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Diagnosis and Clinical Appraisal

Objectives

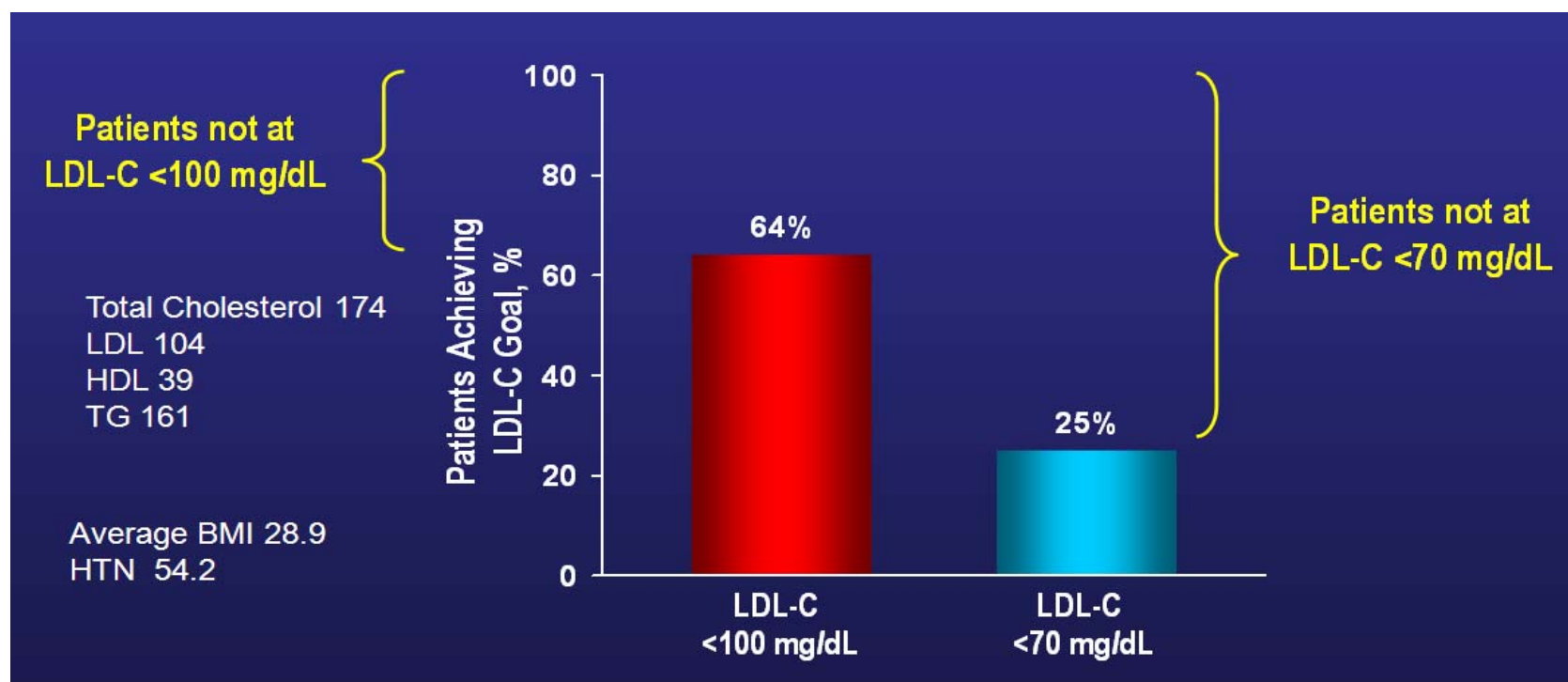
- Compare and contrast the effectiveness of available risk assessment instruments and markers in predicting CV risk in all population groups
- Identify primary and secondary causes of dyslipidemia

Outline

- Risk assessment
- Secondary dyslipidemias
- Genetic (primary) dyslipidemias
- Other risk factors (RF)

GWTG: Patients on Lipid-Lowering Therapy Prior to Hospitalization^a for CHD – Percentage at LDL-C <100 mg/dL or <70 mg/dL¹

Study population included patients with ACS, stable CAD hospitalized for revascularization, and patients with documented CAD hospitalized for reasons other than heart failure

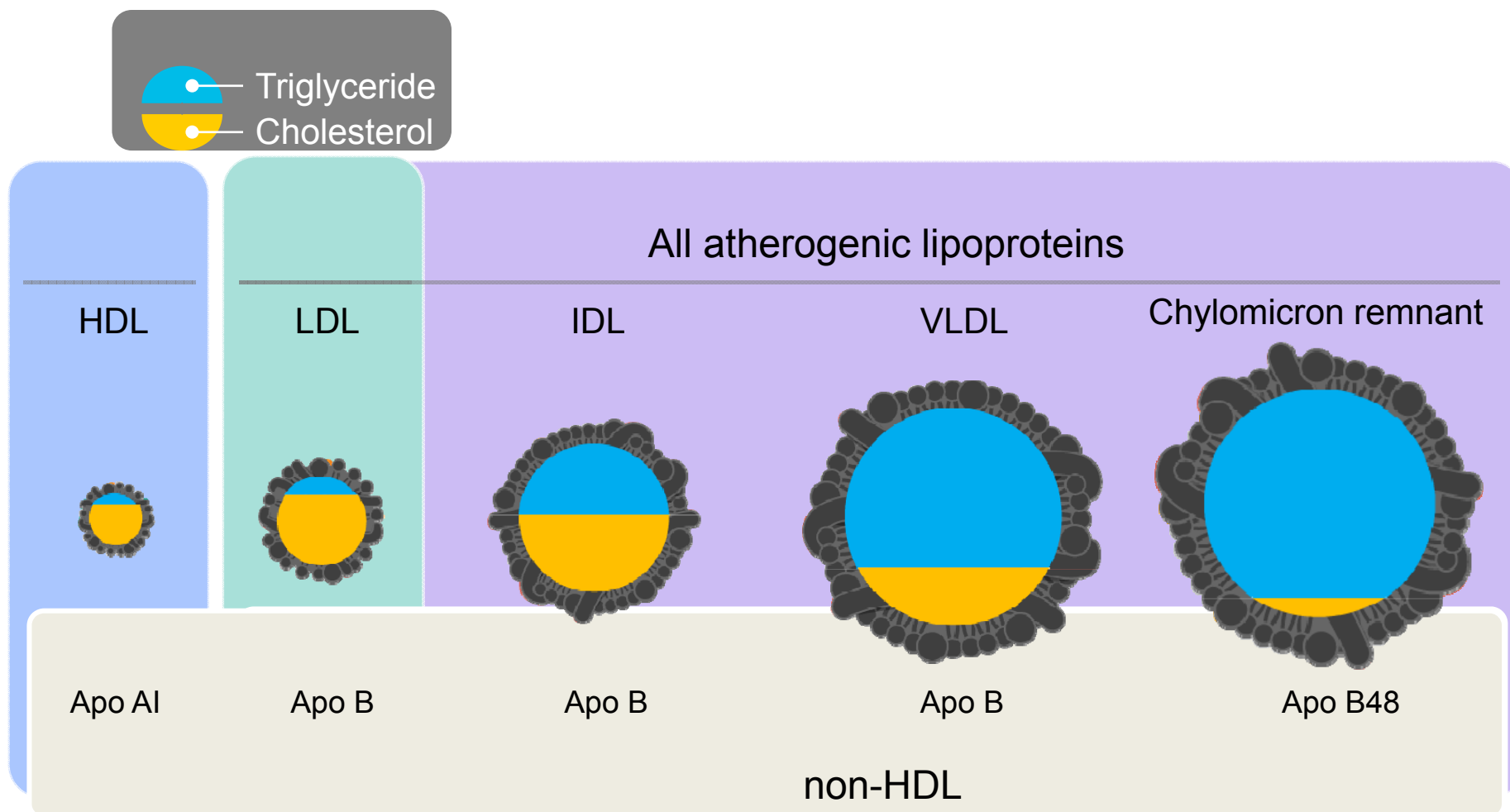


^a(n=28,944)

Adapted from Sachdeva A, et al. *Am Heart J.* 2009;157:111-117. e112.

GWTG= Get With The Guidelines; ACS = acute coronary syndrome; CAD=coronary artery disease

Non-HDL-C Schematic



$$\text{Non-HDL-C} = \text{Total cholesterol} - \text{HDL-C}$$

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

American Diabetes Association/American College of Cardiology Consensus Statement

Treatment Goals in Patients with Cardiometabolic Risk and Lipoprotein Abnormalities

	LDL-C (mg/dL)	Non- HDL-C (mg/dL)	Apo B (mg/dL)
Highest-risk patient – Known CVD – Diabetes plus ≥ 1 additional major CVD risk factor*	<70	<100	<80
High-risk patients – No diabetes or known CVD but ≥ 2 major CVD risk factors* – Diabetes but no other major CVD risk factors*	<100	<130	<90
*Major risk factors beyond dyslipidemia include smoking, hypertension, and family history or premature CHD.			

Evaluations for CHD Risk: Lifetime Risk

- Reflects the cumulative risk of developing CHD during the remainder of an individual's life¹
 - Increases sharply with higher total cholesterol levels at all ages
- Individuals with low or intermediate short-term risk may actually be at high risk in the long term^{2,3}
 - Single risk factor can cause cumulative damage and adverse outcomes if left untreated for many years²
 - Risk factors used to estimate lifetime risk: smoking status, diabetes, hypertension, total cholesterol⁴

1. Lloyd-Jones DM, et al. *Arch Intern Med.* 2003;163:1966-1972.
2. Lloyd-Jones DM, et al. *Am J Cardiol.* 2004;94:20-24.
3. Berry JD, et al. *Circulation.* 2009;119:382-389.
4. Lloyd-Jones DM, et al. *Lancet.* 1999;353: 89-92.

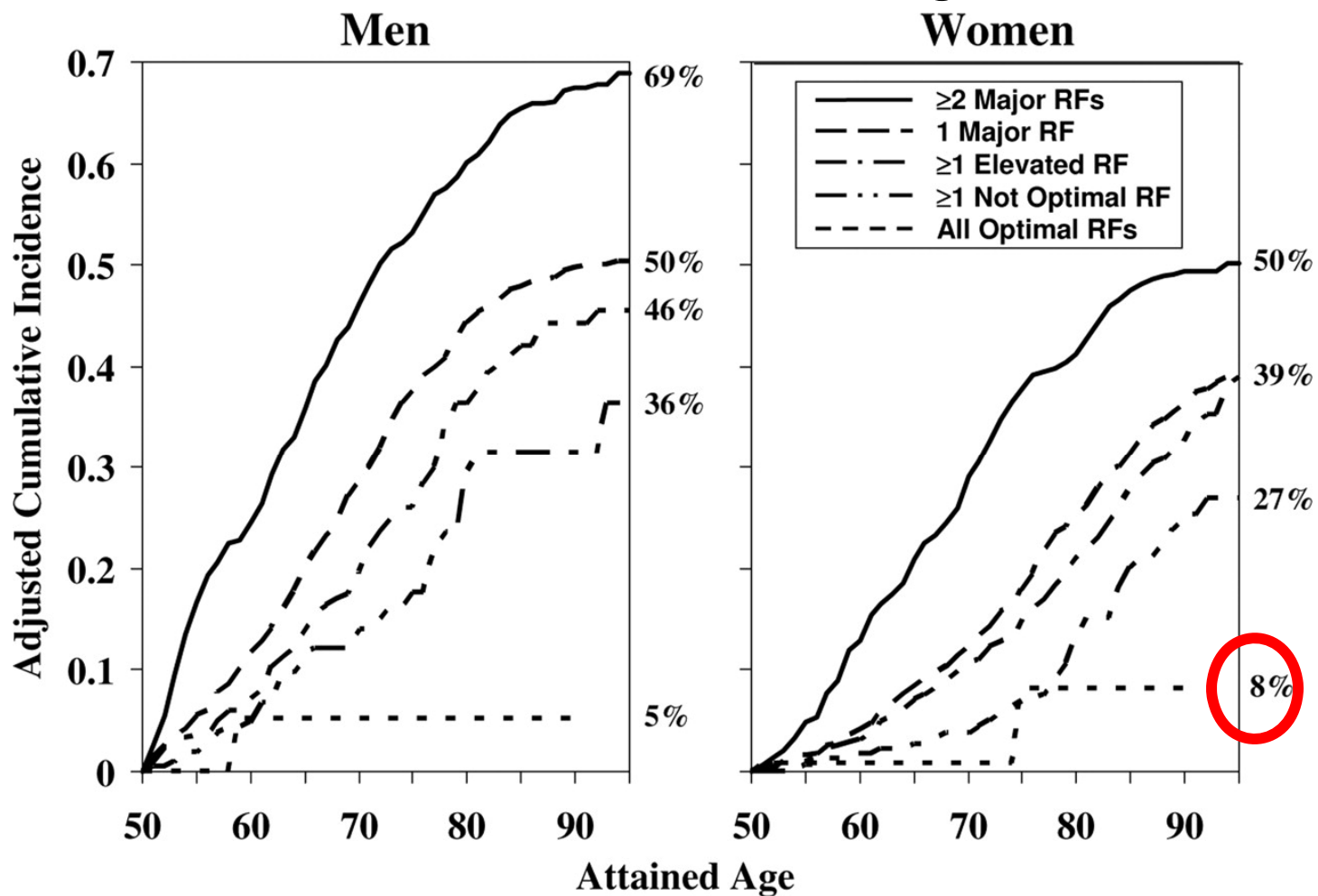
Benefits of Assessing Lifetime Risk

- An important adjunct to short-term (10-year) risk estimation¹
 - Helps identify individuals with hidden long-term risk^{1,2}
 - Improves risk communication
 - Motivates low short-term risk patients to adopt therapeutic lifestyle changes^{1,2}
 - Promotes adherence to medications¹

1. Lloyd-Jones DM, et al. *Curr Opin Lipidol*. 2006;17:619-625.

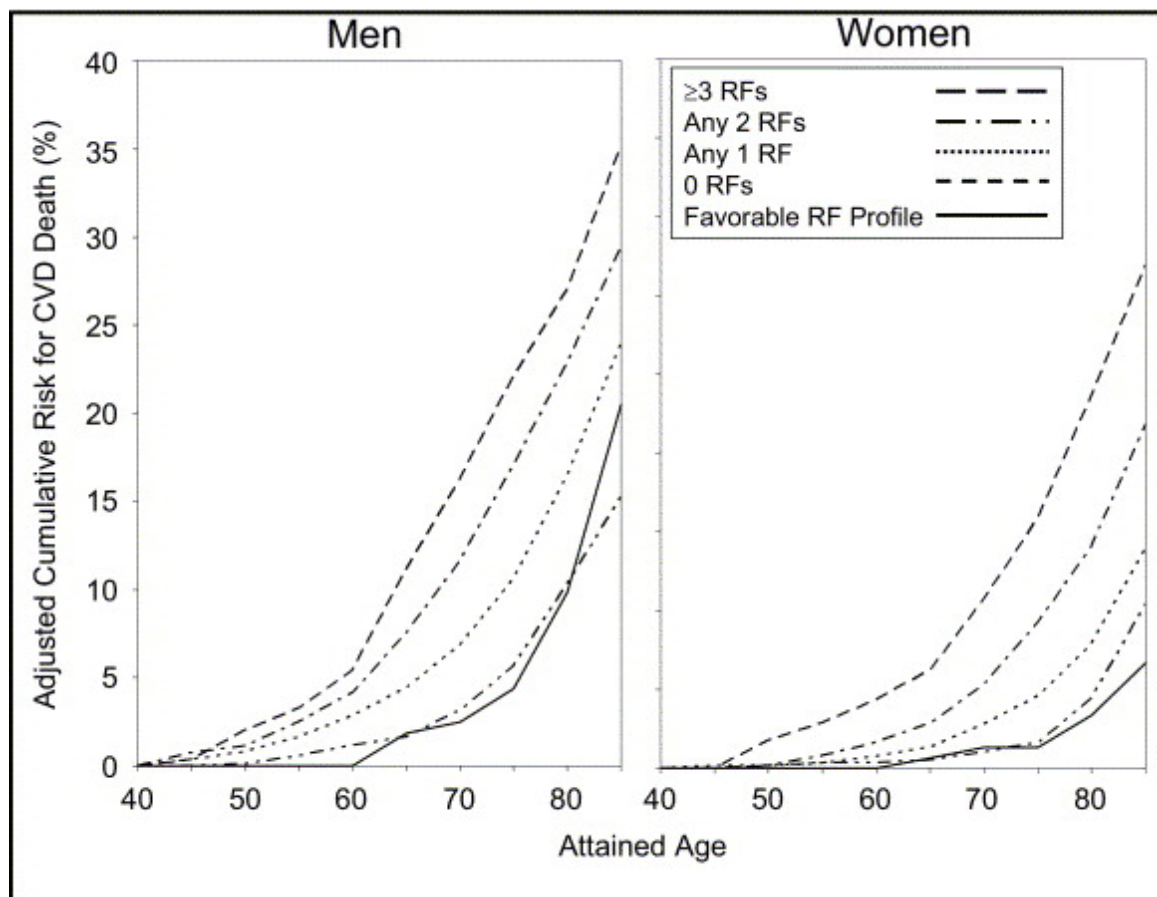
2. Berry JD, et al. *Circulation*. 2009;119:382-389.

Cumulative Incidence of CVD Adjusted for the Competing Risk of Death for Men and Women According to Aggregate Risk Factor (RF) Burden at 50 Years of Age



Lloyd-Jones DM, et al. *Circulation*. 2006;113:791-798.

Cumulative Risks for Death Due to CVD, Adjusted for the Competing Risk for Non-CVD Death, by Risk Factor (RF) Burden in Men and Women Who Were Aged 40 to 59 Years at Baseline



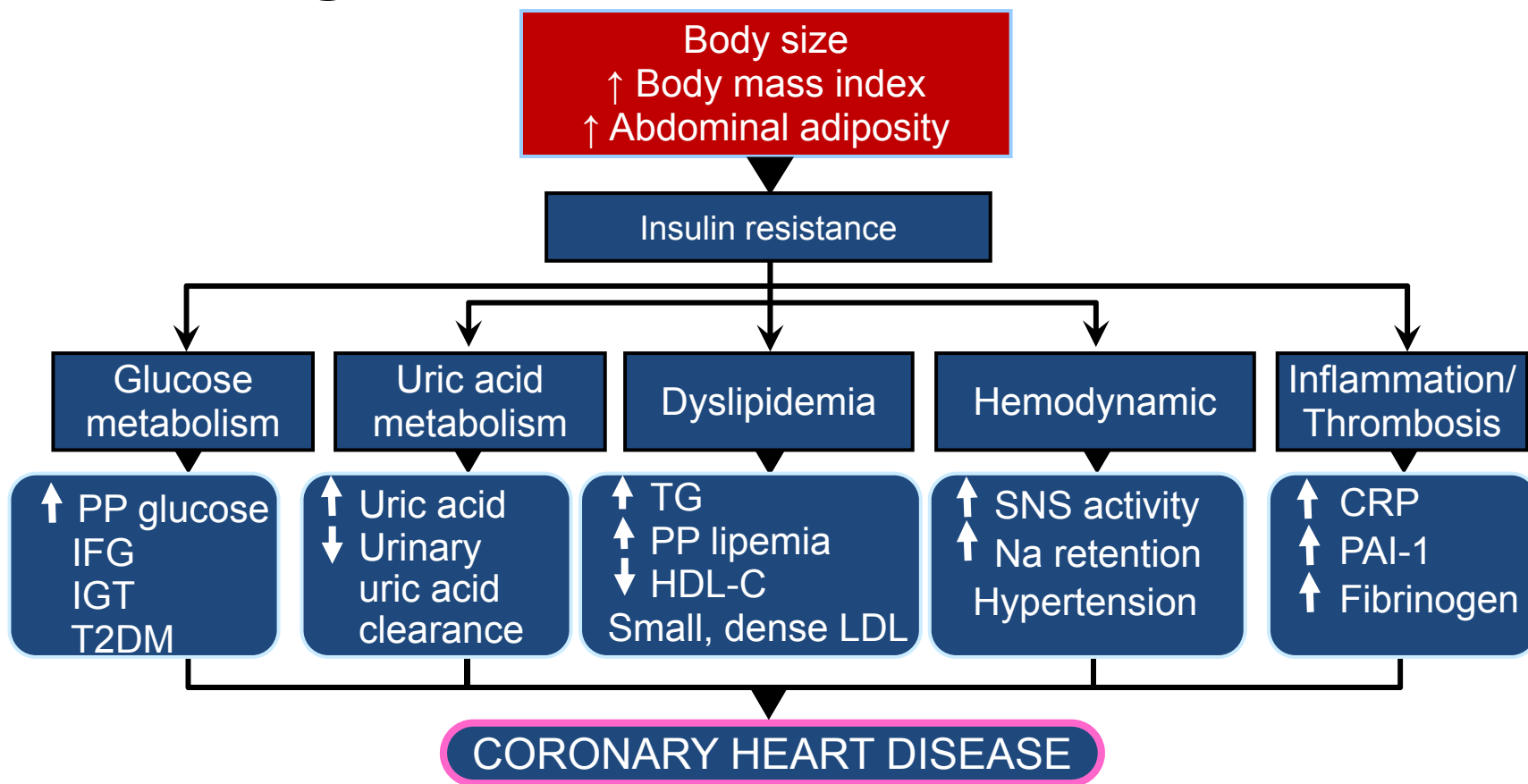
Lloyd-Jones DM, et al. *Am J Cardiol.* 2007;99:535-540.

Friedewald Formula

$$\begin{array}{l} \text{LDL Cholesterol} \\ \text{HDL Cholesterol} \\ + \text{VLDL Cholesterol (Triglyceride/5)} \\ \hline \text{Total Cholesterol} \end{array}$$

$$\begin{array}{l} \text{Total Cholesterol} \\ - \text{HDL Cholesterol} \\ - \text{VLDL Cholesterol (Triglyceride/5)} \\ \hline \text{LDL Cholesterol} \end{array}$$

Obesity and Abdominal Adiposity Are Leading Drivers of Cardiometabolic Risk



PP=postprandial, IFG=impaired fasting glucose, IGT=impaired glucose tolerance, T2DM=type 2 diabetes mellitus, TG=triglycerides, PP lipemia= Post-prandial lipemia, HDL-C=high-density lipoprotein cholesterol, LDL=low-density lipoprotein, SNS=sympathetic nervous system, Na=sodium, CRP=c-reactive protein, PAI-1=plasminogen activator inhibitor

Reaven GM. *Diabetes*. 1988;37:1595-1607;
 Reaven GM. *Drugs*. 1999;58(suppl):19-20.

Clinical Identification of the Metabolic Syndrome (NCEP 2005)*

- Elevated waist circumference
 - Men ≥ 40 in (≥ 102 cm)
 - Women ≥ 35 in (≥ 88 cm)
- TG ≥ 150 mg/dL[†]
- HDL-C
 - Men < 40 mg/dL[†]
 - Women < 50 mg/dL[†]
- BP $\geq 130 / \geq 85$ mm Hg[†]
- Fasting glucose ≥ 100 mg/dL[†]

*Diagnosis is established when ≥ 3 of these factors are present.

[†]Patients must either meet the indicated criteria OR be on drug treatment for that factor.

NCEP=National Cholesterol Education Program
BP=Blood Pressure

National Institutes of Health. May 2001. NIH Publication No. 01-3670.

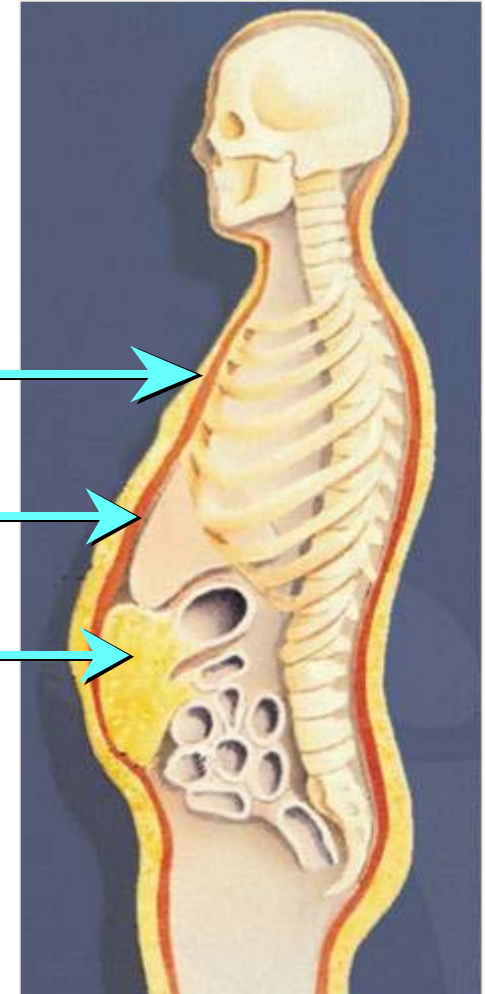
Grundy SM, et al. *Circulation*. 2004;109:551-556.

Grundy SM, et al. *Circulation*. 2005;112:2735-2752.

Abdominal Adiposity: The Critical Adipose Depot



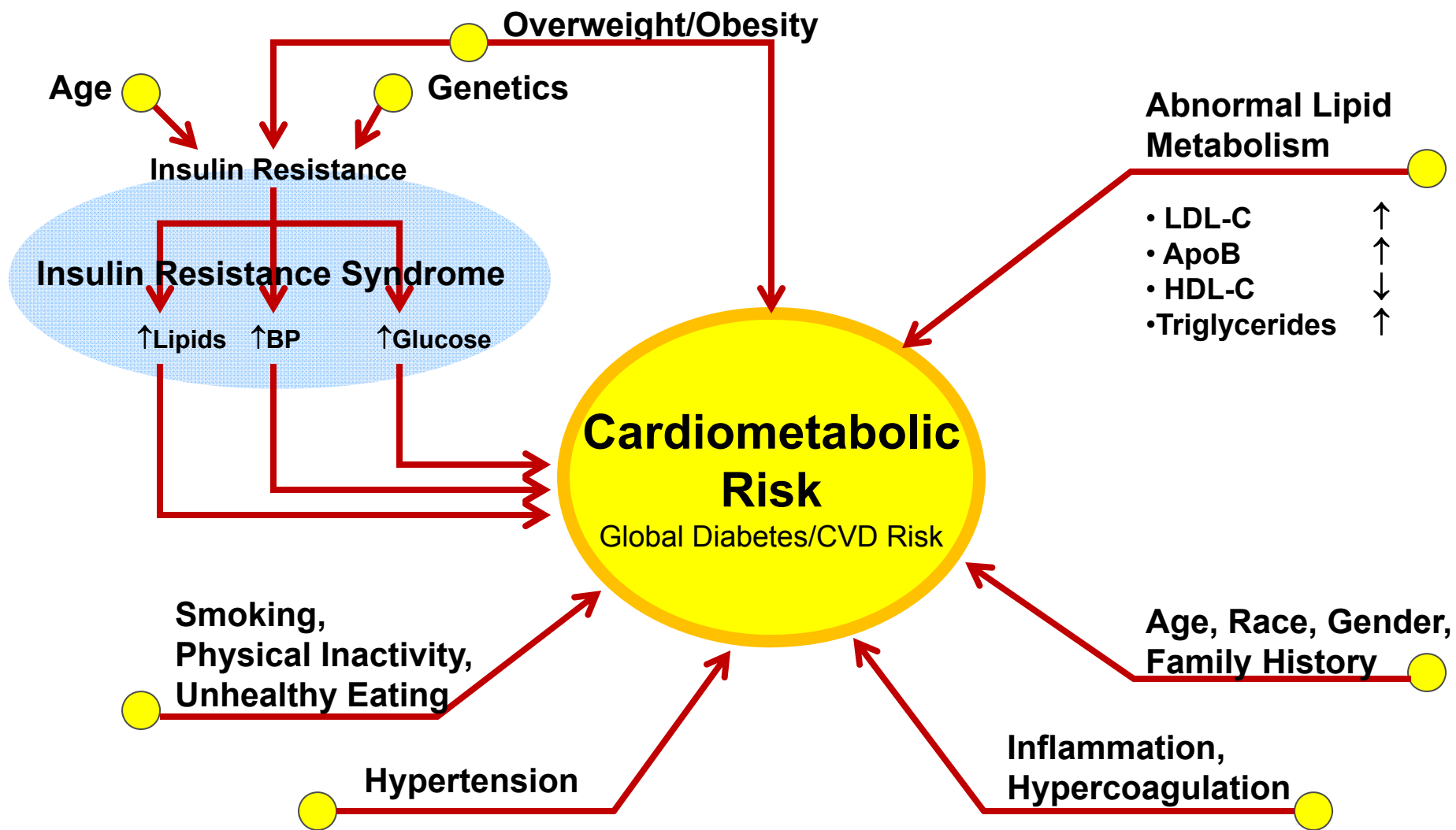
Subcutaneous fat
Abdominal muscle
Intra-layer abdominal fat



Is this where you measure?

Adapted from Despres JP, et al. *BMJ*. 2001;322:716-720.

Factors Contributing: Cardiometabolic Risk

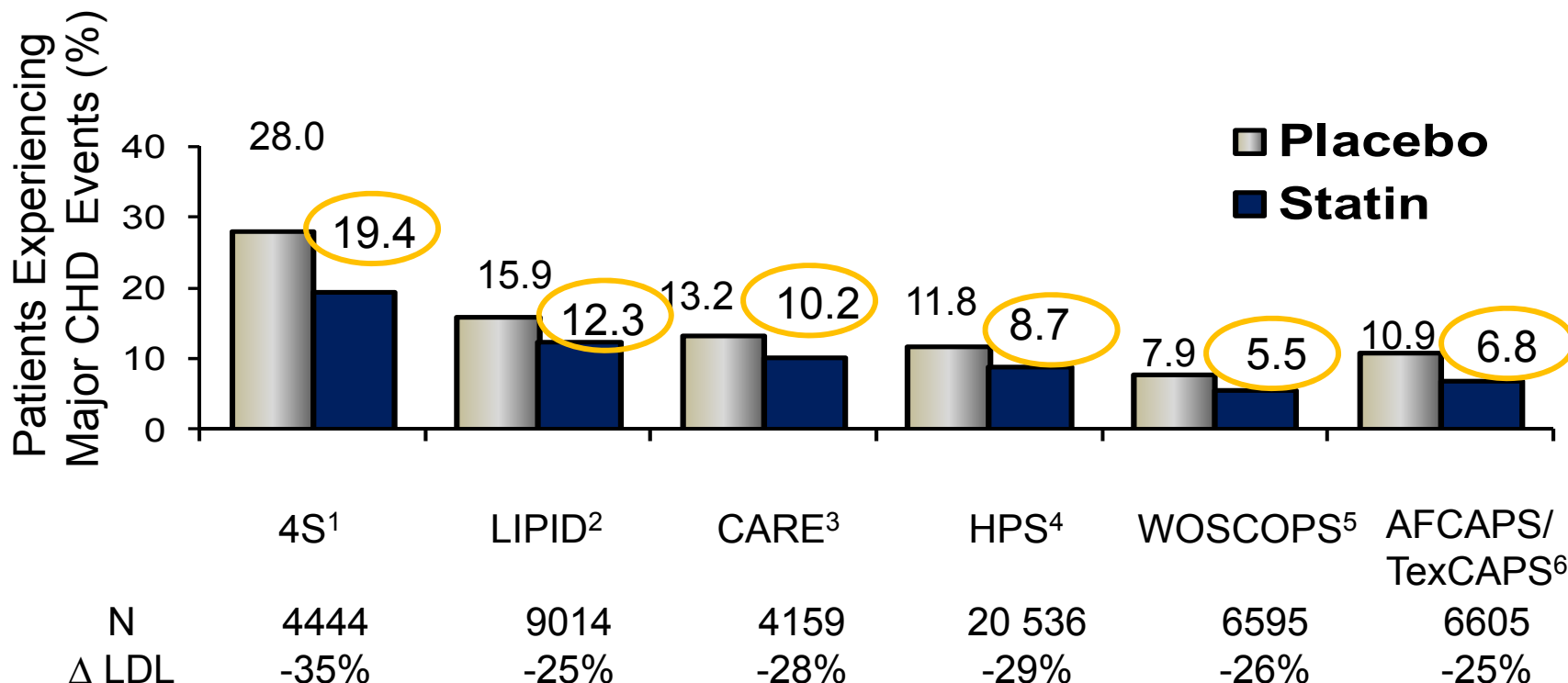


Brunzell JD et al. JACC. 2008;51:1513.

ApoB= Apolipoprotein B

Concept of “Residual Risk” of Cardiovascular Events in patients with Optimal LDL-C Levels

Residual CHD Risk in Statin vs PBO Trials



	4S ¹	LIPID ²	CARE ³	HPS ⁴	WOSCOPS ⁵	AFCAPS/ TexCAPS ⁶
N	4444	9014	4159	20 536	6595	6605
Δ LDL	-35%	-25%	-28%	-29%	-26%	-25%

PBO=Placebo

Secondary

High Risk

Primary

1. 4S Group. *Lancet*. 1994;344:1383-1389.

2. LIPID Study Group. *N Engl J Med*. 1998;339:1349-57.

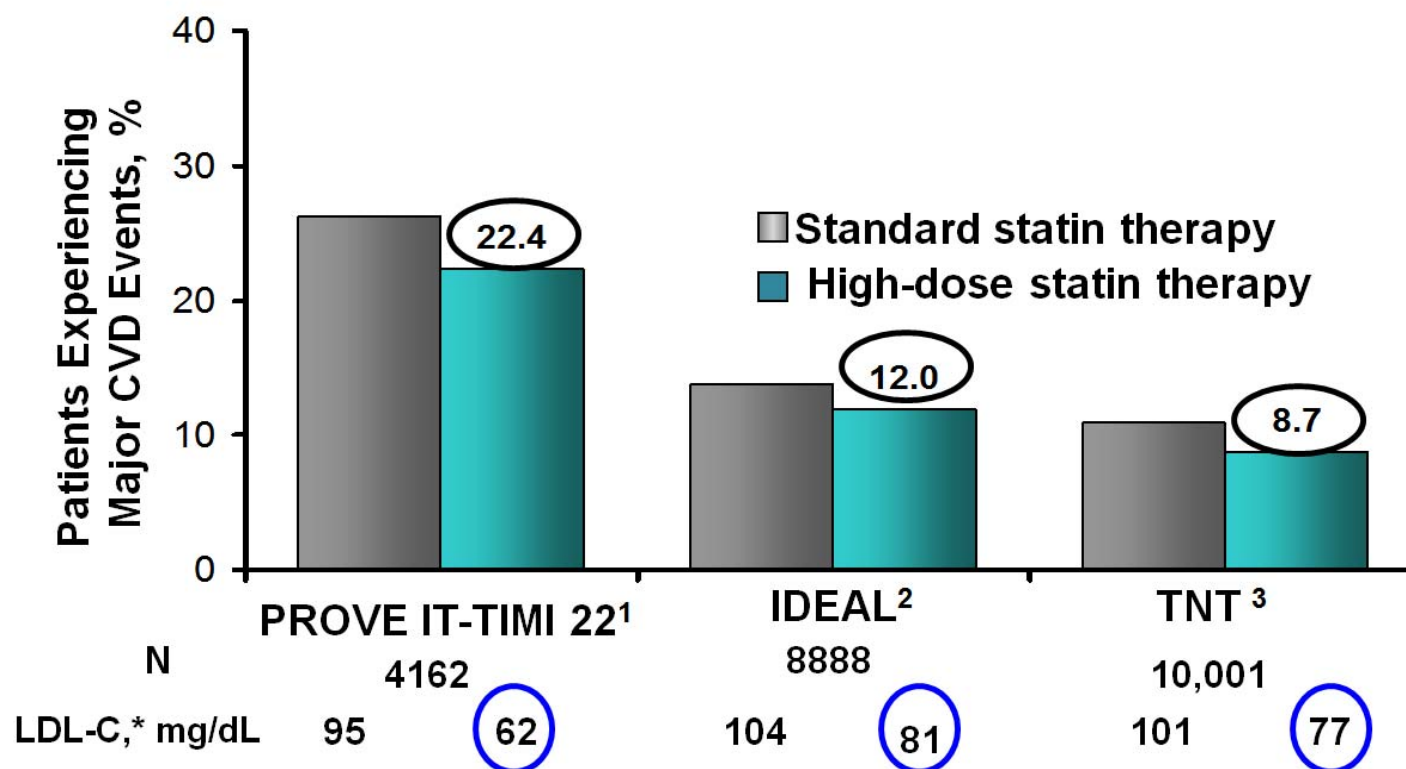
3. Sacks FM, et al. *N Engl J Med*. 1996;335:1001-1009.

4. HPS Collaborative Group. *Lancet*. 2002;360:7-22.

5. Shepherd J, et al. *N Engl J Med*. 1995;333:1301-07.

6. Downs JR, et al. *JAMA*. 1998;279:1615-1622.

Residual CVD Risk in Patients With Intensive Statin Therapy



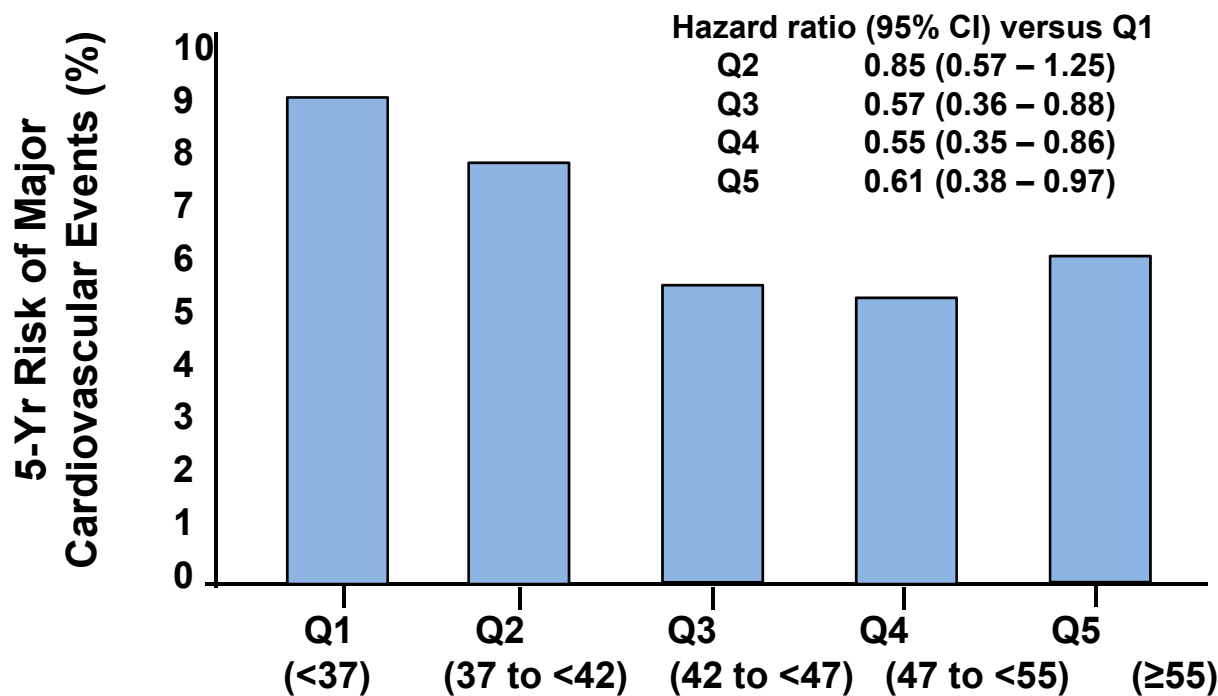
*Mean or median LDL-C after treatment

¹ Adapted from Cannon CP, et al. *N Engl J Med.* 2004;350(15):1495-1504.

² Adapted from Pedersen TR, et al. *JAMA.* 2005;294(19):2437-2445.

³ Adapted from LaRosa JC, et al. *N Engl J Med.* 2005;352(14):1425-1435.

TNT Post-Hoc Analysis: HDL-C Predicts CV Risk at LDL-C <70 mg/dL



	Quintile of HDL Cholesterol Level (mg/dl)				
	Q1 (<37)	Q2 (37 to <42)	Q3 (42 to <47)	Q4 (47 to <55)	Q5 (≥55)
No. of Events	57	50	34	34	35
No. of Patients	473	525	550	569	544

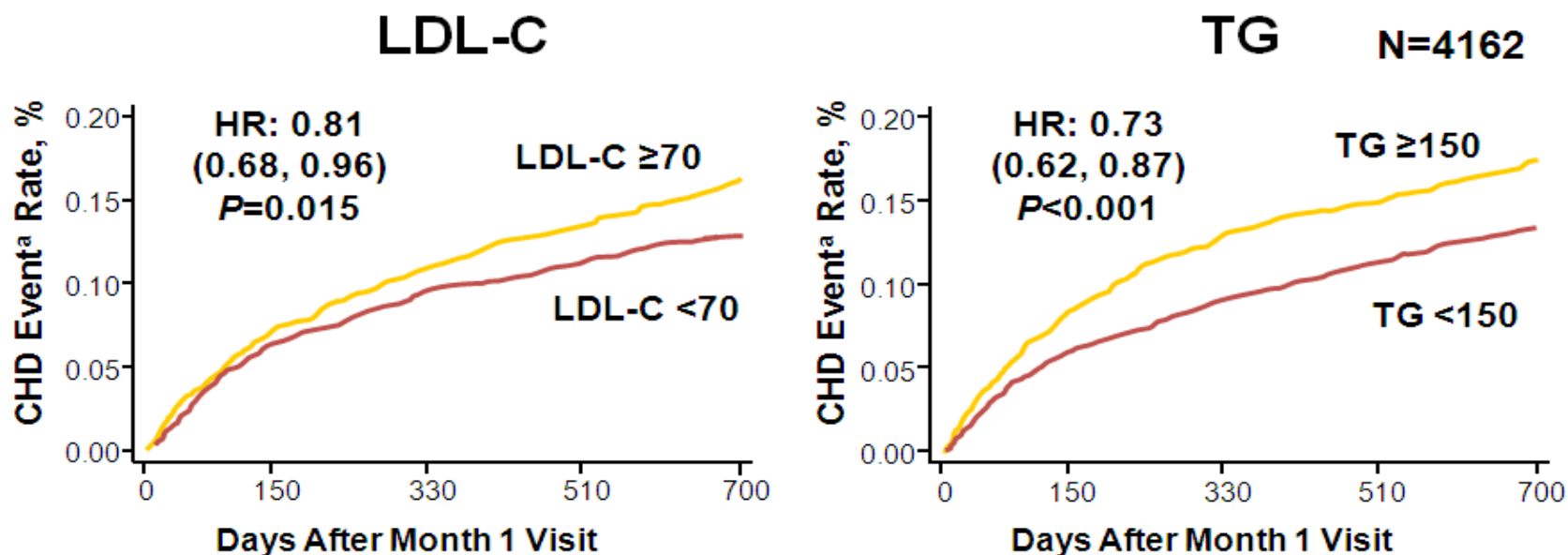
TNT POPULATION
Stable CHD
Age 35-75 y
N = 9,770 with HDL-C

TNT TREATMENT
Atorvastatin 10 mg
Vs.
Atorvastatin 80 mg

TNT= Treating to New Targets

On-Treatment TG >150 mg/dL Predicts CHD Events^a in Patients with ACS^b

PROVE IT-TIMI 22 trial



^aDeath, MI, and recurrent ACS, ^bAtorvastatin 80 mg or pravastatin 40 mg, Lipid values are in mg/dL

ACS= acute coronary syndrome

MI= Myocardial Infarction

PROVE IT-TIMI=Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction

Adapted from Miller M, et al. *J Am Coll Cardiol.* 2008;51(7):724-730.

“Residual Risk”

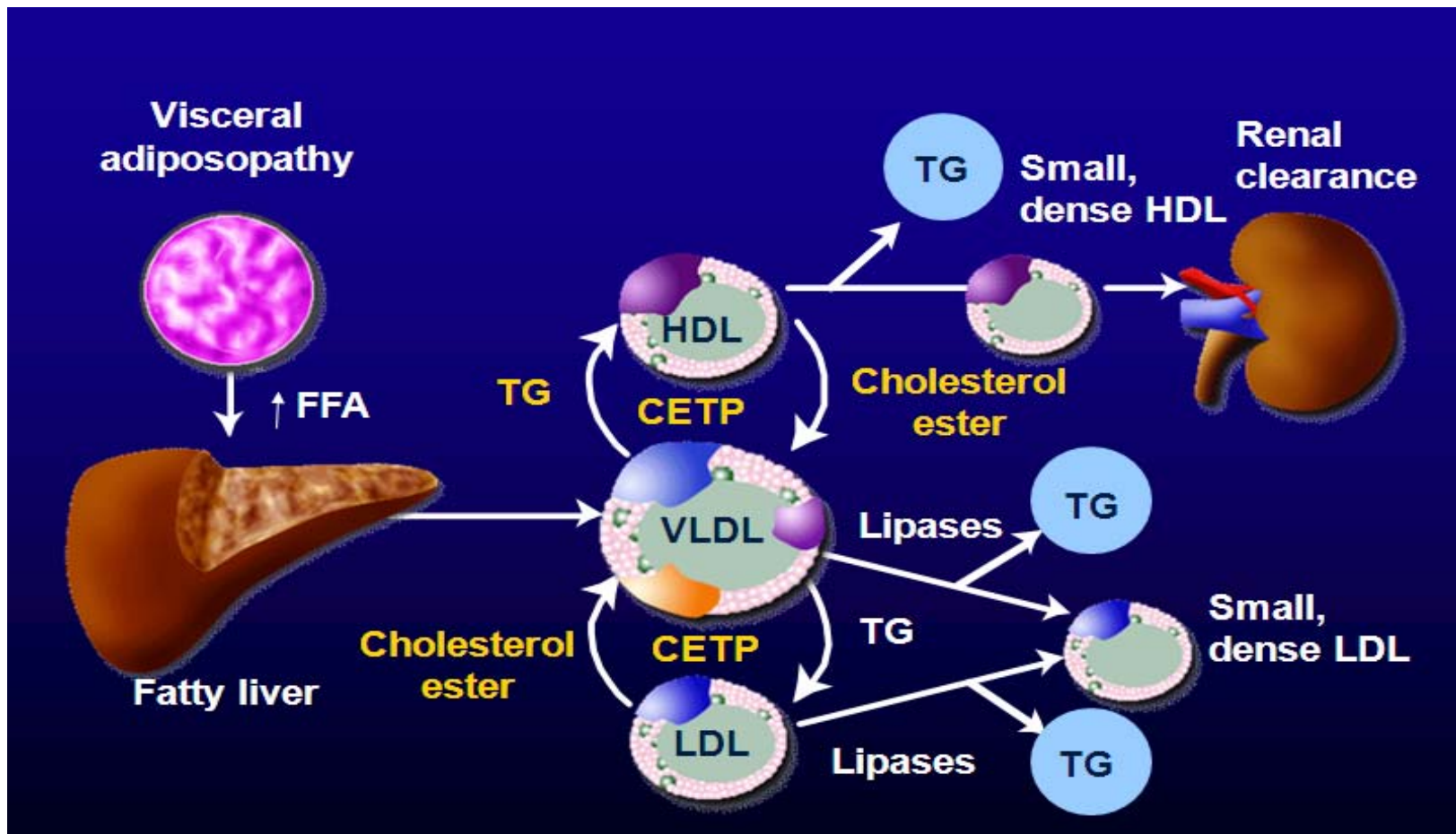
Components

- Disease burden / extent of end-organ damage
- “Non-lipid” risk factors
 - Age / gender / ethnicity
 - Smoking / Alcohol
 - Diet / Physical Activity
 - Obesity
 - Hypertension
 - Diabetes
 - Psychosocial factors
- Lipids and lipoproteins

What Can We “Measure”?

- Age / gender / ethnicity
- Family History
- Diseases
 - Dichotomous
- Lipids and lipoproteins
 - Apo B, Lp(a)
- Non-lipid Biomarkers
 - Serum markers
 - Imaging
- Genetic testing

Elevated Triglycerides Are Metabolically Related to Small LDL and HDL-P



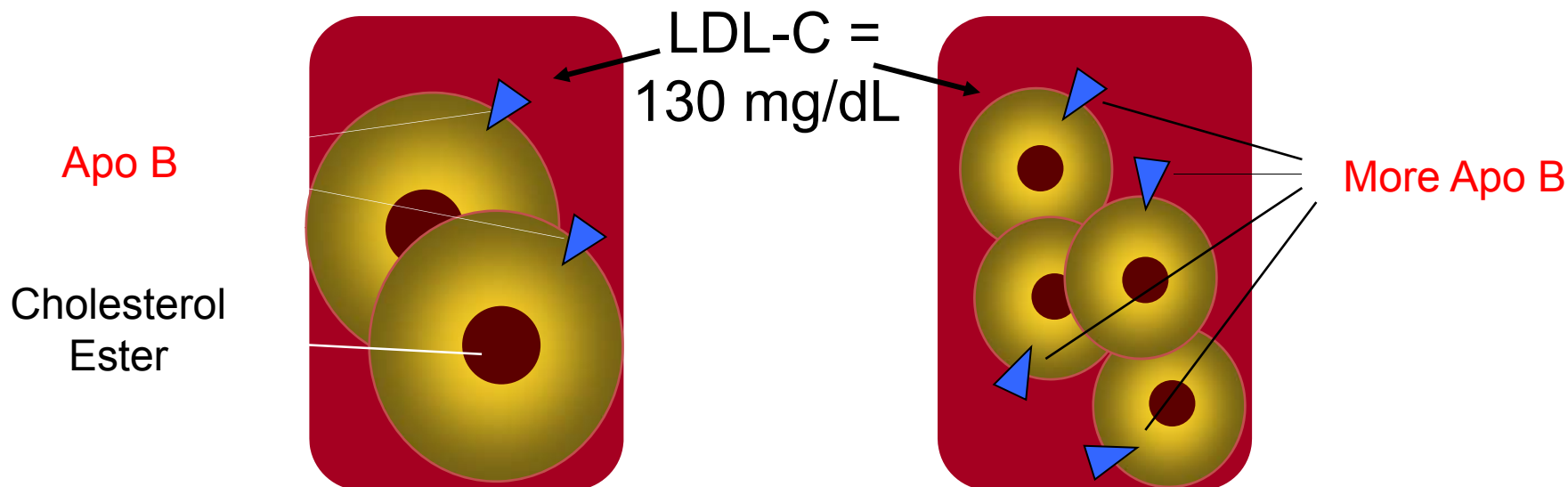
CETP=cholesteryl ester transfer protein
HDL-P= HDL particles

Adapted from Bays H, et al. *Expert Opin Pharmacother.* 2003;4(11):1901-1938.

Same LDL-C Levels, Different Cardiovascular Risk

Fewer Particles

More Particles



Correlates with:

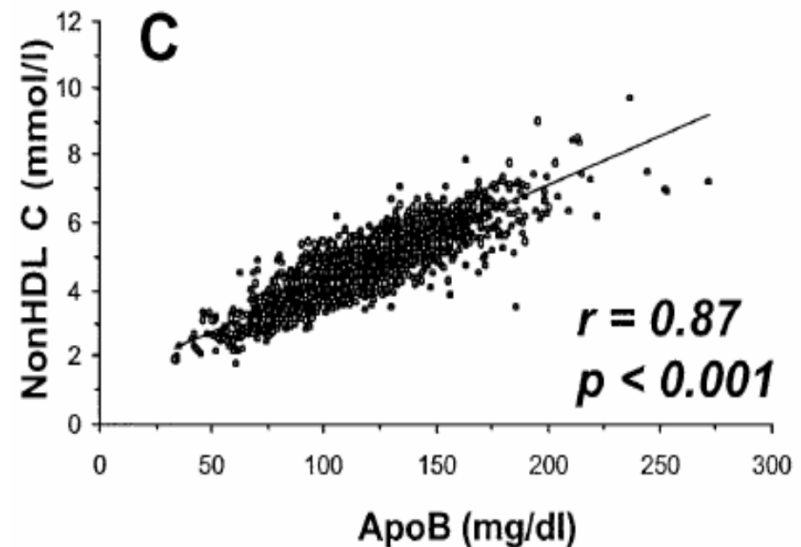
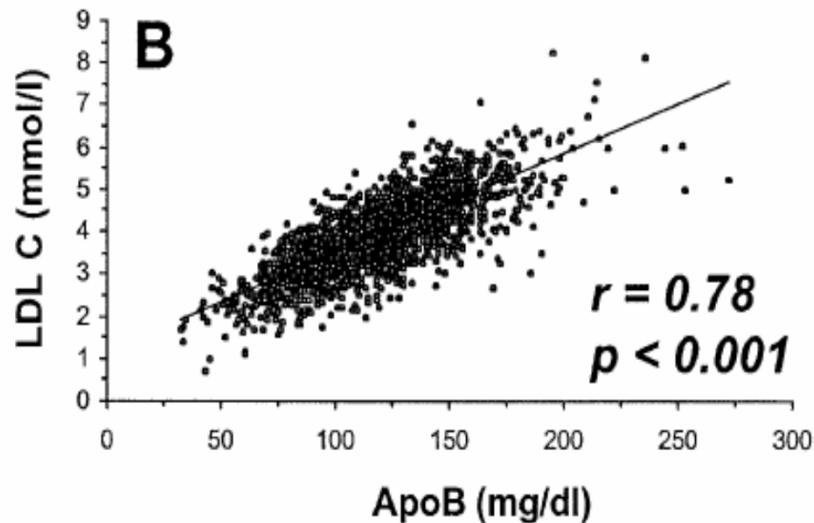
TC	198 mg/dL
LDL-C	130 mg/dL
TG	90 mg/dL
HDL-C	50 mg/dL
Non-HDL-C	148 mg/dL

Correlates with:

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

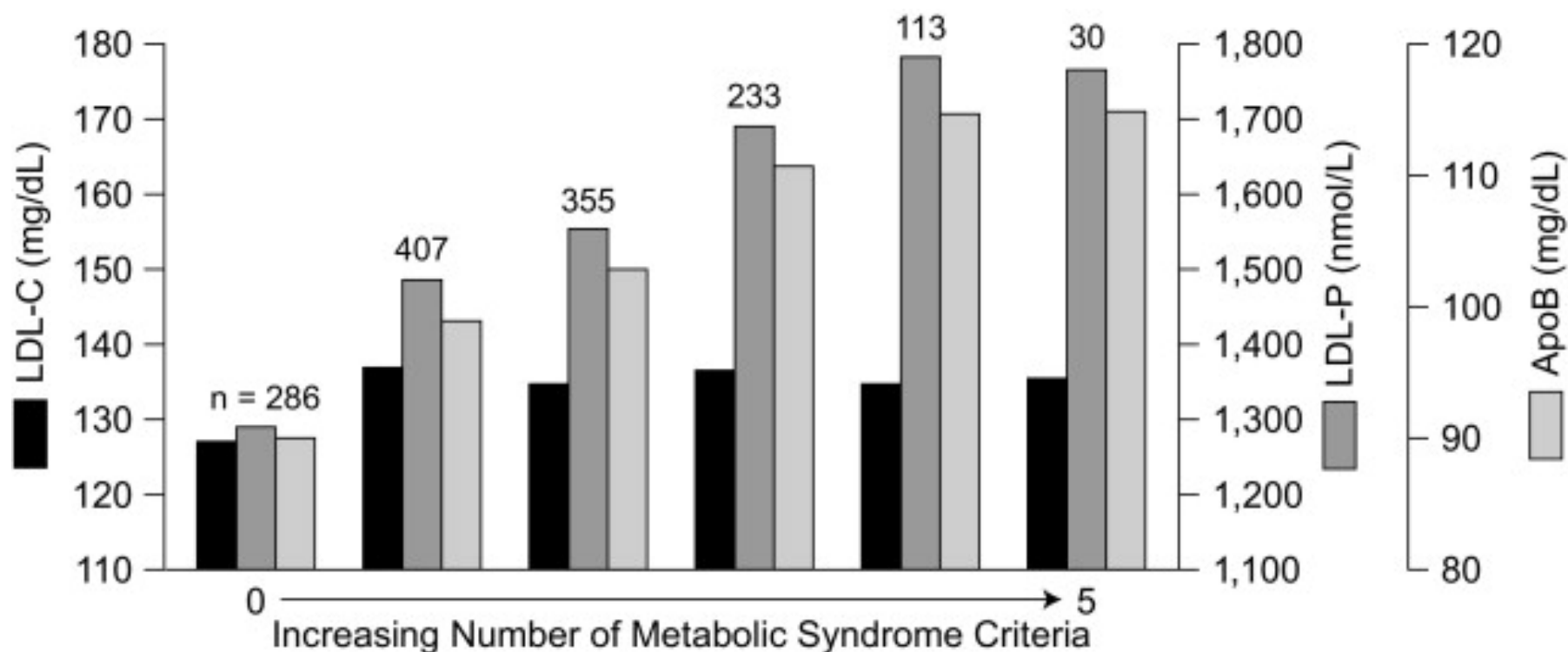
ApoB

- Measurement of the total number of atherogenic particles in plasma
- Apo B correlates more closely with non-HDL-C than with LDL-C:



Adapted from Sniderman AD et al. *AJC*. 2003;91:1173–77.

LDL-C, LDL-P and ApoB in Metabolic Syndrome: Framingham Heart Study



Fruchart JC et al., *Am J Cardiol* 2008;102(suppl); 1K-34K.

Take Home Point:

Atherosclerosis is a multi-factorial disease.

Even if we create the “perfect” lipid / lipoprotein profile, there will be “residual risk”.

What to Do After Lab Data Collection:

- Are the lab results believable?
- Are there secondary causes of hyperlipidemia? Diet, drugs, diseases, metabolic derangements as an explanation? Make a DIAGNOSIS!!!
- Familial lipid disorder?
- What is the risk? Assess near-term risk of CHD, pancreatitis
- What are the goals?
- Treat based on diagnosis, risk and goals

Lipoprotein Evaluation

Technology Used	Selected Lipids/Lipoproteins Measured
Ultracentrifugation – Vertical Auto Profile (VAP)	LDL density: pattern A or B (pattern B referring to a small and dense LDL); IDL and HDL subtypes; VLDL density and lipoprotein (Lp)(a)
Segmented Gradient Gel Electrophoresis (sGGE)	Basic Panel: Apo B (by another technique); LDL (calculated peak particle size and % distribution); 5 subclasses of LDL, 2 subclasses of IDL, and 3 subclasses of VLDL
Nuclear Magnetic Resonance (NMR)	Number, quantity, and size of LDL particles (calculated measurements of 4 LDL subclasses); HDL (large and small); VLDL particle sizes (low, medium, and large)

Adapted from Carmena R, et al. *Circulation*. 2004;109(Suppl III):111-2-111-7.

Overview of Secondary Causes of Dyslipidemia

Secondary cause	High cholesterol High LDL-C	Low HDL-C
Dietary	Saturated fat caloric excess, anorexia	Low-fat diet, high-sugar diet
Drugs	Diuretics, cyclosporine, sirolimus, glucocorticoids, rosiglitazone, fibrates	Anabolic steroids, progestins, β -blockers, cigarettes, retinoic acid
Disorders of metabolism	Hypothyroidism, pregnancy, DM	Obesity, type 2 DM
Diseases	Nephrotic syndrome, biliary obstruction (Lp-X), type 2 DM	Chronic renal failure, dialysis, type 2 DM

Adapted from Stone NJ, Blum CB. *Management of Lipids in Clinical Practice*. 2006.

Overview of Secondary Causes of Dyslipidemia

Secondary Cause	Triglyceride Excess Mild – Mod (High) VLDL	Severe Triglyceride Excess: Chylomicronemia syndrome
Dietary	Weight gain, alcohol, simple carbohydrates	Alcohol, fat plus genetic lipid disorder
Drugs	Retinoic acid, β -blockers, estrogens, glucocorticoids, sirolimus, protease inhibitors	Estrogens, tamoxifen, glucocorticoids plus genetic lipid disorder
Disorders of metabolism	Obesity, type 2 DM, pregnancy (3 rd trimester)	DM, hypothyroidism plus genetic lipid disorder
Diseases	Chronic renal failure \pm dialysis, nephrotic syndrome	Systemic lupus, lymphoma (rare)

Adapted from Stone NJ, Blum CB. *Management of Lipids in Clinical Practice*. 2006.

Secondary Causes of Hypertriglyceridemia (Screen/Treat in All Cases)

Diseases/States

- **Central/visceral adiposity**
 - Insulin resistance/metabolic syndrome
 - PCOS
- **DM-2 (esp. if poor control)**
- **Sedentary Lifestyle**
- **Endocrine disorders/states**
 - **Hypothyroidism**
 - Hypercortisolism
 - Pregnancy
- **Renal disorders**
 - Nephrotic syndrome
 - End-stage renal disease
- **Systemic Inflammation/Infection**
 - Arthritis
 - HIV
 - Other?
- **Psychiatric disorders**

Drugs/Diet

- **Recreational**
 - **Ethanol**
 - Marijuana
- **Diet**
 - ↑**Fructose/sucrose/starch**
 - High fat (when TG >~700)
 - High calories?
- **Hormones**
 - **Oral estrogen (BCP & ERT)**
 - Systemic glucocorticoids (*not* nasal or topical)
- **Blood Pressure/Lipid Rx**
 - Beta blockers (most)
 - Thiazide diuretics
 - Bile-acid sequestrants
- **Miscellaneous**
 - Cyclosporine
 - Retinoic-acid derivatives
 - HAART (PI and others)
 - Atypical anti-psychotics

PI=protease inhibitors.

Modified from Pejic R, et al., *J Am Board Fam Med.* 2006;19:310-316.

Genetic Dyslipidemias Overview

Fredrickson Classification:

Type I = LPL deficiency
 Type I = $<1/10,000$

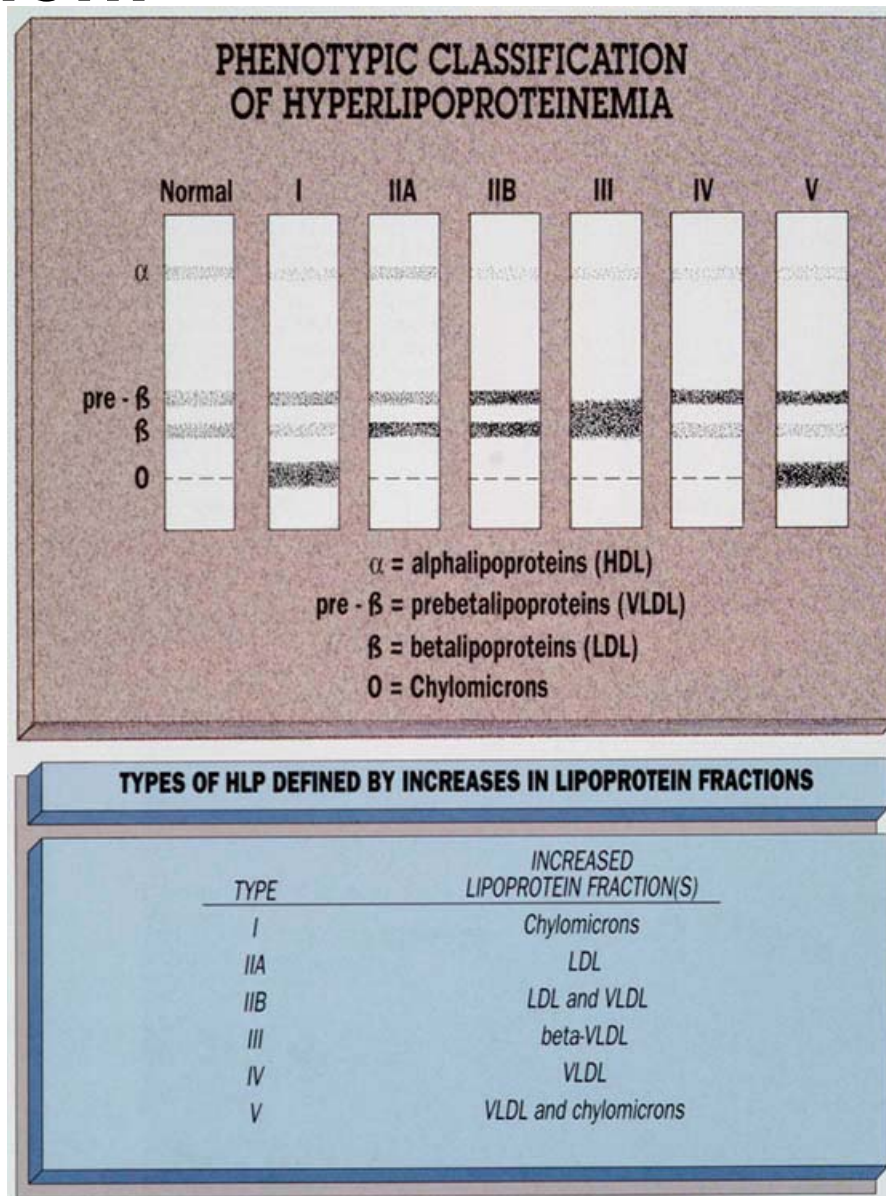
Type II = Familial hypercholesterolemia
 Heterozygous FH = $1/500$

Type III = Dysbetalipoproteinemia
 (Apo E defect)

Familial type III = $1/10,000$

Type IV = Hypertriglyceridemia

Type V = Type I + Type IV



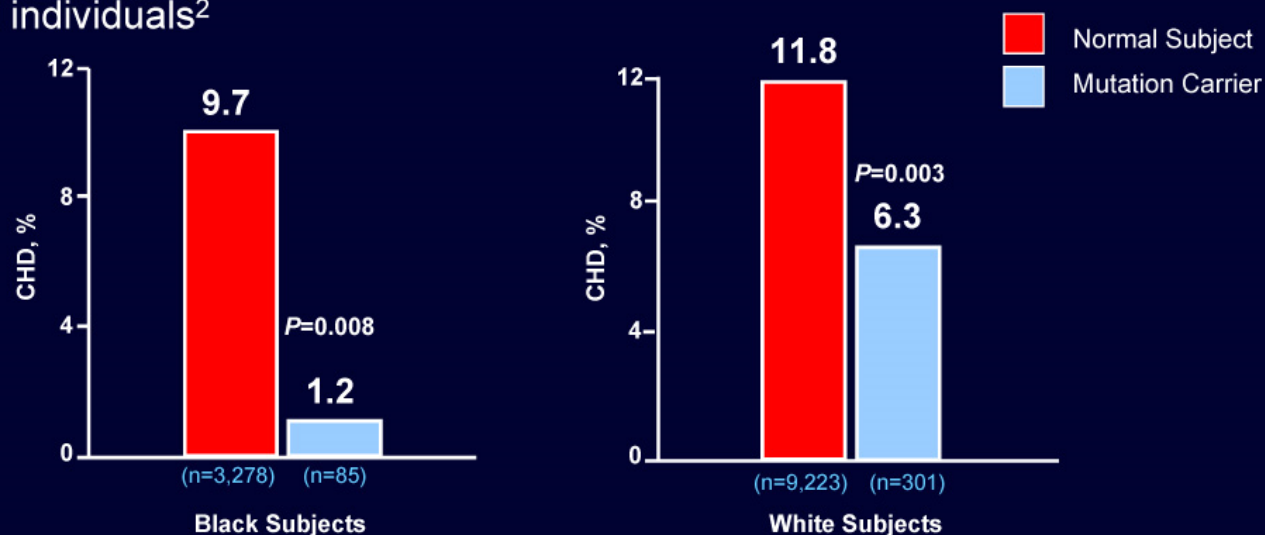
Familial Hypobetalipoproteinemia: Reduced LDL-C and Apo B, and Decreased Morbidity from Myocardial Infarction

- Individuals with this condition have plasma LDL-C and Apo B concentrations <5th percentile for age and sex¹
- Exhibit enhanced LDL particle binding to LDL receptors¹
- Have lower incidence of myocardial infarction²
- Experience increased longevity without adverse events²

1. Burnett JR, et al. *Clin Biochem Rev.* 2008;29:11-26.
2. Glueck CJ, et al. *J Lab Clin Med.* 1976;88:941-957.

PCSK9 Mutations Promoted Genetically Low LDL-C and Reduced CHD Rates

- PCSK9 degrades LDL receptors
- Individuals with PCSK9 loss-of-function mutations had LDL-C levels 15% to 40% lower than normal subjects^{1,2}
- Analysis of a larger cohort showed 47% to 88% reductions in CHD occurrence between PCSK9 mutation carriers and normal individuals²



PCSK9= proprotein convertase subtilisin/kexin type 9 serine protease

1. Cohen J, et al. *Nat Genet.* 2005;37:161-165.
2. Cohen JC, et al. *N Engl J Med.* 2006;354:1264-1272.

Genetic Basis and Phenotypic Presentation of Metabolic Disorders of Dyslipidemia

- Disorders Affecting LDL Receptor (LDLR) Activity
- Disorders of Overproduction of VLDL and LDL
- Familial Metabolic Disorders of TG rich lipoproteins
- Familial Disorders of HDL Metabolism
- Elevated Lp(a)
- Deficiencies in Apo B containing Lipoproteins

Disorders Affecting LDLR Activity

- Familial Hypercholesterolemia (FH): Deficient or defective LDL receptors (chromosome #19); impaired LDL removal from plasma
- Familial Defective Apo B100: Mutant Apo B100 poorly recognized by LDL receptor – impaired LDL removal from plasma
- Autosomal Recessive Hypercholesterolemia: Very rare due to a mutation in the LDL receptor adaptor protein - markedly elevated LDL-C levels

Adapted from Kwiterovich PO, ed. The Johns Hopkins textbook of dyslipidemia. 1st ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2009.

Disorders Affecting LDLR Activity

- Mutation of Proprotein Convertase Subtilisin-like Kexin Type 9 (PCSK9; gain of function mutation): PCSK9 is a serine protease that facilitates the degradation of the LDLR.
- Sitosterolemia: Rare autosomal recessive disorder expressed in childhood and characterized by markedly elevated (>30 fold) plasma level of plant sterols. Persons with this disorder also absorb a higher percentage of dietary cholesterol than normal and secrete less cholesterol into their bile which increases hepatic cholesterol pool, decreases LDLR activity and in turn increases LDL-C levels.

Adapted from Kwiterovich PO, ed. The Johns Hopkins textbook of dyslipidemia. 1st ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2009

Disorders Affecting LDLR Activity

- Deficiency of Cholesterol 7 α -Hydroxylase: Autosomal co-dominant disorder affecting cholesterol 7 α -hydroxylase activity, the first enzyme in the classical pathway for bile acid synthesis. A block in the conversion of cholesterol to bile acids by this rate-limiting enzyme blocks the secretion of cholesterol to bile from the liver, increases hepatic cholesterol and a down-regulation of the LDLR.

Adapted from Kwiterovich PO, ed. The Johns Hopkins textbook of dyslipidemia. 1st ed.
Philadelphia, PA: Lippincott Williams & Wilkins; 2009

Lysosomal Acid Lipase Deficiency (LAL-D)

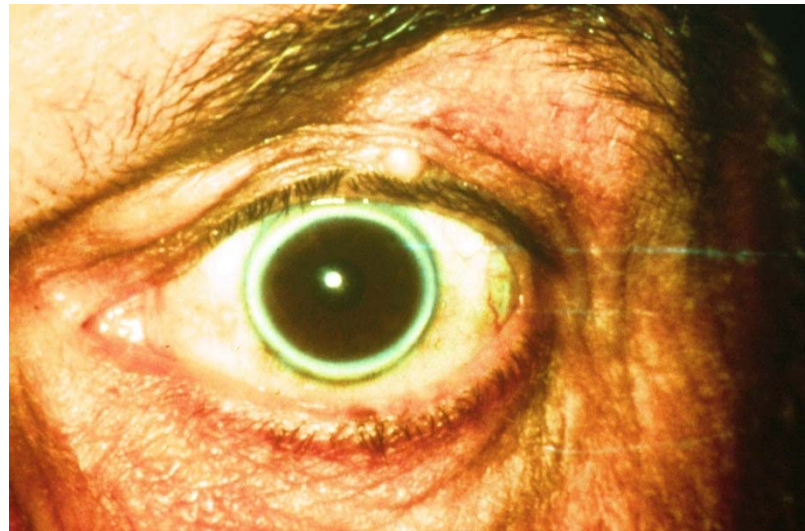
- Also known as **Wolman Disease** or **Cholesterol Ester Storage Disease**
- Underlying cause is the same
 - Autosomal recessive disease affecting lipid metabolism
 - frequency 1/40,000-1/1,000,000
 - Results in lysosomal accumulation of lipids (cholesteryl esters and triglycerides) and multi-organ system damage (liver, GI tract, and blood vessel walls)
- Elevated Total Cholesterol, LDL-C, TG's , Low HDL-C and increased risk of ASCVD ,
- Lack of LAL leads to accumulation of Cholesterol Esters and TG in lysosomes, decrease in free cholesterol , activation of SREBP's, incr. chol. synthesis, lipogenesis and VLDL production. Reduction in LXR expression, dec. cholesterol efflux (ABCA-1) and lower HDL
- Fatty liver, elevated transaminases Liver failure , Cirrhosis , typical pathology microvesicular steatosis, adrenal calcification

1. Patrick AD, Lake BD. Deficiency of an acid lipase in Wolman's disease. *Nature*. 1969;222:1067-8.
2. Burke JA, Schubert WK. Deficient activity of hepatic acid lipase in cholesterol ester storage disease. *Science*. 1972;176:309-10.
3. Cortner JA, et al. Genetic variation of lysosomal acid lipase. *Pediatr Res*. 1976;10:927-32.
4. Goldstein JL, et al. Role of lysosomal acid lipase in the metabolism of plasma low density lipoprotein. *J Biol Chem*. 1975 ;250:8487-95.

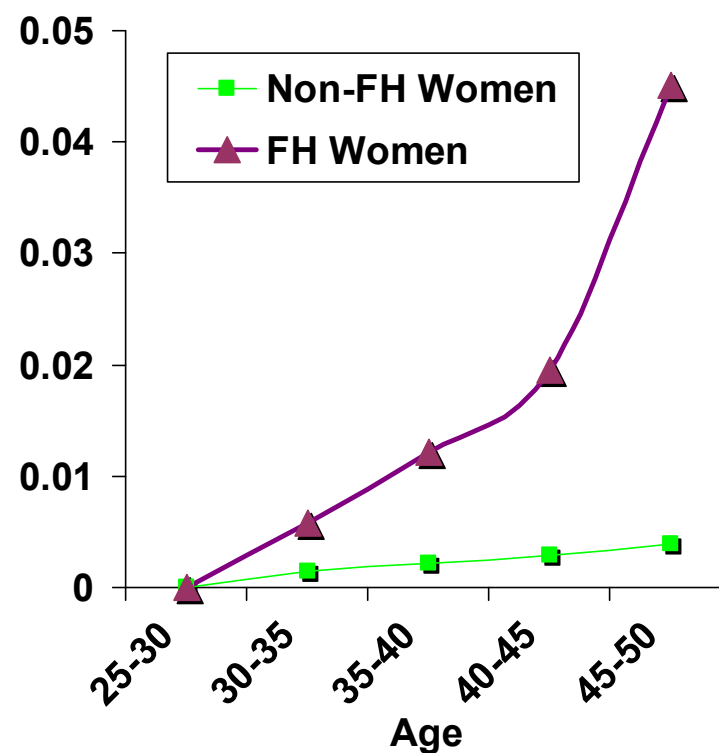
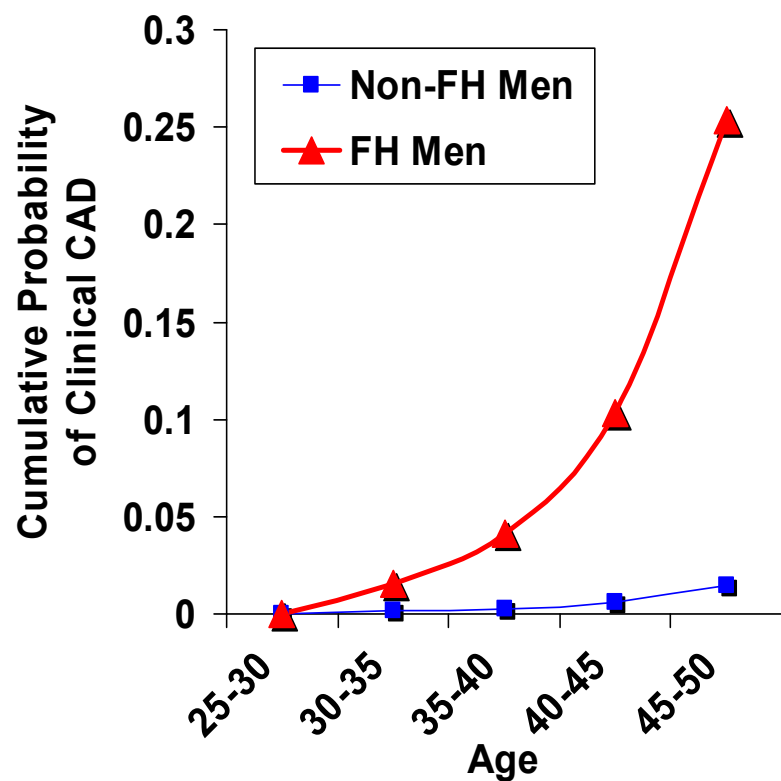
Physical Findings of Familial Hypercholesterolemia (FH)



Eye Findings in FH



Non-Fatal CAD in FH (Utah) vs. General US Population



Hopkins PN, et al. *Am J Cardiol* 2001;87:547 and unpublished observations.

NLA 2011 Familial Hypercholesterolemia (FH) Treatment Recommendations

- **Rationale for treatment**

Individuals with FH have a very high lifetime risk of CHD and are at very high risk of premature onset CHD.

- Early treatment is highly beneficial. Long-term drug therapy of patients with FH can substantially reduce or remove the excess lifetime risk of CHD due to the genetic disorder and can lower CHD event rates in FH patients to levels similar to those of the general population.
- FH requires lifelong treatment and regular follow-up.

NLA FH Risk Evaluation

- Risk stratification algorithms should not be used. Individuals with FH are at high CHD risk. The 10-year CHD risk in the FH patient is not adequately predicted by any conventional risk assessment tools. Therefore, assessment of 10-year risk is not recommended.
- All FH patients require lifestyle management, and very few will not require lipid-lowering drug therapy

Treatment

- Both children and adults with LDL-C >190 mg/dL or Non-HDL-C >220 mg/dL after lifestyle changes will require drug therapy.
- For adult FH patients (>20 years of age), drug treatment to achieve an LDL-C reduction $>50\%$ should be initiated.
- Statins should be the initial treatment for all adults with FH.
- Higher risk patients may need intensification of drug treatment to achieve more aggressive treatment goals (LDL-C, 100 mg/dL and non-HDL-C, 130 mg/dL).

Beyond Statins

- Ezetimibe, niacin, and bile acid sequestrants are reasonable treatment options for intensification of therapy, or for those intolerant of statins.
- The potential benefit of multidrug regimens for an individual patient should be weighed against the increased cost and potential for adverse effects and decreased adherence.

Case 1

- 22-year-old woman. Sexually active, using barrier contraception, not trying to get pregnant
- Father died of myocardial infarction age 52
- Exercises 5 days/week, non-smoker, BMI = 21, Waist Circ. = 29", BP = 110/70, no medical complaints
- Total Cholesterol = 330 mg/dL, LDL-C = 225 mg/dL, HDL-C = 85 mg/dL, TG = 100 mg/dL
- Skin exam and eye exam = within normal limits
- **What is her diagnosis?**
- **What is her 10-year Framingham risk score ?**
- **Should she have her cholesterol treated? And if so how?**

Disorders of Overproduction of VLDL and LDL

- Phenotypes of these disorders vary, but the common denominator is increased LDL – small dense, +/- elevated triglycerides, Apo B, low HDL, insulin resistance, DM, glucose intolerance, hypertension – the phenotype can be accentuated by obesity. Metabolic syndrome is very common in these disorders. The disorders do not appear to be caused by a single gene defect.

Disorders of Overproduction of VLDL and LDL

- Familial Combined Hyperlipidemia (FCHL): Most common inherited lipid disorder.
- Hyperapobetalipoproteinemia (HyperapoB)
- LDL subclass pattern B (small dense LDL)
- Familial Dyslipidemic Hypertension (FDH)
- Syndrome X (Reaven)

Disorders of Overproduction of VLDL and LDL

- The 2-3 fold increase in triglyceride-rich VLDL seen in these disorders requires:
 1. Availability of cholesteryl ester
 2. Increased Apo B – generally due to reduced degradation
 3. Increased biosynthesis of triglycerides [typically due to increased flux of free fatty acids (FFA) to the liver in setting of insulin resistance]

Familial Metabolic Disorders of Triglyceride-rich Lipoproteins

- Lipoprotein Lipase Deficiency/Apo CII Deficiency (Formerly Type I)
- Familial Hypertriglyceridemia (Formerly Type IV)
- Type V Hyperlipoproteinemia
- Dysbetalipoproteinemia (Formerly Type III)

Lipoprotein Lipase Deficiency/ Apo CII Deficiency

- Lipoprotein lipase deficiency (formerly Type I) is a rare cause of very high triglyceride levels (triglycerides well over 1000 mg/dL – due to chylomicrons) can be caused by production of inactive LPL molecules or absence of LPL molecules.
- Type I can also be caused by Apo CII deficiency (Apo CII activates LPL).
- Defect generally discovered in infancy – acute pancreatitis – treat with total fat restriction.
- Hemorrhagic pancreatitis is the major life-threatening risk for persons with type I hyperlipoproteinemia.



Eruptive xanthomata of buttocks in patient with chylomicronemia.

Familial Hypertriglyceridemia (Type IV and Type V Hyperlipoproteinemia)

- **Familial hypertriglyceridemia (type IV):** TC, LDL-C, Apo B levels are normal, Chylomicrons are absent, and VLDL-C and TG are elevated – TG are >95 percentile. VLDL and Apo B are not overproduced (as they are in FCHL) – rather they are not hydrolyzed normally. May be accompanied by glucose intolerance, PVD, hyperuricemia and obesity. Inherited as an autosomal dominant disorder with incomplete penetrance.
- **Type V hyperlipoproteinemia:** elevated TG due to both VLDL and chylomicrons. Increased synthesis and/or decreased clearance. Associated with glucose intolerance, eruptive xanthomas, lipemia retinalis, PVD, CAD

Type III Hyperlipoproteinemia (Familial Dysbetalipoproteinemia)

- Characterized by an accumulation of VLDL remnants – due to defective Apo E (Apo 2/2 phenotype)
- See elevation in both cholesterol and triglycerides (usually 250-500 mg/dL)
- Most common mutation: Apo E-2, arg158→cys has a gene frequency of 10%. Homozygosity occurs in 1% of population but type III occurs in 0.01-0.04% of population – thus Apo E mutation is necessary, but not sufficient [can be precipitated by obesity, alcohol, DM, hypothyroidism (hypothyroidism can suppress LDL receptor synthesis)]

Type III Dysbetalipoproteinemia



Tuberous xanthomata of elbow of patient with type III dysbetalipoproteinemia



Striate palmar xanthomata in type III hyperlipoproteinaemia

Courtesy Prof PN Durrington. © Copyright Science Press Ltd 2002

Case 2

A 35 year old woman presents to the lipid clinic upon referral by her OB/GYN physician for evaluation of severe hypercholesterolemia. Her past medical history is unremarkable. Both her parents died with premature CHD (father age 58 and mother age 57). She is 5'6", 198 lbs. She had difficulty with fertility and, with therapy, delivered healthy triplets. During pregnancy, she had gestational diabetes. After her pregnancy, she continued to gain a considerable amount of weight and now weighs 60 lbs more than her pre-pregnancy weight.

Case 2

- A lipid profile performed 4 weeks prior to her visit was TC = 1000 mg/dL (verified by repeat analysis, highest level of detection) and TG = 4544 mg/dL (also verified by repeat measures). HDL and LDL-C were not performed due to the fact that specimen was unsuitable for assay due to lipemia. She was placed on fenofibric acid 135 mg and prescription omega-3 fatty acids 4 g/day and referred for further evaluation. Her repeat lipid profile was as follows:

Case 2

Lab Values

Total Cholesterol	643 mg/dL
Triglycerides	1277 mg/dL
HDL-C	N/A
LDL-C	N/A
Glucose	108 mg/dL
AST	23 u/L (N = 10–30 u/L)
ALT	30 u/L (N = 6–40 u/L)

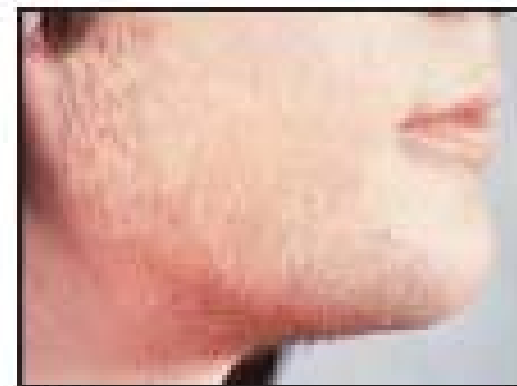
Which of the Following Physical Findings Depicted in Photographs A–E Is/Are Consistent with this Patient’s Medical History and Laboratory Findings?



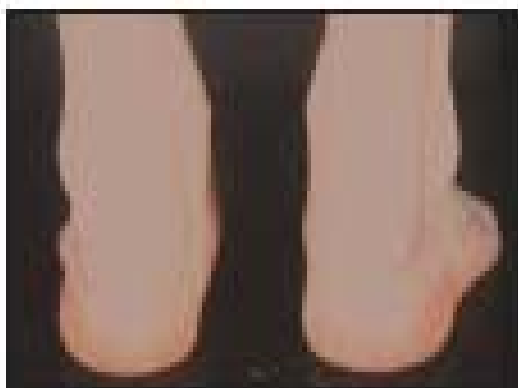
(A)



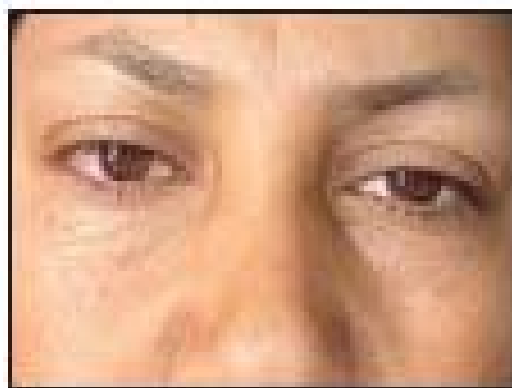
(B)



(C)



(D)



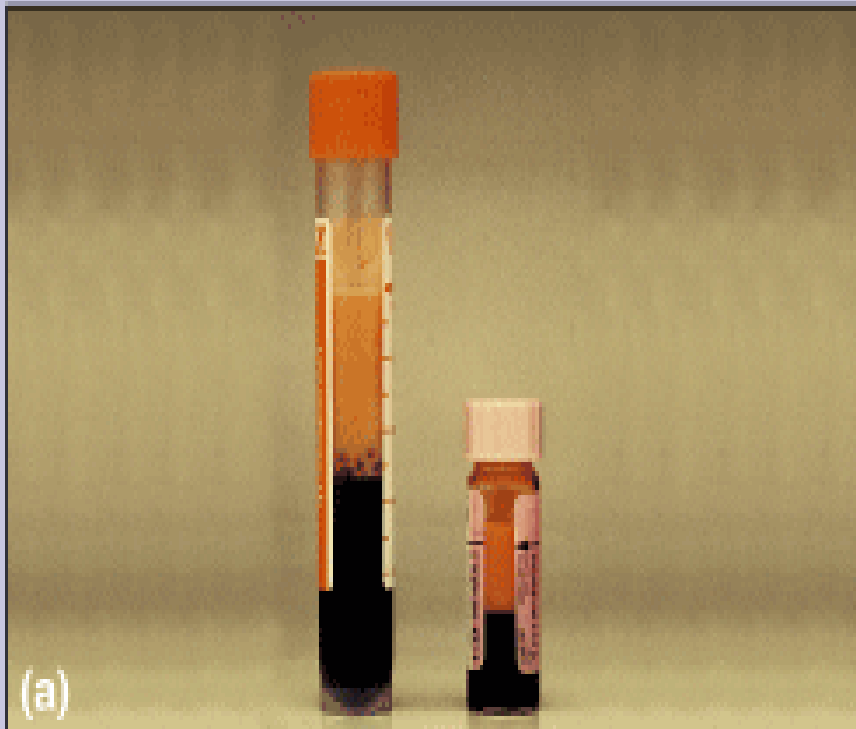
(E)

Genetic TGRL Disorders

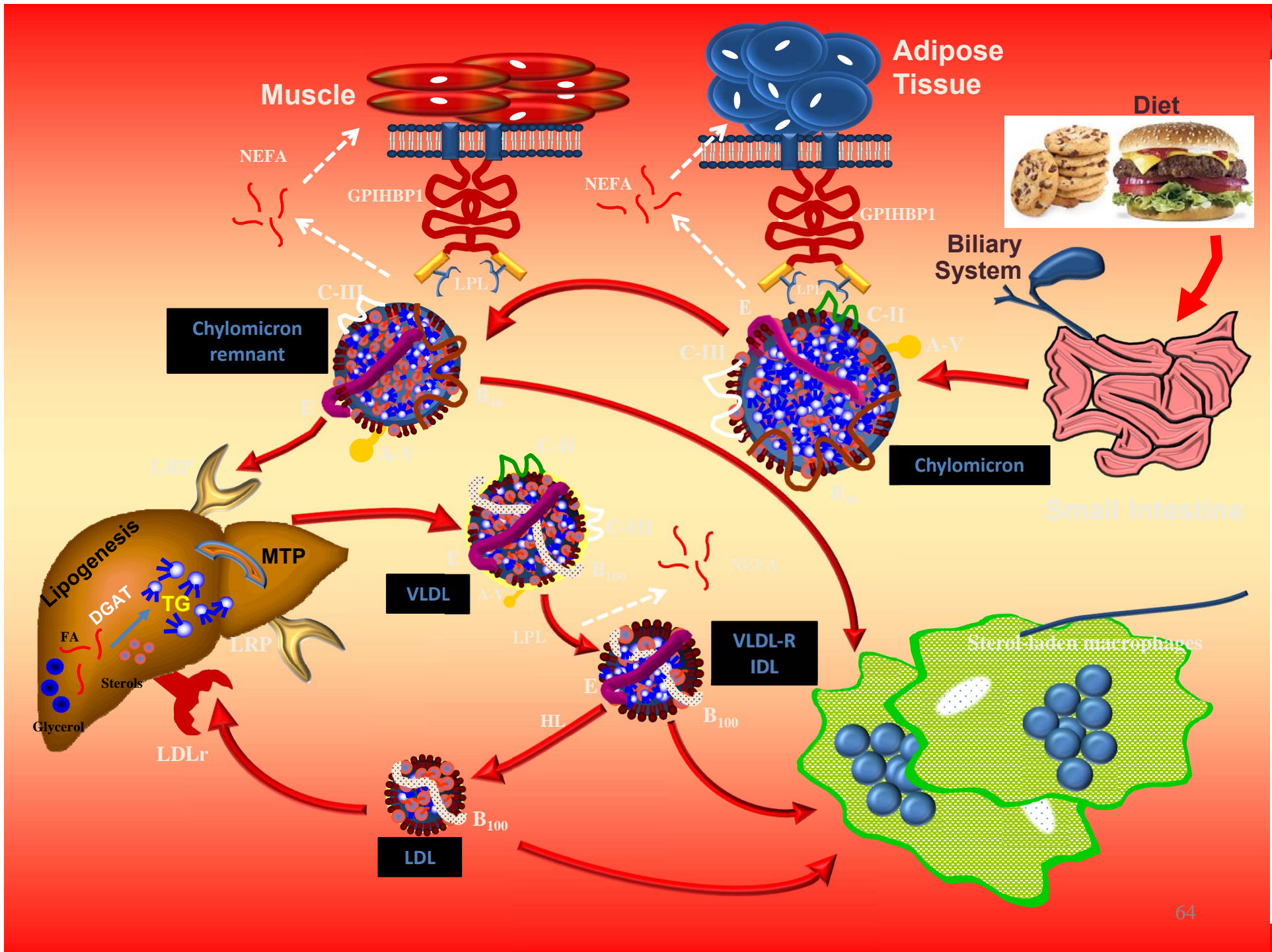
<u>Name</u>	<u>Mechanism</u>	<u>Phenotype</u>	<u>Athero</u>
Familial Hyperchyl (Type I)	LPL Defic	↑↑↑TG, ↓↓HDL	nl (vs. ↑hets?)
Fam HTG (Type IV/V)	↓TG clear, ↑TG PR	↑↑TG, ↓HDL	↑/↑↑
FCHL	Ins Resist ↓TG clear/ ↑TG PR	↑TG and/or ↑LDL, ↓HDL	↑↑
Type III	↓Rem clear	C-rich VLDL	↑↑↑

After Alawadhi M, et al. *Curr Athero Rep.* 2005;7:196-203

Manifestations of severe hypertriglyceridaemia



Courtesy Prof PN Durrington.



Genetic HDL Disorders

<u>Name</u>	<u>Mechanism</u>	<u>Δ HDL-C</u>	<u>Athero</u>
Apo AI Mut	Abn AI struct	↓ to 0 HDL-C	↑/nl/↓
Apo AI Milano	Apo AI Arg173Cys	sl ↓ HDL-C	↓
Tangier Dis	Abn ABCA1 transporter	↓ to ↓ ↓ HDL-C	↑
LCAT Def/ Fish Eye	LCAT def total or HDL only	↓ ↓ HDL-C	↑
Niemann-Pick	?	↓ HDL-C	↑
PON Defic	↓ antiox effects	?	↑/nl
CETP Defic	↓ chol loss to TGRL	↑ ↑ HDL-C	↑/nl/↓?
Fam ↑ α	↓ HDL catabolism	↑ ↑ HDL-C	↓ ↓

No clinical value: monogenic dis. rare, polygenic not understood

Alawadhi M, et al. *Curr Athero Rep.* 2005;7:196-203.

Summary: HDL-Deficiency

Diagnosis

- HDL-C level likely best/sufficient
- Apo AI, HDL-P, HDL₂-C good, *not* needed

Causes

- *Common*: insulin resistance, hypertriglyceridemia (moderate-severe), *poor* lifestyle (cigarettes, sedentary, central obesity), polygenic factors
- *Rare*: monogenic, androgen abuse

Consequences

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

Treatment *difficult* (by TLC or drug)

Disorders of HDL Metabolism

- The most common cause of depressed HDL is secondary to insulin resistance, increased flux of FFA to the liver, VLDL overproduction, and the subsequent formation of low levels of HDL in conjunction with elevated TG and increased small, dense LDL particles. There are however a number of primary HDL disorders.

Disorders of HDL Metabolism

- Hypoalphalipoproteinemias:
 - Deletions and Nonsense Mutations in Apo AI:
 - Result in little if any biosynthesis of Apo AI by liver and intestines – early CVD – may also see peripheral cholesterol deposition – cataracts, planar xanthomas.
 - Missense Mutations in Apo AI:
 - Result in low HDL-C, but impact on CVD less clear. Example: Apo AI Milano results from a mutation in the Apo AI gene at codon 173, Arg to Cys, and alters the structure of Apo AI heterozygotes have low HDL-C due to increased turnover of Apo AI, but surprisingly manifest little CVD.

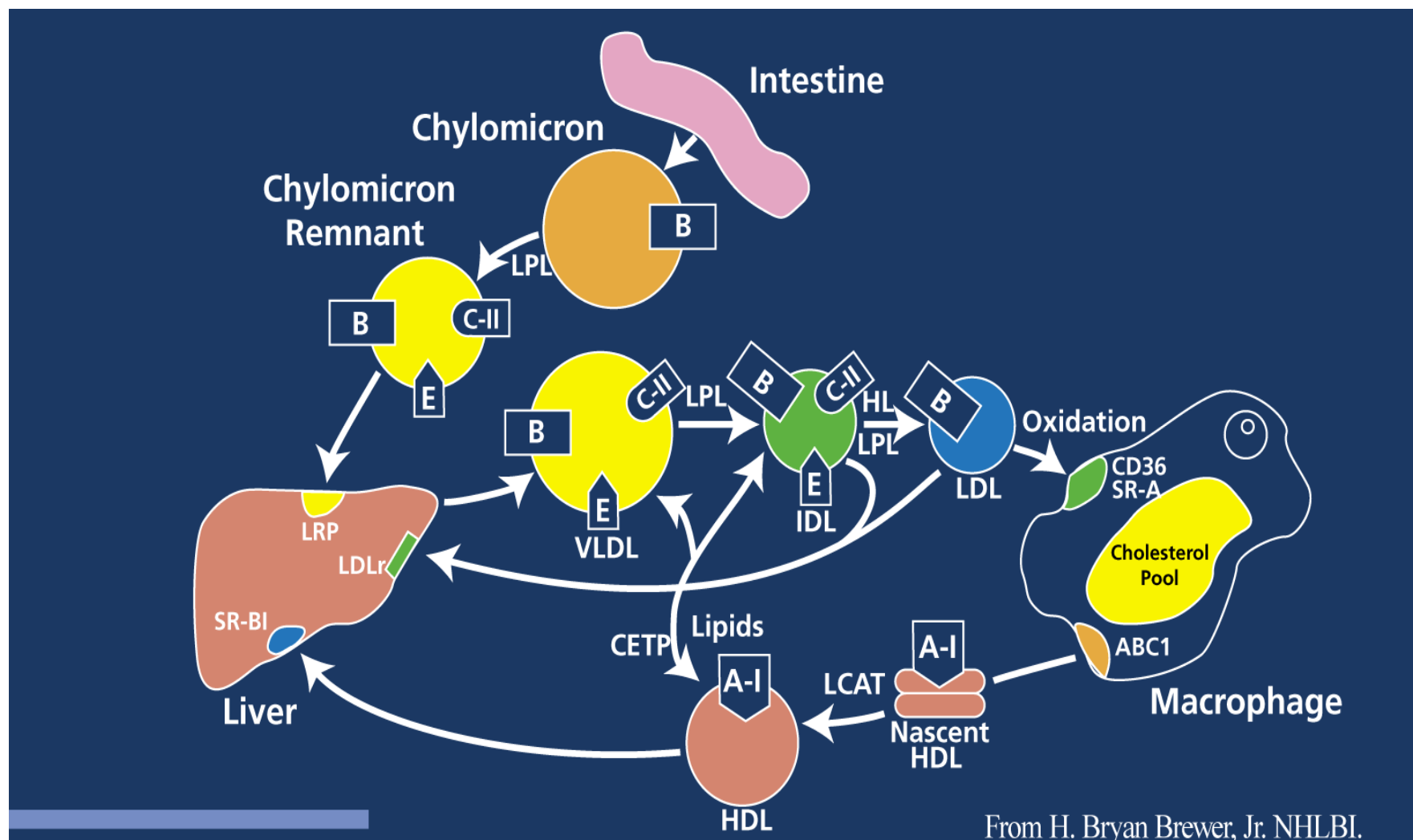
Disorders of HDL Metabolism

- Hypoalphalipoproteinemias:
 - Tangier Disease: Results from a defect in cholesterol and phospholipid efflux from cells to Apo A1. Poorly lipidated Apo A1 is then rapidly removed by the kidney. Basic defect is in double dose mutation in *ABCA1* gene. HDL markedly abnormal. Chylomicron-like particles are sequestered by the reticular endothelial cells (yellow tonsils). Early atherosclerosis is not a major feature.

Disorders of HDL Metabolism

- Hypoalphalipoproteinemias:
 - LCAT Deficiency and Fish Eye Disease: Free cholesterol must be esterified to produce a spherical HDL; esterification is achieved via LCAT.
 - Patients with LCAT deficiency have markedly reduced HDL-C. (Other lipoproteins are also abnormal).
 - Clinical findings include glomerulosclerosis, normochromic anemia, and corneal opacities.
 - Although CAD is not prominent, it has been reported.
 - Classic LCAT deficiency – both α and β LCAT deficient – all lipoproteins abnormal. If only α LCAT is abnormal – fish eye disease – a major finding is corneal opacities.

Summary of Lipoprotein Metabolism



Adapted from H. Bryan Brewer, Jr. NHLBI.

Disorders of HDL Metabolism

- Hyperalphalipoproteinemias:
 - **CETP Deficiency:** Homozygotes for CETP deficiency can have HDL-C ≥ 120 mg/dL (large HDL). It is not clear whether this is always protective against CVD. Recent genome-wide association studies have found that variation at the CETP gene locus is one of the most important factors influencing HDL-C levels in the general population.
 - **Familial Hyperalphalipoproteinemia:** Generally defined as HDL-C > 95 percentile for age and gender. Considered as present if other family members have the phenotype. Etiology is diverse: CETP deficiency; lower SR-B1; loss-of-function mutation of endothelial lipase

Elevated Levels of Lipoprotein(a) - Lp(a)

- Apo(a) is very similar to plasminogen and has many homologous kringle 4 regions.
- Variation in kringle 4 regions is under genetic control; there is an inverse relationship between the size of Apo(a) and level of Lp(a).
- Consistent with this observation, hepatic synthesis of apo(a) is higher in those with smaller Apo(a) isoforms.
- Lp(a) is now measured by immunochemical methods, (normal <74 nmol/L), or in terms of its cholesterol content (normal <10 mg/dL).
- Elevated Lp(a) is familial and can be strongly associated with premature CVD.
- Children with stroke often have elevated Lp(a).

Deficiencies in Apo B-Containing Lipoproteins

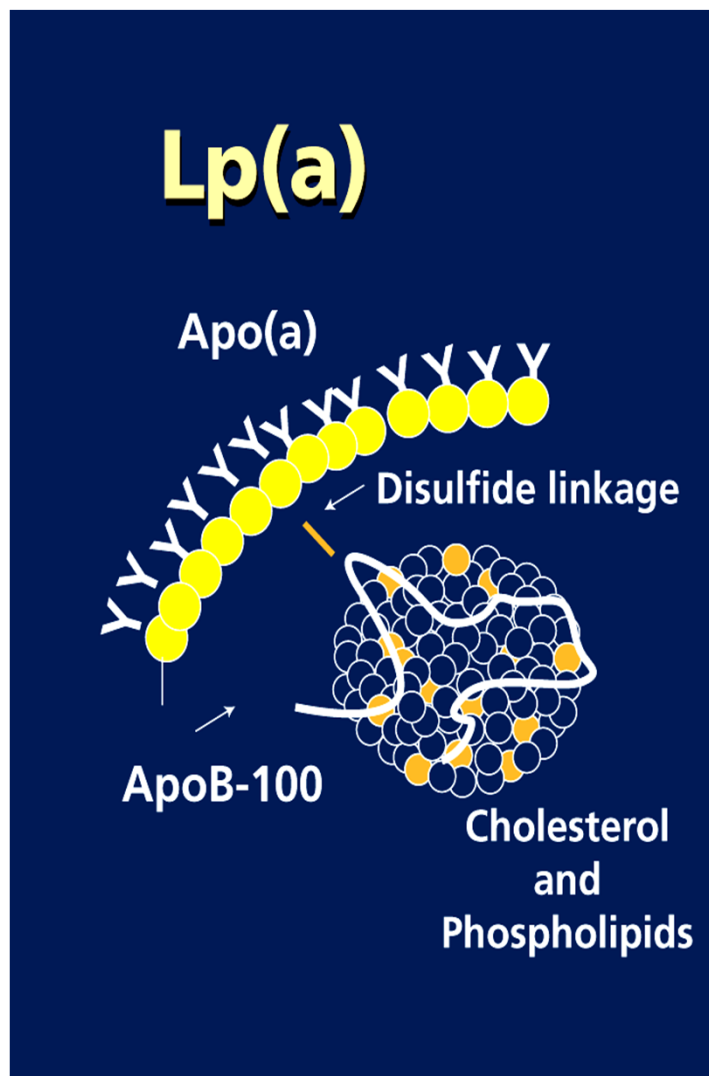
- Hypobetalipoproteinemia:
 - **Familial Hypobeta:** Autosomal dominant – mutations of the Apo B gene generally produce a stop codon and truncated Apo B100 – one normal gene – very low VLDL, IDL, LDL – generally asymptomatic – low risk of CVD, + longevity. Occasionally increased hepatic fat.
 - **Loss-of-function Mutations in PCSK9:** Ineffective degradation of LDLR. LDL-C levels reduced. Reduced risk of CAD.

Deficiencies in Apo B-Containing Lipoproteins

- Hypobetalipoproteinemia:
 - **Abetalipoproteinemia (abeta) (Bassen-Kornzweig Syndrome):** Rare autosomal recessive disorder – clinical manifestations in childhood including fat malabsorption, severe hypolipidemia, retinitis pigmentosa, cerebellar ataxia. All major Apo B containing lipoproteins missing (chylomicrons, VLDL, IDL, LDL).
 - Not caused by defective Apo B gene – defect in MTP in both intestines and liver. This causes a failure of intracellular transport of membrane associated lipids and their association with Apo B.
 - Defects associated with this disorder result from defects in the absorption and transport of fat-soluble vitamins A, D, E, K.

Deficiencies in Apo B-Containing Lipoproteins

- Hypobetalipoproteinemia:
 - **Abetalipoproteinemia (abeta) – also called Bassen-Kornzweig Syndrome:**
 - Treatment:
 - Reduce total fat to 5-20 g per day (decreases steatorrhea and improves growth)
 - Supplementation with linoleic acid (5 g corn oil or safflower oil per day)
 - High-dose fat soluble vitamins – especially vitamin E



- Genetically determined
- Marked elevation after acute ischemic coronary syndromes
- Structurally homologous to plasminogen
- Competes with plasminogen binding sites on endothelial cell surfaces
- Oxidized Lp(a) promotes atherosclerosis
- Simulates PAI-1 synthesis
- Risk factor for CHD events in men (Lipid Research Clinic) and women (Framingham Heart Study)

Modified from Stein JH, Rosenson RS. *Arch Intern Med.* 1997;157:1170-1176.

Key Take-Away Messages: Major Dyslipidemias

- Chylomicrons and chylo remnants (Apo B48, etc.)
 - Mainly for transport of dietary TG (energy)
 - Seen in fasting plasma *only* if TG > 500 mg/dL (T ½ = mins)
 - Increased risk of pancreatitis when TG > 1000 mg/dL
 - ~Always due to decreased clearance (↓LPL)
 - *Minor* role in atherogenesis (chylo remnants only)
- VLDL+IDL (Apo B100, Apo Cs, Apo E)
 - Common/moderate TG increase (TG 200-500 mg/dL)
 - Due to ↑production (fatty liver) + ↓clearance (↓LPL)
 - *Moderate* role in atherogenesis
- LDL (Apo B100)—also Lp(a) variant
 - Mainly for cholesterol transport
 - *Major* atherogenic factor
 - Oxidation/Inflammation
 - Endothelial dysfunction
- HDL (Apo AI, etc)
 - Major atheropreventive (blocks/reverses ~all adverse effects of VLDL, IDL, LDL)

Key Take-Away Messages: Major Dyslipidemias

Not associated w/ Insulin-resistance

- ↑LDL alone (Type IIa)—common and high-risk
 - Familial Hypercholesterolemia (tendon xanthomas)
 - Other polygenic (more common, usually without xanthomas)

Associated w/ Insulin-resistance

- ↑LDL+ ↑VLDL (types IIb + IV = IIb/mixed dyslip)—common and high-risk
- ↓HDL-C—common and high-risk (often seen w/ IIb, IV or V, but may be “isolated” ↓HDL)

Key Take-Away Messages: Minor Dyslipidemias

- Type I (↑chylomicrons only)
 - Severe TG
 - ↑Pancreatitis
 - Very Rare
- Type III (↑chol-enriched VLDL, familial dysbetalipoproteinemia)
 - ↓ Remnant removal (Apo E defect + ?)
 - Bad (premature) atherosclerosis
 - Orange palmar creases
 - Relatively rare
- ↑Lp(a)—no type #
 - LDL + Apo(a)
 - Poorly cleared
 - Highly oxidized
 - Very atherogenic
 - Relatively *uncommon*