Evolution of Lipid Guidelines
Where We Have Been – Where Should We Be Going?

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Major Lipid Guideline History

- **National Cholesterol Education Program**
  - NCEP ATP I 1987
  - NCEP ATP-II 199
  - NCEP ATP-III 2001 with 2004 addendum
- AHA Secondary Prevention Guidelines
  - 2001
  - 2006 update

Past

- ADA/ACC Consensus Statement 2008
- AACC 2009

Present

- NCEP ATP-IV 2010

Future

Cardiovascular Disease Risk Reduction, Adults
Cholesterol Guidelines Update, ATP IV
Hypertension Guidelines Update, JNC 8
Obesity Guidelines Update, Adults

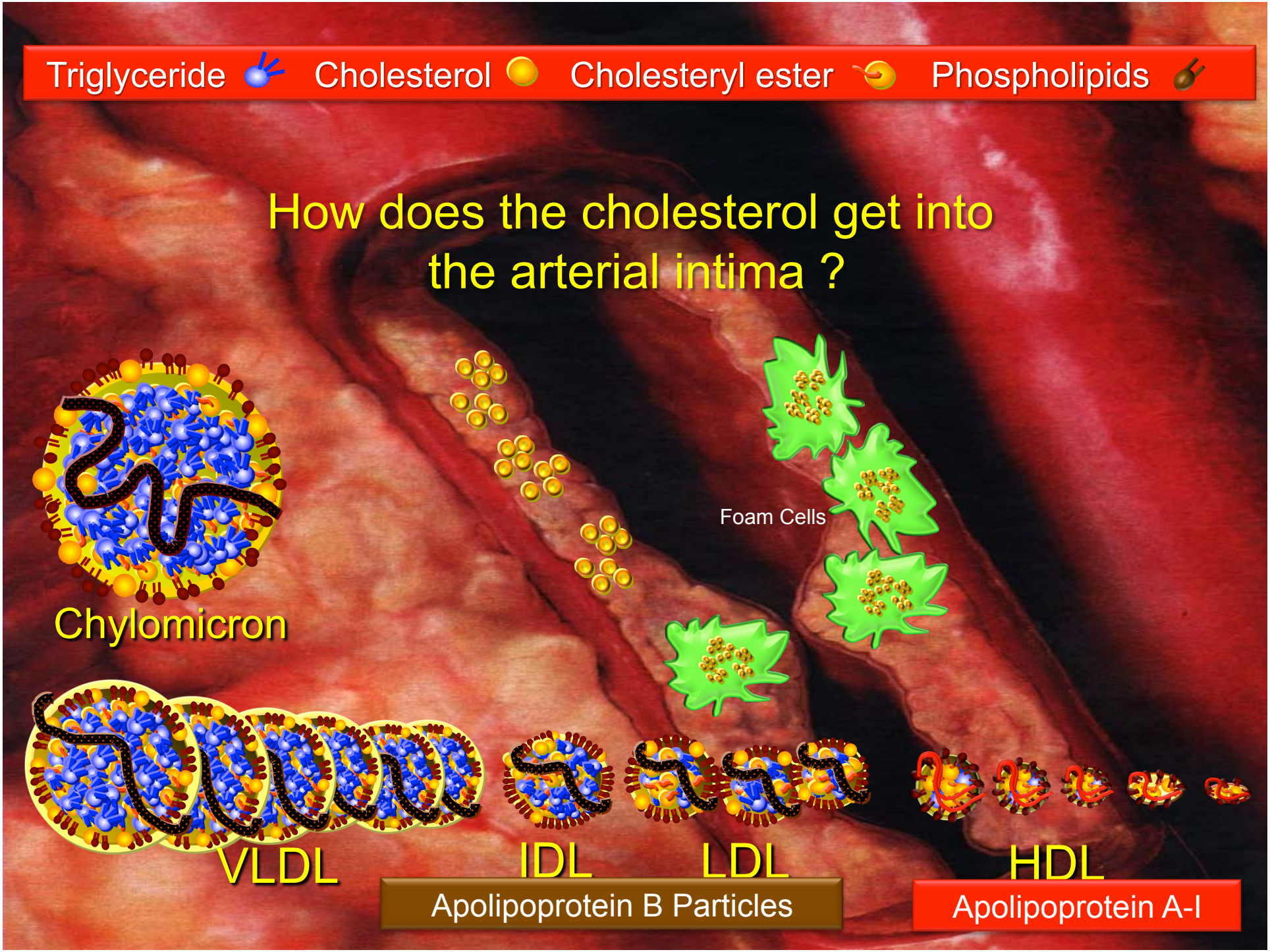
Unlike previous guideline panels, which have focused their efforts on developing individual guidelines in one specific area (e.g., cholesterol assessment and treatment), this guideline development effort will focus on developing a comprehensive integrated guideline across all CV risk factors to more closely mimic "real world" clinical scenarios faced by individuals and clinicians.

Concurrent with the development of the integrated CV risk reduction guideline, NHLBI will update existing guidelines on the prevention, detection, evaluation, and treatment of high blood cholesterol/ dyslipidemia (ATP III), hypertension (JNC7) and overweight/obesity (Obesity Guidelines)

Summer 2010

http://www.nhlbi.nih.gov/guidelines/cholesterol/atp4/

Atherogenesis: Lipids and Lipoproteins


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

Response to Retention Model for 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

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.§

BETHESDA, MARYLAND

THE subjects of this review are the plasma lipoproteins, their structure and functions and the ways in which they are disordered in certain diseases. The intent is not to discuss lipoproteins for their own sake, however, but to exploit their potential for illuminating the common and often frustrating clinical problem of hyperlipidemia. The finding of an abnormal concentration in plasma of cholesterol, glycerides or a given class of the lipoproteins often raises questions of cause and relief that have no certain answer. These will not necessarily be forthcoming in this report. What will be attempted is the reduction of current information about fat transport and metabolism to the minimum terms needed by a physician to obtain a rational approach to the patient with hyperlipidemia and to keep abreast of new developments in this rapidly expanding field.

The integration of information and concepts about normal mechanisms and clinical disorders will proceed from more theoretical to more practical grounds. The first part of the review will outline the normal tasks of fat transport and describe how the several plasma lipids and certain proteins interact in their performances. The proteins that have evolved mainly to participate in transport of esterified lipids and the lipoproteins that they form will be closely examined. This will include analysis of several inheritable diseases in which one of these proteins is deficient to gain perspective on the functions that they apparently serve.

A detailed discussion of hyperlipidemia will follow. This will be based on an approach developed primarily for the study of genetically determined abnormalities, but acquired or nonfamilial disorders, including changes in lipid concentrations secondary

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poпro-

teinemia 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 nomenclature is offered since the older terminology

Classic 5 part NEJM series that put lipidology on the map

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January 5,1967 MEDICAL PROGRESS Volume 276

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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

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transport and metabolism to the
needed by a physician to obtain a
to the patient with hyperlipidem
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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

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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.

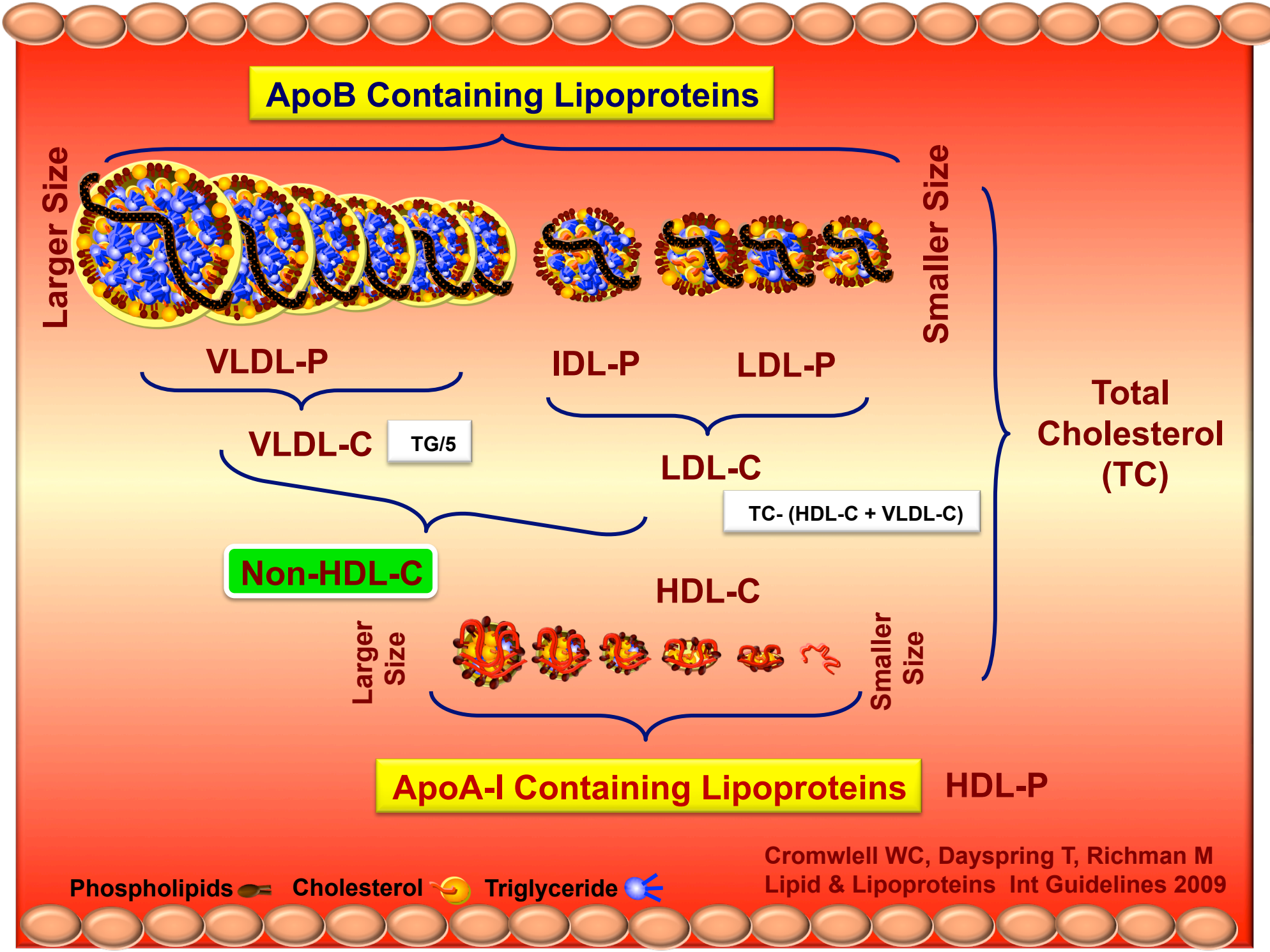
This presumes that cholesterol is the most important lipoprotein-related proatherogenic risk variable.

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


ApoB Containing Lipoproteins
Larger Size
Smaller Size
VLDL-P
IDL-P
LDL-P
VLDL-C
TG/5
LDL-C
TC- (HDL-C + VLDL-C)
Non-HDL-C
HDL-C
Larger Size
Smaller Size
ApoA-I Containing Lipoproteins
HDL-P
Total Cholesterol (TC)
Phospholipids
Cholesterol
Triglyceride
Cromwlell WC, Dayspring T, Richman M
Lipid & Lipoproteins Int Guidelines 2009

Guidelines

Where We Have Been

Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults

The Expert Panel

• **This report of an expert panel of the National Cholesterol Education Program provides new guidelines for the treatment of high blood cholesterol in adults 20 years of age and over. Total cholesterol levels are classified as follows: <200 mg/dL—"desirable blood cholesterol"; 200 to 239 mg/dL—borderline-high blood cholesterol; ≥240 mg/dL—high blood cholesterol. The guidelines detail which patients should go on to have lipoprotein analysis, and which should receive cholesterol-lowering treatment on the basis of their low density lipoprotein (LDL)-cholesterol levels and status with respect to other coronary heart disease risk factors. Dietary therapy is the primary cholesterol-lowering treatment. The report specifies the LDL-cholesterol levels at which dietary therapy should be started and the goals of therapy, and provides detailed guidance on the nature of the recommended dietary changes. If, after six months of intensive dietary therapy, LDL-cholesterol exceeds specified levels, drug treatment should be considered.**

(*Arch Intern Med* 1988;148:36-69)

OVERVIEW AND SUMMARY

Increased blood cholesterol levels, or, more specifically, increased levels of low density lipoprotein (LDL)-cholesterol, are causally related to an increased risk of coronary heart disease (CHD). Coronary risk rises progressively with an increase in cholesterol level, particularly when cholesterol levels rise above 200 mg/dL (for Système International [SI] conversions throughout text, refer to Appendix I, Table 1). There is also substantial evidence that lowering total and LDL-cholesterol levels will reduce the incidence of CHD.

Two approaches can be used to lower blood cholesterol levels. The first is the subject of this report: a patient-based approach that seeks to identify individuals at high risk who will benefit from intensive intervention efforts. The goal here is to establish criteria that define the candidates for medical intervention and to provide guidelines on how to detect, set goals for, treat, and monitor these patients over time. The second approach, the population (public health) strategy, aims to shift the distribution of cholesterol levels in the entire population to a lower range. These two approaches are complementary and, together, represent a coordinated strategy aimed at reducing cholesterol levels and coronary risk.

Case finding: Initial Classification by Total Blood Cholesterol (Table 1)

Serum total cholesterol should be measured in all adults 20 years of age and over at least once every five years; this measurement may be made in the nonfasting state. Levels below 200 mg/dL are classified as "desirable blood cholesterol," those 200 to 239 mg/dL as "borderline-high blood cholesterol," and those 240 mg/dL and above as "high blood cholesterol." The cutpoint that defines high blood cholesterol (240 mg/dL) is a value above which risk of CHD rises steeply, and corresponds approximately to the 75th percentile for the adult US population. The cutpoints recommended in this report are uniform for adult men and women of all ages.

Accepted for publication Sept 28, 1987.

From the National Cholesterol Education Program, National Heart, Lung, and Blood Institute, Bethesda, Md.

Reprint requests to Coordinator, National Cholesterol Education Program, National Heart, Lung, and Blood Institute, Bldg 31, Room 4A 06, Bethesda, MD 20892 (Dr Cleeman).

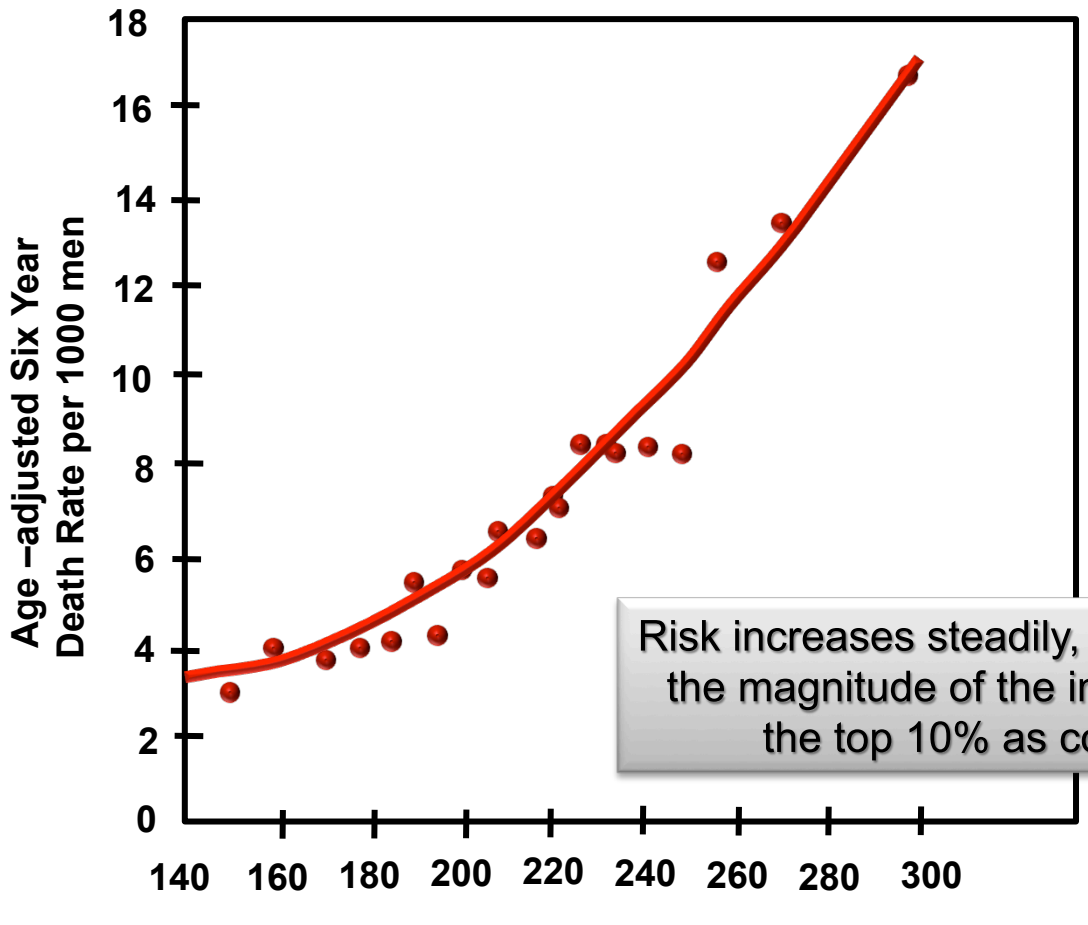
ATP-I

January 1988
Arch Internal Med
1988;148:36-69

National Cholesterol Education Program

Adult Treatment Panel I NCEP-ATP I

Cholesterol and CHD Death Rate



Relationship of serum cholesterol to CHD death in 361,662 men 35-57 years of age during an average of 6 year follow up. Each point represents median-value for 5% of the population

Risk increases steadily, particularly above 200 mg/dL and the magnitude of the increased risk is large, fourfold in the top 10% as compared to the bottom 10%

Arch Internal Med 1988;148:36-69

National Cholesterol Education Program

Adult Treatment Panel I NCEP-ATP I

Total Cholesterol Classification

Classification and Treatment Decisions Based on LDL-C

Risk factors = male sex, family history premature CHD, smoking, HTN, low HDL-C, DM, ASCVD or PVD or obesity

Classification, mg/dL

< 130	----------	Desirable LDL-C
130 to 159	----------	Borderline high-risk LDL-C
≥ 160	----------	High Risk LDL-C

Dietary treatment	Initiation level mg/dL	Minimal Goal mg/dL
Without CHD or 2 risk factors	≥ 160	< 160
With CHD or 2 other risk factors	≥ 130	< 130
Drug treatment		
Without CHD or 2 risk factors	≥ 190	< 160
With CHD or 2 other risk factors	≥ 160	< 130

Arch Internal Med 1988;148:36-69

National Cholesterol
Education Program

Second Report of the Expert Panel on

Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II)

ATP-II

March 1994
Circulation1994;89:3
1329-1445

National Cholesterol Education Program

Adult Treatment Panel II NCEP-ATP II

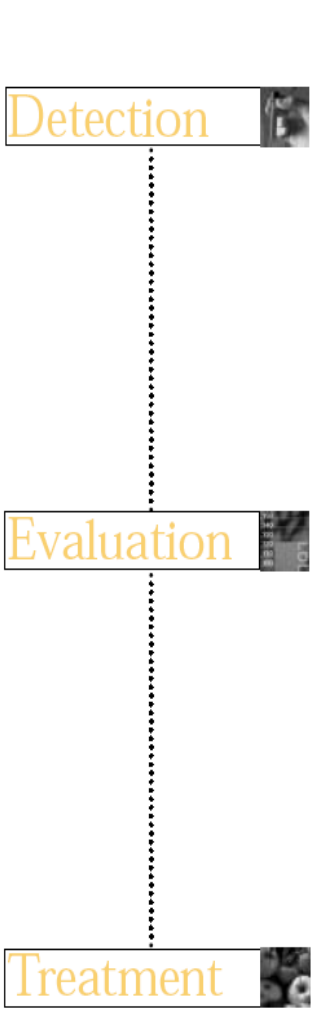
Treatment Decisions

	Initiation level	LDL-C Goal
Dietary treatment		
Without CHD and fewer than 2 risk factors	≥ 160 mg/dL	< 160 mg/dL
Without CHD and with 2 or more risk factors	≥ 130 mg/dL	< 130 mg/dL
With CHD	≥ 100 mg/dL	< 100 mg/dL
	Consideration Level	**LDL-C Goal**
Drug treatment		
Without CHD and fewer than 2 risk factors	≥ 190 mg/dL	< 160 mg/dL
Without CHD and with 2 or more risk factors	≥ 160 mg/dL	< 130 mg/dL
With CHD	≥ 130 mg/dL	< 100 mg/dL

In men < 35 years old and premenopausal women with LDL-C of 190 – 219 mg/dL, drug therapy should be delayed except in high-risk patients such as those with diabetes.

In patients with CHD and LDL-C of 100-129 mg/dL, the physician should exercise clinical judgment in deciding whether to initiate drug therapy

Circulation1994;89:31329-1445



Final Report Circulation 2002;106:3143-3421

378 pages long

National Cholesterol Education Program

National Heart, Lung, and Blood Institute

National Institutes of Health

NIH Publication No. 02-5215
September 2002

SPECIAL COMMUNICATION

12 pages long

Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III)

Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults

THE THIRD REPORT OF THE Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III, or ATP III) constitutes the National Cholesterol Education Program's (NCEP's) updated clinical guidelines for cholesterol testing and management. The full ATP III document is an evidence-based and extensively referenced report that provides the scientific rationale for the recommendations contained in the executive summary. ATP III builds on previous ATP reports and expands the indications for intensive cholesterol-lowering therapy in clinical practice. It should be noted that these guidelines are intended to inform, not replace, the physician's clinical judgment, which must ultimately determine the appropriate treatment for each individual.

BACKGROUND

The third ATP report updates the existing recommendations for clinical management of high blood cholesterol. The NCEP periodically produces ATP clinical updates as warranted by advances in the science of cholesterol management. Each of the guideline reports—ATP I, II, and III—has a major thrust. ATP I outlined a strategy for primary prevention of coronary heart disease (CHD) in persons with high levels of low-density lipoprotein (LDL) cholesterol (≥160 mg/dL) or those with borderline high LDL cholesterol (130-159 mg/dL) and multiple (2+) risk factors. ATP II affirmed the importance of this approach and added a new feature: the intensive management of LDL cholesterol in persons with established CHD. For patients with CHD, ATP II set a new, lower LDL cholesterol goal of ≤100 mg/dL. ATP III adds a call for more intensive LDL-lowering therapy in certain groups of people, in accord with recent clinical trial evidence, but its core is based on ATP I and ATP II. Some of the important features shared with previous reports are shown in Table A in the APPENDIX.

While ATP III maintains attention to intensive treatment of patients with CHD, its major new feature is a focus on primary prevention in persons with multiple risk factors. Many of these persons have a relatively high risk for CHD and will benefit from more intensive LDL-lowering treatment than recommended in ATP II. TABLE 1 shows the new features of ATP III. (Note: To convert cholesterol to mmol/L, divide values by 38.7).

LDL CHOLESTEROL: THE PRIMARY TARGET OF THERAPY

Research from experimental animals, laboratory investigations, epidemiology, and genetic forms of hypercholesterolemia indicate that elevated LDL cholesterol is a major cause of CHD. In addition, recent clinical trials robustly show that LDL-lowering therapy reduces risk for CHD. For these reasons, ATP III continues to identify elevated LDL cholesterol as the primary target of cholesterol-lowering therapy. As a result, the primary goals of therapy and the cutpoints for initiating treatment are stated in terms of LDL.

RISK ASSESSMENT: FIRST STEP IN RISK MANAGEMENT

A basic principle of prevention is that the intensity of risk-reduction therapy should be adjusted to a person's absolute risk. Hence, the first step in selection of LDL-lowering therapy is to assess a person's risk status. Risk assessment requires measurement of LDL cholesterol as part of lipoprotein analysis and identification of accompanying risk determinants.

In all adults aged 20 years or older, a fasting lipoprotein profile (total cholesterol, LDL cholesterol, high-density lipoprotein [HDL] cholesterol, and triglyceride) should be obtained once every 5 years. If the testing opportunity is nonfasting, only the values for total choles-

See also p 2508 and Patient Page.

Corresponding Author and Reprints: James I. Cleeman, MD, National Cholesterol Education Program, National Heart, Lung, and Blood Institute (NHLBI), 31 Center Dr, Room 4A16, MSC 2480, Bethesda, MD 20892-2480 (e-mail: cleemanj@nih.gov).
The Full Report of ATP III is available online on the NHLBI Web site at www.nhlbi.nih.gov.
Members of the NCEP Expert Panel are listed at the end of this article.

NCEP JAMA 2001;285:2486

National Cholesterol Education Program

Adult Treatment Panel III NCEP-ATP III

Global Risk Assessment

Circulation 2004;110:227-239

National Cholesterol Education Program

Adult Treatment Panel III NCEP-ATP III

Framingham Risk Scoring

Step One: Age
Points increase from age 20-79
Step Two: Total Cholesterol
Points increase depending on levels at different ages 20-79
Step Three: HDL Cholesterol
Points increase as levels decrease
Step Four: Systolic Blood pressure
Points increase as levels increase and if on treatment
Step Five: Smoking Status
Points increase in smokers depending on age

NCEP JAMA 2001;285:2486 Final Report Circulation 2002;106:3143-3421

National Cholesterol Education Program
Adult Treatment Panel III NCEP-ATP III

Risk Factors For Atherosclerosis

The robust relationship between total cholesterol and CHD found in epidemiological trials strongly implies that an **elevated LDL-C is a powerful risk factor**

LDL-C makes up 60 to 70% of total cholesterol

NCEP JAMA 2001;285:2486 Final Report Circulation 2002;106:3143-3421

National Cholesterol Education Program

Adult Treatment Panel III NCEP-ATP III

Risk of Triglycerides

Risk Classification of Serum Triglycerides

Normal	<150 mg/dL
Borderline high	150–199 mg/dL
High	200–499 mg/dL
Very high	≥500 mg/dL

NCEP JAMA 2001;285:2486 Final Report Circulation 2002;106:3143-3421

National Cholesterol Education Program

Adult Treatment Panel III NCEP-ATP III

Risk of Low HDL-C

Evidence statement

A low HDL cholesterol level is strongly and inversely associated with risk for CHD

NCEP JAMA 2001;285:2486 Final Report Circulation 2002;106:3143-3421

National Cholesterol Education Program

Adult Treatment Panel III NCEP-ATP III LDL-C Goals

Risk Category	LDL Goal (mg/dL)	LDL Level at Which to Initiate Therapeutic Lifestyle Changes (TLC) (mg/dL)	LDL Level at Which to Consider Drug Therapy (mg/dL)
CHD or CHD Risk Equivalents (10-year risk >20%)	<100	≥100	≥130 (100–129: drug optional)
2+ Risk Factors (10-year risk ≤20%)	<130	≥130	10-year risk 10–20%: ≥130
			10-year risk <10%: ≥160
0–1 Risk Factor	<160	≥160	≥190 (160–189: LDL-lowering drug optional)

NCEP ATPIII. JAMA 2001;285:2486-2497

National Cholesterol Education Program

Adult Treatment Panel III NCEP-ATP III

Risk of Diabetes

Evidence statement

Diabetes is a major independent risk factor for CHD and should be treated as a CHD risk equivalent

NCEP JAMA 2001;285:2486 Final Report Circulation 2002;106:3143-3421

National Cholesterol Education Program

Adult Treatment Panel III NCEP-ATP III

The Metabolic Syndrome

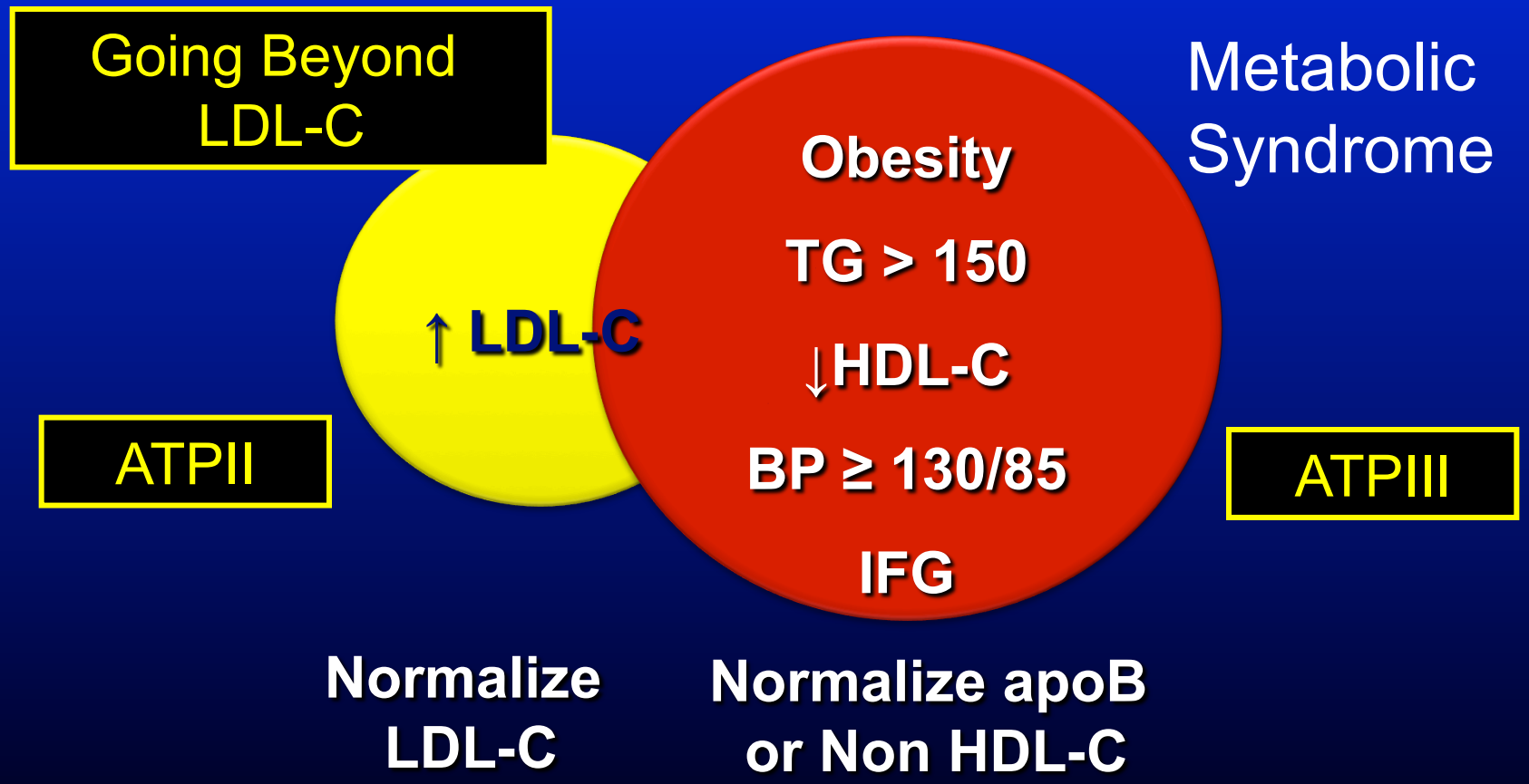
- The diagnosis is suggested by the presence of **three or more** of the following features:
  - Waist >40 inches in men or >35 in women
  - **Triglycerides >150 mg/dl**
  - **HDL-C <40 mg/dL** in men and **<50 mg/dL** in women
  - SBP ≥130 or DBP ≥ 85 mm Hg
  - Fasting plasma glucose >110 mg/dL
- Consider **specific therapy** of these features to mitigate cardiovascular risk

NCEP JAMA 2001;285:2486 Final Report Circulation 2002;106:3143-3421

National Cholesterol Education Program

Adult Treatment Panel III NCEP-ATP III

Global Risk Assessment



Circulation 2004;110:227-239

National Cholesterol Education Program

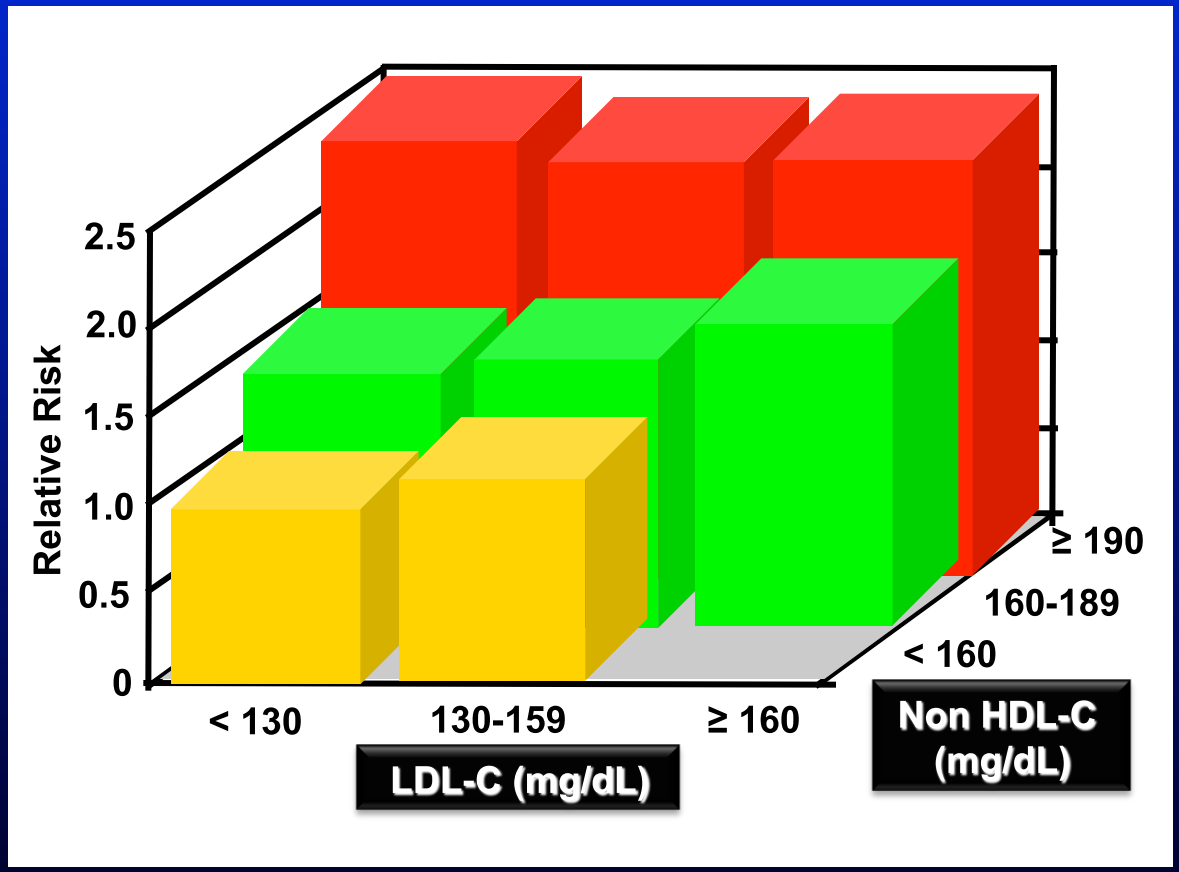
Adult Treatment Panel III NCEP-ATP III

Risk Categories: LDL-C and Non HDL-C Goals

Risk Category	LDL-C Goal (mg/dL)	Non-HDL-C Goal (mg/dL)
CHD and CHD Risk Equivalent (10-year risk for CHD >20%)	<100	<130
Multiple (2+) Risk Factors (10-year risk <20%)	<130	<160
0–1 Risk Factor (10 year risk <10%)	<160	<190

NCEP JAMA 2001;285:2486 Final Report Circulation 2002;106:3143-3421

Framingham Heart Study: Non HDL-C and VLDL-C and Their Risk Predictive Values in Coronary Heart Disease



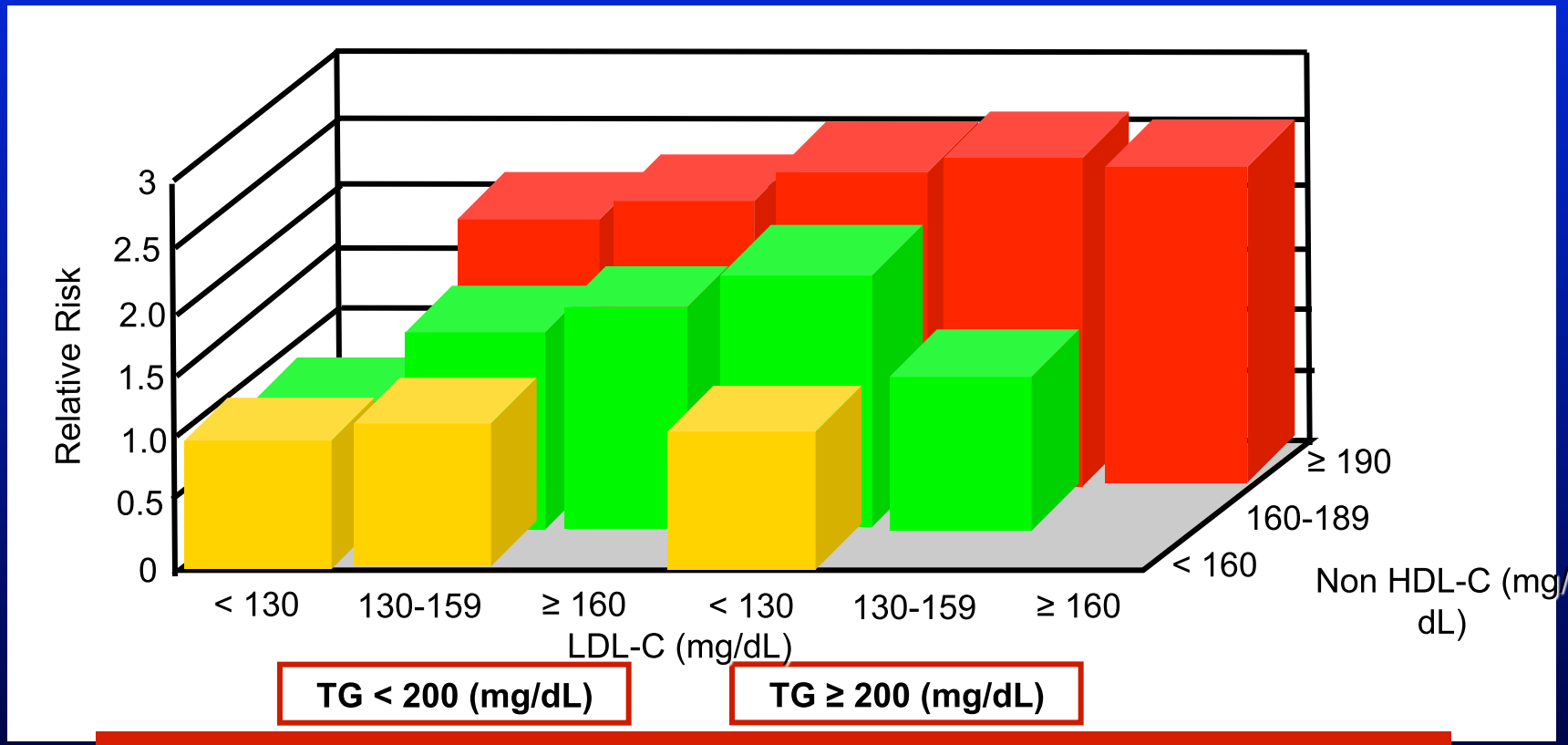
Within non HDL cholesterol levels, **no association** was found between LDL-C and the risk for incident CHD.

In contrast, a strong positive and graded association between non-HDL-C and risk for CHD incidence occurred within every level of LDL-C

That is, non HDL-C appears to be a better predictor of CHD incidence.

Jian Liu, -- Scott Grundy et al. Am J Cardiol 2006;98:1363-1368

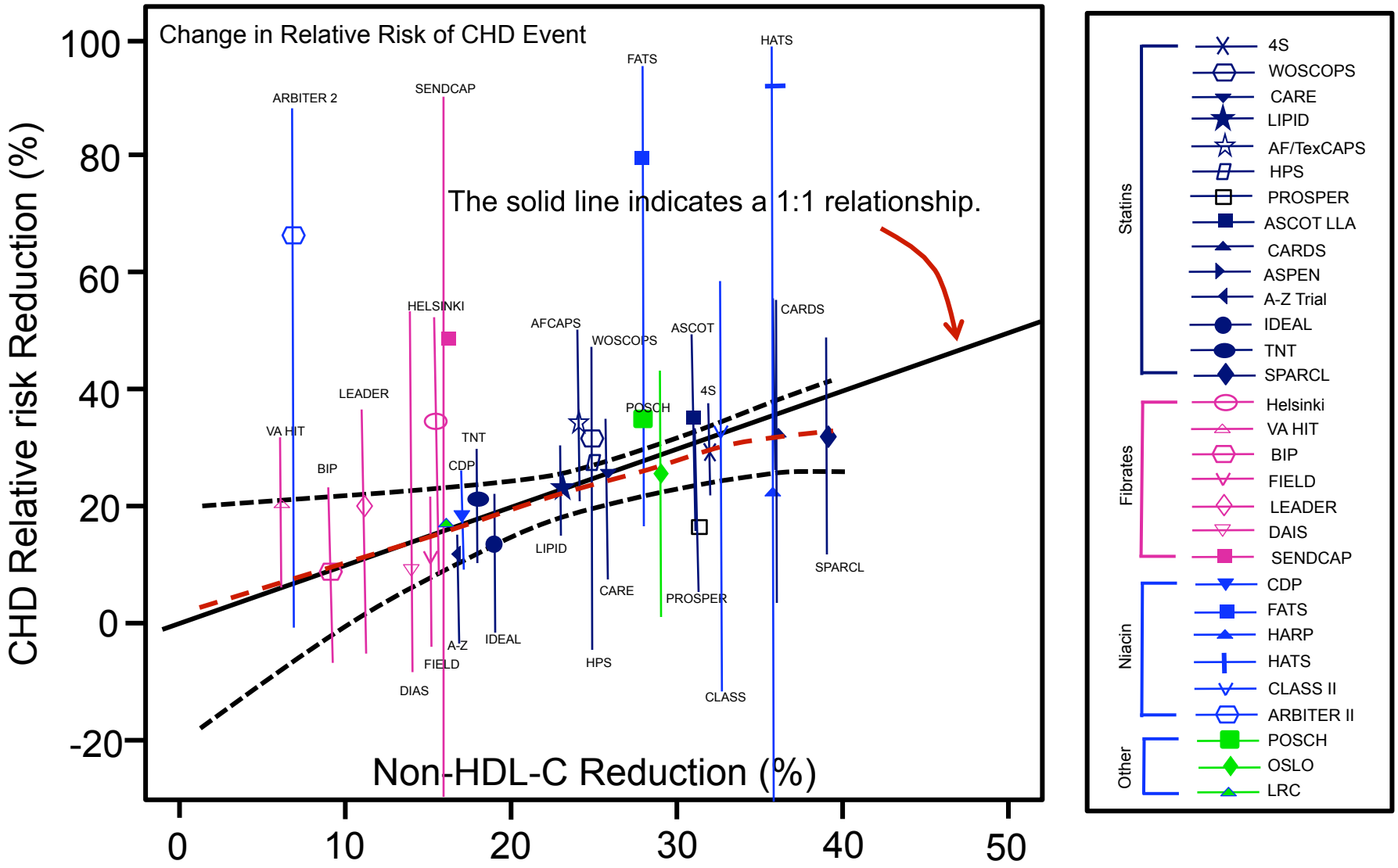
Non HDL-C and VLDL-C and Their Risk Predictive Values in Coronary Heart Disease



The association with CHD incidence was stronger for non-HDL cholesterol within every level of LDL cholesterol than that for LDL cholesterol within each level of non-HDL cholesterol, regardless of TG levels.

Jian Liu, -- Scott Grundy et al. Am J Cardiol 2006;98:1363-1368

Non-HDL-cholesterol



The crude risk estimates from the individual studies are plotted along with their associated 95% confidence intervals. Statin trials are in black; fibrate trials are in pink; niacin trials are in blue (UCSF-SCOR was not plotted); and the POSCH, Oslo, and LRC trials are in green. The relative risks from the 3 trials, POSCH, Oslo, and LRC, were plotted but they are not included in the modeling.

Robinson J et al. J Am Coll Cardiol 2009;53:316–22

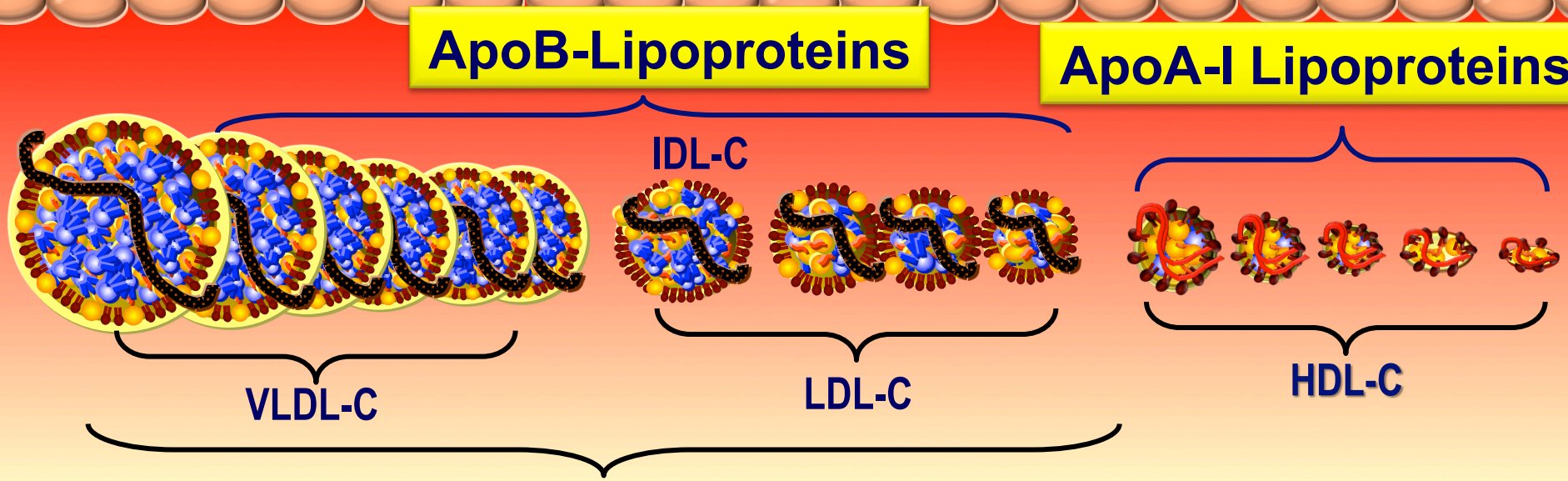
Non-HDL-cholesterol

In summary, there is a direct, consistent relationship between the magnitude of non–HDL-C lowering and cardiovascular risk reduction.

These findings support the use of non–HDL-C as an important target of therapy as recommended by both the NCEP ATP III and the ADA/ACC consensus report on lipoprotein management.

Robinson J et al. J Am Coll Cardiol 2009;53:316–22

Determinants of Non-HDL-C



Non-HDL-C = ApoB-cholesterol

- Non HDL-C can be increased by:
  - High LDL-C
  - Low HDL-C
  - High VLDL-C → VLDL-C = TG/5

National Cholesterol Education Program

Adult Treatment Panel III NCEP-ATP III

Treatment of Triglycerides

What is the NCEP ATP III **goal for TG therapy,** if baseline TG is 200-500 mg/dL?

1) Normalize LDL-C
2) Normalize the non HDL-C value

} ↓ **ApoB**

TG are surrogates for apoB

NCEP JAMA 2001;285:2486 Final Report Circulation 2002;106:3143-3421

National Cholesterol Education Program

Adult Treatment Panel III NCEP-ATP III

Treatment of Low HDL-C

- **Low HDL-C: is defined as <40 mg/dL**
  No specific goal defined for raising HDL-C

- Targets of therapy:
  - Normalize LDL-C in all
  - Those with TG 200–499 mg/dL: achieve **non–HDL-C goal** as secondary priority

↓ **ApoB**

JAMA 2001;285 :2331-2338

National Cholesterol Education Program

Adult Treatment Panel III NCEP-ATP III

Non HDL-C: Treatment

If the non HDL-C is elevated on a statin, it should be normalized with the use of a fibrate or niacin.

COMBINATION THERAPY

NCEP JAMA 2001;285:2486 Final Report Circulation 2002;106:3143-3421

National Cholesterol Education Program
Adult Treatment Panel III NCEP-ATP III

Emerging Risk Factors in 2001

- Triglycerides
- Remnant lipoproteins
- Lipoprotein (a)
- Small LDL
- HDL subspecies
- Apolipoproteins
- TC/HDL-C ratio
- Homocysteine
- Hemostatic factors
- Inflammatory factors
- Impaired fasting glucose

NCEP JAMA 2001;285:2486 Final Report Circulation 2002;106:3143-3421

AHA/ACC Scientific Statement

AHA/ACC Guidelines for Preventing Heart Attack and Death in Patients With Atherosclerotic Cardiovascular Disease: 2001 Update

A Statement for Healthcare Professionals From the American Heart Association and the American College of Cardiology

Sidney C. Smith, Jr, MD; Steven N. Blair, PED; Robert O. Bonow, MD; Lawrence M. Brass, MD; Manuel D. Cerqueira, MD; Kathleen Dracup, RN, DNSc; Valentin Fuster, MD, PhD; Antonio Gotto, MD, DPhil; Scott M. Grundy, MD, PhD; Nancy Houston Miller, RN, BSN; Alice Jacobs, MD; Daniel Jones, MD; Ronald M. Krauss, MD; Lori Mosca, MD, PhD; Ira Ockene, MD; Richard C. Pasternak, MD; Thomas Pearson, MD, PhD; Marc A. Pfeffer, MD, PhD; Rodman D. Starke, MD; Kathryn A. Taubert, PhD

September 2001
Circulation Volume 104 pp 1577 –1579.

AHA/ACC Guidelines for Preventing MI and Death in CHD patients

LDL-C <100 mg/dL (baseline or on-treatment)

- Further LDL-C lowering not required
- Consider fibrate or niacin (if low HDL-C or high TG)

LDL-C 100-129 mg/dL (baseline or on-treatment)

- Intensify LDL-C lowering therapy (statin or resin*)
- Fibrate or niacin (if low HDL-C or high TG)
- Consider combined drug therapy (statin + fibrate or niacin) (if low HDL-C or high TG

LDL-C ≥130 mg/dL (baseline or on-treatment)

- Intensify LDL-C lowering therapy (statin or resin*)
- Add or increase drug therapy with lifestyle therapies

*The use of resin is relatively contraindicated when TG >200 mg/dL

Smith SC, et al. Circulation. 2001;104:1577-1579.

NCEP Report

Implications of Recent Clinical Trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines

Scott M. Grundy; James I. Cleeman; C. Noel Bairey Merz; H. Bryan Brewer, Jr; Luther T. Clark; Donald B. Hunninghake*; Richard C. Pasternak; Sidney C. Smith, Jr; Neil J. Stone; for the Coordinating Committee of the National Cholesterol Education Program

Endorsed by the National Heart, Lung, and Blood Institute, American College of Cardiology Foundation, and American Heart Association

Circulation. 2004;110:227-239

Addendum

National Cholesterol Education Program

Adult Treatment Panel III NCEP-ATP III

2004 Addendum

Risk Category	If LDL-C is:	LDL-C	Non HDL-C
Very High: CVD + ACS, diabetes, MS, ↑BP, smoking,	≥ 100, initiate TLC & consider drugs	< 70 (optional)	< 100
High: CVD or diabetes or CHD equivalent	≥ 100, initiate TLC & consider drugs	< 100	< 130
Moderately High: ≥2 risk factors with 10-20% MI risk	≥ 130, initiate TLC & consider drugs 100-129	< 130 (<100 optional)	160 (<130 option)
Moderate: 2 or more risk factors with <10% MI risk	≥ 130, initiate TLC & ≥ 160 consider drugs	< 130	160
Low: Zero or 1 risk factor	≥ 160, initiate TLC & ≥ 190 consider drugs	< 160	190

Circulation 2004;110:227-239

AHA/ACC Guidelines for Secondary Prevention for Patients with CHD

- LDL-C should be < 100 mg/dL and
- Further reduction of LDL-C to < 70 mg/dL is reasonable
- If baseline LDL-C is ≥ 100 mg/dL, initiate drug therapy
  May require drug combination therapy
  if baseline LDL-C is 70-100 mg/dL, treat to LDL-C < 70 mg/dL
- Further reduction of non-HDL-C to < 100 mg/dL is reasonable
- If TG ≥ 500 mg/dL options are fibrate or niacin before LDL-C lowering therapy and treat LDL-C after TG-lowering therapy. Achieve non-HDL-C < 130 mg/dL if possible

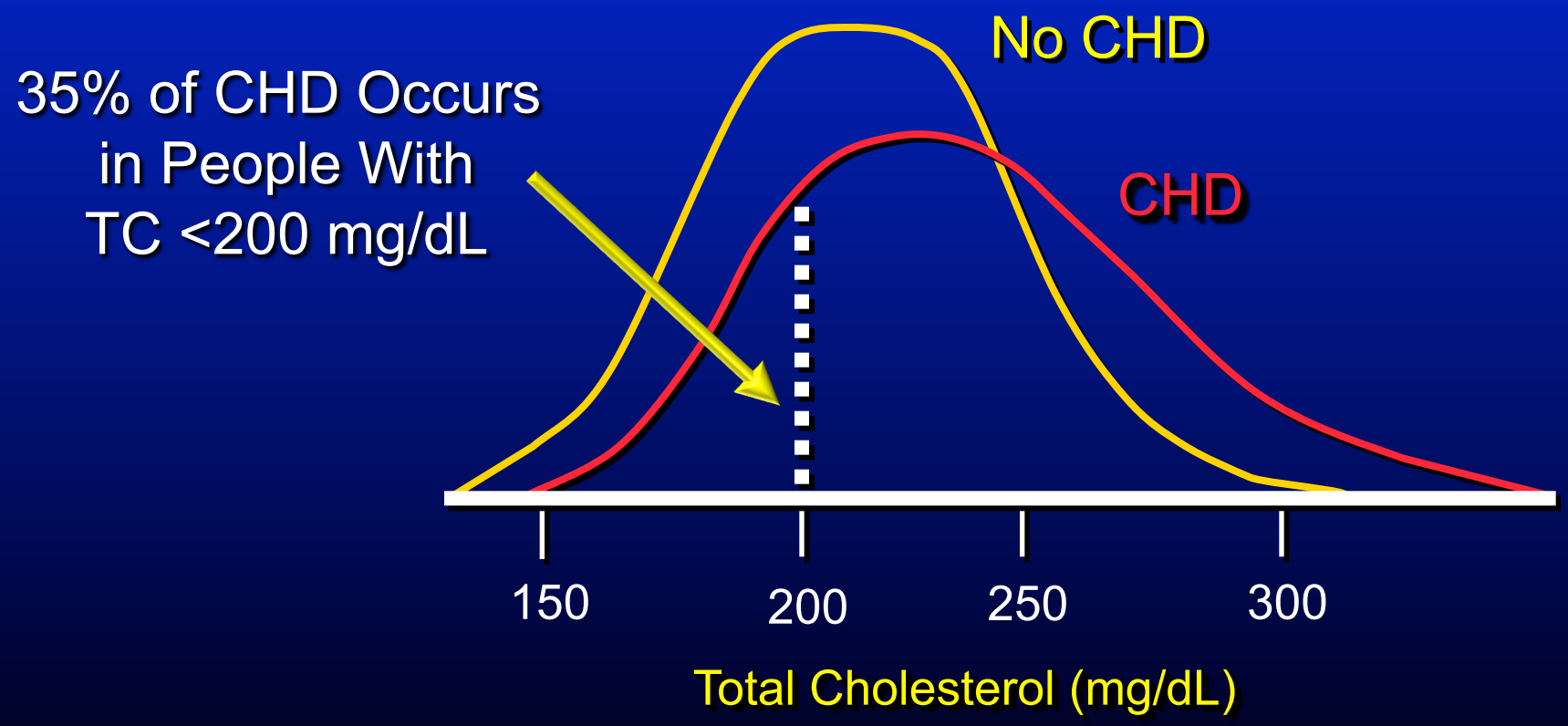
JACC 2006;47:2130 –9.

Guidelines

Where We need to Go

Total Cholesterol Distribution: CHD vs Non-CHD Population

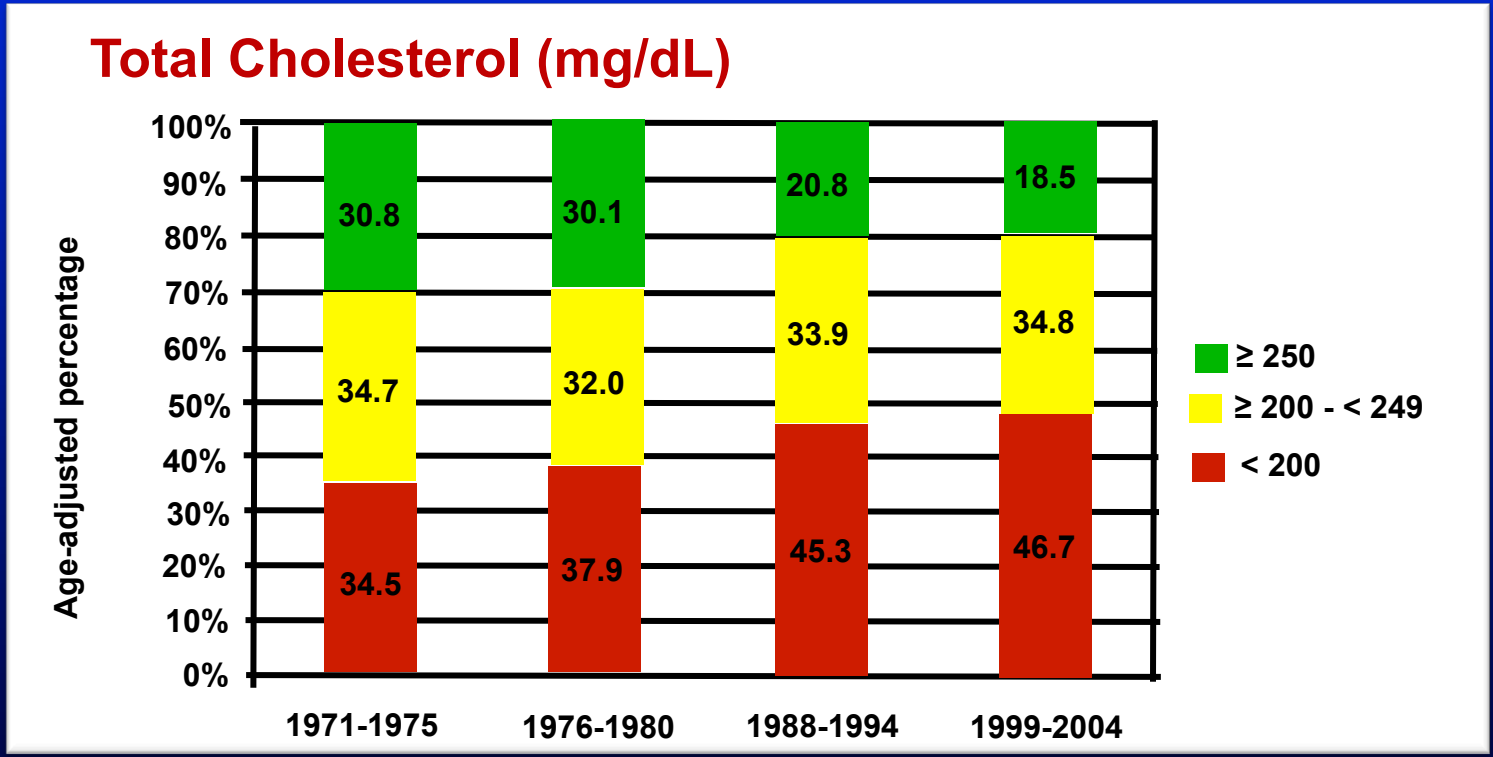
Framingham Heart Study—26-Year Follow-up



Adapted from Castelli. *Atherosclerosis.* 1996;124(suppl):S1-S9.

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

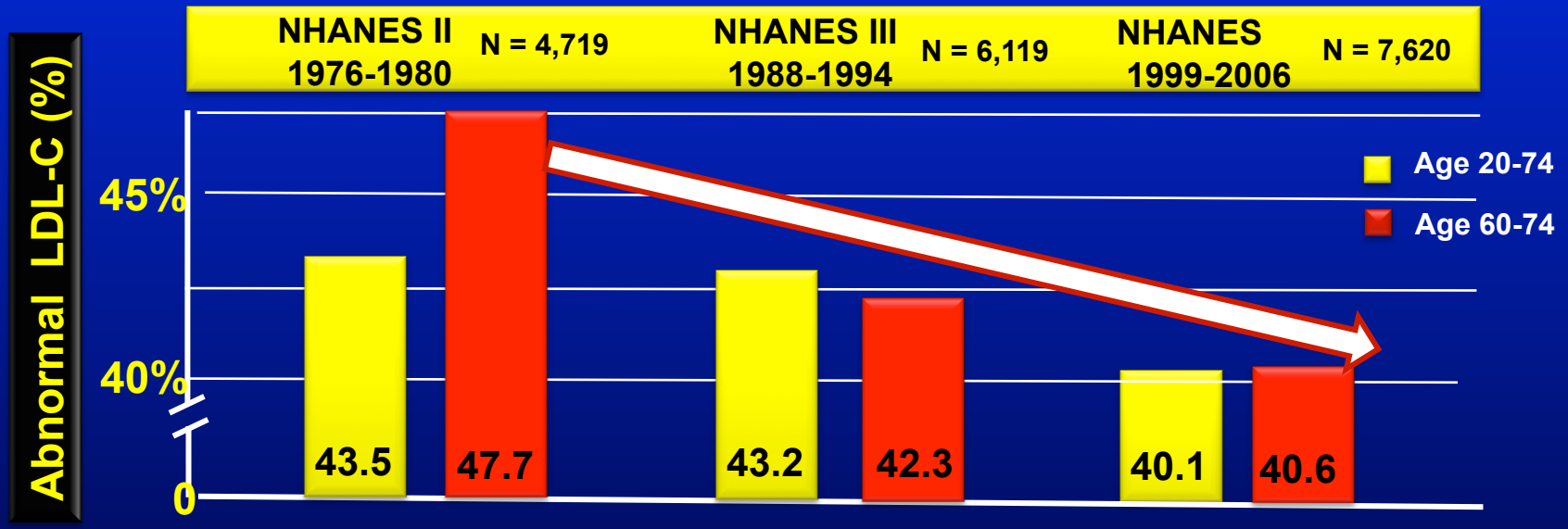
Prevalence of Total Cholesterol Risk Factor Burden



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

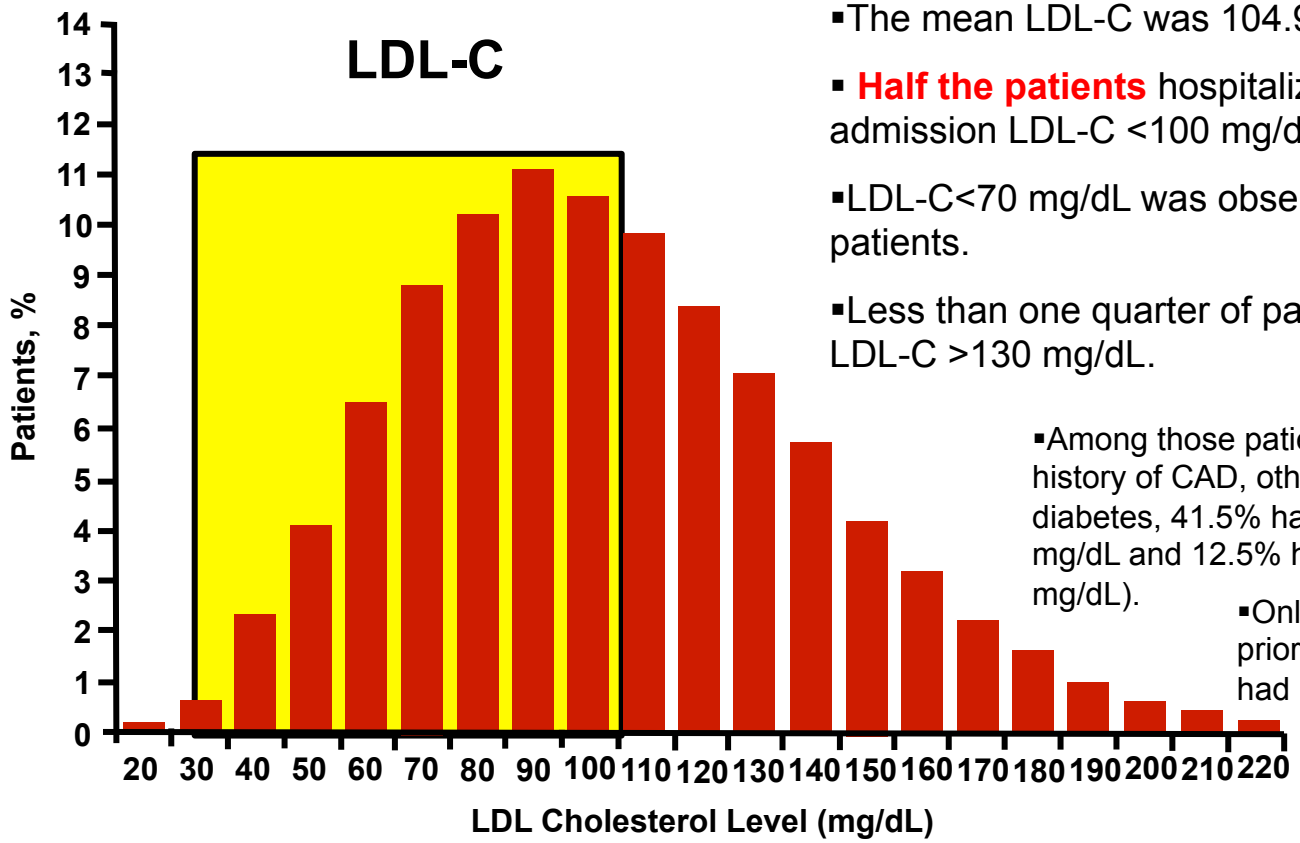


LDL-C values have been dropping

NHANES II 1976-1980	N = 1785	NHANES III 1988-1994	N = 1462	NHANES 1999-2006	N = 1817

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
- 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

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

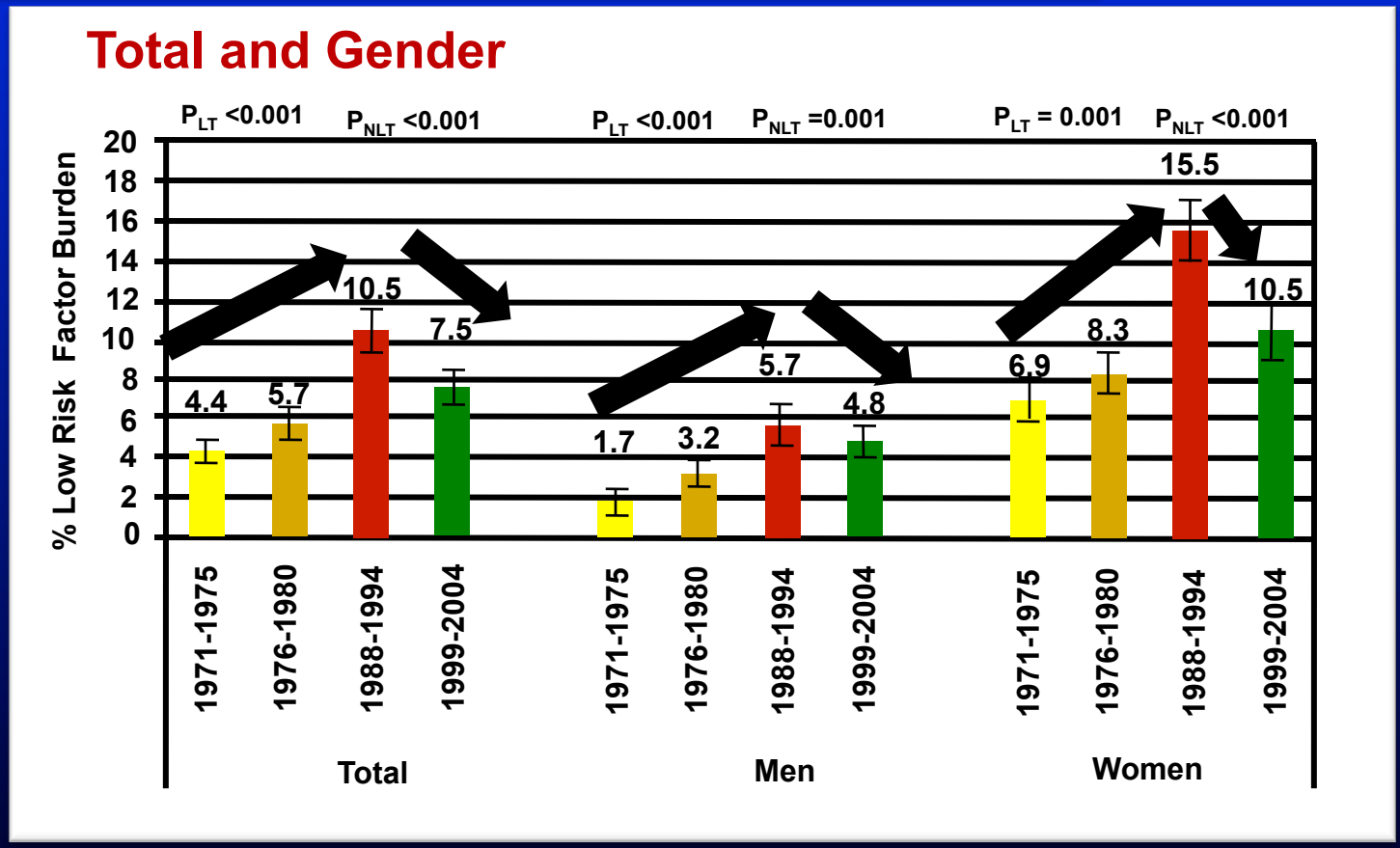
National Health And Nutrition Examination Survey (NHANES) 1971-2004

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.

% of low risk persons has been dropping since early 1990's



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

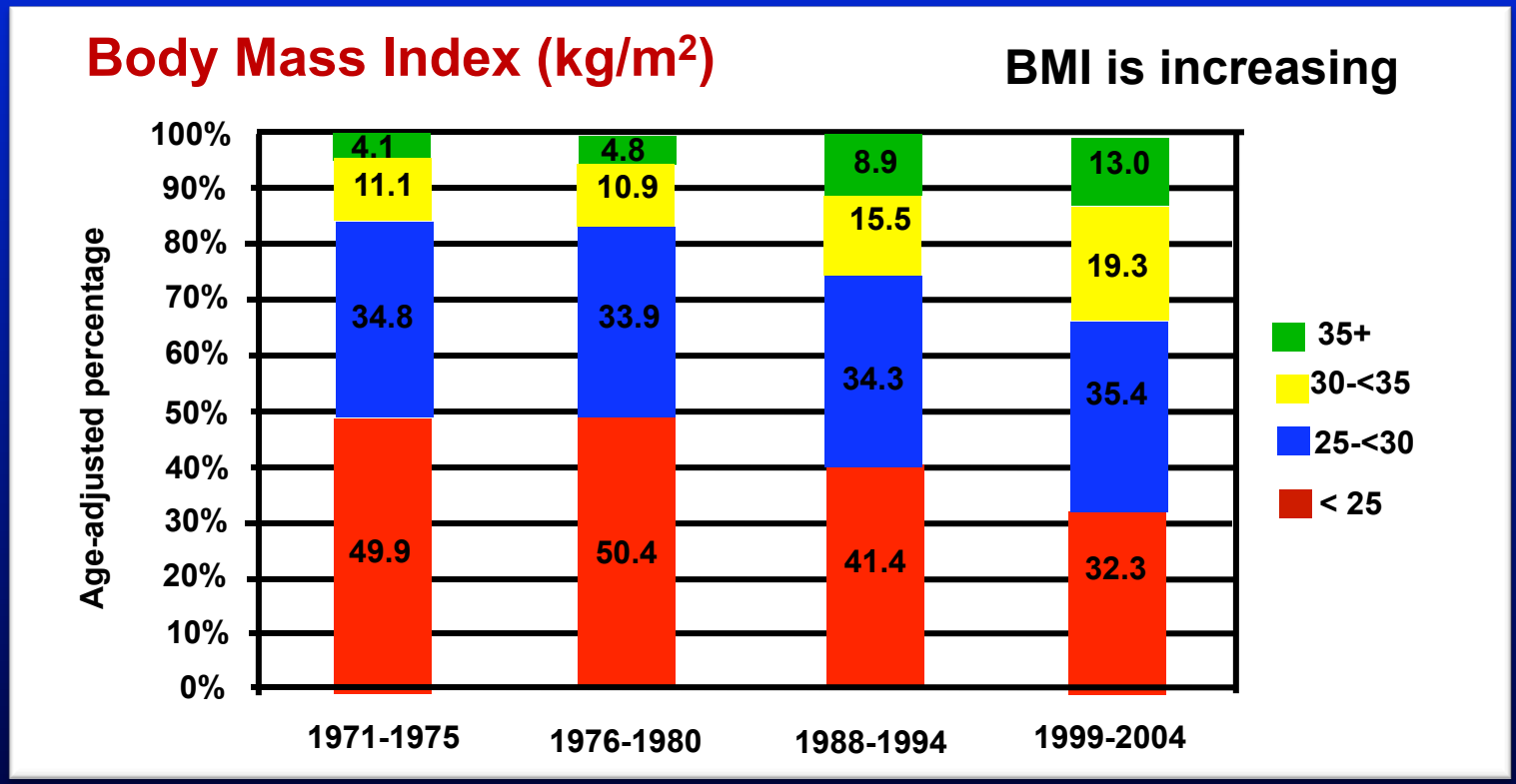
Conclusion: The prevalence of low risk factor burden for cardiovascular disease is low.

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

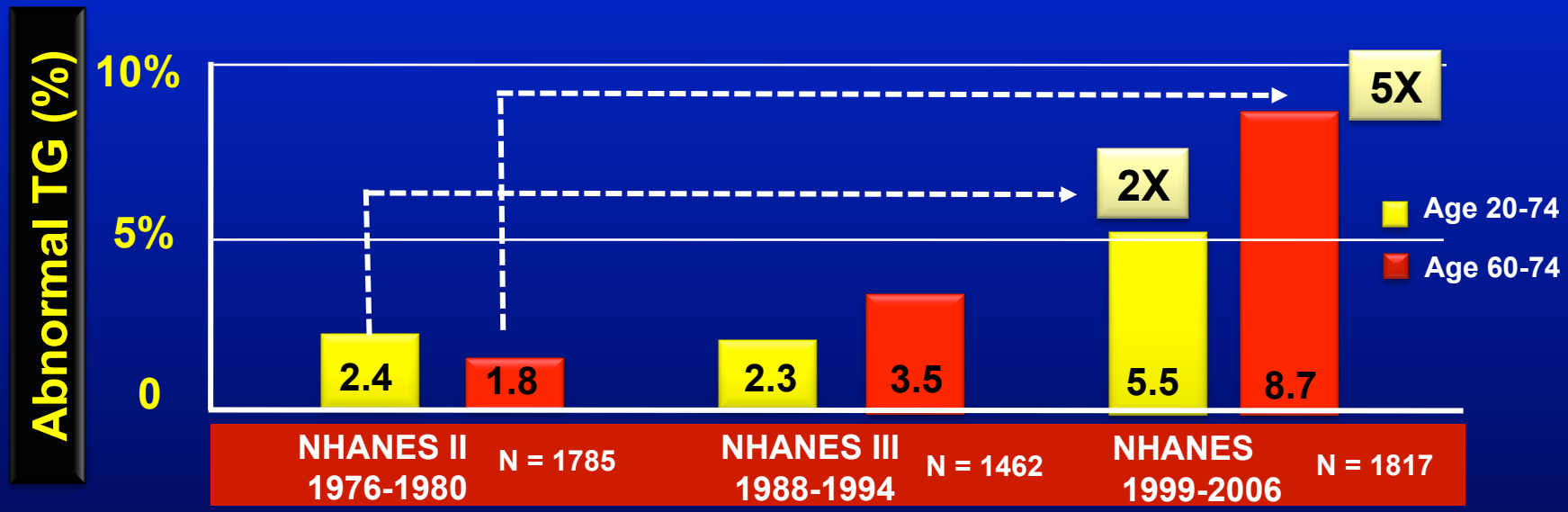
Prevalence of BMI Risk Factor Burden



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.

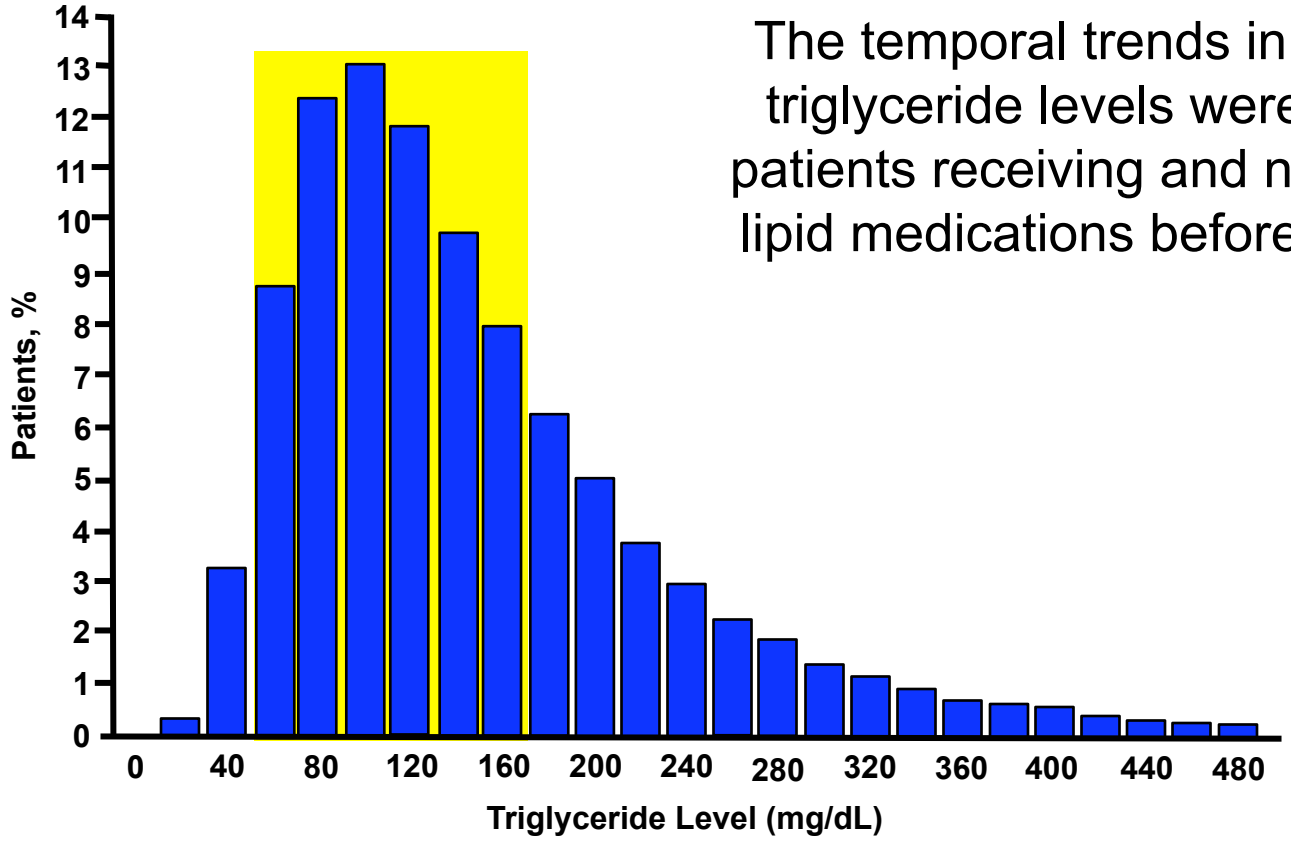
National Health And Nutrition Examination Survey (NHANES) Lipid Changes 1976 - 2006



TG values have been rising

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.

n > 136,000

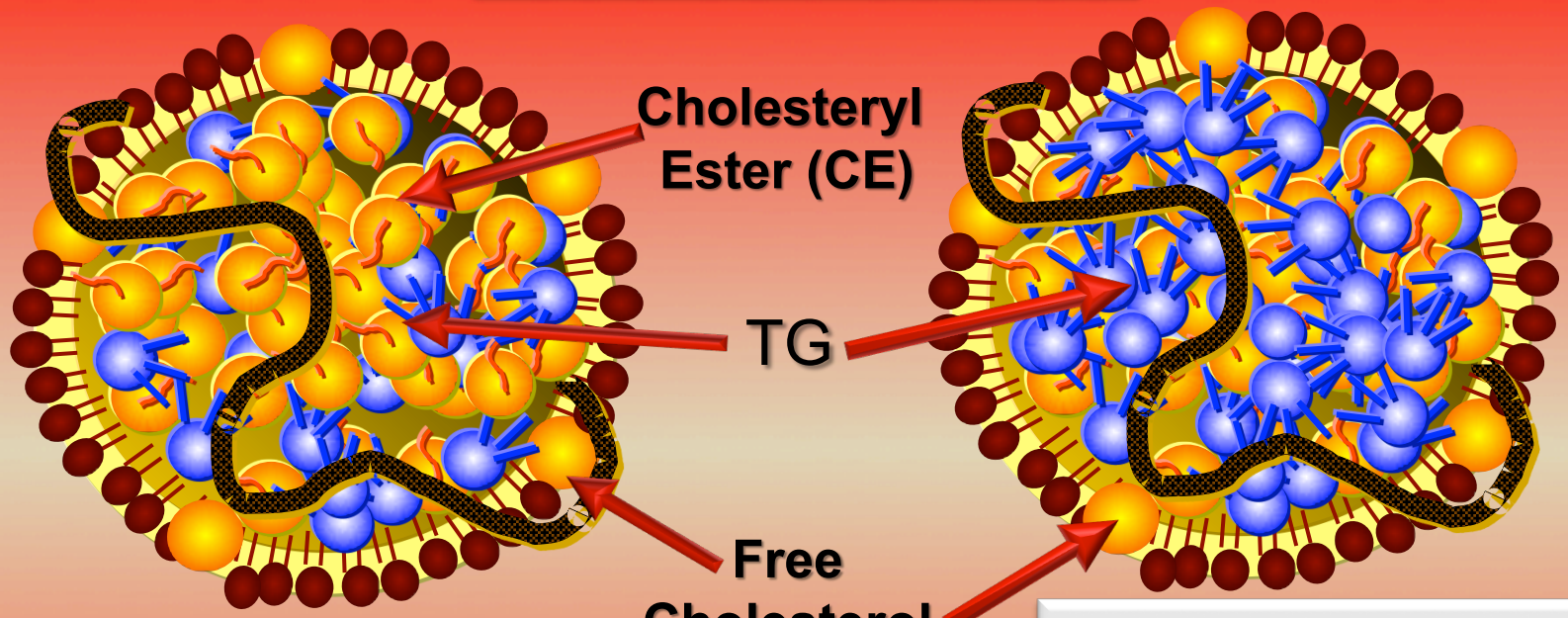
Sachdeva A, et al. Am Heart J 2009;157:111-7.e2

LDL Particle Composition

Low Ratio

Normal CE/TG ratio is >4

Low Ratio

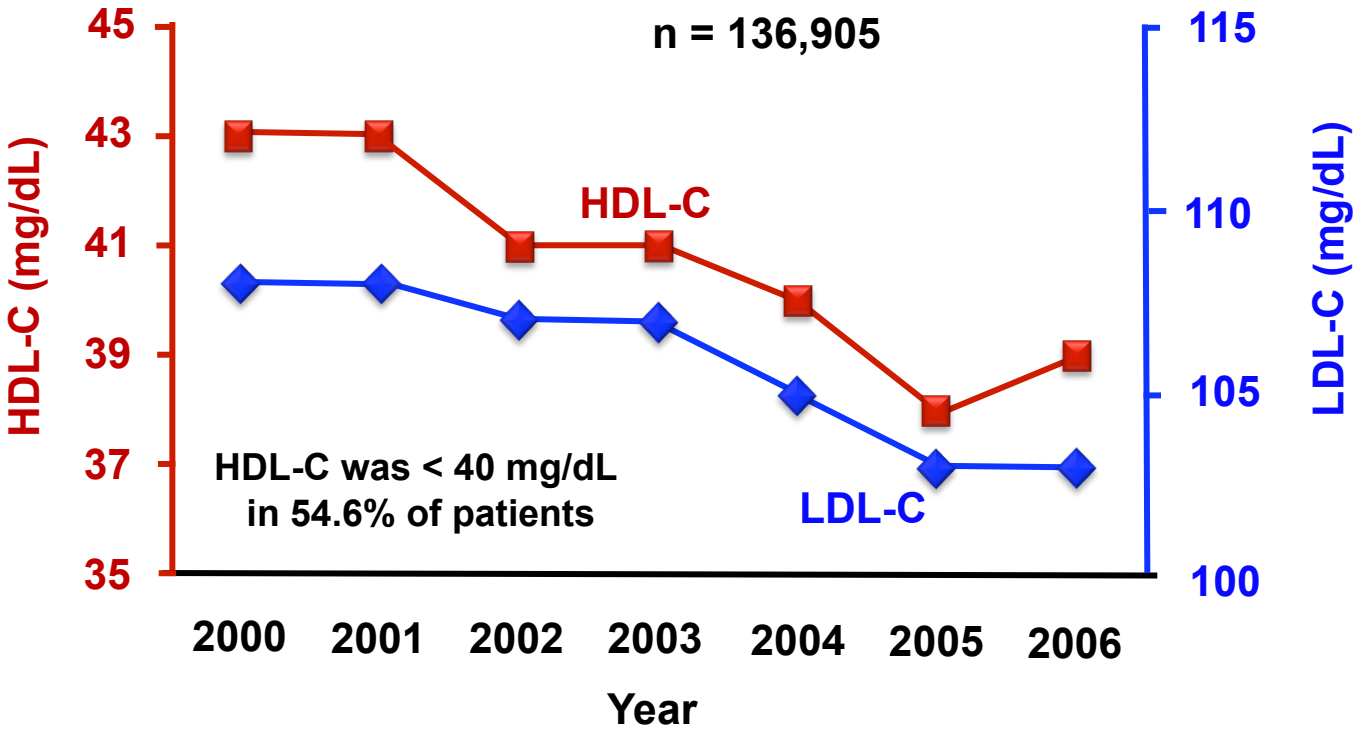


A CE-rich, particle

A TG-rich, cholesterol poor particle

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

Lipid Levels in Patients Hospitalized with Coronary Artery Disease



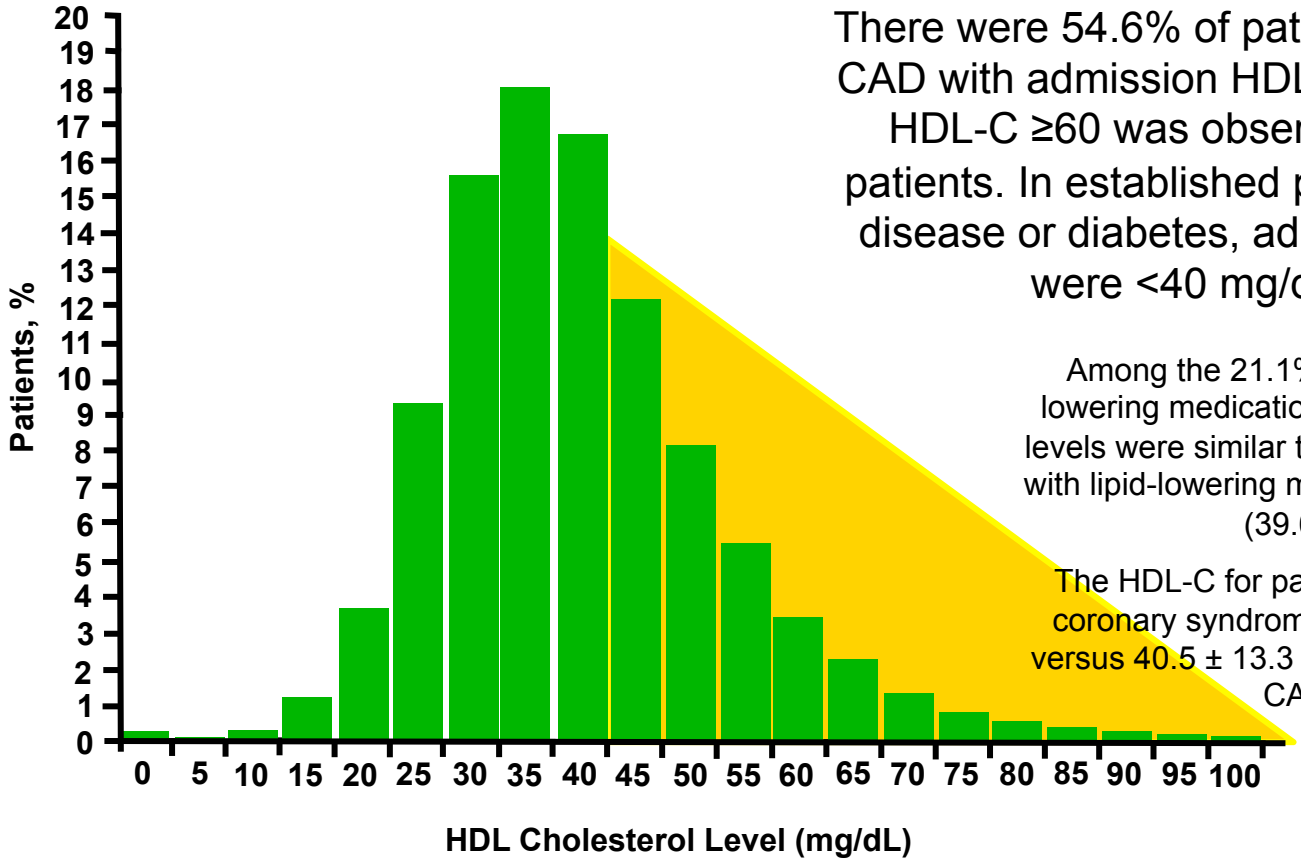
During the period 2000–2006, there was a 10% (p 0.001) decrease in the levels of HDL cholesterol from a mean of 43 mg/dL to 39 mg/dL

.Over the same period, a proportionately smaller but statistically significant decrease in LDL cholesterol 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 **apoB.**

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

Lipoproteins

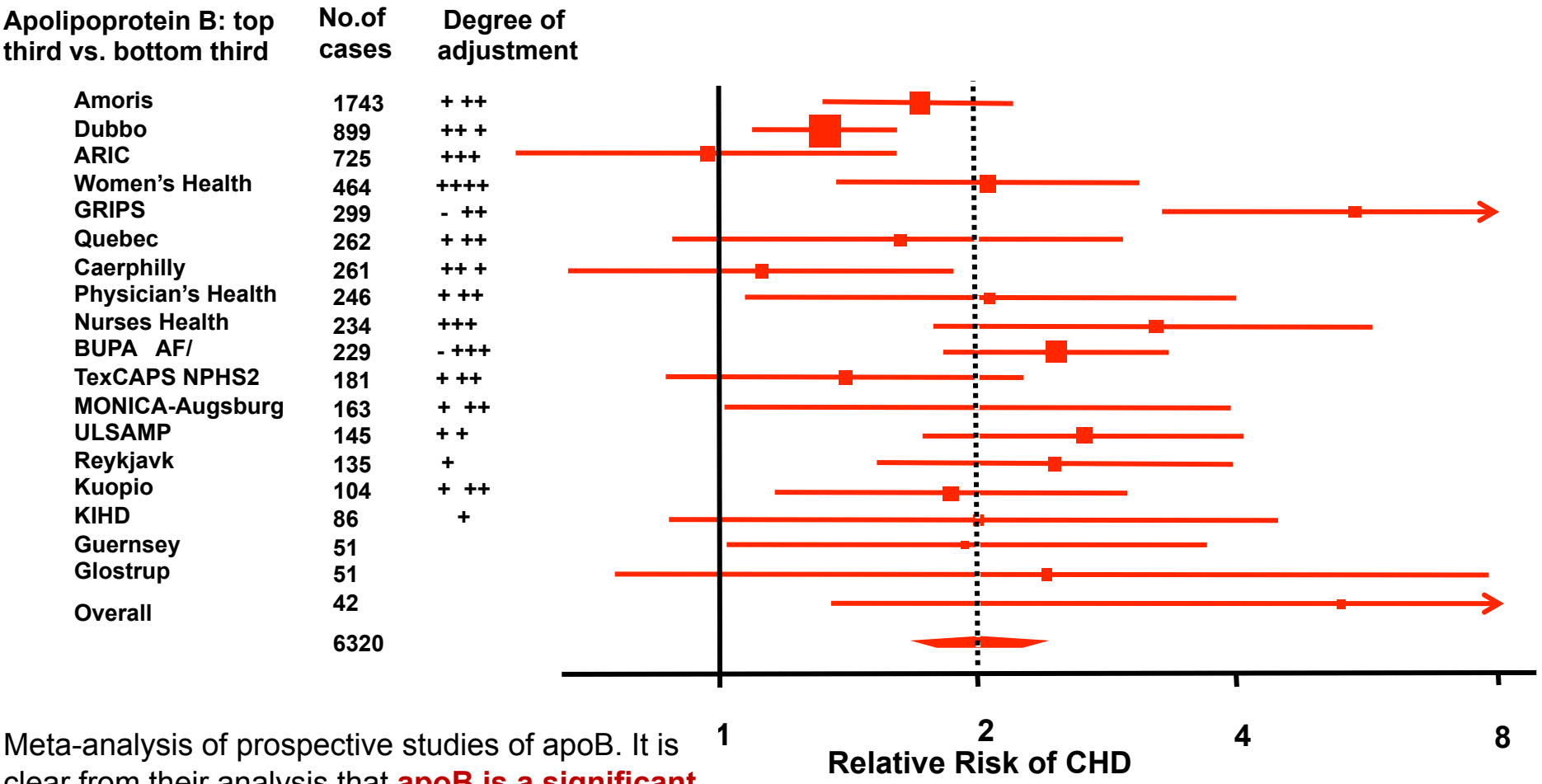
W. Virgil Brown MD

"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

Prospective Studies of Apolipoprotein B and CHD Risk



Meta-analysis of prospective studies of apoB. It is clear from their analysis that **apoB is a significant predictor of CHD,** with an overall relative risk of about 2.0 for the upper vs the lower tertile.
J Intern Med 2006;259:481–92.

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

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

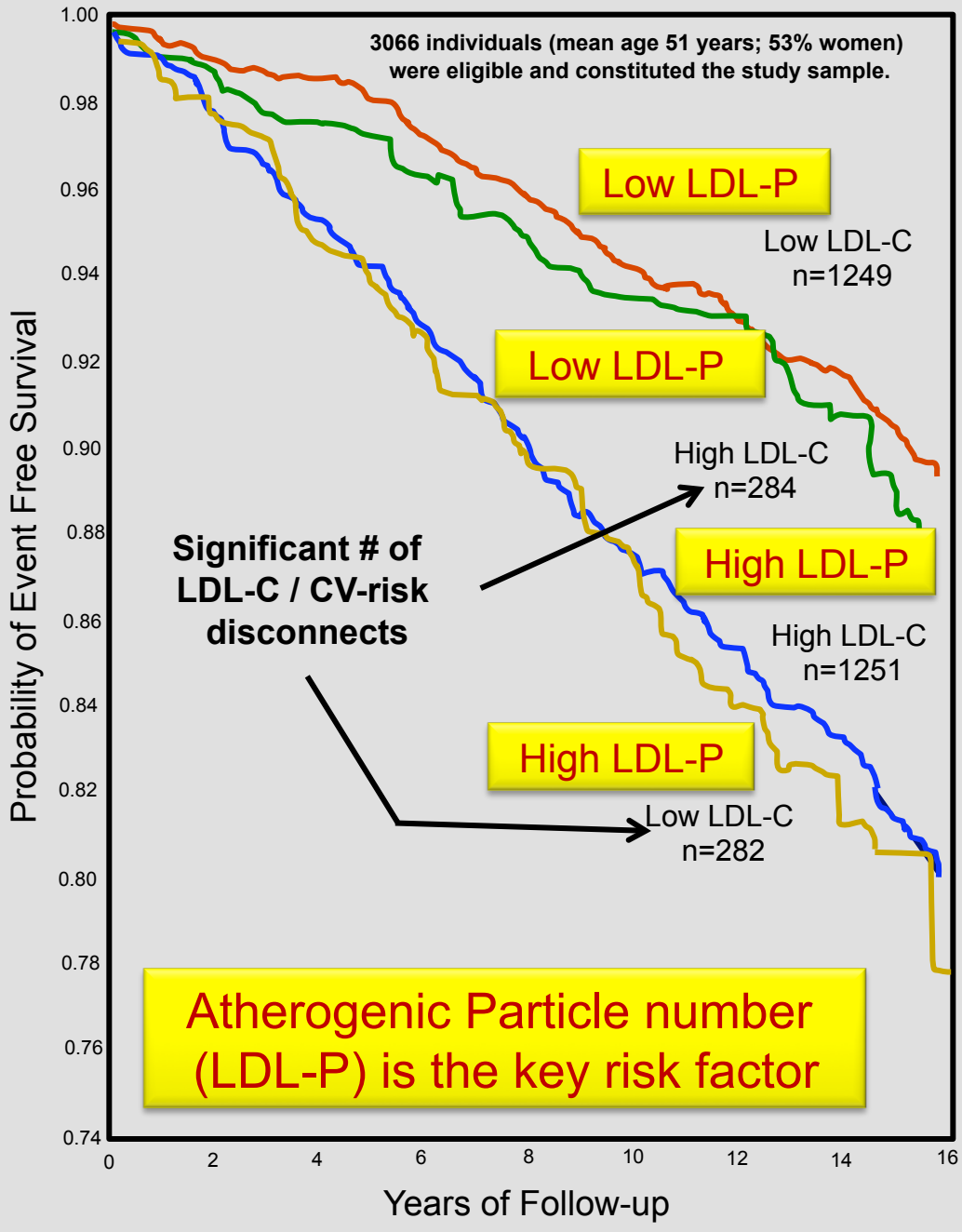
Journal of Clinical Lipidology

Changing Face of 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



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

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]

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

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

- The panel concludes that routine use of non-HDL-C constitutes a better index than LDL-C for identifying high risk patients
- When both non-HDL-C and apoB are measured, the two are highly correlated, but only moderately concordant
- At any given level of non-HDL-C there will be wide variations of apoB levels and vice versa indicating the correlation is of limited value for assessing individual risk
  - This lack of concordance is particularly marked in patients with elevated triglyceride levels

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

ADA and ACC Consensus Statement on Lipoprotein Management

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
- LDL-P as measured by NMR appears equally informative as apoB
- The panel recommends that the apoB goal be reached

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

ADA and ACC Consensus Statement on Lipoprotein Management

TREATMENT GOALS	LDL-C (mg/dL)	Non-HDL-C (mg/dL)	ApoB (mg/dL)
High-risk patients, 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
Highest-risk patients, 1) known CVD or 2) Diabetes plus one or more additional CVD risk factor	< 70	< 100	< 80

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

American Association of Clinical Chemistry

Clinical Chemistry 55:3
407-419 (2009)

Lipids, Lipoproteins, and Cardiovascular Risk Factors

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

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."
- "We believe that the medical decision cutpoints should be set so that the apoB and LDL-P cutpoints are equivalent to those for LDL-C in terms of population percentiles."

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

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

- "Because therapies with 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors reduce LDL-C to a greater extent than they do LDL particles, apoB or LDL-P appear to provide a better assessment of on-treatment residual risk than LDL-C measurement."
- "Importantly, on-treatment non-HDL-C concentrations may not reflect residual risk associated with increased LDL particle number."
- "In light of the mounting evidence, the members of this working group of the Lipoproteins and Vascular Diseases Division of the AACC believe that **apoB and alternate measures of LDL particle concentration should be recognized and included in guidelines, rather than continuing to focus solely on LDL-C**."

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

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
	< 70	< 80	
< 80	< 100	< 120	< 1100
< 100	< 130	< 150	< 1400

Significant reductions in non-HDL-C goals compared to NCEP ATP-III

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

Journal of the American College of Cardiology

Published by Elsevier Inc.

EDITORIAL COMMENT

We Must Prevent Disease, Not Predict Events*

Allan D. Sniderman, MD

Montreal, Quebec, Canada

We KNOW what causes disease within our arteries but can only guess at what precipitates clinical events.

It follows that prevention of coronary disease would be much simpler and much more effective if we focused on PREVENTING disease developing within our arteries rather than trying to predict who is just about to become a victim and then trying frantically, at what may be just one minute before their final midnight, to rescue them

If we prevent the disease, we will prevent the events.

JACC, 52(4) 2008. 300-301.

Journal of the American College of Cardiology

Published by Elsevier Inc.

EDITORIAL COMMENT

We Must Prevent Disease, Not Predict Events*

Allan D. Sniderman, MD

Montreal, Quebec, Canada

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It follows that prevention of coronary disease would be much simpler and much more effective if we focused on PREVENTING disease de to predict who is just tically, at what may to rescue them

Take away the apoB particles and you take away atherosclerosis.

If we prevent the disease, we will prevent the events.

JACC, 52(4) 2008. 300-301.

GUIDELINES

"Guidelines are just that—guidelines. They are meant to provide clinicians with the best summary of evidence-based therapy and expert opinion."

"However, they are not intended to replace patient-centered decision making by experienced clinicians."

Raymond J. Gibbons Circulation. 2010;121:194-196