Image purchased

canstockphoto.com

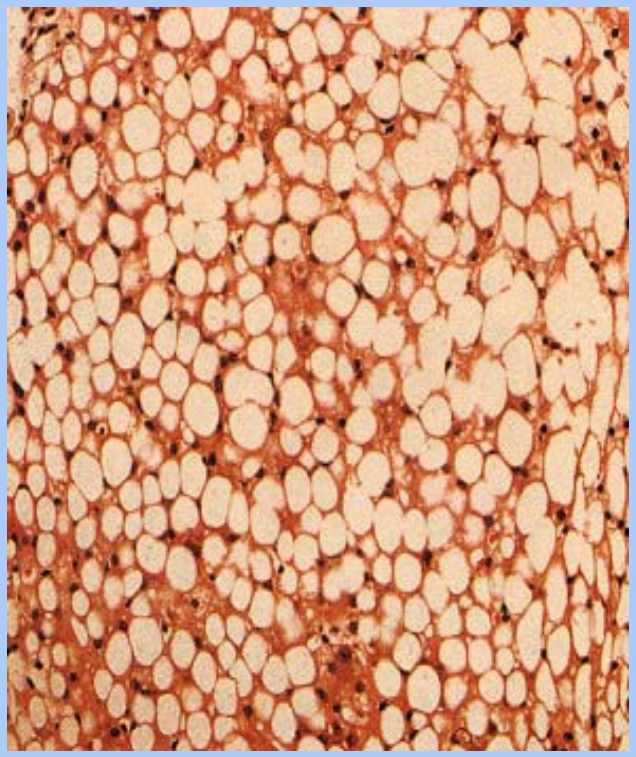
Non-alcoholic Fatty Liver Disease (NAFLD)

- Alcohol-like liver disease characterized by hepatic triglyceride accumulation in individuals who do not consume excessive alcohol
- Clinical course of NAFLD dictated by histopathology
  - NAFL – Simple steatosis - Benign
  - NASH – Steatosis + inflammation (steatohepatitis) - Aggressive

Non-alcoholic Fatty Liver (NAFL) Steatosis



Simple Steatosis



www.gastroslides.org

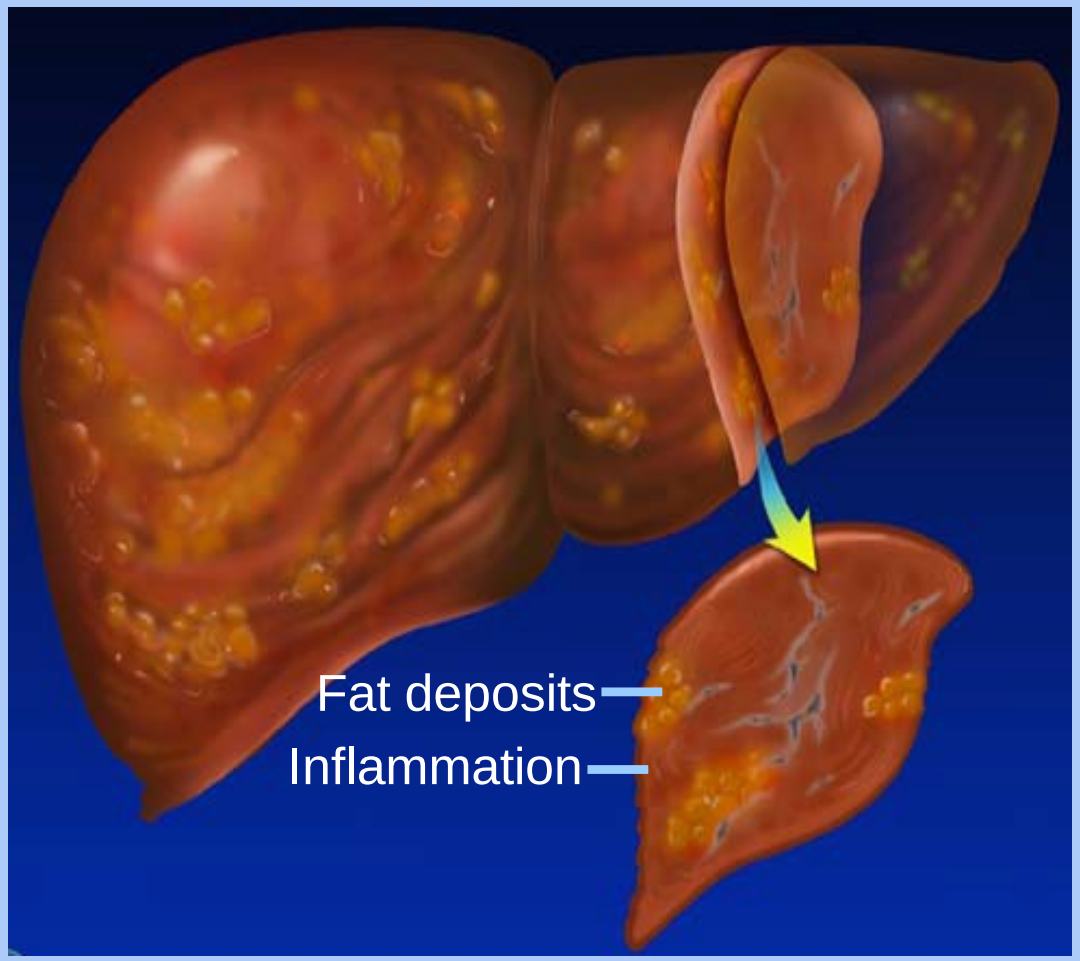
Non-alcoholic Steatohepatitis (NASH)

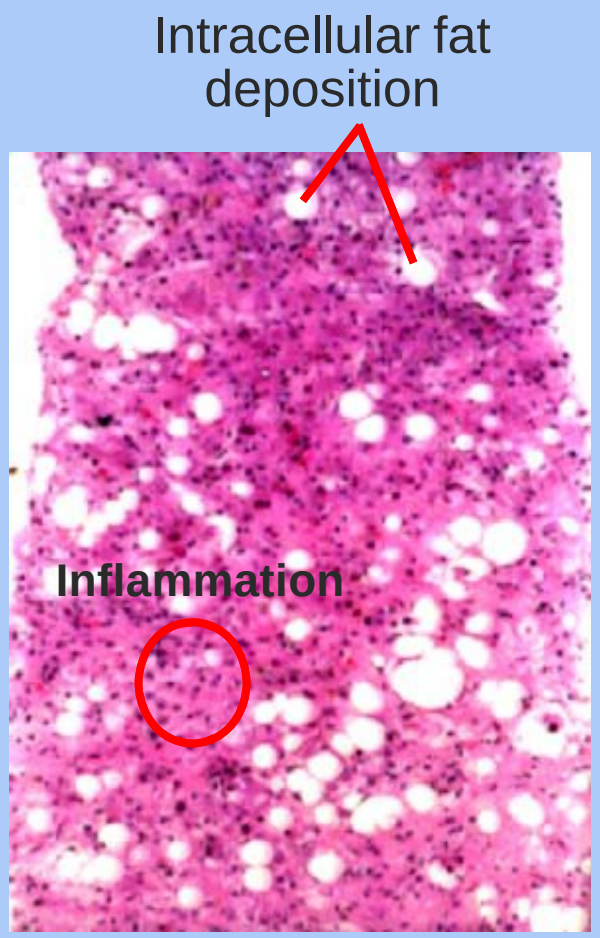
- Often called “silent” liver disease
  - Resembles alcoholic liver disease, but occurs in people who drink little or no alcohol
- Major feature: fat in the liver; inflammation and damage
  - Can lead to cirrhosis
- Affects 2 to 5% of Americans

Causes	Still not clear; most often occurs in persons who are middle-aged and overweight or obese
Symptoms	Few or no symptoms; patients generally feel well in the early stages and only begin to have symptoms (i.e., fatigue, weight loss, and weakness) once disease is more advanced

http://digestive.niddk.nih.gov/ddiseases/pubs/nash/. Accessed June 16, 2014.

Non-alcoholic Steatohepatitis (NASH)





www.gastro.org

Cirrhosis[1]

- Slowly progressing disease in which healthy liver tissue is replaced with scar tissue, eventually preventing the liver from functioning properly
  - Scar tissue blocks the flow of blood through the liver and slows the processing of nutrients, hormones, drugs, and naturally produced toxins
- 12th leading cause of death by disease

Most Common Causes	Hepatitis C, fatty liver, and alcohol abuse
Symptoms	Loss of appetite, lack of energy (fatigue), which may be debilitating, weight loss or sudden weight gain, bruises, yellowing of skin or the whites of eyes (jaundice), itchy skin, fluid retention (edema) and swelling in the ankles, legs, and abdomen (often an early sign)

1. http://www.webmd.com/digestive-disorders/cirrhosis-liver?page=2. Accessed July 1, 2014.

Cirrhosis

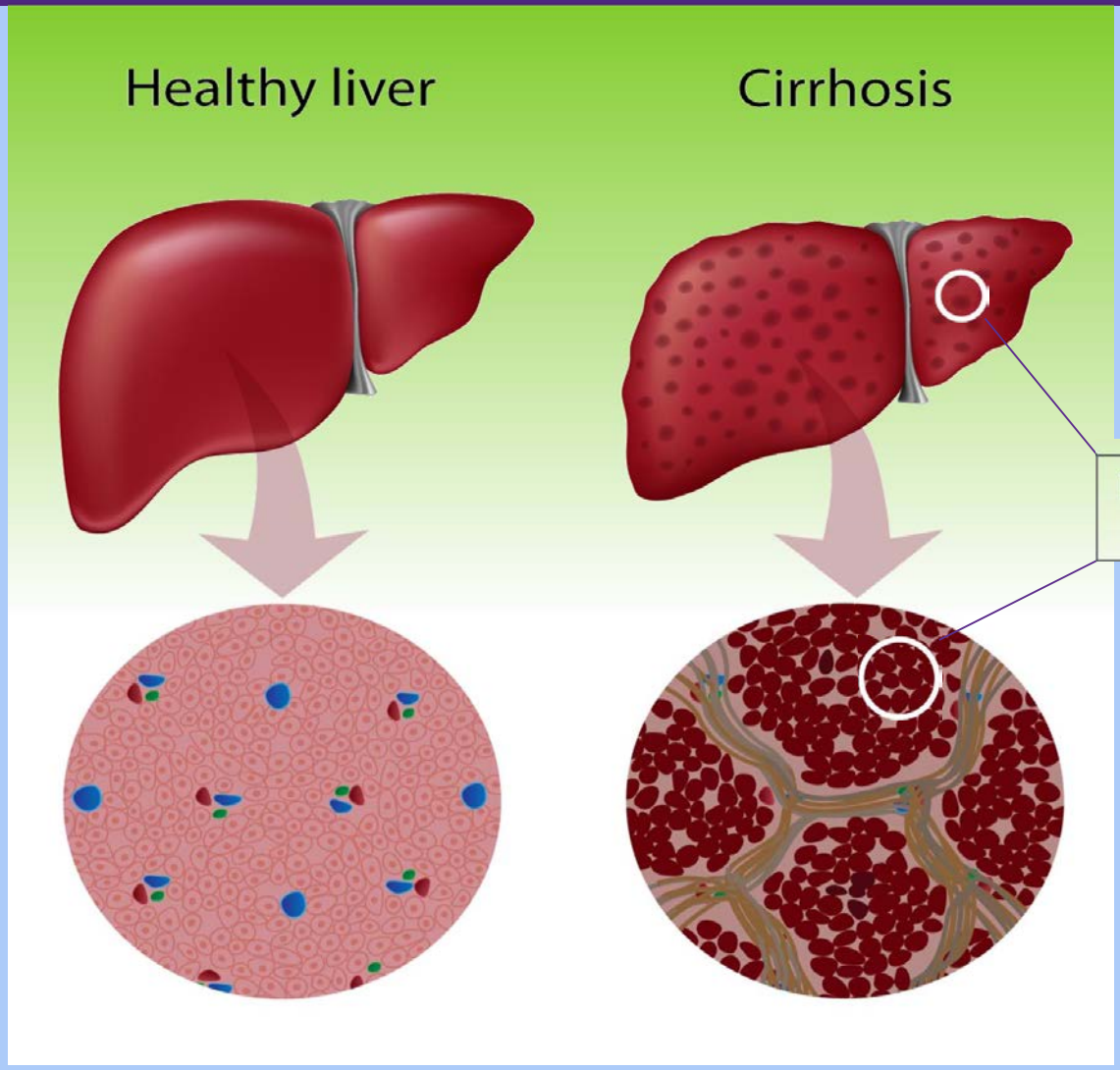


Image purchased from canstockphoto.com

Summary