Are Lipid Measurements Falling Short ? Lipidology vs Lipoproteinology

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Fellow of the National Lipid Association
North American Menopause Society Certified Menopause Practitioner

Director: North Jersey Institute of Menopausal Lipidology
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National Health And Nutrition Examination Survey (NHANES) 1971-2004

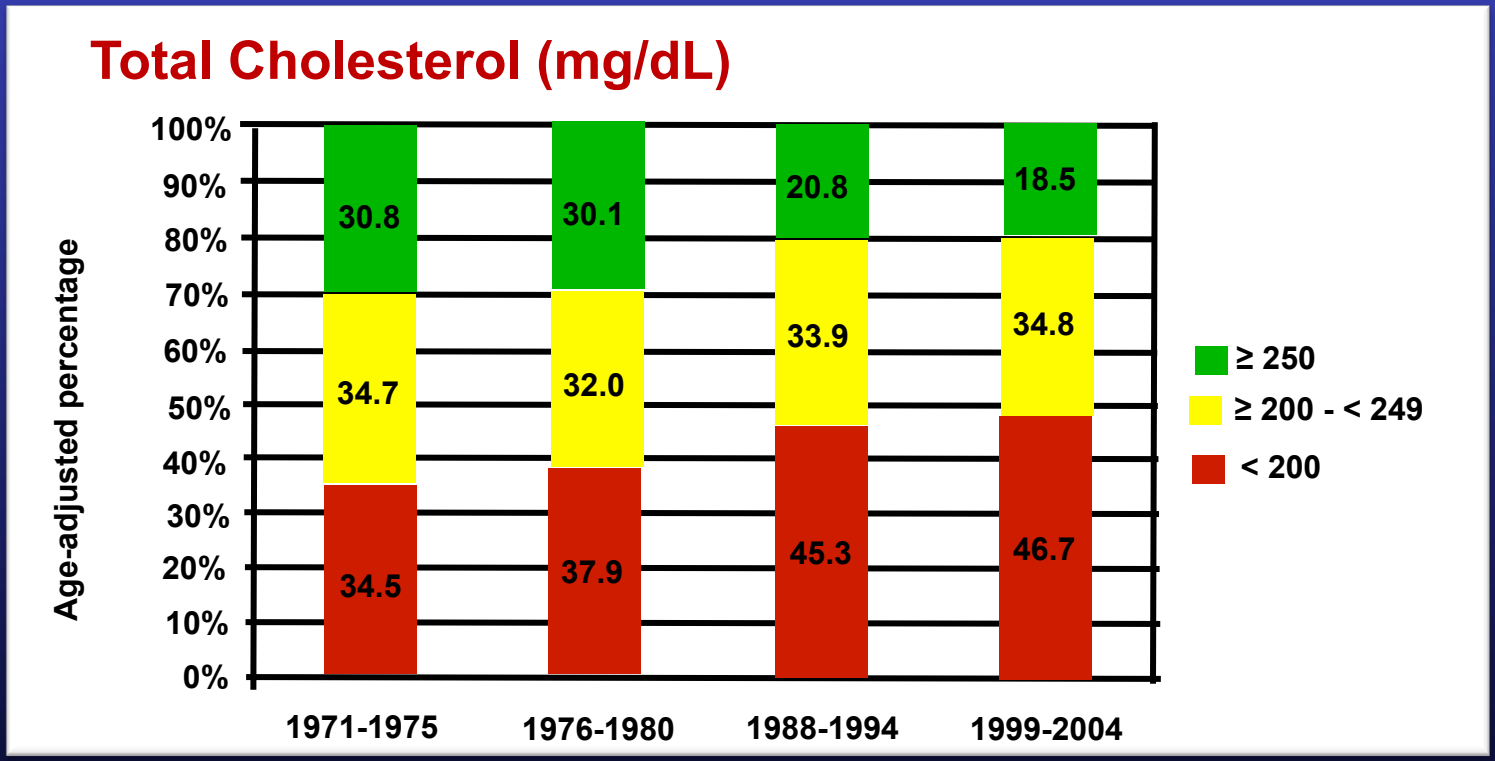
Prevalence of Low Risk Factor Burden

- The objective was to examine the prevalence and trends in low risk factor burden for cardiovascular disease among adults in the US population.
- Data from adults 25 to 74 years of age who participated in 4 national surveys was used. An index of low risk was created from the following variables:
  - Not currently smoking,
  - Total cholesterol 200 mg/dL and not using cholesterol-lowering medications,
  - Systolic blood pressure 120 mm Hg and diastolic blood pressure 80 mm Hg and not using antihypertensive medications,
  - Body Mass Index 25 kg/m2, and
  - Not having been previously diagnosed with diabetes mellitus.

Ford ES et al Circulation. 2009;120:1181-1188.

National Health And Nutrition Examination Survey (NHANES) 1971-2004

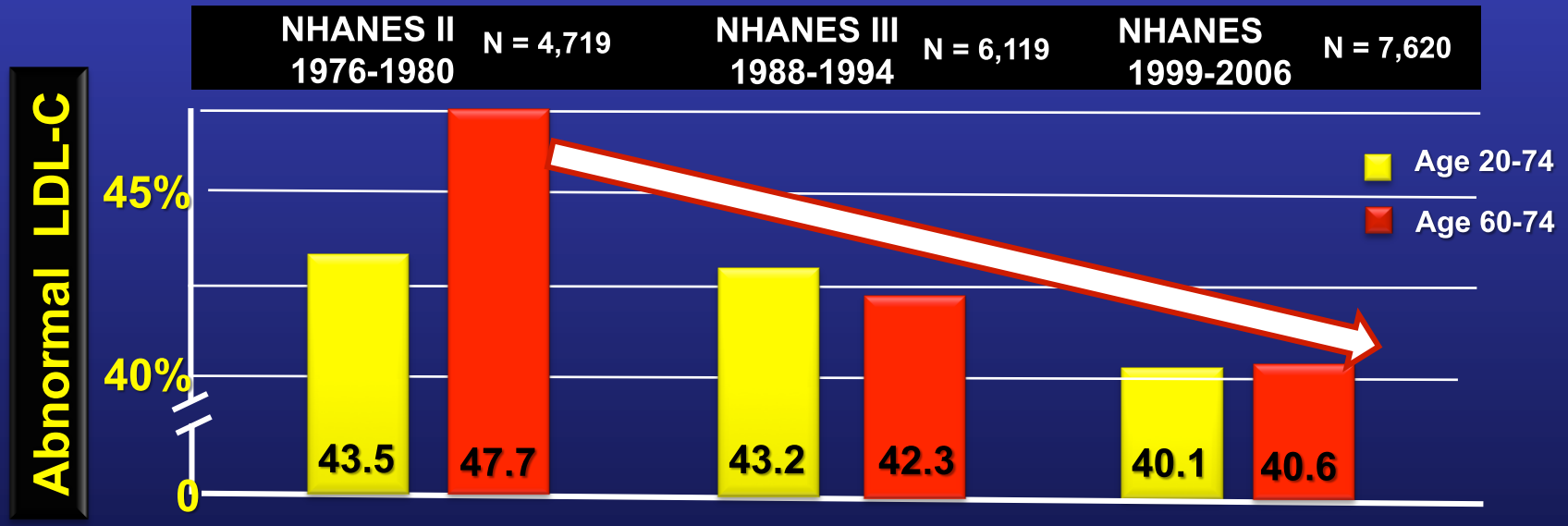
Prevalence of Total Cholesterol Risk Factor Burden



Trends in the age-adjusted prevalence of categories of total cholesterol (mmol/L) among adults not using cholesterol-lowering medications

Ford ES et al Circulation. 2009;120:1181-1188.

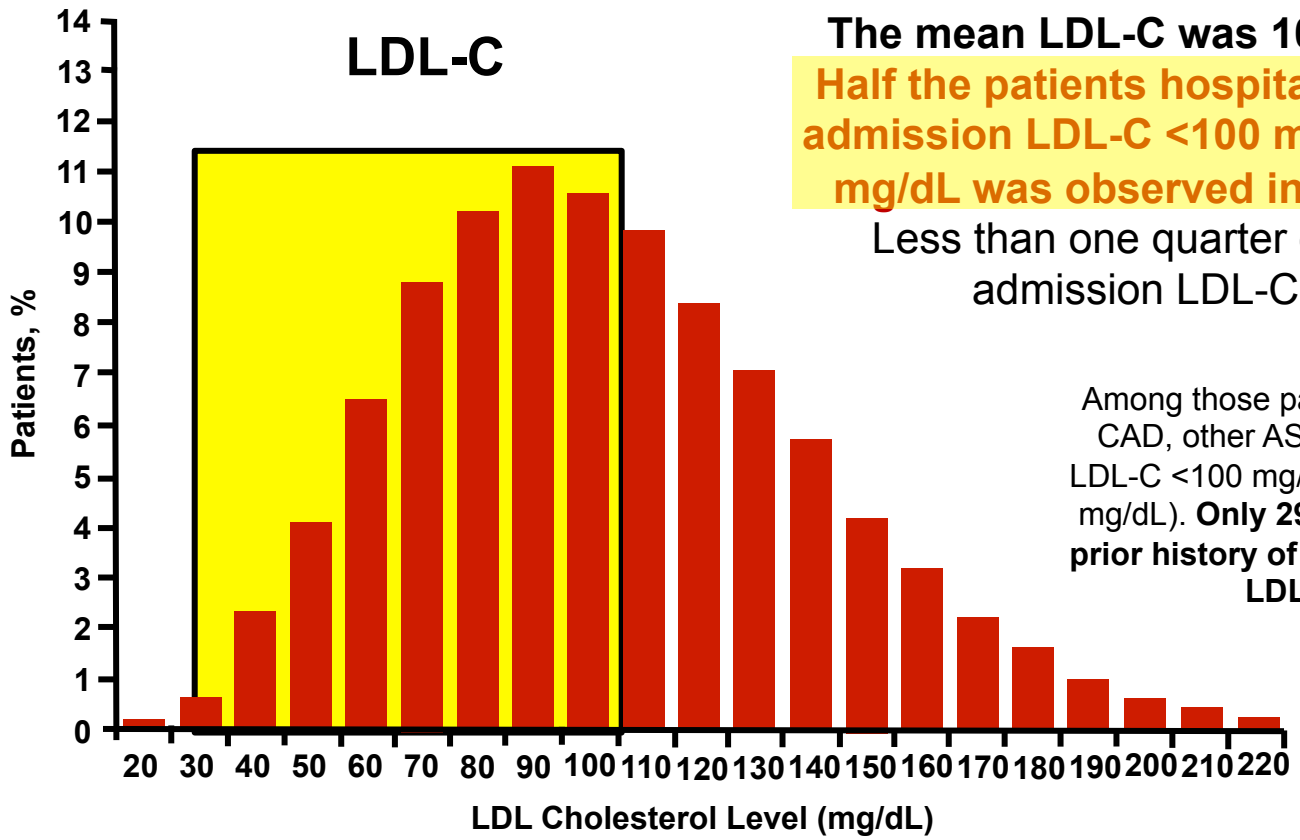
National Health And Nutrition Examination Survey (NHANES) Lipid Changes 1976 - 2006



LDL-C values have been dropping

Cohen J, et al. Circulation AHA Scientific Sessions 11/2008 New Orleans

Lipid Levels in Patients Hospitalized with Coronary Artery Disease



The mean LDL-C was 104.9 ± 39.8 mg/dL.

Half the patients hospitalized with CAD had admission LDL-C <100 mg/dL, and LDL-C<70 mg/dL was observed in 17.6% of patients.

Less than one quarter of patients had an admission LDL-C >130 mg/dL.

Among those patients without prior history of CAD, other ASHD, or diabetes, 41.5% had LDL-C <100 mg/dL and 12.5% had LDL-C <70 mg/dL). **Only 29.2% of the patients without prior history of ASHD or diabetes had LDL –C ≥ 130 mg/dL.**

n > 136,000

Get with the Guidelines Study

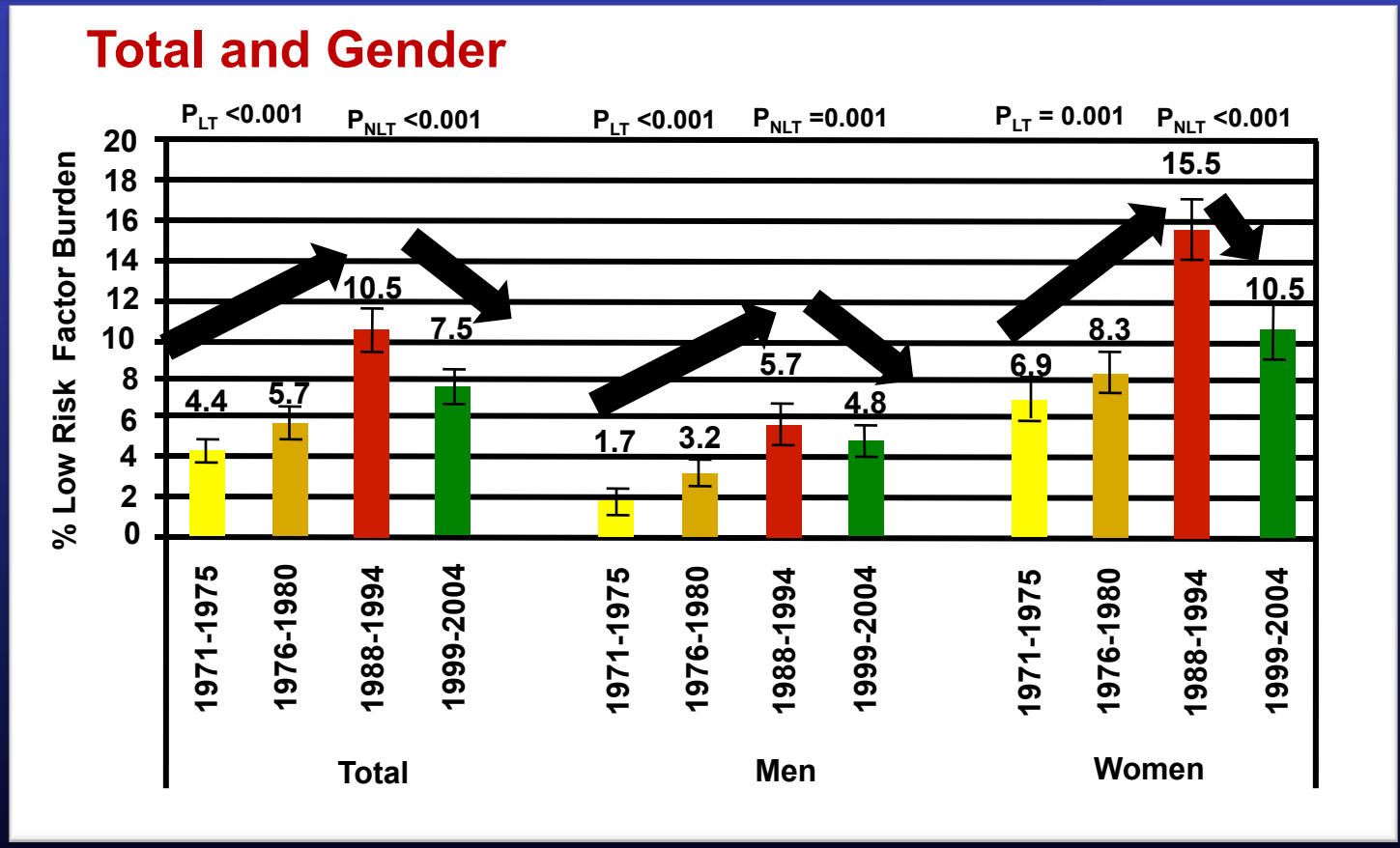
Sachdeva A, et al. Am Heart J 2009;157:111-7.e2

National Health And Nutrition Examination Survey (NHANES) 1971-2004

Prevalence of Low Risk Factor Burden

PLT = p value for linear trend for model containing a single term for time

PNLT = p value for quadratic term for model containing a term for time and its squared term.



Trends in the age-adjusted prevalence (95% confidence interval) of low risk factor burden for cardiovascular disease among US adults 25 to 74 years of age.

Ford ES et al Circulation. 2009;120:1181-1188.

National Health And Nutrition Examination Survey (NHANES) 1971-2004

Prevalence of Low Risk Factor Burden

Conclusion:

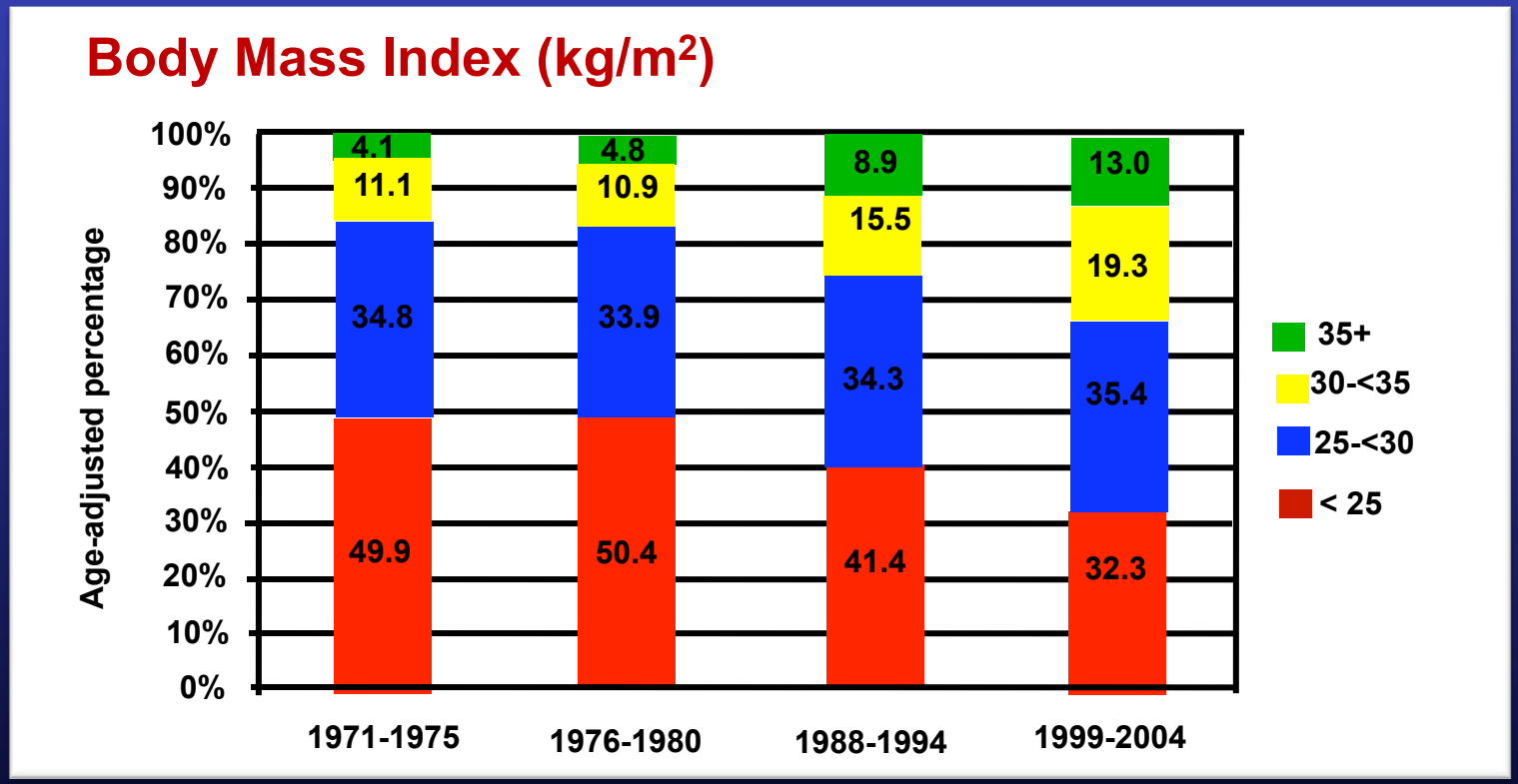
The prevalence of low risk factor burden for cardiovascular disease is low.

The progress that had been made during the 1970s and 1980s reversed in recent decades.

Ford ES et al Circulation. 2009;120:1181-1188.

National Health And Nutrition Examination Survey (NHANES) 1971-2004

Prevalence of BMI Risk Factor Burden



Trends in the age-adjusted prevalence of categories of BMI among adults not using cholesterol-lowering medications

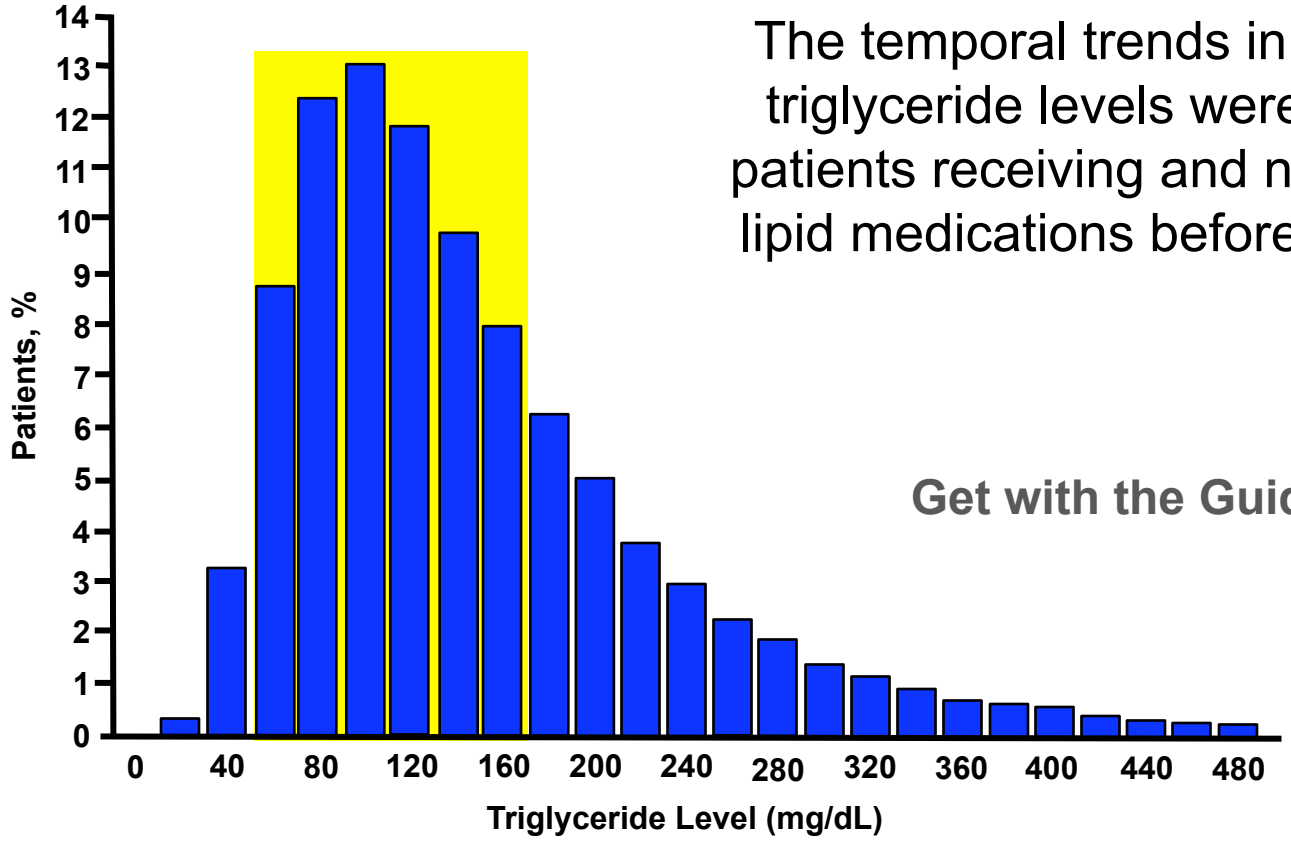
Ford ES et al Circulation. 2009;120:1181-1188.

National Health And Nutrition Examination Survey (NHANES) Lipid Changes 1976 - 2006

As LDL-C values have been dropping, TG values have been increasing

Cohen J, et al. Circulation AHA Scientific Sessions 11/2008 New Orleans

Lipid Levels in Patients Hospitalized with Coronary Artery Disease



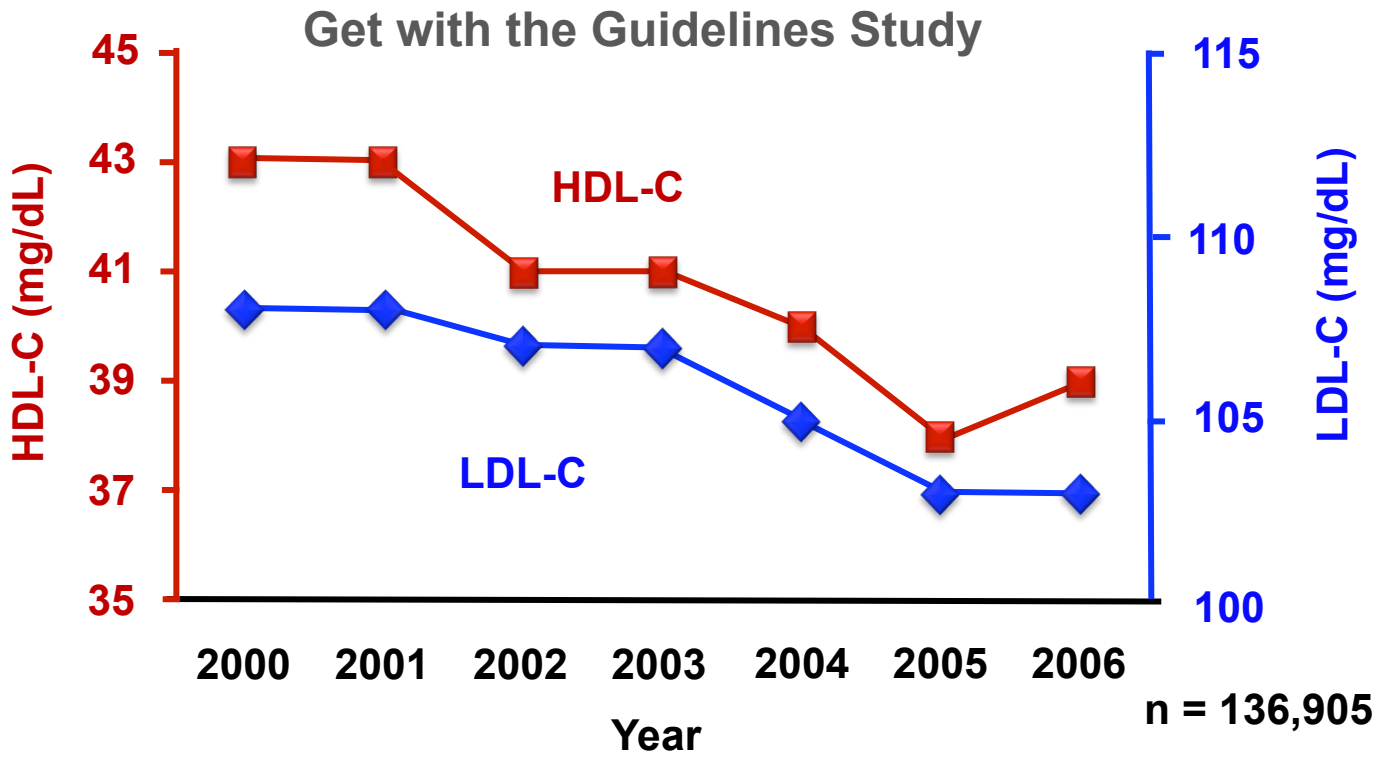
The temporal trends in admission triglyceride levels were similar in patients receiving and not receiving lipid medications before admission.

Get with the Guidelines Study

n > 136,000

Sachdeva A, et al. Am Heart J 2009;157:111-7.e2

Lipid Levels in Patients Hospitalized with Coronary Artery Disease



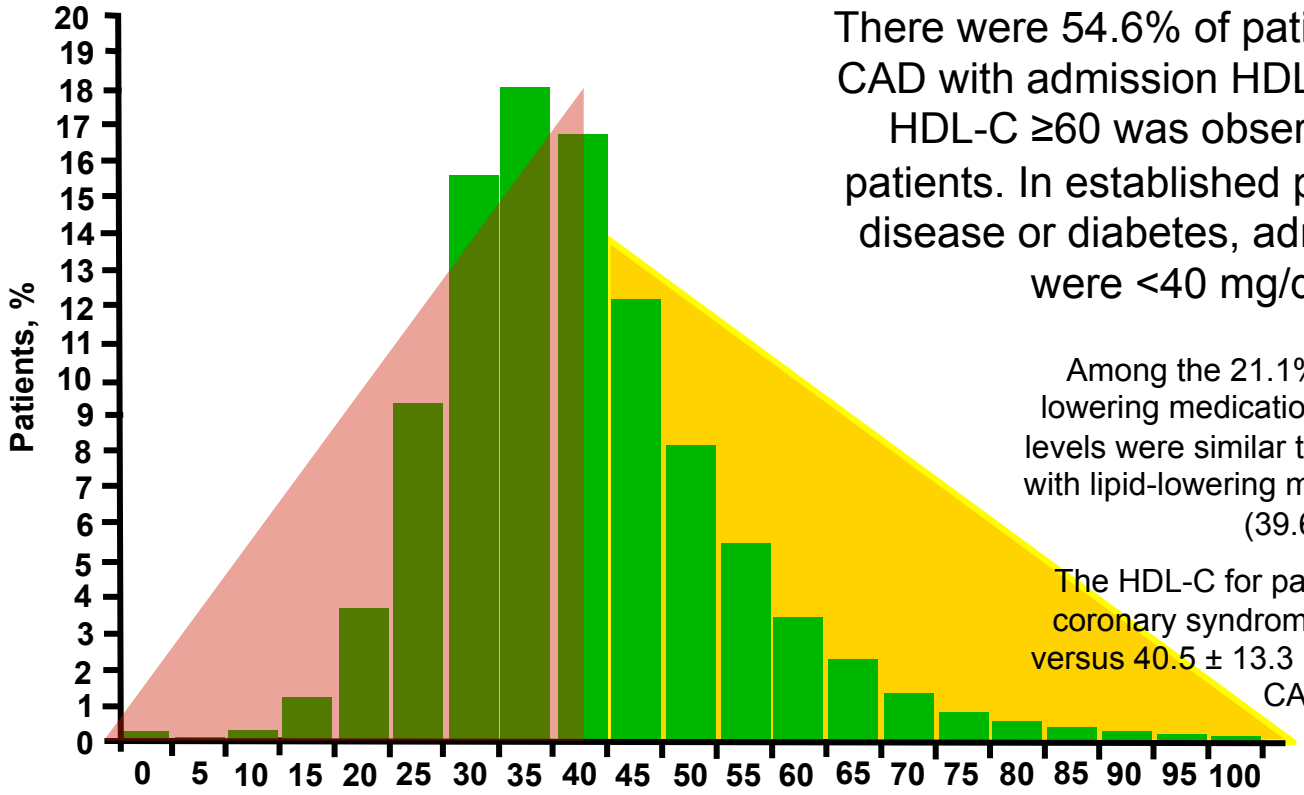
During the period 2000–2006, there was a 10% ($p < 0.001$) decrease in the levels of HDL cholesterol from a mean of 43 mg/dL to 39 mg/dL .

Over the same period, a proportionately smaller but statistically significant decrease in LDL-C levels was also observed

As the prevalence of obesity and metabolic syndrome continues to increase in many societies, it is reasonable to expect that HDL-C levels will continue to decrease among patients with ACS as well as those with other manifestations of CAD, and that low HDL may become the dominant manifestation of dyslipidemia in many of these patients.

Sachdeva A, et al. Am Heart J 2009;157:111-7.e2

Lipid Levels in Patients Hospitalized with Coronary Artery Disease



There were 54.6% of patients hospitalized with CAD with admission HDL-C levels <40 mg/dL. HDL-C ≥60 was observed in just 7.8% of patients. In established patients with vascular disease or diabetes, admission HDL-C level were <40 mg/dL in 56.9%.

Among the 21.1% of patients receiving lipid-lowering medications before admission, HDL-C levels were similar to those not previously treated with lipid-lowering medications (39.6 ± 2.6 mg/dL).

The HDL-C for patients presenting with acute coronary syndromes were 39.5 ± 13.2 mg/dL, versus 40.5 ± 13.3 mg/dL for patients with stable CAD diagnoses.

n > 136,000

There was a 10% decrease in admission HDL-C levels over the 6-year period is quite notable and may reflect increasing rates of obesity, insulin resistance, and diabetes.

Sachdeva A, et al. Am Heart J 2009;157:111-7.e2

National Health And Nutrition Examination Survey (NHANES) 1998-2004

Insulin Resistance, Metabolic Variables, and CAD

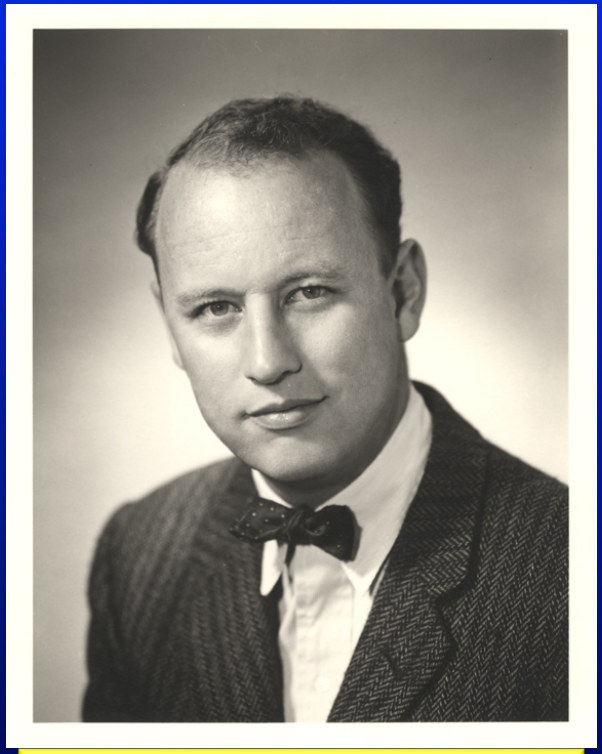
►Of the risk factors that are sufficiently well studied to permit quantitative analysis, insulin resistance is the most important single risk factor for CAD. Our results indicate that insulin resistance is responsible for approximately 42% of myocardial infarctions.

►Its effect on CAD is indirect, mediated through its effects on other variables such as SBP, HDL-cholesterol, triglycerides, glucose, and **apolipoprotein B.**

Eddy D et al. Diabetes Care 32:361–366, 2009

The Fathers of Modern Lipidology

Robert I Levy



Donald S Fredrickson

Robert S Lees

Circulation

MARCH 1965
VOL. XXXI NO. 3

AN OFFICIAL JOURNAL of the AMERICAN HEART ASSOCIATION

Editorial

A System for Phenotyping Hyperlipoproteinemia

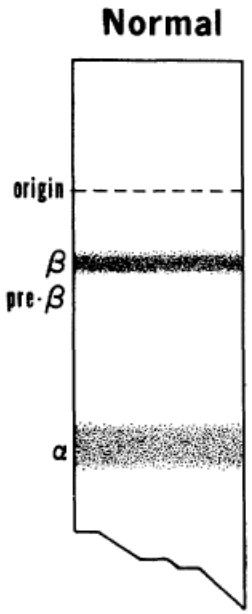
IT HAS been well established that the lipids in plasma do not circulate free but combine in orderly arrangements with protein. Most of the lipid is combined with two major proteins, the α and β polypeptides, to form lipoproteins that extend over a wide density range, from greater than 1.21 to that of fat itself, about 0.9 Gm. per ml. Changes in this lipoprotein spectrum occur in many diseases. In many instances the lipoprotein abnormality appears to be the primary expression of a biochemical defect. These disorders are usually familial, relatively common, and of particular interest in relation to atherogenesis and coronary heart disease. Despite their relative importance, the present understanding of these hereditary defects is meager and their classification chaotic.

For the determination and study of such abnormalities a number of methods have been available for some time. The minimum is a determination of plasma cholesterol and glyceride content. The maximum in resolving power is offered by the ultracentrifuge, which is capable of measuring changes within small increments of the density spectrum. When one is concerned particularly with familial hyperlipoproteinemia, necessitating screening of large kindreds, neither of these approaches has proved ideal. Measurement of triglycerides is tedious. Furthermore, even after considerable experience, knowledge of both cholesterol and triglyceride concentrations is inadequate for distinguishing all of the familial syndromes. The ultracentrifugal techniques also do not meet current needs because they are time-consuming, costly, and not sufficiently available to clinicians.

In the present state of knowledge of fat transport, most clinical studies require only rough quantitation of four groups of lipoproteins known to be related to independent metabolic processes and therefore possibly subject to specific inborn errors. These are the soluble alpha and beta lipoproteins and the two groups of lipoprotein or particles that transport, respectively, glycerides of exogenous or dietary origin (chylomicrons) and of endogenous, mainly hepatic, origin (pre-beta lipoproteins).

These lipoprotein groups can be separated by a rapid and simple method, a modification of established technics for paper electrophoresis.[1] By its application to a large number of subjects with familial hyperlipoproteinemia, we have so far been able to detect what appear to be five different phenotypes, more than have been ordinarily considered in the past.[2] It has also been possible to follow such patients through various dietary and metabolic studies much more easily than heretofore. Of particular value has been the ability to make a tentative diagnosis of fat or carbo-

From the section on Molecular Disease, Laboratory of Metabolism, National Heart Institute, Bethesda, Maryland.



The Normal Plasma Lipoprotein Pattern

CHYLOMICRONS

BETA LIPOPROTEINS
PRE-BETA LIPOPROTEINS

ALPHA LIPOPROTEINS

Paper Electrophoresis

Fredrickson D, Lees R.
Circulation 1965;31:321-327

January 5,1967 MEDICAL PROGRESS Volume 276

FAT TRANSPORT IN LIPOPROTEINS – AN INTEGRATED APPROACH TO MECHANISMS AND DISORDERS*

DONALD S. FREDRICKSON, M.D.† ROBERT I. LEVY, M.D.‡ AND ROBERT S. LEES, M.D.§

HYPERLIPOPROTEINEMIA

Definitions

Up to this point we have concentrated on laying the support for 2 generalizations. The first is that, with the exception of free fatty acid concentrations, which have no lipoprotein equivalents, all abnormalities in plasma lipid concentrations or *dyslipidemia* can be translated into *dyslipoproteinemia*. The second is that the shift of emphasis to lipoproteins offers distinct advantages in the recognition and management of such disorders. We have already

THE su
protein
ways in w
eases. The
their own s
tial for illu
ing clinical
of an abno
terol, glyce
often raises
no certain
forthcoming
is the reduction of current inform
transport and metabolism to the
needed by a physician to obtain a
to the patient with hyperlipidem
abreast of new developments in
panding field.

formation and concepts about
d clinical disorders will pro-
eoretical to more practical
of the review will outline the
nsport and describe how the
nd certain proteins interact in
e proteins that have evolved
transport of esterified lipids
at they form will be closely
clude analysis of several in-
hich one of these proteins is
pective on the functions that

All these disorders are translated into *hyperlipoproteinemia* on the premise – for which supporting evidence will be presented – that lipoprotein patterns offer necessary information not provided by analyses of plasma lipids alone. Some simple new

*From the Laboratory of Molecular Dise
Institute.
†Director and chief, Laboratory of Molecu
Heart Institute.
‡Head, Section on Lipoproteins, Laboratory of Molecular Diseases, National Heart Institute.
§Assistant professor and associate physician, Rockefeller University.

evidence will be presented – that lipoprotein patterns offer necessary information not provided by analyses of plasma lipids alone. Some simple new nomenclature is offered since the older terminology

CONSENSUS STATEMENT

Lipoprotein Management in Patients With Cardiometabolic Risk

Consensus statement from the American Diabetes Association and the American College of Cardiology Foundation

April 2008

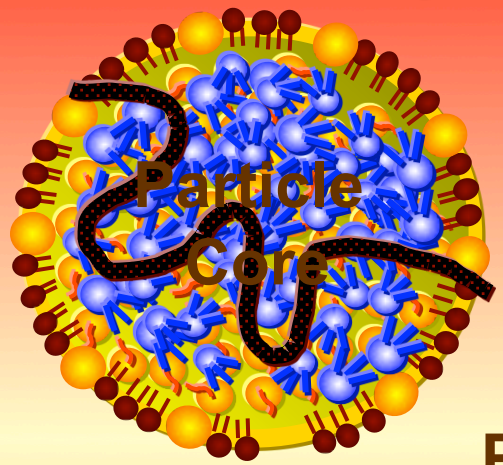
John D. Brunzell, MD, FACP[1]
Michael Davidson, MD, FACC[2]
Curt D. Furberg, MD, PHD[3]
Ronald B. Goldberg, MD[4]
Barbara V. Howard, PHD[5]
James H. Stein, MD, FACC, FACP[6]
Joseph L. Witztum, MD[7]

41 Years after the NEJM article

Diabetes Care 2008;31:811-822
JACC 2008;51:1512–24

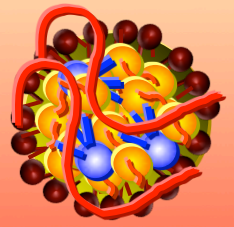
Lipoprotein Makeup

Apolipoprotein B (one molecule)



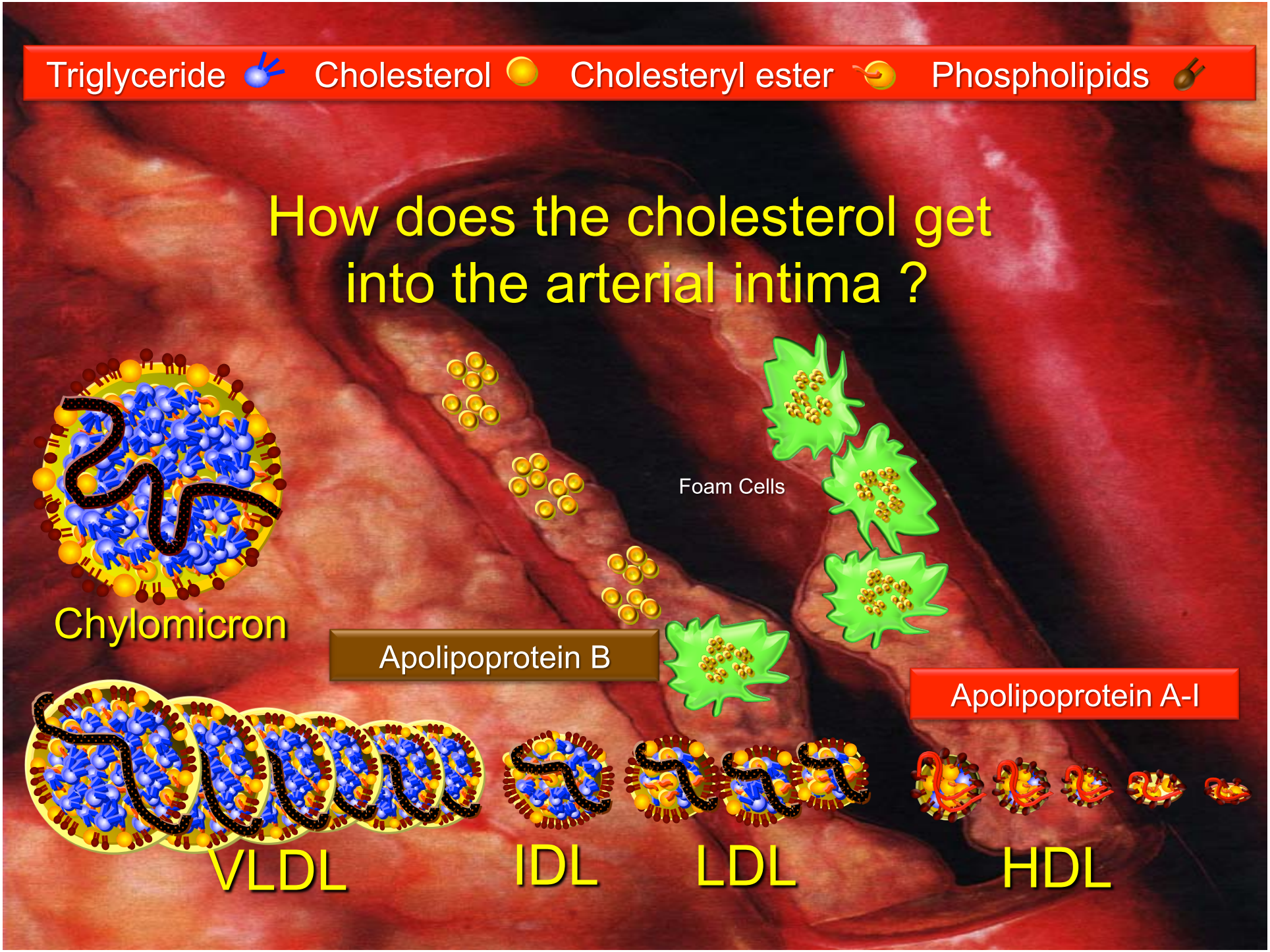
Core cholesteryl ester (CE)
Core triglycerides (TG)

Phospholipid surface
Free cholesterol surface



Apolipoprotein A-I (two to four molecules)

Phospholipids Cholesterol Triglyceride


Triglyceride
Cholesterol
Cholesteryl ester
Phospholipids
How does the cholesterol get into the arterial intima ?
Chylomicron
Foam Cells
Apolipoprotein B
Apolipoprotein A-I
VLDL
IDL
LDL
HDL

Atherogenesis

►**The key initiating process in atherogenesis is the subendothelial retention of apolipoprotein B–containing lipoproteins.**

►Local biological responses to these retained lipoproteins, including a chronic and maladaptive macrophage and T-cell– dominated inflammatory response, promote subsequent lesion development.

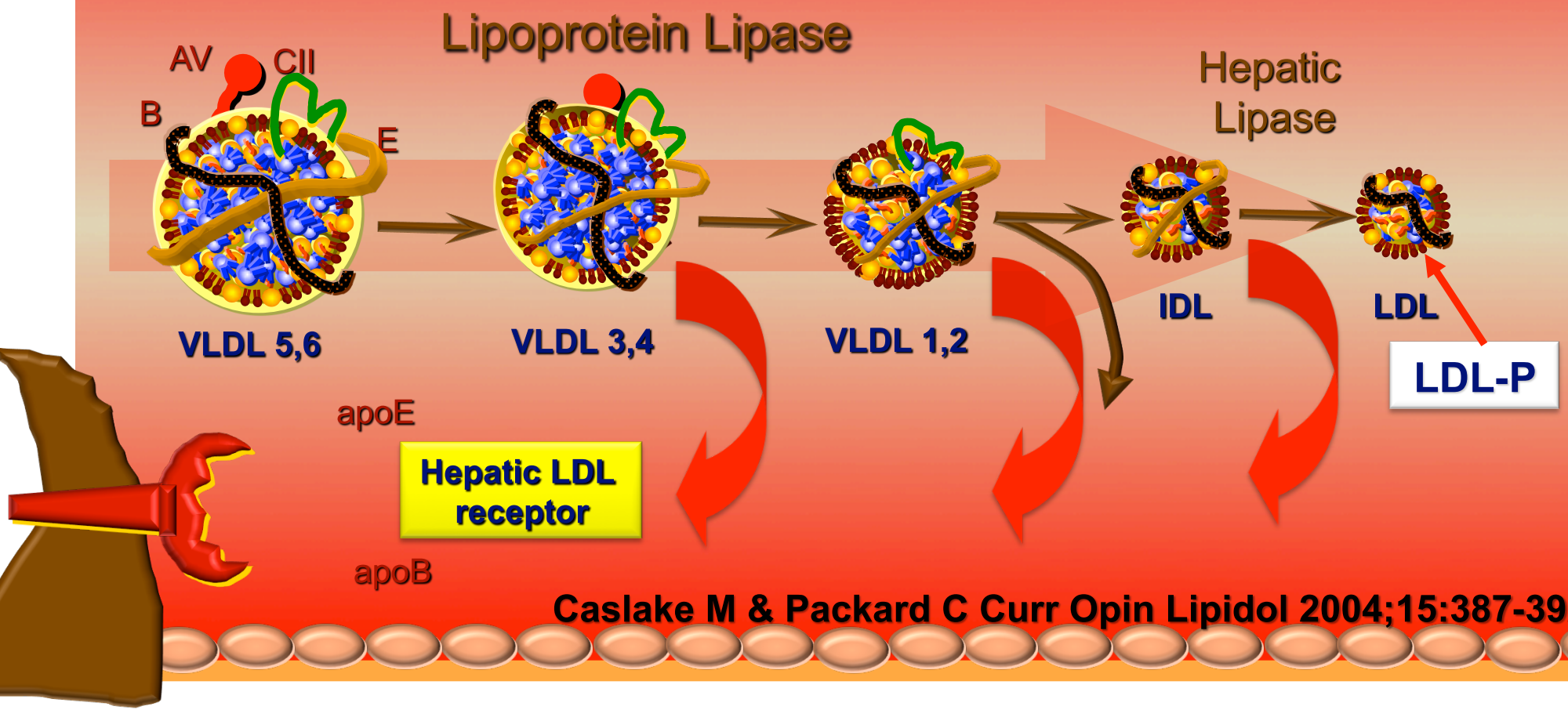
►The most effective therapy against atherothrombotic cardiovascular disease to date—low density lipoprotein–lowering drugs—is based on the principle that decreasing circulating apolipoprotein B lipoproteins decreases the probability that they will enter and be retained in the subendothelium.

►Ongoing improvements in this area include more aggressive lowering of low-density lipoprotein and other atherogenic lipoproteins in the plasma and initiation of low-density lipoprotein–lowering therapy at an earlier age in at-risk individuals.

Tabas I et al. Circulation. 2007;116:1832-1844

Normal VLDL Lipolysis

In patients with normal triglycerides,
VLDL lipolysis (hydrolysis of TG) is rapid (2-6 hours)



Caslake M & Packard C Curr Opin Lipidol 2004;15:387-392

Journal of Internal Medicine 2006; 259: 247–258 doi:10.1111/j.1365-2796.2006.01616.x

REVIEW

Apo B versus cholesterol in estimating cardiovascular risk and in guiding therapy: report of the thirty-person/ten-country panel

P. J. BARTER[1], C. M. BALLANTYNE[2], R. CARMENA[3], M. CASTRO CABEZAS[4], M. JOHN CHAPMAN[5], P. COUTURE[6], J. DE GRAAF[7], P. N. DURRINGTON[8], O. FAERGEMAN[9], J. FROHLICH[10], C. D. FURBERG[11], C. GAGNE[12], S. M. HAFFNER[13], S. E. HUMPHRIES[14], I. JUNGNER[15,16], R. M. KRAUSS[17], P. KWITEROVICH[18], S. MARCOVINA[19], C. J. PACKARD[20], T. A. PEARSON[21], K. SRINATH REDDY[22], R. ROSENSON[23], N. SARRAFZADEGAN[24], A. D. SNIDERMAN[25], A. F. STALENHOEF[7], E. STEIN[26], P. J. TALMUD[14], A. M. TONKIN[27], G. WALLDIUS[28] & K. M. S. WILLIAMS[13]

From the [1]Heart Research Institute, Camperdown, Sydney, NSW, Australia; [2]Baylor College of Medicine, Houston, TX, USA; [3]Department of Endocrinology and Nutrition, Facultad de Medicina y Hospital Clinico Universitario, Valencia, Spain; [4]St Franciscus Gasthuis, Rotterdam, the Netherlands; [5]Hôpital de la Pitié, Paris, France; [6]Centre Hospitalier Universitaire de Québec, Ste-Foy, Québec, Canada; [7]Radboud University Nijmegen Medical Center, Nijmegen, the Netherlands; [8]Division of Cardiovascular and Endocrine Science, Department of Medicine, Manchester Royal Infirmary, University of Manchester, Manchester, UK; [9]Aarhus Amtssygehus University Hospital, Aarhus C, Denmark; [10]University of British Columbia, St Paul's Hospital, Vancouver, BC, Canada; [11]Wake Forest University School of Medicine, Winston-Salem, NC, USA; [12]Université de Laval, Laval, Québec, Canada; [13]University of Texas Health Science Center, San Antonio, TX, USA; [14]Royal Free and University College Medical School, London, UK; [15]Clinical Epidemiology Unit, Department of Medicine, Karolinska Institute, Stockholm; [16]CALAB Research, Stockholm, Sweden; [17]Children's Hospital Oakland Research Institute, Oakland, CA; [18]The Johns Hopkins Medication Institutions, Baltimore, MD; [19]University of Washington, Seattle, WA, USA; [20]Glasgow Royal Infirmary, Glasgow, UK; [21]University of Rochester, Rochester, NY, USA; [22]All India Institute of Medical Sciences, New Delhi, India; [23]Northwestern University, Chicago, IL, USA; [24]Isfahan Cardiovascular Research Center, Isfahan, Iran; [25]Mike Rosenbloom Laboratory for Cardiovascular Research, McGill University Health Sciences Centre, Montreal, Québec, Canada; [26]Metabolic and Atherosclerosis Research Center, Cincinnati, OH, USA; [27]Monash University, Victoria, Australia; and [28]King Gustaf V Research Institute and Karolinska Institute, Stockholm, Sweden

Abstract. Barter PJ, Ballantyne CM, Carmena R, Castro Cabezas M, John Chapman M, Couture P, de Graaf J, Durrington PN, Faergeman O, Frohlich J, Furberg CD, Gagne C, Haffner SM, Humphries SE, Jungner I, Krauss RM, Kwiterovich P, Marcovina S, Packard CJ, Pearson TA, Srinath Reddy K, Rosenson R, Sarrafzadegan N, Sniderman AD, Stalenhoef AF, Stein E, Talmud PJ, Tonkin AM, Walldius G, Williams KMS (Heart Research Institute, Sydney, NSW, Australia; Baylor College of Medicine, Houston, TX, USA; Hospital Clinico Universitario, Valencia, Spain; St Franciscus Gasthuis, Rotterdam, the Netherlands; Hôpital de la Pitié, Paris, France; Centre Hospitalier Universitaire de Québec, Québec, Canada; Radboud University Nijmegen Medical Center, Nijmegen, the Netherlands; University of Manchester, Manchester, UK; Aarhus Amtssygehus University Hospital, Aarhus C, Denmark; University of British Columbia, St Paul's Hospital, Vancouver, BC, Canada; Wake Forest University School of Medicine, Winston-Salem, NC, USA; Université de Laval, Laval, Québec, Canada; University of Texas Health Science Center, San Antonio, TX, USA; Royal Free and University College Medical School, London, UK; Karolinska Institute, Stockholm; CALAB Research, Stockholm, Sweden; Children's Hospital Oakland Research Institute, Oakland, CA; The Johns Hopkins Medication Institutions, Baltimore, MD; University of Washington, Seattle, WA, USA; Glasgow Royal Infirmary, Glasgow, UK; University of Rochester,

All of the national and transnational screening and therapeutic guidelines are based on total or LDL cholesterol.

This presumes that cholesterol is the most important lipoprotein-related proatherogenic risk variable.

On the contrary, risk appears to be more directly related to the number of circulating atherogenic particles that contact and enter the arterial wall than to the measured concentration of cholesterol in these lipoprotein fractions.

Each of the atherogenic lipoprotein particles contains a single molecule of apolipoprotein (apo) B and therefore the concentration of apo B provides a direct measure of the number of circulating atherogenic lipoproteins.

Evidence from fundamental, epidemiological and clinical trial studies indicates that apo B is superior to any of the cholesterol indices to recognize those at increased risk of vascular disease and to judge the adequacy of lipid-lowering therapy.

Barter PJ et al. J Intern Med 2006;249:247-258

American Association of Clinical Chemistry

Clinical Chemistry
2009;55:407-419

Apolipoprotein B and Cardiovascular Disease Risk: Position Statement from the AACC Lipoproteins and Vascular Diseases Division Working Group on Best Practices

John H. Contois,[1*†] Joseph P. McConnell,[2] Amar A. Sethi,[3] Gyorgy Csako,[3] Sridevi Devaraj,[4] Daniel M. Hoefner,[5] and G. Russell Warnick[6]

Contois JH, et al. Clinical Chemistry 2009; 55:407-419

Lipoproteins

W. Virgil Brown MD

"In 2009, several trends are developing in the management of lipoproteins as contributors to the risk of arteriosclerotic vascular disease."

"The risk of developing vascular disease in large populations is continuous and positively related to low-density and very–low-density **lipoprotein** concentrations throughout the range of values observed in surveys."

J Clin Lipidol 2009;3:151-152

Laboratory Analysis

Lipids

Standard Lipid Profile

LIPIDS	mg/dL	Optimal	Near or above optimal	Borderline-high	High	Very High
LDL-C (calculated)	**101**	<100	100 - 129	130 - 159	160 - 189	≥190

	mg/dL	
HDL-C	**56**	Desirable ≥ 40
Triglycerides	**72**	Desirable <150
Total Cholesterol	**171**	Desirable <200

LDL-C cannot be reported if triglycerides are 400 mg/dL. LDL-C will be inaccurate if the sample is nonfasting.

The cholesterol within all of the HDLs per dL of plasma

The TG within all of the lipoproteins per dL of plasma, although normally most are in VLDLs

The cholesterol within all of the lipoproteins per dL of plasma,

The cholesterol within all of the LDLs per dL of plasma

Friedewald formula

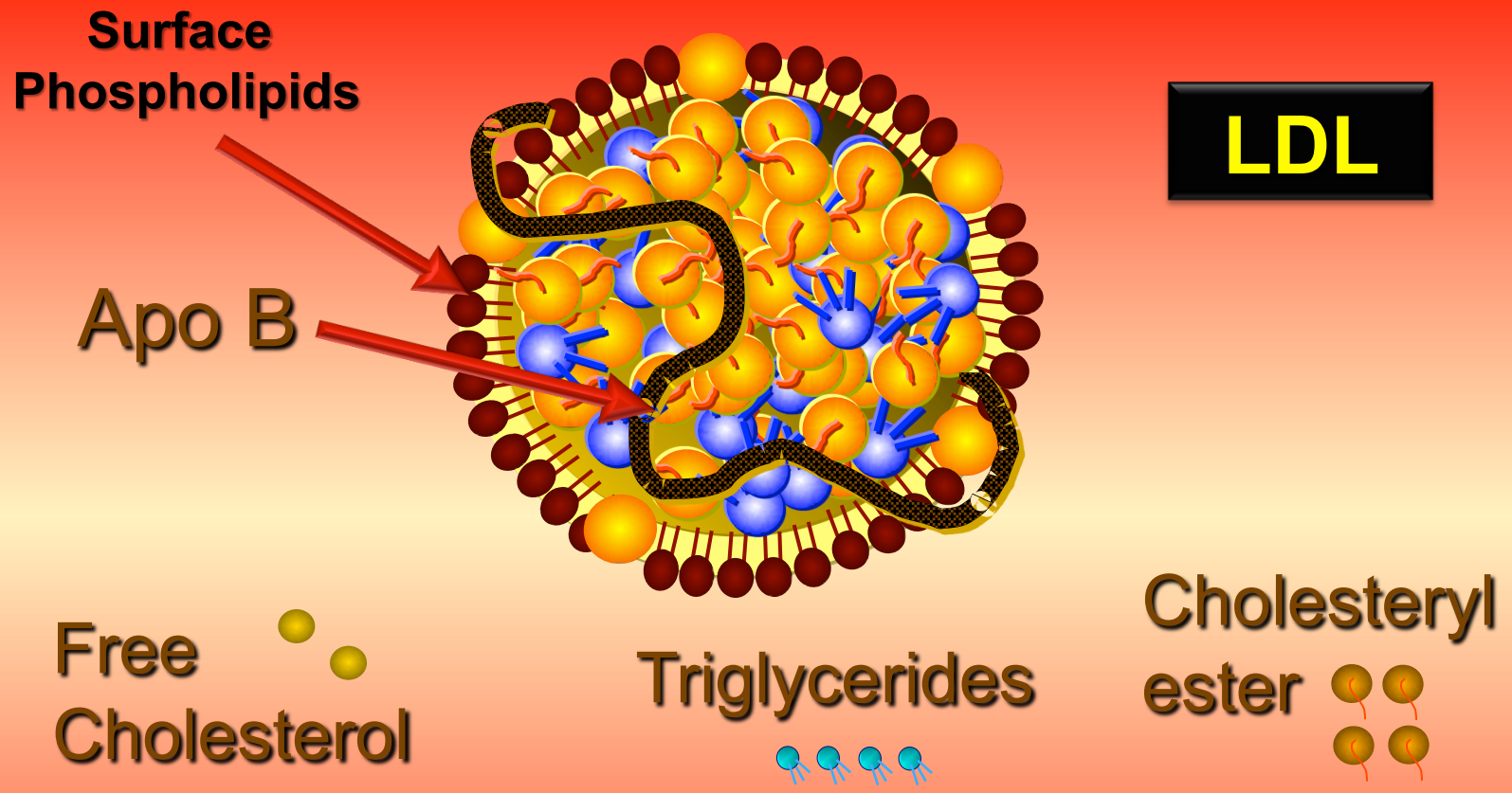
LDL-C = Total Cholesterol - ([HDL-C] + [VLDL-C])

VLDL-C = TG/5


Assaying LDL
LDL-C

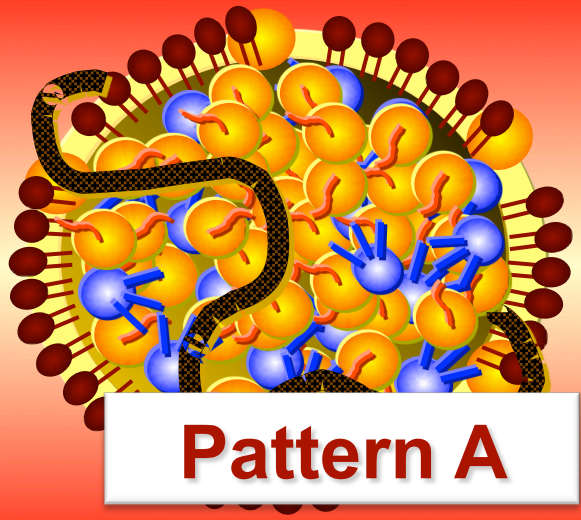
Low Density Lipoprotein

Low Density Lipoprotein (LDL) is one of several human lipoproteins

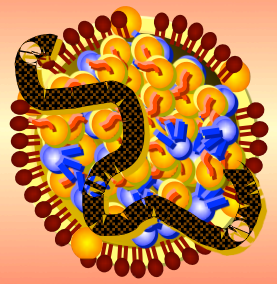


A beta-lipoprotein with a core composition of > 80-90% cholesterol and 10-20% TG

LDL-cholesterol



Pattern A



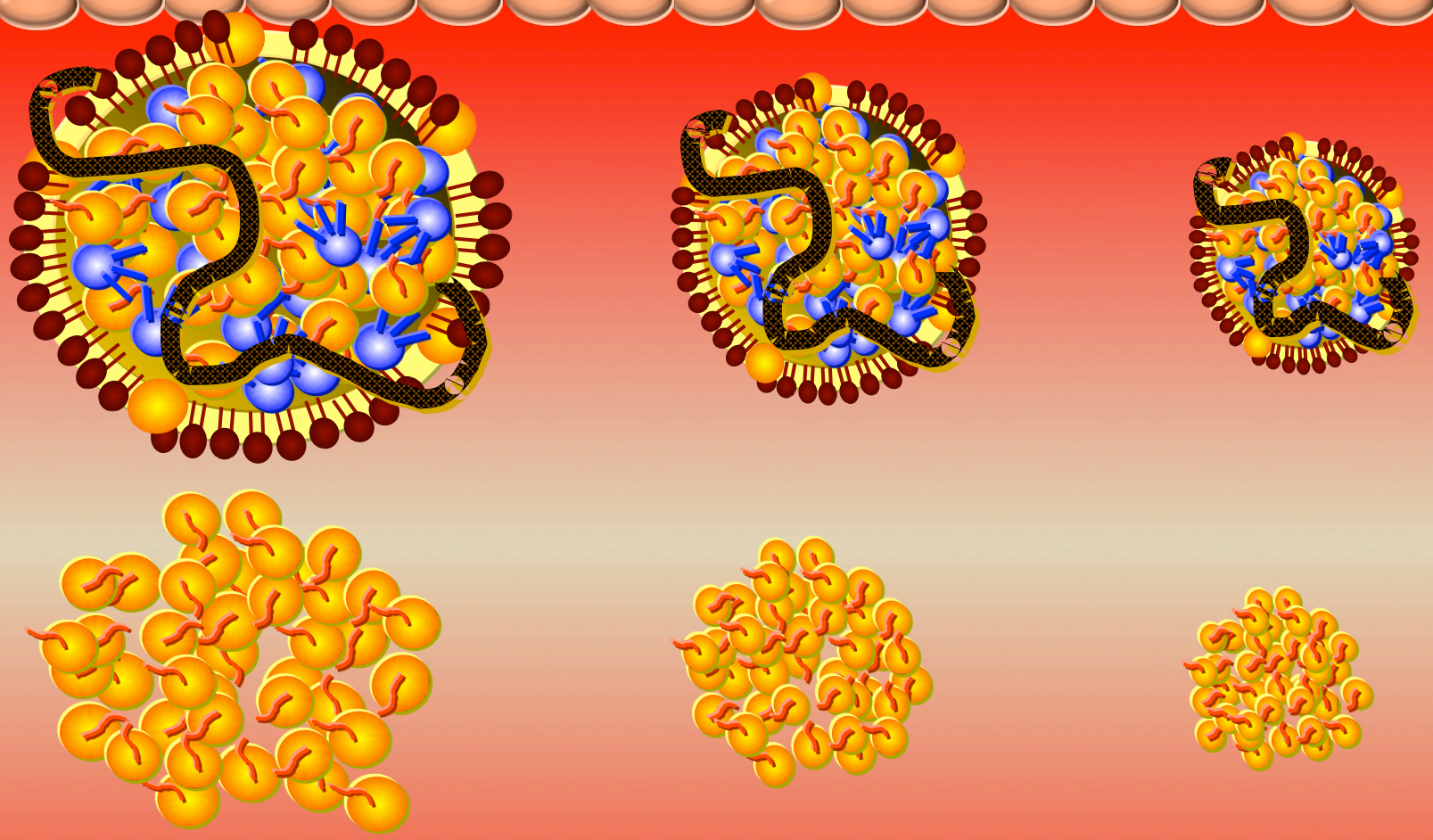
Pattern B

LDL-C = TC – [HDL-C + VLDL-C)

- LDL particles are a heterogeneous mixture of particles of varying composition and size, each with a single molecule of apoB
- The larger, more buoyant particles are termed Phenotype or Pattern A
- The smaller, denser, less buoyant particles are termed Phenotype or Pattern B
- LDL-C is the sum of the cholesterol within all of the LDL particles per/ dL of serum

Handbook of Lipoprotein Testing 2000 AACC Press

Evaluating LDL-C in the Laboratory



LDL-C is the cholesterol within all of the LDL particles that exist in a dL of plasma

Population Distributions of LDL-C in Framingham Offspring Study and the Multi-Ethnic Study of Atherosclerosis (MESA)

Percentile	LDL-C (mg/dL)	LDL-C (mg/dL)	
2	70		2nd Percentile Cutpoint
5	78	70	5th Percentile Cutpoint
10	88	81	
20	100	93	20th Percentile Cutpoint
30	111	103	
40	120	110	
50	130	118	50th Percentile Cutpoint
60	139	125	
70	149	133	
80	160	143	
90	176	160	
95	191	171	

MESA in red font
FOS in black


Assaying LDL
LDL-P

ADA and ACC Consensus Statement on Lipoprotein Management In Patients with Cardiometabolic Risk

Statement on LDL-P

- A more accurate way to capture the risk posed by LDL may be to measure the number of LDL particles directly using nuclear magnetic resonance (NMR).
- Many cross-sectional and prospective studies show that LDL particle number is a better discriminator of risk than is LDL cholesterol.
- LDL particle number as measured by NMR appears equally informative as apoB.

Brunzell JD, Davidson M, Furberg CD et al. Diabetes Care 2008;31:811-822

Population Distributions of LDL-P in Framingham Offspring Study and the Multi-Ethnic Study of Atherosclerosis (MESA)

Percentile	LDL-C (mg/dL)	LDL-C (mg/dL)	LDL-P (nmol/L)	LDL-P (nmol/L)	
2	70		720		2nd Percentile Cutpoint
5	78	70	850	770	5th Percentile Cutpoint
10	88	81	940	940	
20	100	93	1100	1000	20th Percentile Cutpoint
30	111	103	1220	1070	
40	120	110	1330	1100	
50	130	118	1440	1190	50th Percentile Cutpoint
60	139	125	1540	1280	
70	149	133	1670	1480	
80	160	143	1820	1610	
90	176	160	2020	1790	
95	191	171	2210	1980	

MESA in red font
FOS in black

Recommendations from AACC Lipoproteins and Vascular Diseases Division Working Group on Best Practices

Suggested Treatment Goals

	LDL-C, mg/dL		LDL-P, nmol/L
Very High Risk	< 70	2nd percentile	
High Risk	< 100	20th percentile	< 1100
Lower Risk	< 130	50th percentile	< 1400

Population cutpoints are from Framingham Offspring Study

Contois JH, et al. Clinical Chemistry 2009; 55:407-419

The LipoScience Report Form
LDL Particle Concentration

NMR LipoProfile® test

		Reference Range [1]				
	Percentile[1]	20th	50th	80th	95th	
	nmol/L	Low	Moderate	Borderline-High	High	Very High
LDL-P (LDL Particle Number)	1350	<1000	1000-1299	1300-1599	1600-2000	>2000

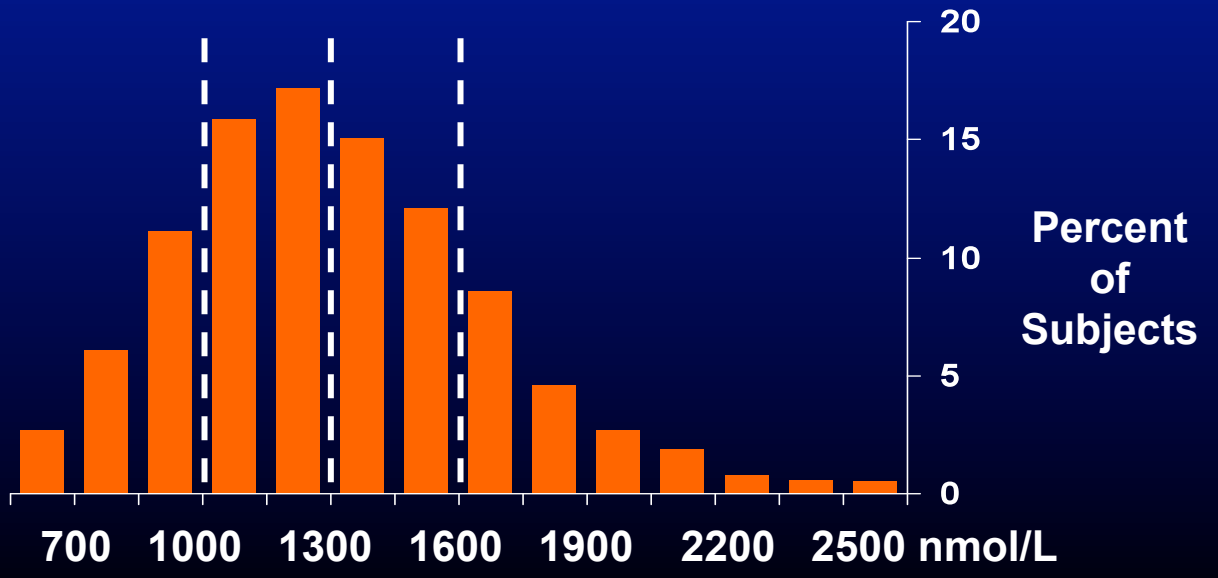
1. Reference population compromises 5,362 men and women not on lipid medication enrolled in the Multi-Ethnic Study of Atherosclerosis (MESA). Mora et al. Atherosclerosis 2007

Now FDA Approved

Percentile: 20th 50th 80th

MESA

LDL Particle Number



www.liposcience.com

NMR LipoProfile® test

Reference Range [1]

		Percentile[1]	20th	50th	80th	95th
	nmol/L	Low	Moderate	Borderline-High	High	Very High
LDL-P (LDL Particle Number)	1350	<1000	1000-1299	1300-1599	1600-2000	>2000

Lipids

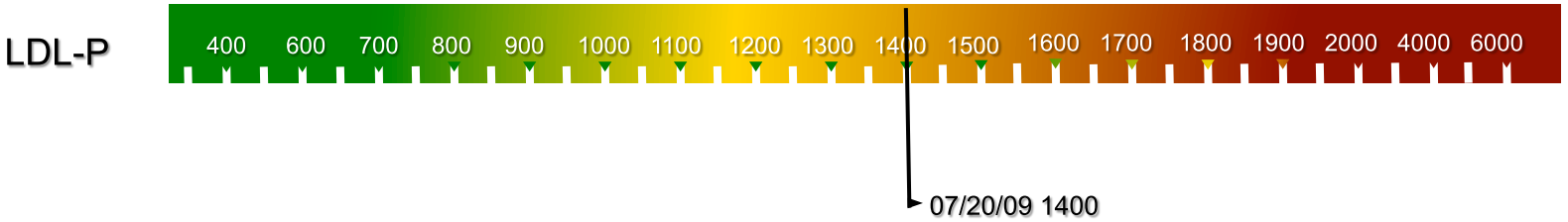
		Optimal	Near or above optimal	Borderline-High	High	Very High
	mg/dL					
LDL-C (calculated)	***	<100	100-129	130-159	160-200	>200

	mg/dL		mg/dL		mg/dL
HDL-C	42	Triglycerides	410	Total Cholesterol	185
	Desirable ≥ 40		Desirable < 150		Desirable < 150

**** Test not ordered

*** LDL-C cannot be calculated if triglycerides are > 400. LDL-C will be inaccurate if patient is nonfasting

Historical Reporting



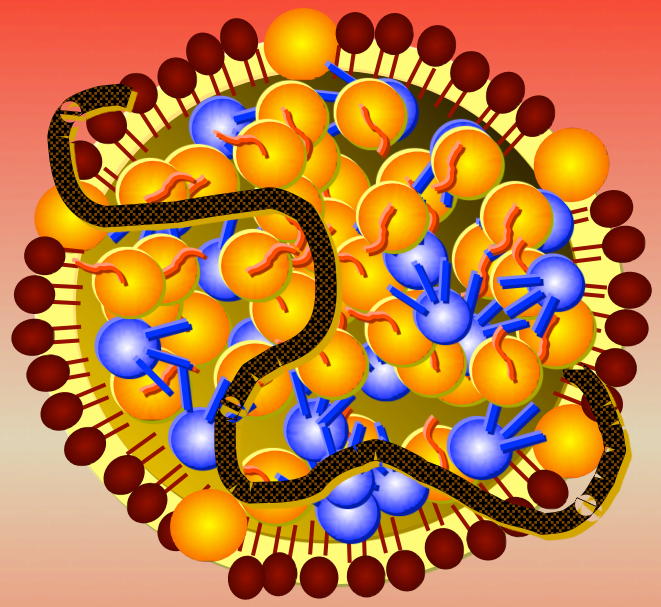
1. Reference population compromises 5,362 men and women not on lipid medication enrolled in the Multi-Ethnic Study of Atherosclerosis (MESA). More et al. Atherosaclerosis 2007

www.liposcience.com

Evaluating LDL in the Laboratory

LDL-P is the TOTAL number (nmol) of LDL particles per liter of plasma

- LDL-P via NMR* (available at LipoScience or LabCorp)



- Every single LDL particle contains one molecule of apolipoprotein B100
- The core contains variable amounts of TG and cholesteryl ester (CE)

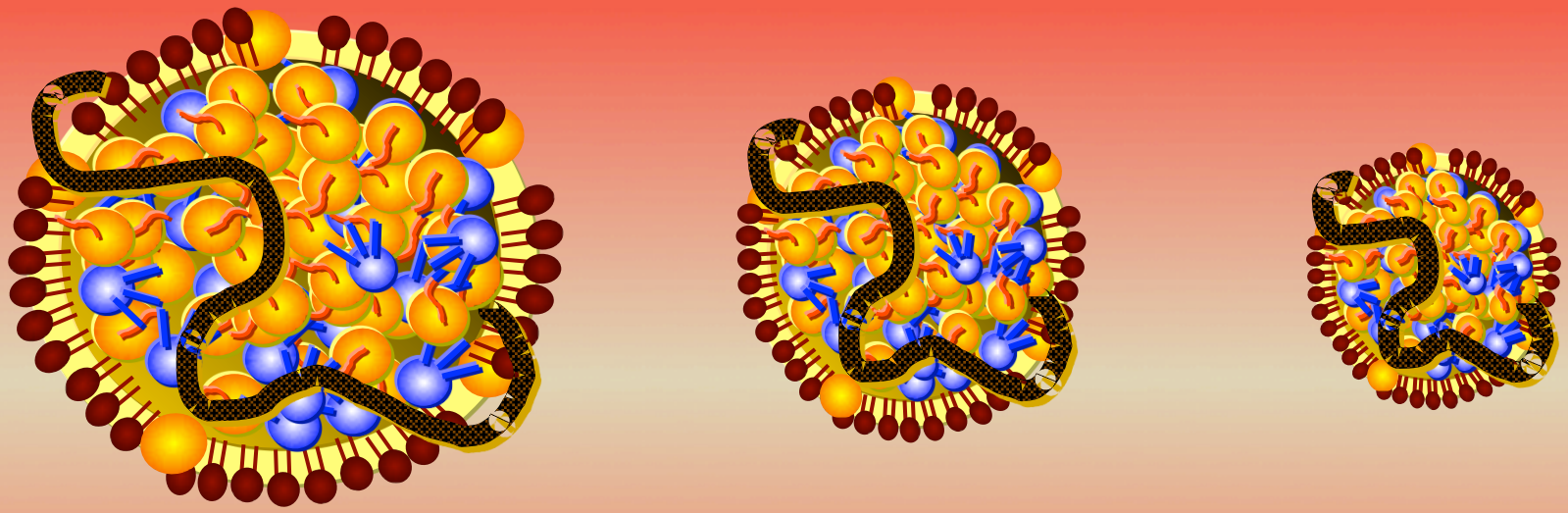
- LDL particles are a heterogeneous mixture of particles of varying composition and size, each with a single molecule of apoB
- Depending on size and core TG, each LDL particle traffics a different number of cholesterol molecules

*Nuclear magnetic resonance spectroscopy

Evaluating LDL in the Laboratory

LDL-P is the TOTAL number (nmol) of LDL particles per liter of plasma

- LDL-P via NMR* (available at LipoScience or LabCorp)



- LDL particles are a heterogeneous mixture of particles of varying composition and size, each with a single molecule of apoB
- Depending on size and core TG, each LDL particle traffics a different number of cholesterol molecules

*Nuclear magnetic resonance spectroscopy


Assaying LDL
Apo B

Recommendations from AACC Lipoproteins and Vascular Diseases Division Working Group on Best Practices

Options for Measurement of LDL Particle Concentration

- "Although it is often considered to be a distinct risk factor, apoB is better considered an alternate measure of LDL-related risk because it largely reflects LDL particle concentration."

Contois JH, et al. Clinical Chemistry 2009; 55:407-419

ADA and ACC Consensus Statement on Lipoprotein Management In Patients with Cardiometabolic Risk

Particle Quantification

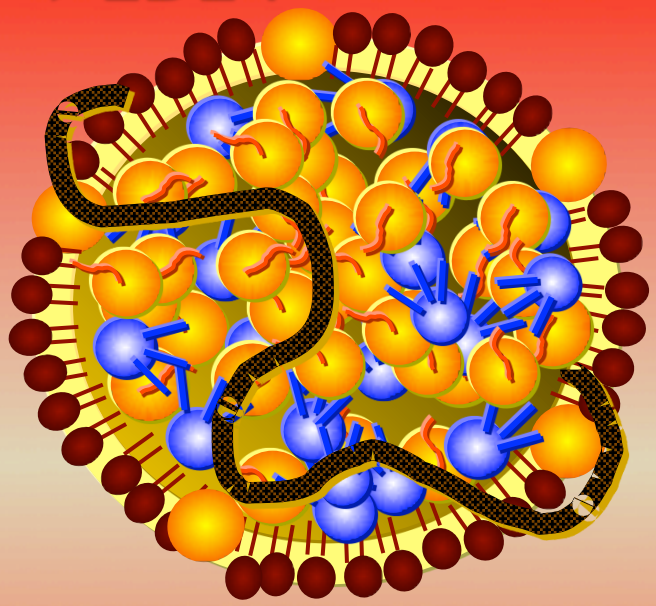
- Measurement of apoB is warranted in patients with cardiometabolic risk on pharmacologic treatment
- In particular apoB should be used to guide adjustments to therapy
- The panel recommends that the apoB goal be reached

Brunzell JD, Davidson M, Furberg CD et al. Diabetes Care 2008;31:811-822

Evaluating LDL in the Laboratory

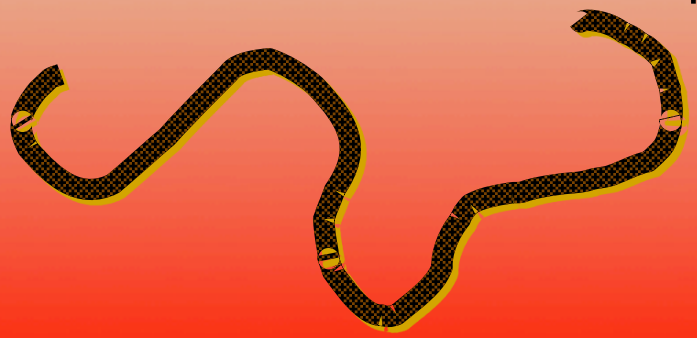
LDL-P is the number (nmol) of LDL particles per liter of plasma

►LDL-P



- Every single LDL particle contains one molecule of apolipoprotein B100
- Because of its much longer half life, compared to VLDLs and IDLs, > 90 % of apoB particles are LDLs
- Apolipoprotein B assay is a protein immunoassay where the epitopes on the apoB molecule are recognized by the paratopes on the reagent.

►ApoB



Population Distributions of LDL-C, non-HDL-C, ApoB and LDL-P in Framingham Offspring Study

Percentile	LDL-C (mg/dL)	Non-HDL-C (mg/dL)	LDL-P (nmol/L)	ApoB (mg/dL)	
2	70		720	54	2nd Percentile Cutpoint
5	78		850	62	
10	88		940	69	
20	100		1100	78	20th Percentile Cutpoint
30	111		1220	85	
40	120		1330	91	
50	130		1440	97	50th Percentile Cutpoint
60	139		1540	103	
70	149		1670	110	
80	160		1820	118	
90	176		2020	130	
95	191		2210	140	

ADA and ACC Consensus Statement on Lipoprotein Management in Patients with Cardiometabolic Risk

TREATMENT GOALS	LDL-C (mg/dL)	Non-HDL-C (mg/dL)	ApoB (mg/dL)
Highest-risk patients, including those with 1) known CVD or 2) Diabetes plus one or more additional CVD risk factor	< 70	< 100	< 80
High-risk patients, including those with 1) no diabetes or known clinical CVD but 2 or more additional major CVD risk factors or 2) Diabetes but no other CVD risk factors	< 100	< 130	< 90

Brunzell JD, Davidson M, Furberg CD et al. Diabetes Care 2008;31:811-822

Recommendations from AACC Lipoproteins and Vascular Diseases Division Working Group on Best Practices

Suggested Treatment Goals

	ApoB, mg/dL	LDL-C, mg/dL	LDL-P, nmol/L	
Very High Risk		< 70		2nd percentile
High Risk	< 80	< 100	< 1100	20th percentile
Lower Risk	< 100	< 130	< 1400	50th percentile

Population cutpoints are from Framingham Offspring Study

Contois JH, et al. Clinical Chemistry 2009; 55:407-419

Lipid and Lipoprotein Disorders:

Current Clinical Solutions

International Guidelines Center

Expert Reviewers:

William Cromwell, MD, FAHA, FNLA
Diplomate, American Board of Clinical Lipidology
Chief, Division of Atherosclerosis and Lipoprotein Disorders
Presbyterian CV Institute
Adjunct Associate Professor
Wake Forest University School of Medicine

Thomas Dayspring, MD, FACP, FNLA
Diplomate, American Board Clinical Lipidology
North Jersey Institute of Menopausal Lipidology
Clinical Assistant Professor of Medicine
University of Medicine and Dentistry of New Jersey
New Jersey Medical School

Michael Richman, MD, FACS, FCCP
Diplomate, American Boards of Surgery and Thoracic Surgery
CEO, Medical Director
The Center for Cholesterol Management
Los Angeles, California

Key Points

Diagnosis and Assessment of Disease

Selecting a Treatment Regimen

www.lipidcenter.com

Cromwell, Dayspring, Richman Pocket Guide

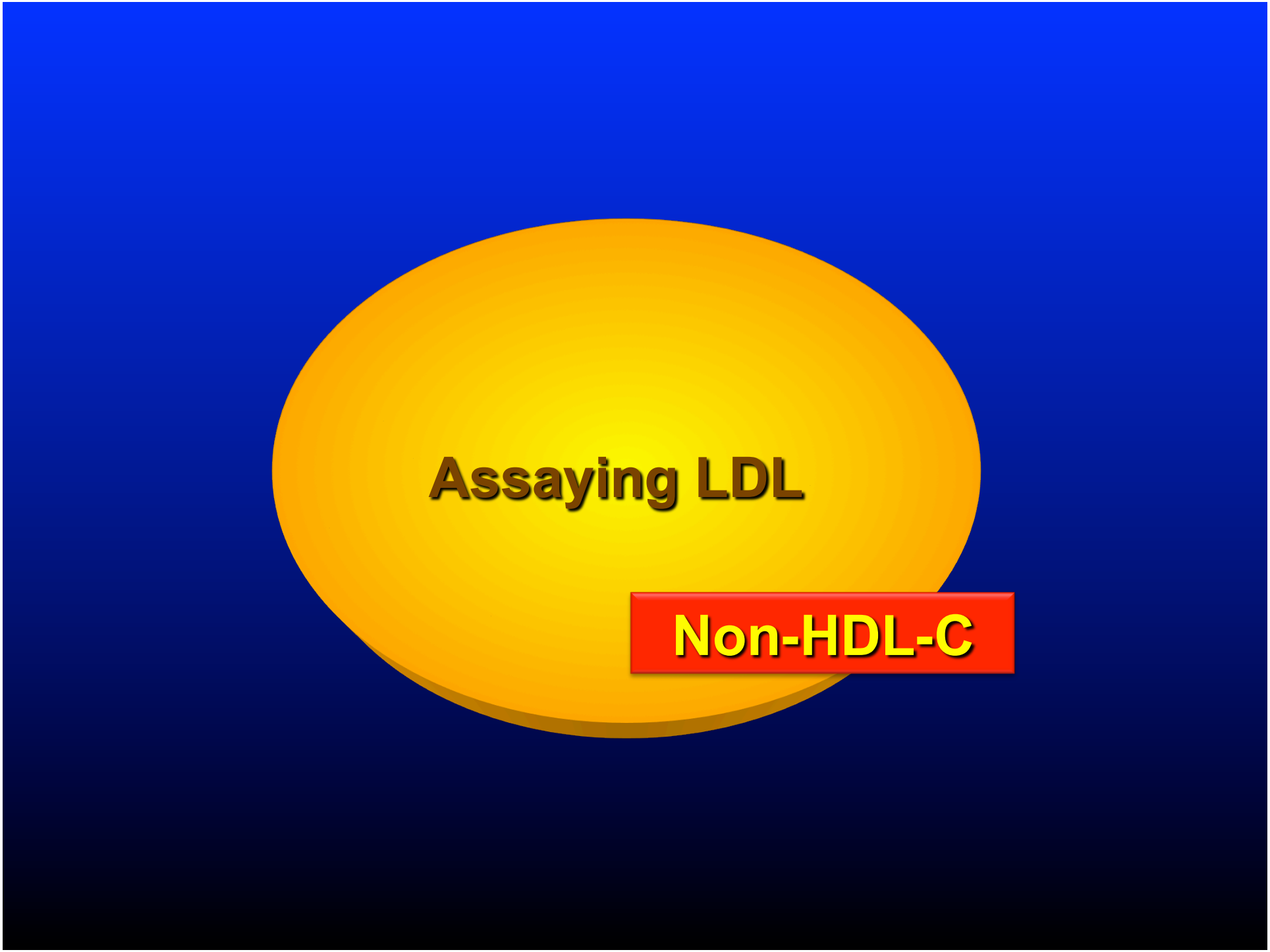
Goals of Therapy

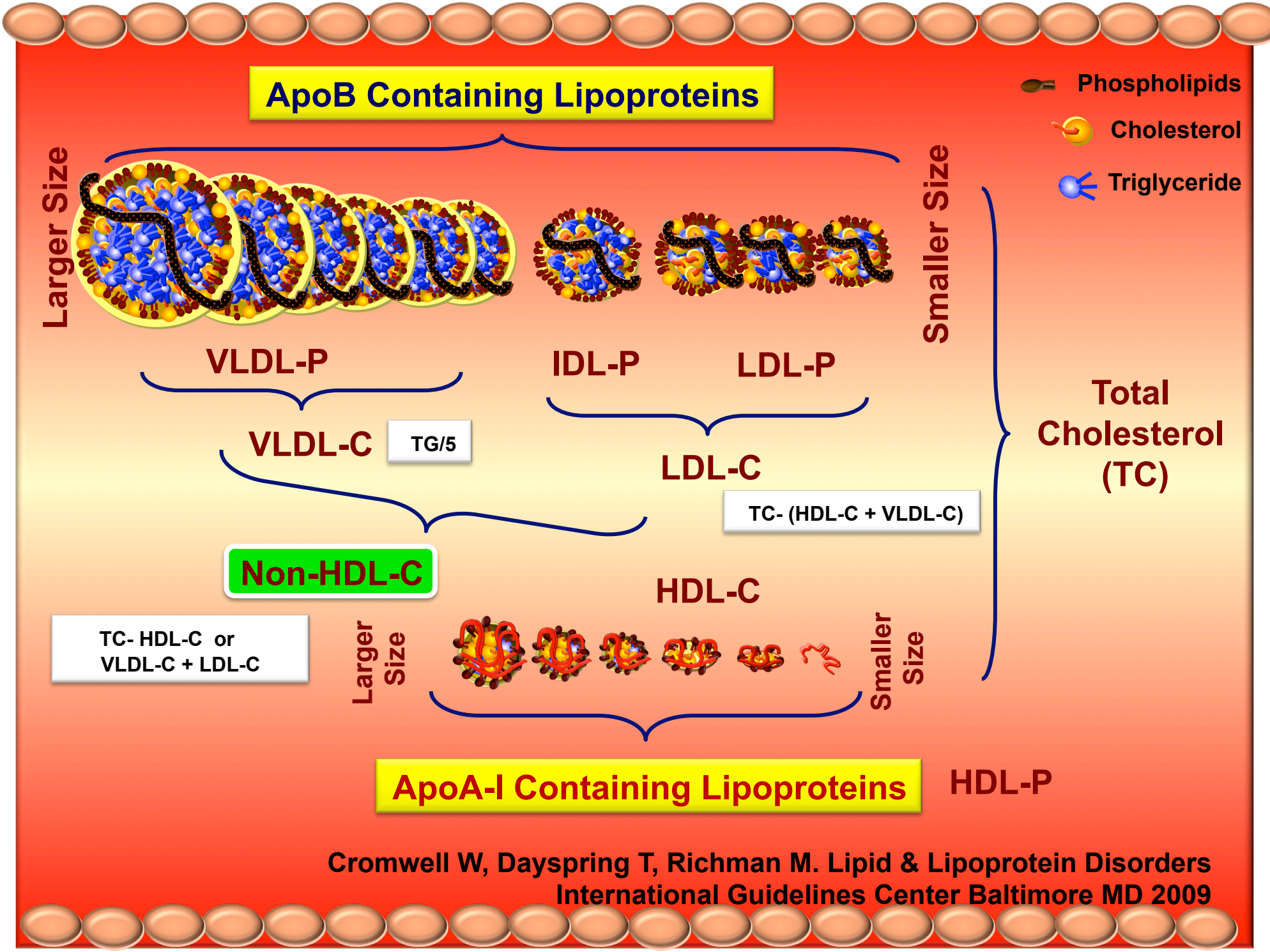
		LDL Particle Number (Measured ApoB or NMR LDL-P)[2,4,5]			
LDL-C (mg/dL)	Non-HDL-C* (mg/dL)	Measured ApoB[2] (mg/dL)	NMR LDL-P[5] (nmol/L)	HDL-C (mg/dL)	TG (mg/dL)
Very High Risk					
< 100 (consider < 70)	< 130 (consider < 100)	< 80†	< 1000†	> 40 Male or > 50 Female	< 150
High Risk					
< 100 (optional < 70)	< 130 (optional < 100)	< 80	< 1000	> 40 Male or > 50 Female	< 150
Moderately High Risk					
< 130 (optional < 130)	< 160 (optional < 130)	< 100 (optional < 80)	< 1300 (optional < 1000)	> 40 Male or > 50 Female	< 150
Moderate Risk					
< 130	< 160	< 100	< 1300	> 40 Male or > 50 Female	< 150
Low Risk					
< 160	< 190	< 120	< 1600	> 40 Male or > 50 Female	< 150

* Calculated as TC minus HDL-C (if TG > 200 mg/dL)

† More aggressive LDL lowering may be needed based on clinical judgment

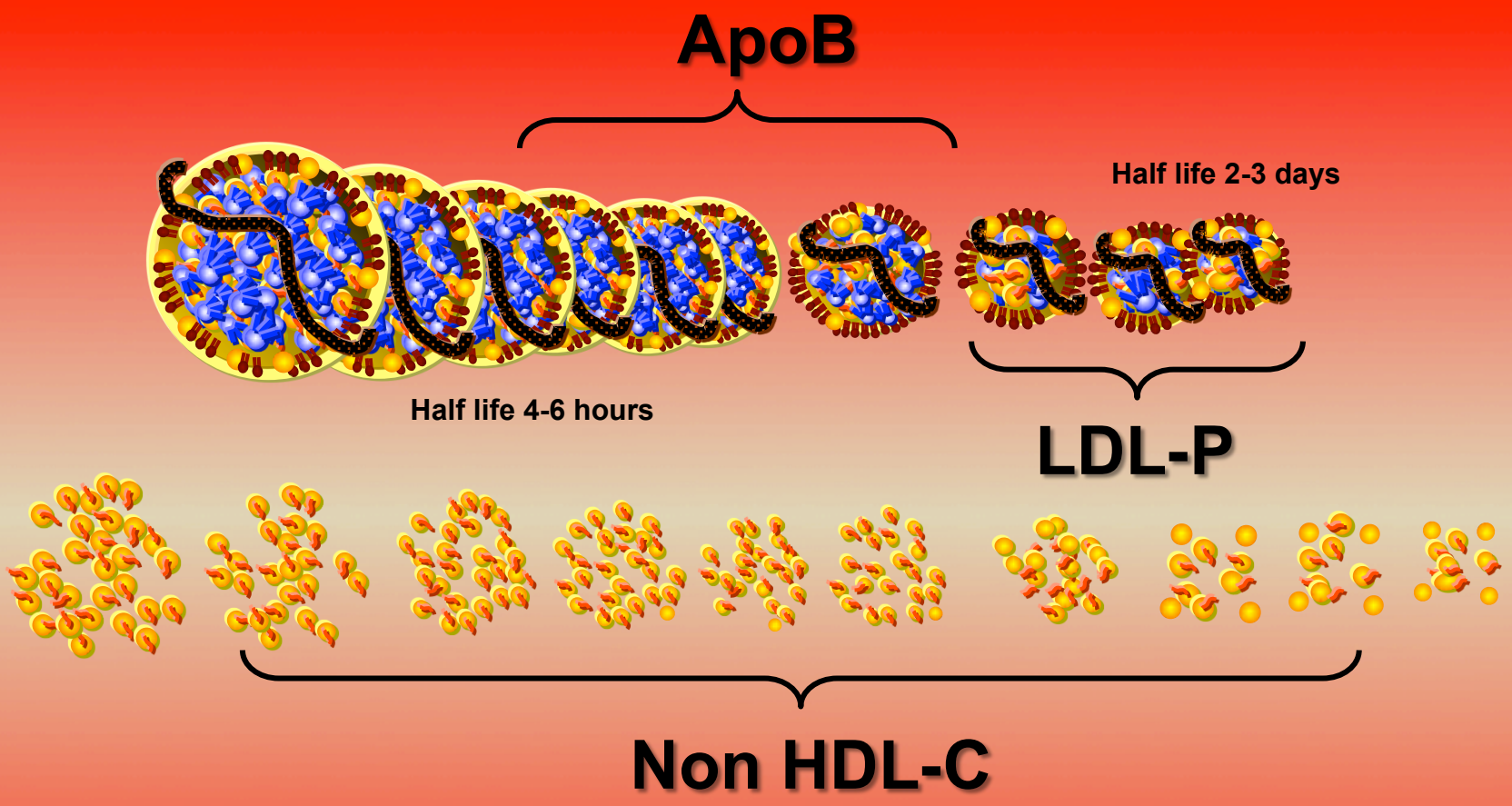
www.lipidcenter.com


Assaying LDL
Non-HDL-C



Cromwell W, Dayspring T, Richman M. Lipid & Lipoprotein Disorders International Guidelines Center Baltimore MD 2009

Atherogenic Lipoproteins



Since LDL-P makes up more than 90% of apoB particles,
Non HDL-C is in effect an LDL-P surrogate

Population Distributions of LDL-P, ApoB & Non-HDL-C in Framingham Offspring Study & the Multi-Ethnic Study of Atherosclerosis (MESA)

Percentile	Non-HDL-C (mg/dL)	Non-HDL-C (mg/dL)	LDL-P (nmol/L)	ApoB (mg/dL)	
2	78	83	720	54	2nd Percentile Cutpoint
5	90	94	850	62	5th Percentile Cutpoint
10	100	104	940	69	10th Percentile Cutpoint
20	113	119	1100	78	20th Percentile Cutpoint
30	123	132	1220	85	
40	132	143	1330	91	
50	140	153	1440	97	50th Percentile Cutpoint
60	148	163	1540	103	
70	158	175	1670	110	
80	169	187	1820	118	
90	187	205	2020	130	
95	202	224	2210	140	

MESA in red font
FOS in black

Recommendations from AACC Lipoproteins and Vascular Diseases Division Working Group on Best Practices

Suggested Treatment Goals

	ApoB, mg/dL	LDL-C, mg/dL	Non-HDL-C, mg/dL	LDL-P, nmol/L	
Very High Risk		< 70	< 80		2nd percentile
High Risk	< 80	< 100	< 120	< 1100	20th percentile
Lower Risk	< 100	< 130	< 150	< 1400	50th percentile

Population cutpoints are from Framingham Offspring Study

< 78	2nd percentile
< 113	20th percentile
< 140	50th percentile

MESA Cutpoints

Contois JH, et al. Clinical Chemistry 2009; 55:407-419

Recommendations from AACC Lipoproteins and Vascular Diseases Division Working Group on Best Practices

Use of ApoB and LDL Particle Number in Clinical Management

- Data from several prospective studies show non–HDL-C to be a better predictor of cardiovascular events than LDL-C.
- However, apoB has been more extensively validated in epidemiological studies and clinical trials than non-HDL-C, and non-HDL-C, like LDL-C, reflects the cholesterol content of atherogenic particles and **not the number of atherogenic particles**.
- Importantly, on-treatment non-HDL-C concentrations may not reflect residual risk associated with increased LDL particle number

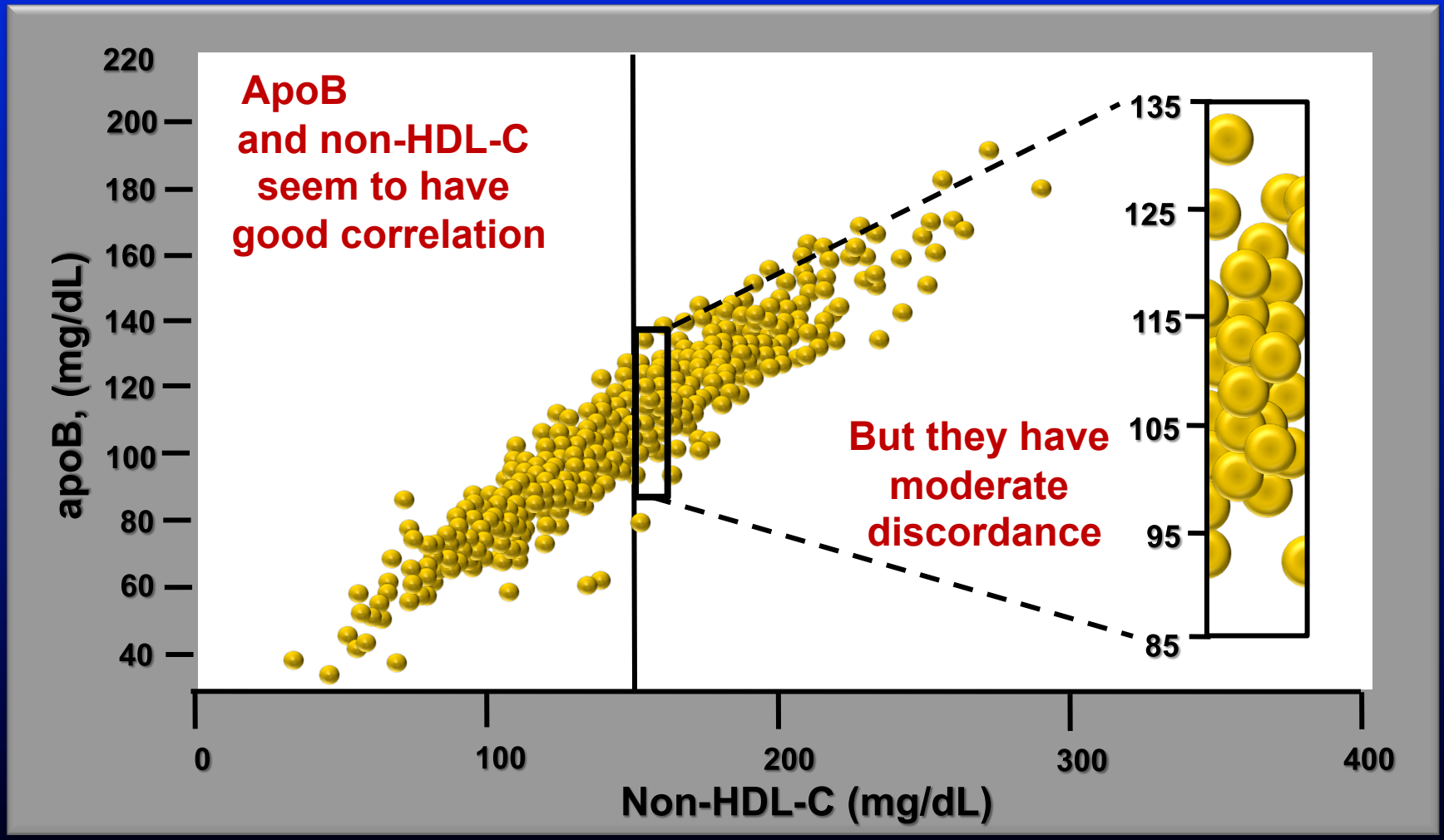
Contois JH, et al. Clinical Chemistry 2009; 55:407-419

Recommendations from AACC Lipoproteins and Vascular Diseases Division Working Group on Best Practices

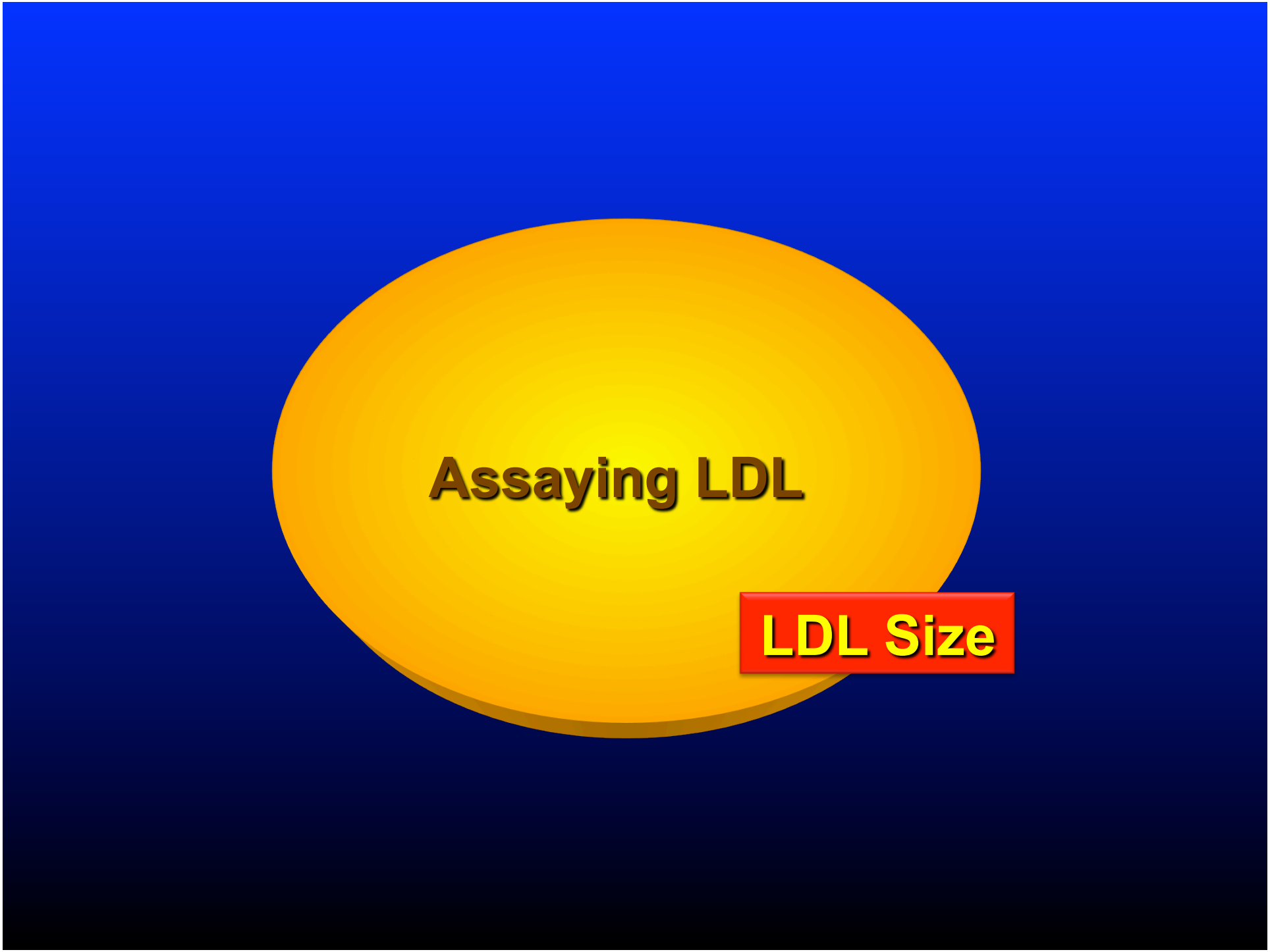
- "LDL-C, non-HDL-C, LDL-P, and total apoB are all, to varying degrees, measures of LDL related risk."
- "These cholesterol and particle measures are highly intercorrelated, which explains why they have all been implicated as predictors of CVD risk in epidemiologic studies, but biologically they reflect different entities."
- "Despite a high correlation, these markers are only modestly concordant, **indicating that one cannot simply substitute for another** in classifying patients into risk categories."

Contois JH, et al. Clinical Chemistry 2009; 55:407-419

National Health And Nutrition Examination Survey (NHANES) 2005-2006



Sniderman et al. Curr Athero Rep 2009;11:358-363 http;//www.cdc.gov/nchs/data/nhanes/nhanes_05_06/nhanes_2005_2006_codebook_description.pdf


Assaying LDL
LDL Size

Evaluating LDL Size

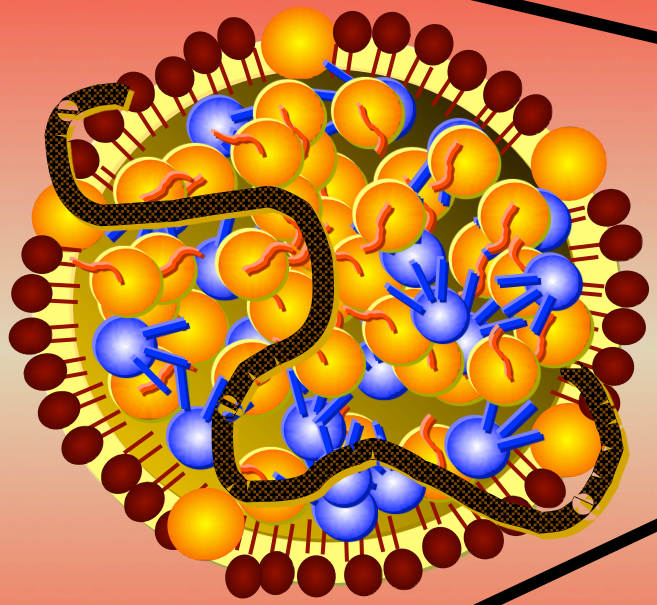
LDL size is measured in nanometers (nm)

23.0 – 20.6

Large
(Pattern A)

20.5 – 18.0

Small
(Pattern B)



▶LDL-P

▶LDL size

Very large,
Large,
Small

- Average diameter (nm) of the patient's LDL particles.
- A predominance of small LDL particles is associated with metabolic syndrome and insulin resistance

Multi-Ethnic Study of Atherosclerosis (MESA)

- Contrary to current opinion, both small and large LDL were significantly associated with subclinical atherosclerosis independent of each other, traditional lipids, and established risk factors, with **no association between LDL size and atherosclerosis** after accounting for the concentrations of the two subclasses.

Mora S, Szklo S, Otvos JD et al. Atherosclerosis 2006;

European Prospective Investigation into Cancer and Nutrition- Norfolk Study (EPIC-Norfolk)

- Whereas LDL size was related to Coronary Artery Disease risk, this relationship was abolished after adjusting for LDL-P.

Karim El Harchaoui, et al. J. Am. Coll. Cardiol. 2007;49;547-553

Assaying LDL

LDL-C vs LDL-P

Journal of Clinical Lipidology (2007) 1, 583–592

Journal of Clinical Lipidology

Original Contributions

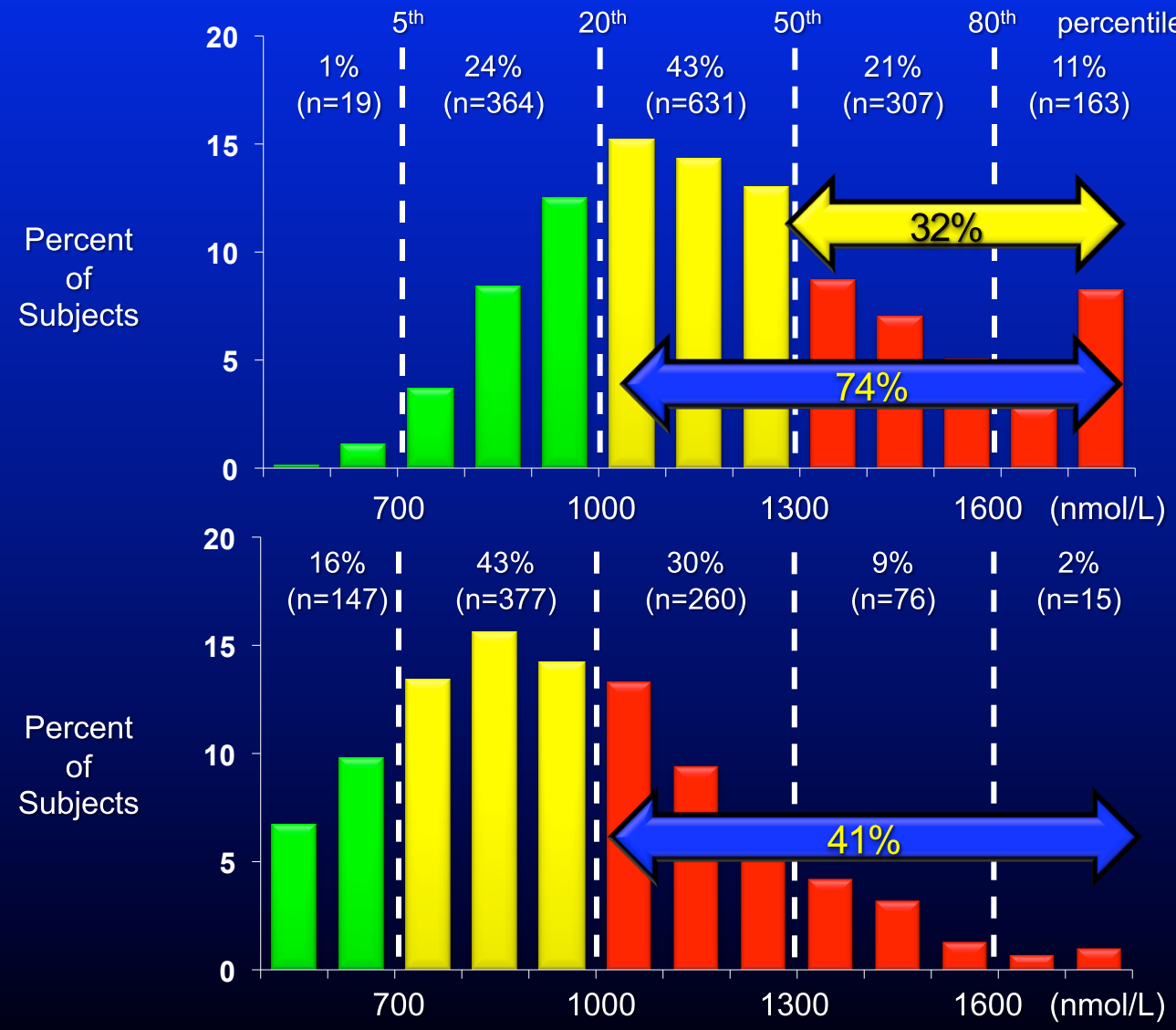
LDL particle number and risk of future cardiovascular disease in the Framingham Offspring Study—Implications for LDL management

William C. Cromwell, MD,* James D. Otvos, PhD, Michelle J. Keyes, PhD, Michael J. Pencina, PhD, Lisa Sullivan, PhD, Ramachandran S. Vasan, MD, Peter W. F. Wilson, MD, Ralph B. D'Agostino, PhD

Changing Face of Lipidology

J Clin Lipidol 2007;1:583-592

LDL Particle Number Distribution in T2DM Subjects with Normal, at Goal LDL-C

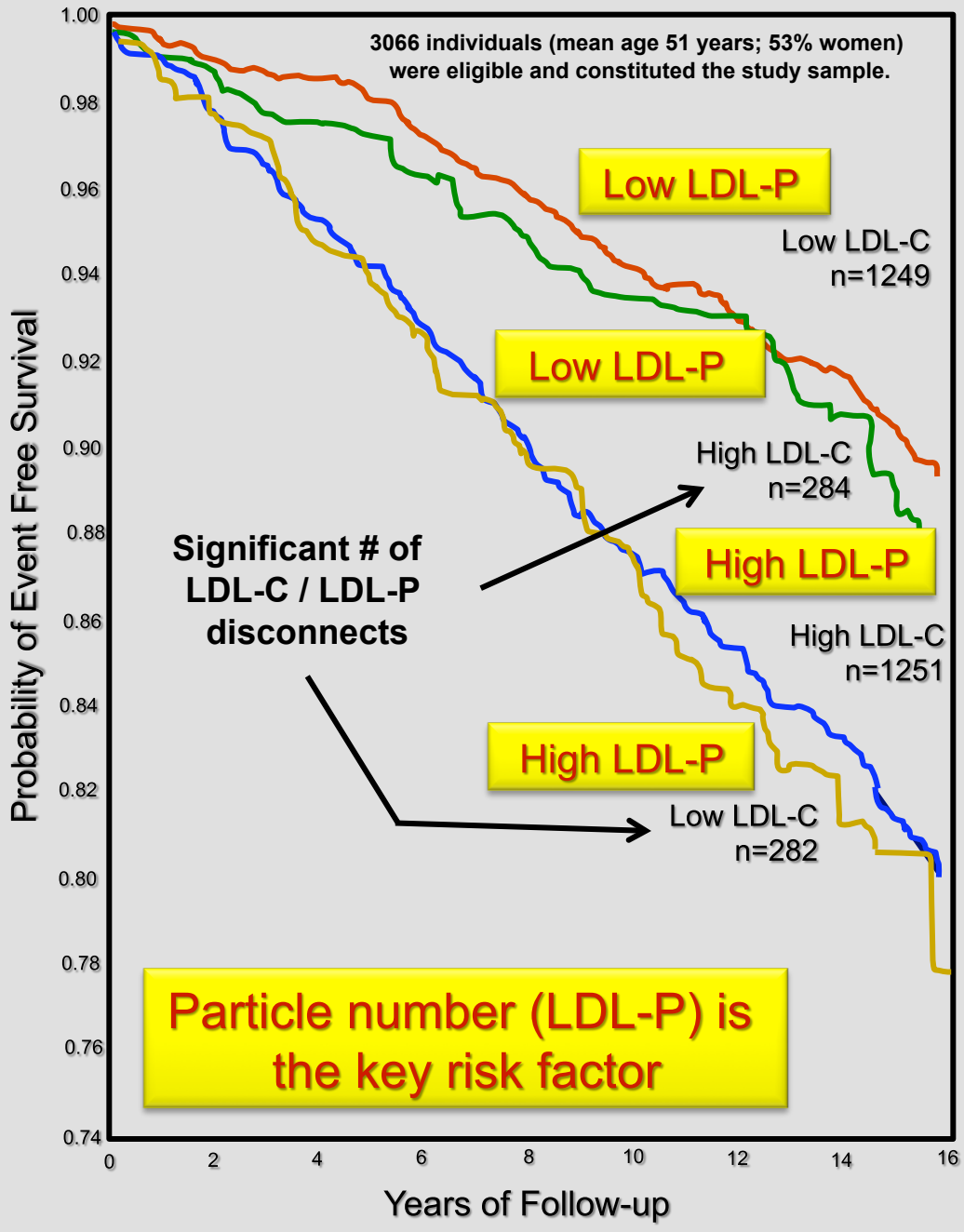


LDL-C
71-99 mg/dL
(n=1,484)

LDL-C
< 70 mg/dL
(n=871)

Cromwell W & Otvos J (Am J Cardiol 2006;98:1599 –1602

Framingham Heart Study Offspring Cohort



Event-free survival among participants with low-density lipoprotein cholesterol (**LDL-C**) and LDL particle number (**LDL-P**) above or below the median.

Median values were 131 mg/dL for LDL-C and 1414 nmol/L for LDL-P.

LDL-P was strongly associated with increased CVD risk in both men and women ($p<0.0001$)

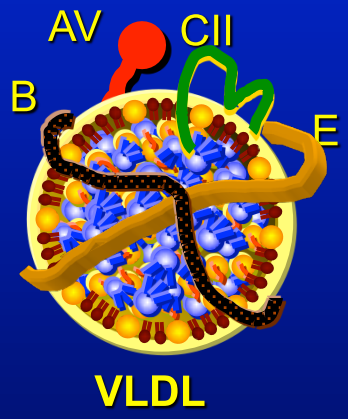
When data for men and women were combined, LDL-P was approximately twice as strongly related to CVD incidence as LDL-C

Cromwell W et al. J Clin Lipidol 2007;1:583-592

Framingham Heart Study
Offspring Cohort

VLDL-C and VLDL-P

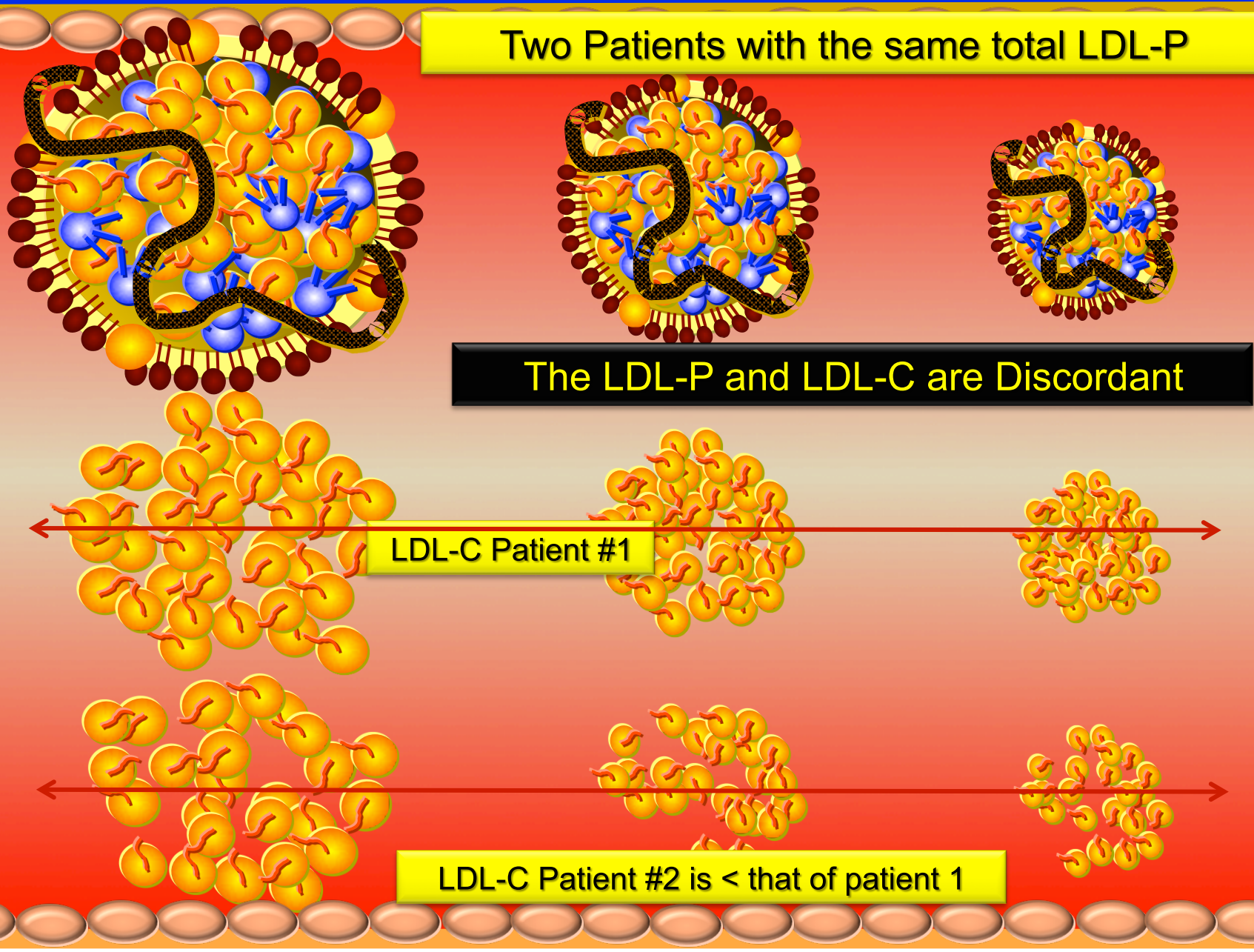
►Non-HDL-C, which includes contributions from the cholesterol in VLDL as well as LDL, was more strongly associated with CVD than LDL-C in both men and women, but was less predictive of CVD events than LDL-P.



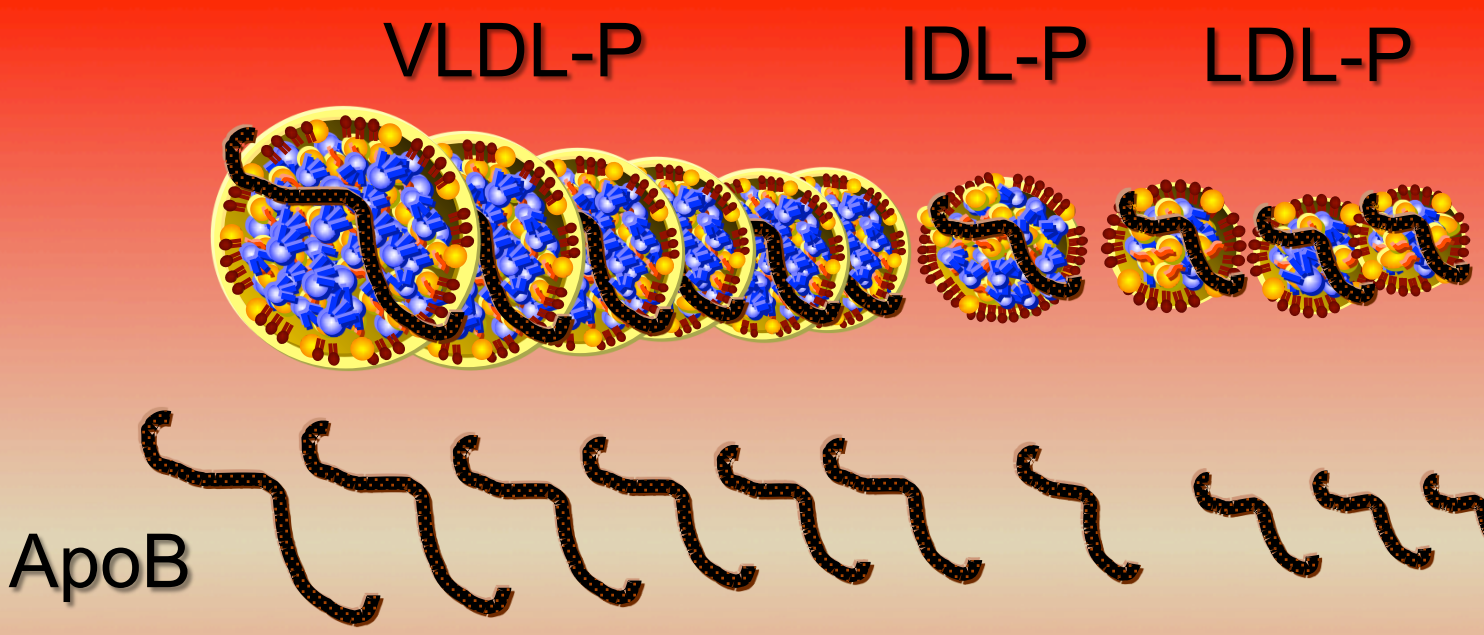
►Adding VLDL-P to LDL-P only very marginally strengthened CVD associations compared to LDL-P alone.

Cromwell W et al. J Clin Lipidol 2007;1:583-592

Evaluating LDL in the Laboratory



Lipid and Lipoprotein Evaluation

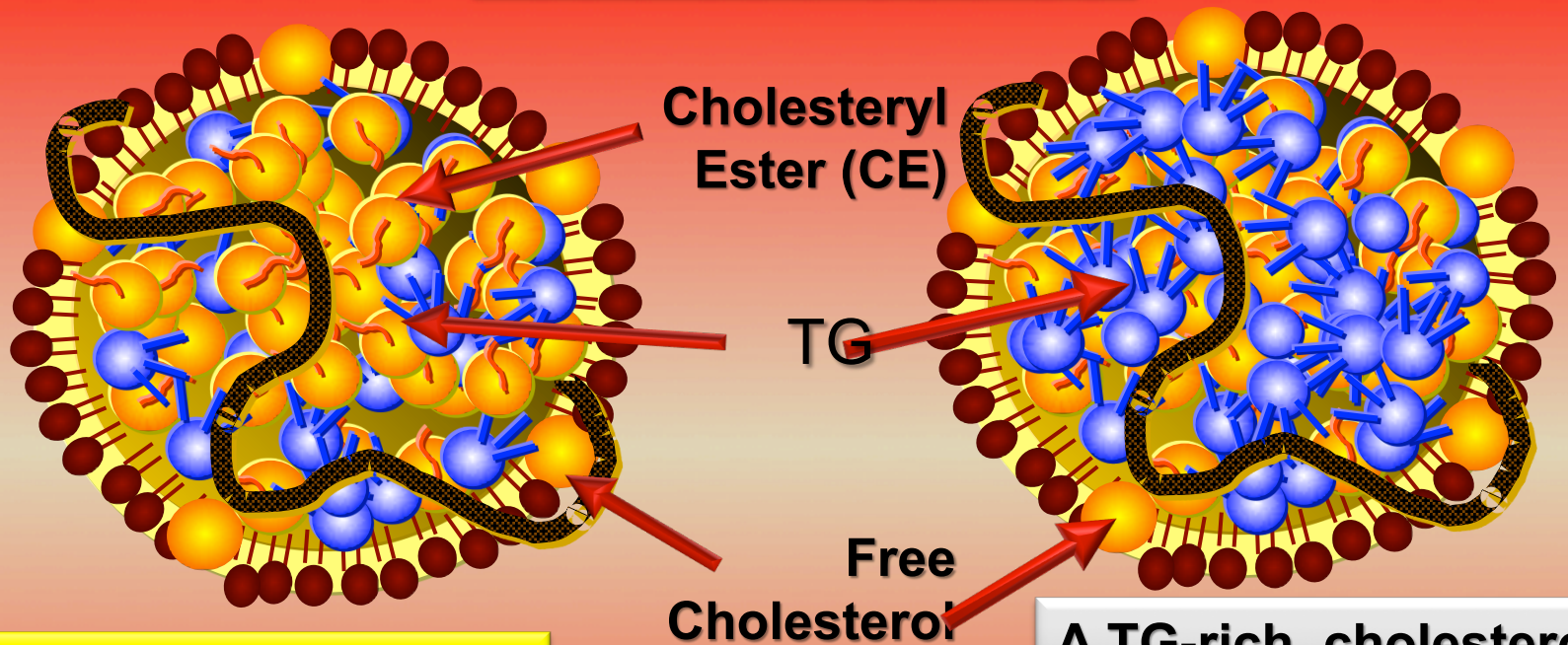


Triglycerides and LDL Particle Composition

High Ratio

Normal CE/TG ratio is >4

Low Ratio



A CE-rich, particle

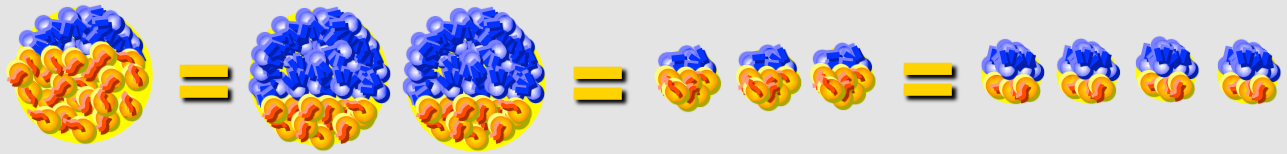
A TG-rich, cholesterol poor particle

Rising TG is associated depleting LDL particles of their CE, thus often reducing LDL-C

LDL-C Often Fails to Reflect the Number of LDL Particles or LDL-P

- LDL particles can be large or small, and the amount of cholesterol and triglycerides (core composition) contained within these particles varies widely.
- For this reason, LDL cholesterol often fails to reflect the number of LDL particles.

LDL-C = whatever mg/dL



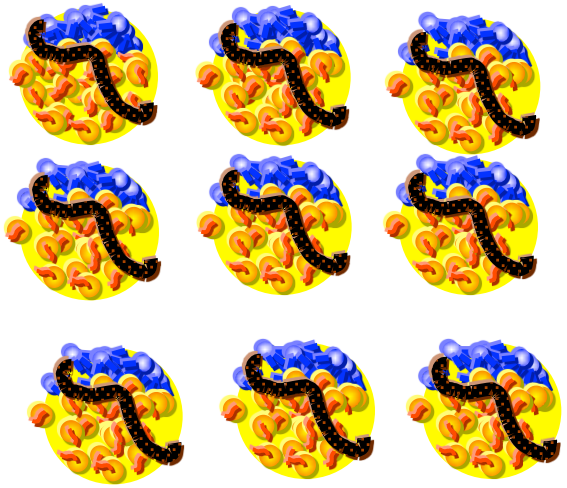
LDL-P = X **LDL-P > X** **LDL-P = >> X** **LDL-P >>> X**

LDL-P in nmol/L

Otvos JD, Jayarajah E, Cromwell, WC. *AJC* 2002;90(8A):22i-29i

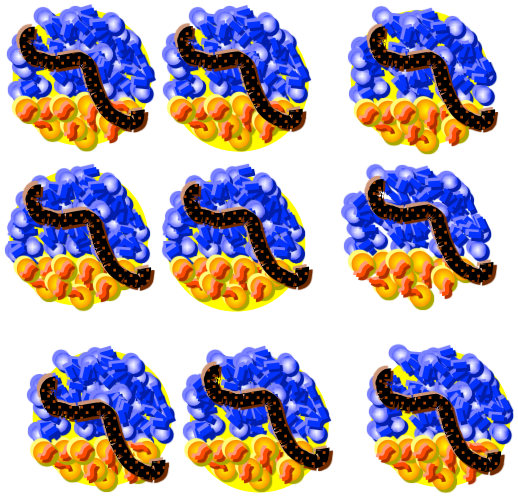
The Influence of TG Composition on LDL-P and LDL-C Levels

LDL-P is Identical in Both Patients



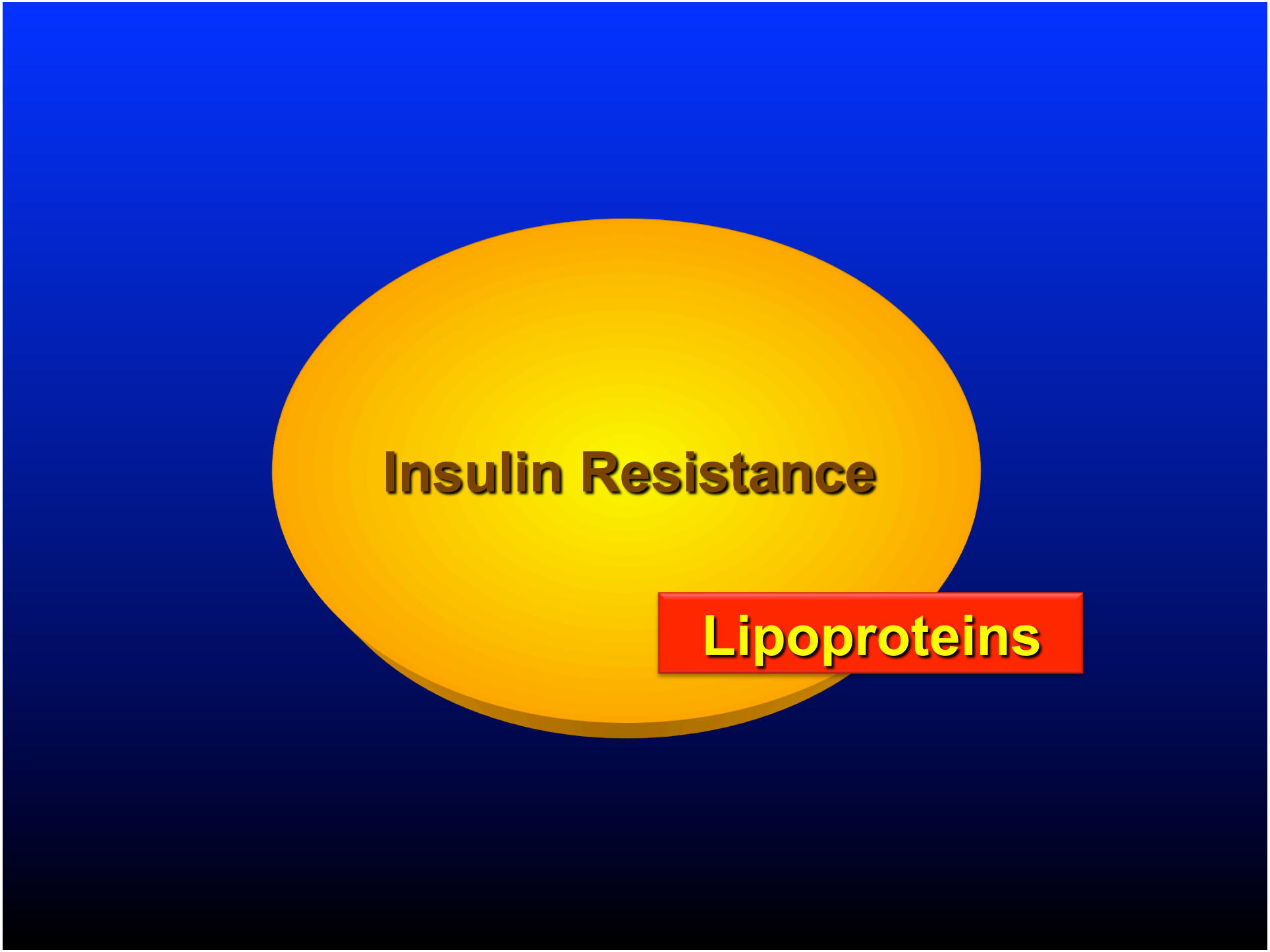
Normally composed cholesterol-rich LDLs

LDL-C is X



TG-rich, cholesterol poor LDLs

LDL-C is < X


Insulin Resistance
Lipoproteins

Lipoprotein Insulin Resistance Score

►This section includes the six lipoprotein markers associated with insulin resistance and type 2 diabetes risk, and are included in the calculation for the **LP-IR score.**

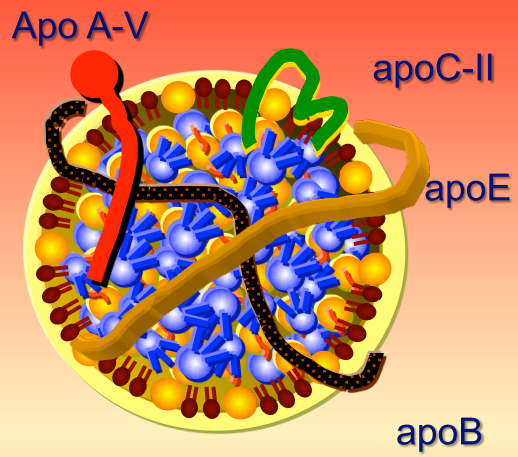
The Lipoprotein Insulin Resistance Score **(LP-IR)** assesses the patient's insulin resistance level and T2DM risk.

This score (0-100) is derived using the results from the six lipoprotein markers listed.

Therapeutic lifestyle changes may reduce the score.

Lipoprotein Abnormalities in Hypertriglyceridemic States

TG-rich VLDL

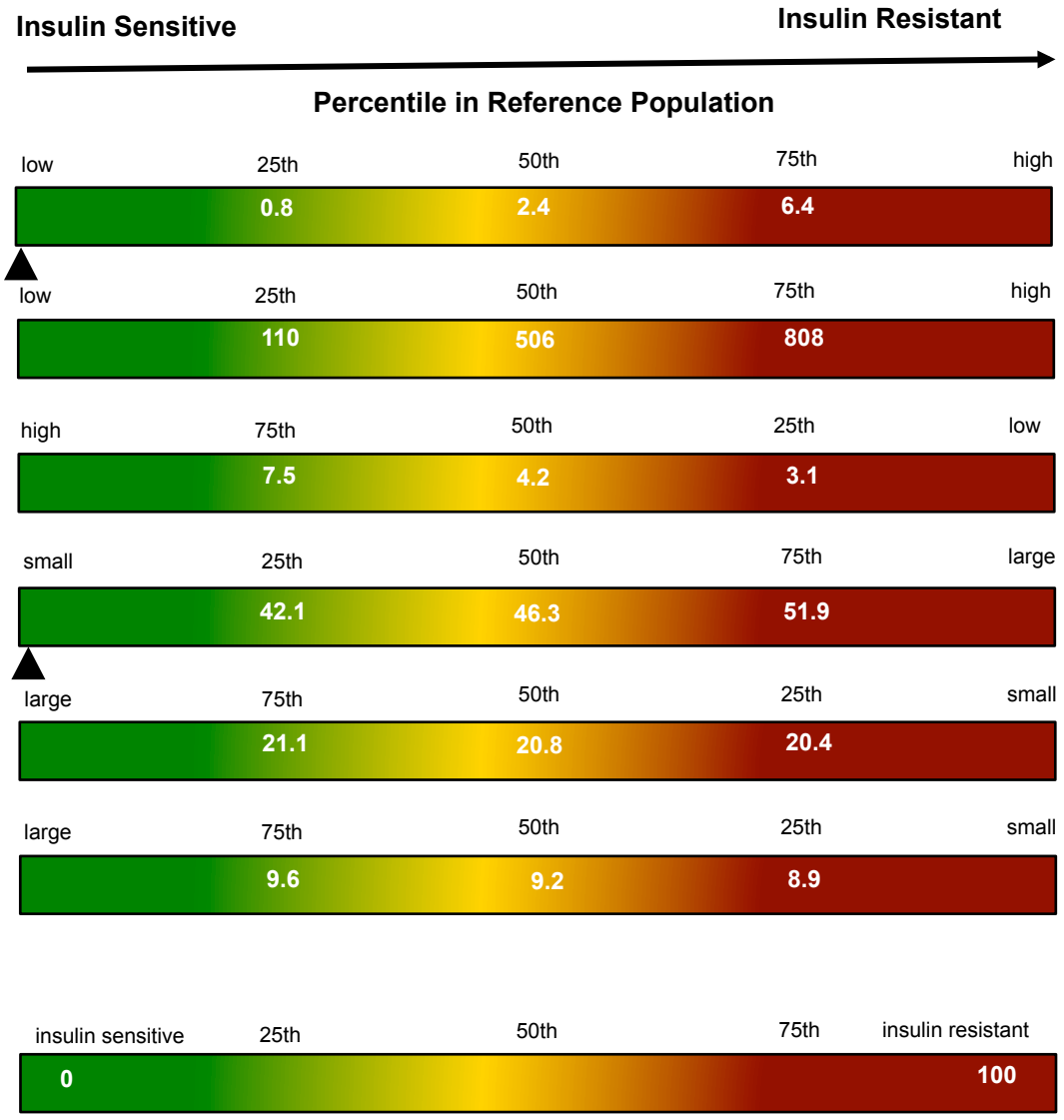


Large VLDL

Increased VLDL size

Triglyceride Cholesteryl ester

LIPOPROTEIN MARKERS ASSOCIATED WITH INSULIN RESISTANCE[1,2]



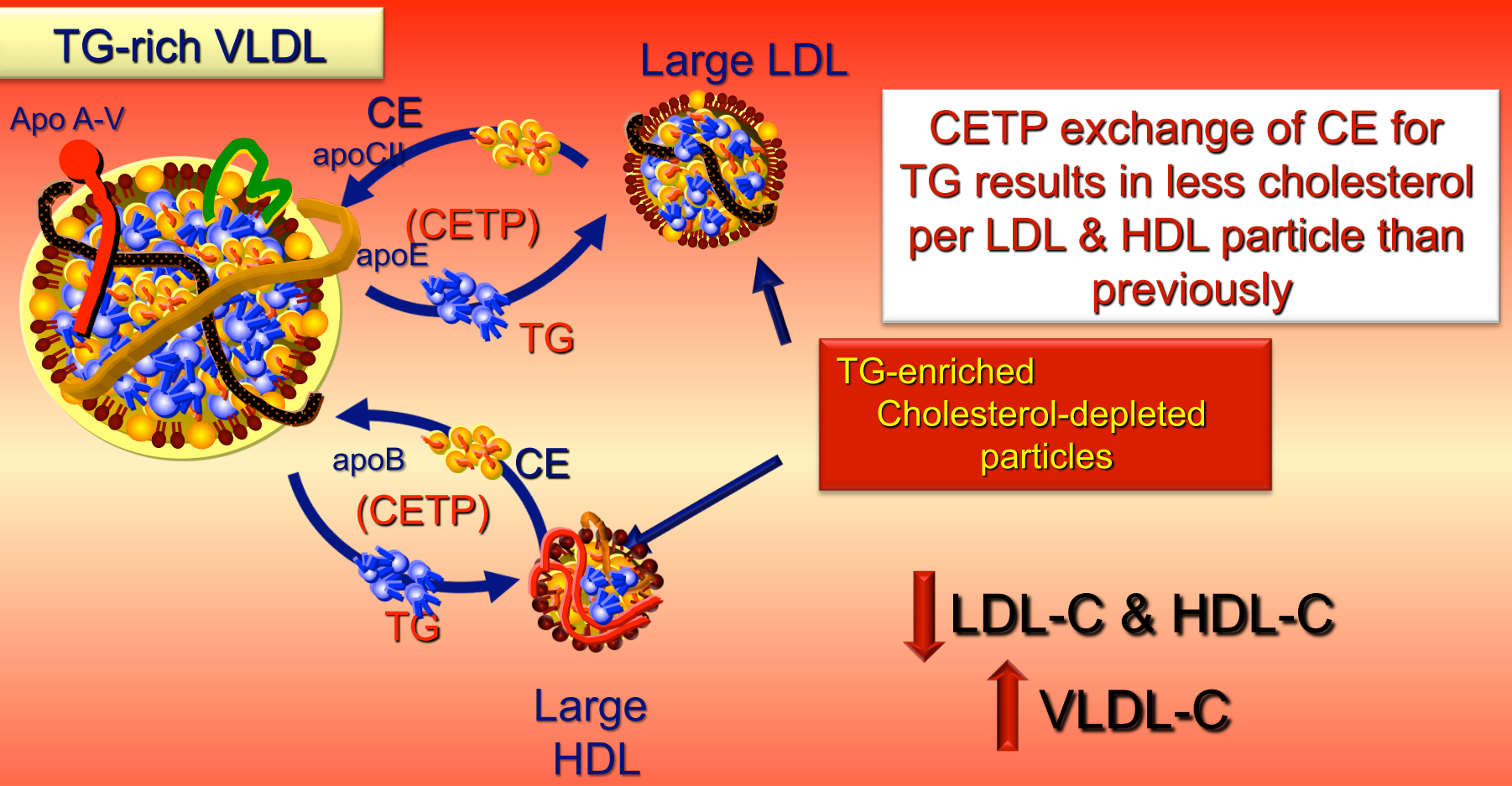
INSULIN RESISTANCE SCORE

**** The LP-IR SCORE combines the information from the 6 lipoprotein markers to give improved prediction of insulin resistance****

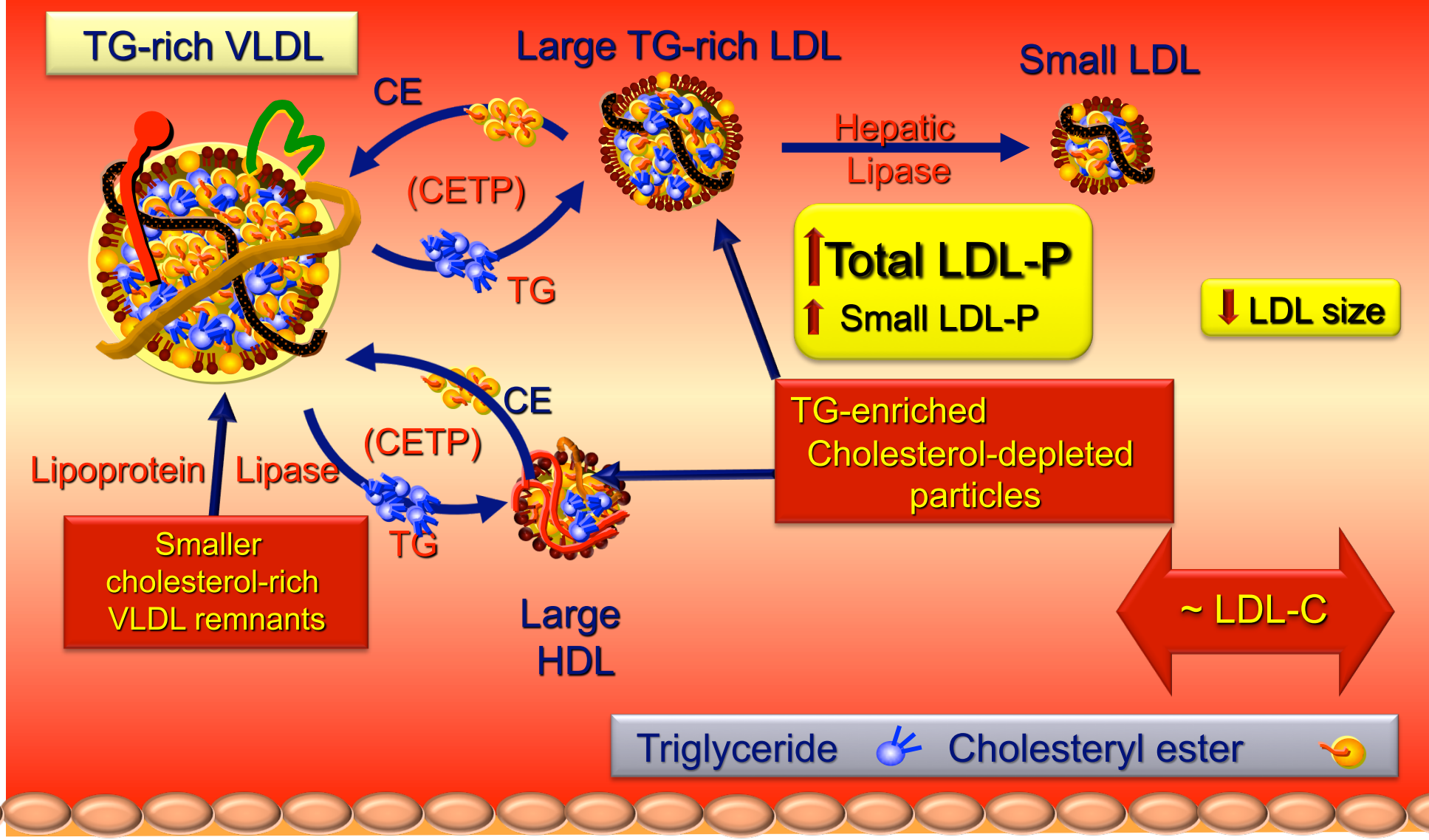
These laboratory assays validated by LipoScience have not been cleared by the US Food and Drug Administration. The clinical utility of these laboratory values has not been fully established.

1.Garvey WT et al. Diabetes 2003;532:453-462
2. Goff DC. et al. Metabolism. 2005;54:264-270

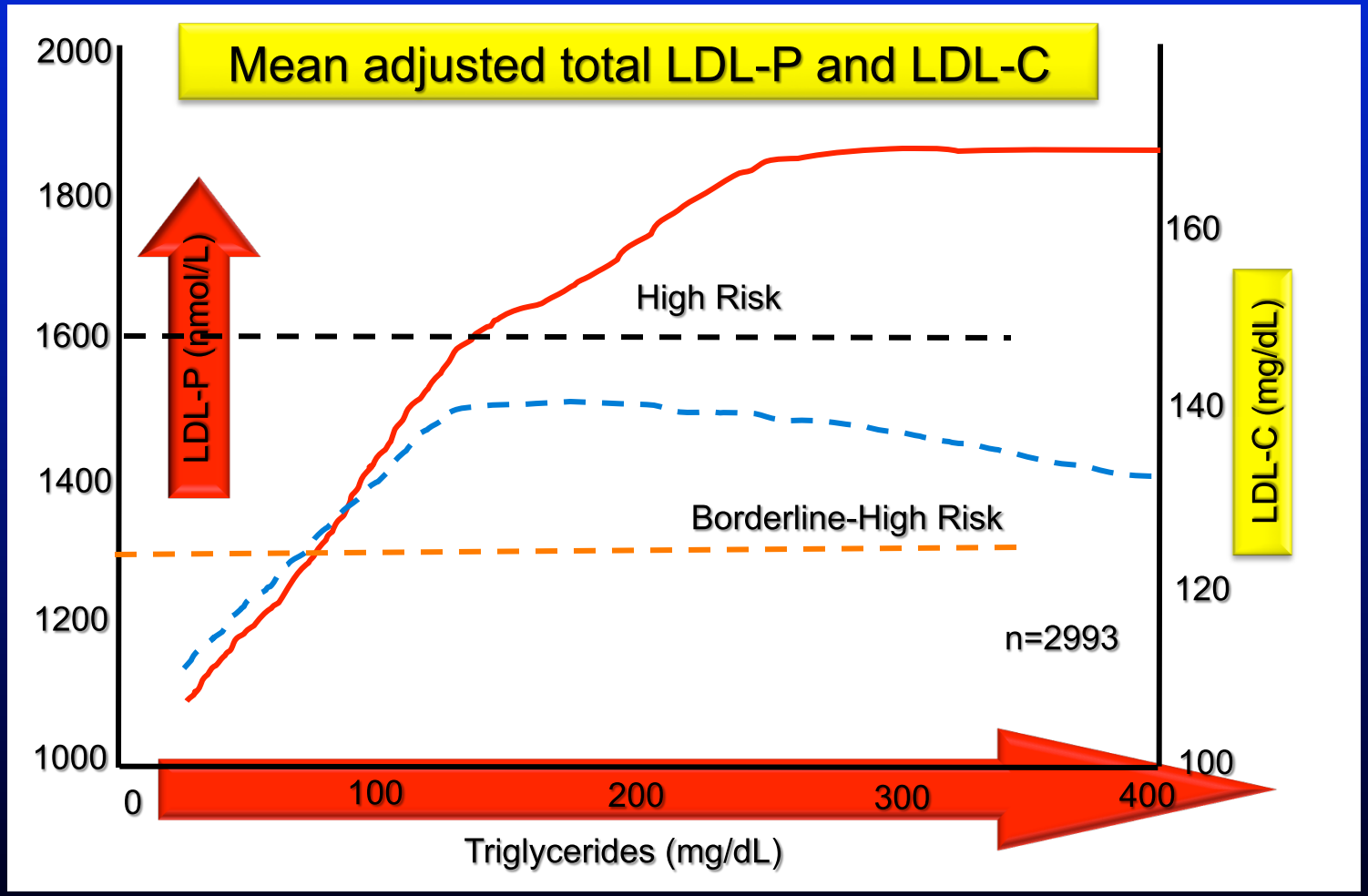
Lipoprotein Abnormalities in Hypertriglyceridemic States



LDL Particle Abnormalities in Hypertriglyceridemic States



Framingham Offspring Study
LDL-P and Metabolic Syndrome



Kathiresan S, Otvos JD, Sullivan LM et al. Circulation. 2006;113:20-29.

LIPOPROTEIN MARKERS ASSOCIATED WITH INSULIN RESISTANCE[1,2]

Insulin Sensitive → Insulin Resistant

Percentile in Reference Population

		low	25th	50th	75th	high
LARGE VLDL-P	nmol/L: 8.2		0.8	2.4	6.4	
SMALL LDL-P	nmol/L: 830	low	25th	50th	75th	high
			110	506	808	
	µmol/L:	high	75th	50th	25th	low
			7.5	4.2	3.1	
VLDL SIZE	nm: 50.4	small	25th	50th	75th	large
			42.1	46.3	51.9	
LDL SIZE	nm: 20.2	large	75th	50th	25th	small
			21.1	20.8	20.4	
	nm:	large	75th	50th	25th	small
			9.6	9.2	8.9	

INSULIN RESISTANCE SCORE

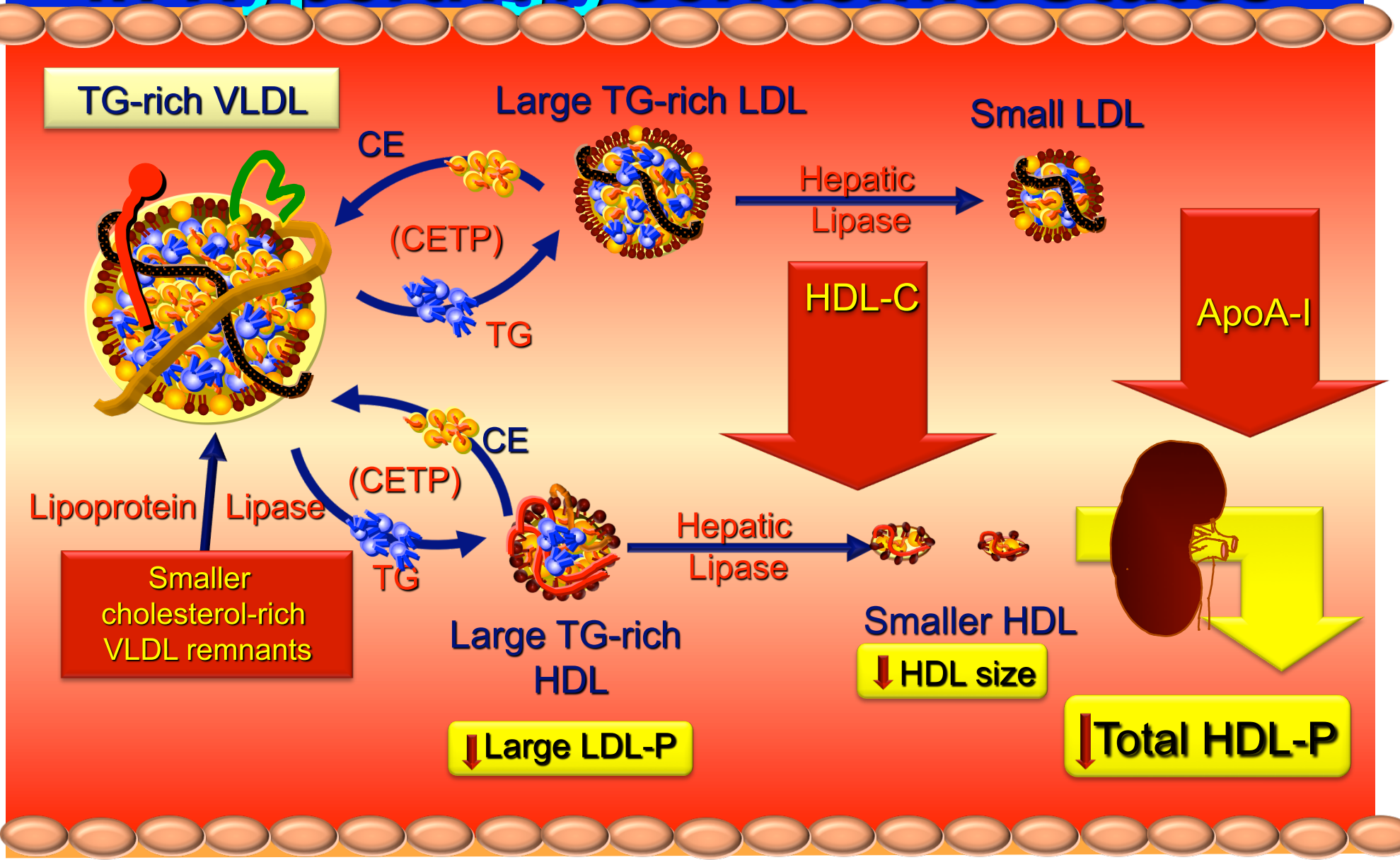
		insulin sensitive	25th	50th	75th	insulin resistant
LP-IR SCORE**	0-100:	0				100

**** The LP-IR SCORE combines the information from the 6 lipoprotein markers to give improved prediction of insulin resistance****

These laboratory assays validated by LipoScience have not been cleared by the US Food and Drug Administration. The clinical utility of these laboratory values has not been fully established.

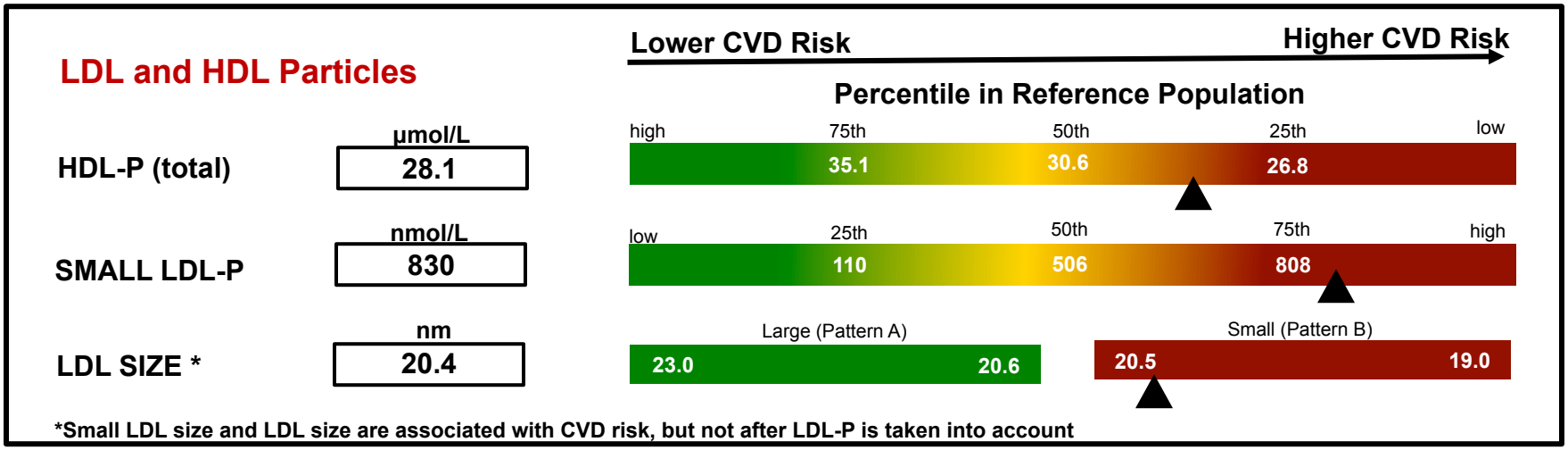
1.Garvey WT et al. Diabetes 2003;532:453-462
2. Goff DC. et al. Metabolism. 2005;54:264-270

HDL Particle Abnormalities in Hypertriglyceridemic States



The New LipoScience Report Form Particle Concentrations and Size

Particle Concentration and Size



The particle concentration and size is now provided on a separate report. In addition to small LDL-P (nmol/L) and LDL size (nm), **total HDL-P is reported** (μmol/L).

www.liposcience.com

LIPOPROTEIN MARKERS ASSOCIATED WITH INSULIN RESISTANCE[1,2]

Insulin Sensitive → Insulin Resistant

Percentile in Reference Population

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LARGE VLDL-P	nmol/L: 8.2		0.8	2.4	6.4	
SMALL LDL-P	nmol/L: 830		110	506	808	
LARGE HDL-P	µmol/L: 2.7		7.5	4.2	3.1	
VLDL SIZE	nm: 50.4		42.1	46.3	51.9	
LDL SIZE	nm: 20.2		21.1	20.8	20.4	
HDL SIZE	nm: 8.7		9.6	9.2	8.9	

		insulin sensitive	25th	50th	75th	insulin resistant
LP-IR SCORE**	0-100	0				100

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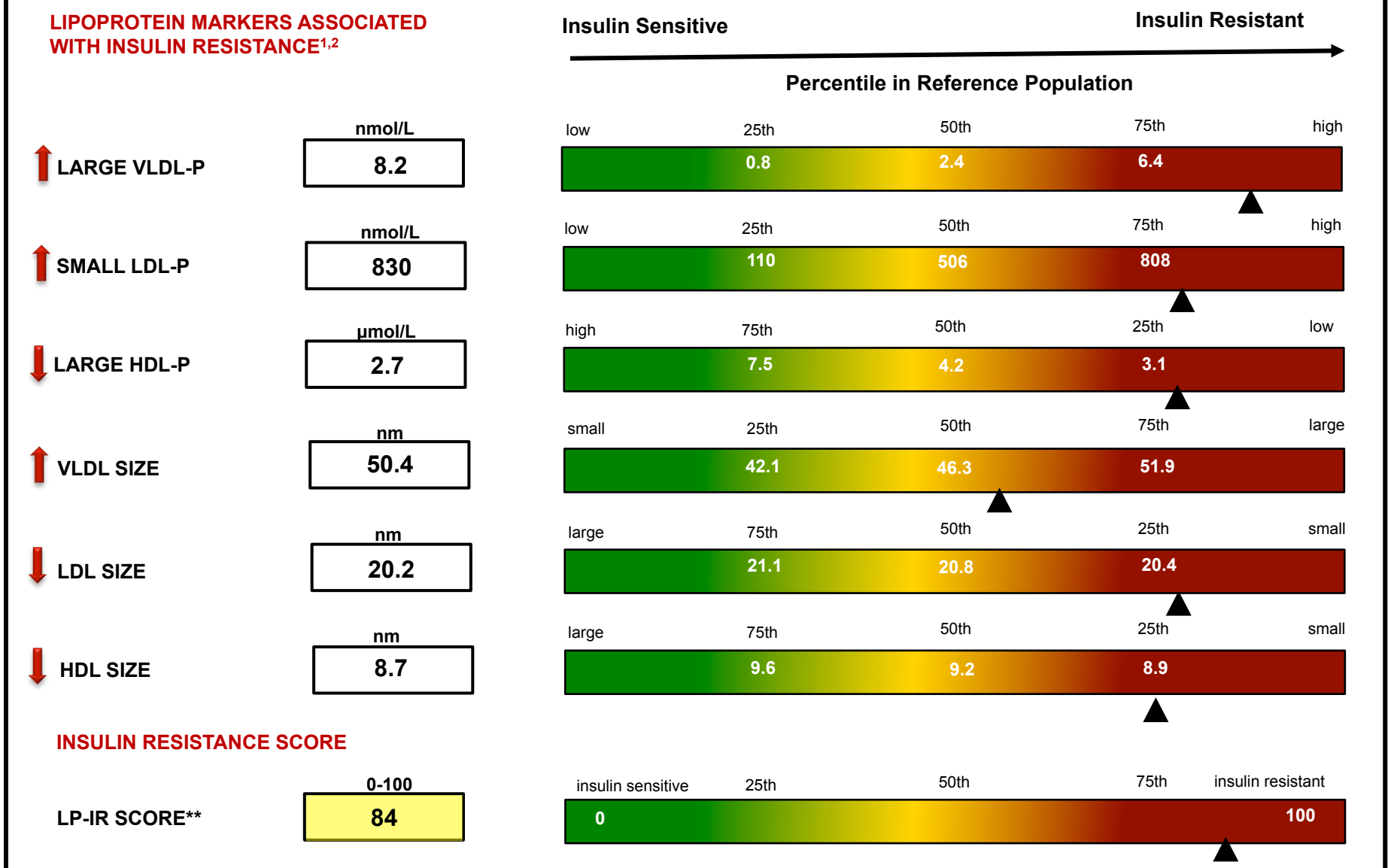

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Labcorp Report: Insulin resistance markers

		Large (Pattern) A		Small (Pattern) B
LDL particle size	**19.4**	23.0 – 20.6		20.5 – 18.0
		Low Risk	**Intermediate**	**High Risk**
Large HDL-P	**3.5**	> 9.0	4.0-9	< 4.0
		Low Risk	**Intermediate**	**High Risk**
Large VLDL-P	**11.9**	> 0.5	0.5 – 5.0	> 5.0

Small LDL size (≤ 20.5 nm) ✓

Low Large HDL-P (< 4.0 umol/L) ✓

High Large VLDL-P (> 5.0 nmol/L) ✓

Metabolic Syndrome Markers **These markers increase the risk of developing Type 2 diabetes mellitus**

None of these markers are goals of therapy

Goals Of Therapy

Framingham Heart Study: Offspring Cohort

- The data show that persons with this LDL-P / LDL-C disconnect have higher CVD risk.
  - It is therefore reasonable to anticipate that such discordant individuals would derive clinical benefit from more intensive LDL lowering than would have been indicated by their LDL-C level.

Cromwell W et al. J Clin Lipidol 2007;1:583-592

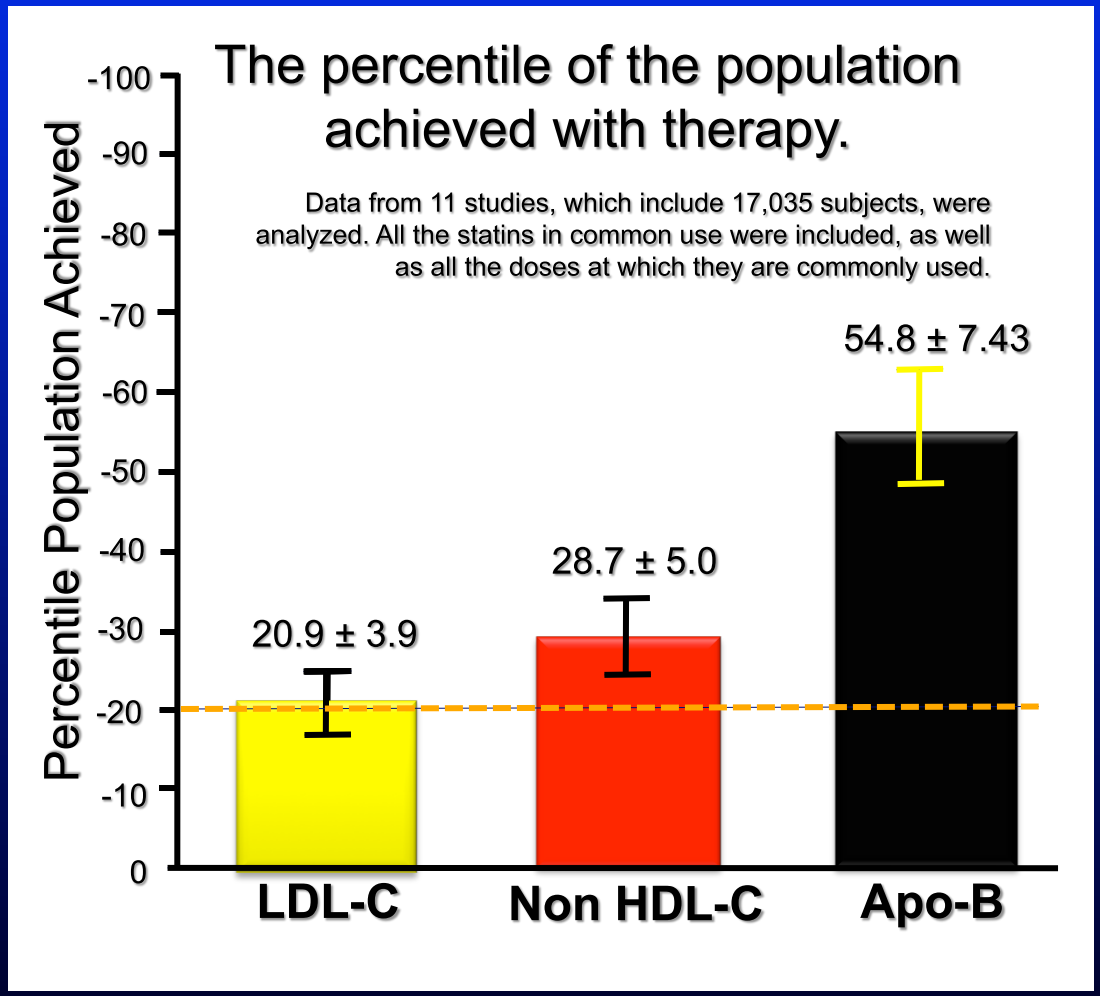
Recommendations from AACC Lipoproteins and Vascular Diseases Division Working Group on Best Practices

Use of LDL Particle Number in Clinical Management

- "Statins are highly effective in reducing serum cholesterol through inhibition of HMG-CoA reductase, which upregulates LDL receptors and leads to increased clearance of LDL particles from the circulation."
- "However, the reduction in serum apoB or LDL-P concentration is not as dramatic as the reduction in LDL-C or non HDL-C."
- "As a result, patients treated to goal for LDL-C may not have achieved correspondingly low LDL particle concentrations, leading them with potential residual risk."

Contois JH, et al. Clinical Chemistry 2009; 55:407-419

On Therapy LDL-C vs Non HDL-C vs ApoB



LDL-C, on average, was reduced to a level equal to the 22nd percentile of the reference population.

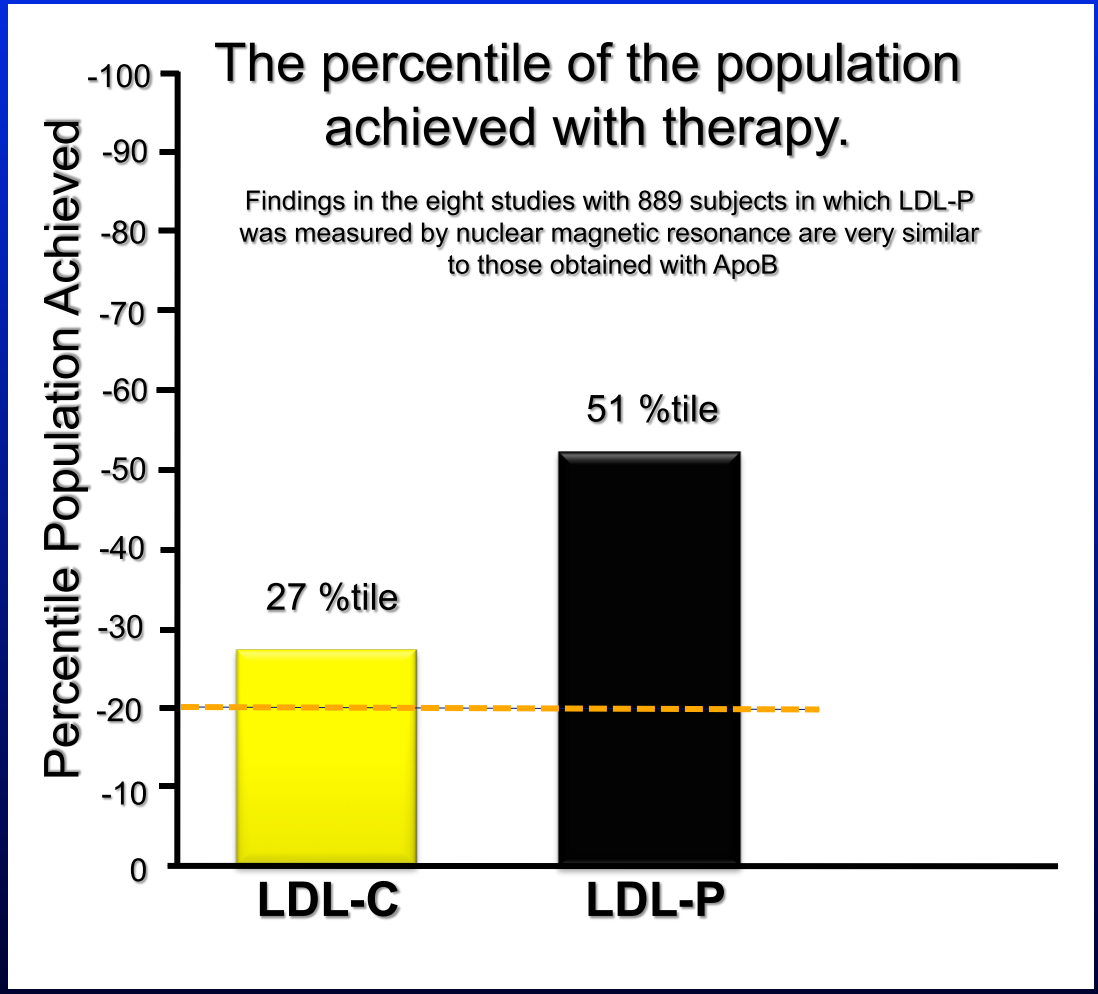
The corresponding average concentration achieved for non HDL-C was the 29th percentile value, which was a significantly lesser change than achieved with LDL-C (P 0.001).

Both differ substantially with the findings obtained for ApoB.

ApoB was only decreased to the 55th percentile of the population, a drop that is significantly less than achieved with LDL-C or non HDL-C (P 0.001 in both comparisons).

Sniderman, AD Journal of Clinical Lipidology (2008) 2, 36–42

On Therapy LDL-C vs LDL-P



Very similar results were obtained in eight studies of LDL lowering in 889 subjects in which the responses of LDL-C and LDL particle number (LDL-P) assessed by nuclear magnetic resonance spectroscopy were compared.

LDL-C was reduced to the 27th percentile of the population, whereas LDL-P was only reduced to the 51st percentile of the population ($P<0.007$).

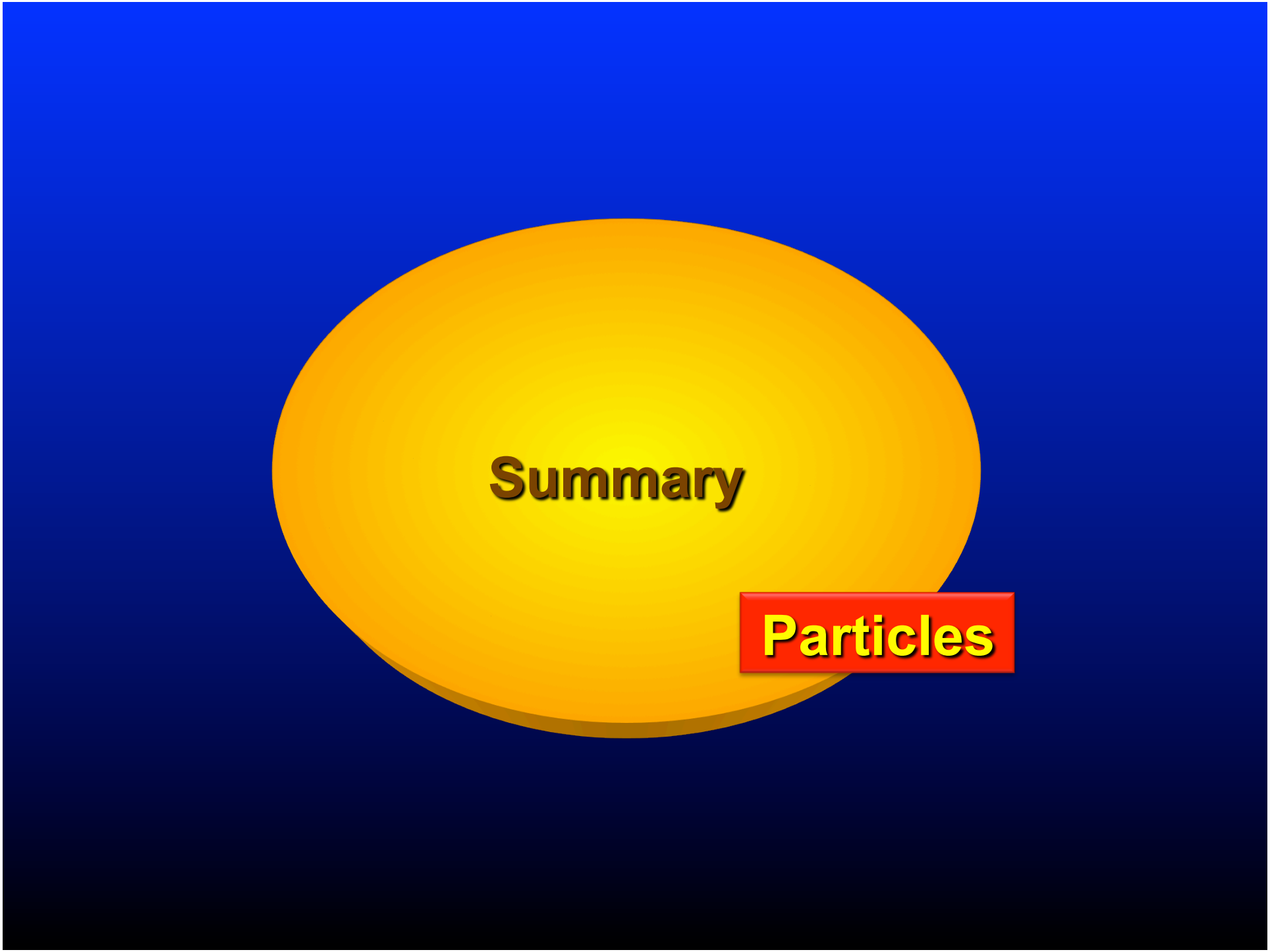
Thus, the reduction in LDL-P was significantly less than LDL-C.

Sniderman, AD Journal of Clinical Lipidology (2008) 2, 36–42

LDL-C vs Non HDL-C vs ApoB

- Statin therapy results in triglyceride enrichment and cholesterol depletion of LDL particles. Because triglycerides persist within the particle core, LDL composition, but not LDL size, changes.
- Changes in core lipid composition of LDL can, therefore, be driven not only by VLDL triglyceride elevation, ie, the usual model, but also by LDL-C reduction, ie, the statin model.
- These data establish that basing LDL-lowering therapy only on the cholesterol indexes results in a treatment gap in a large group of patients—a treatment gap that can be recognized and closed with more intensive therapy only if the atherogenic particle number is measured.

Sniderman AD Journal of Clinical Lipidology (2008) 2, 36–42


Summary
Particles

Endocrinology and Metabolic Clinics of North America
March 2009;38:1–31

Advanced Lipoprotein Testing: Recommendations Based on Current Evidence

Joe F. Lau, MD, PhD[a], Donald A. Smith, MD, MPH[b,*]

►Numerous studies have shown that the LDL cholesterol level as determined by the Friedewald formula is not the most sensitive measure of lipid- and lipoprotein-associated risk for ischemic CVD, especially in patients who have cardiometabolic risk factors including high triglycerides levels, low HDL cholesterol levels, and high numbers of LDL particles.

►The non-HDL cholesterol level is a better alternative goal,

►But the apoB level and the number of NMR-measured LDL particles are the most powerful single lipid and lipoprotein measures and should be ordered with discretion by physicians seeking to use them to improve lipid-altering therapies.