Advanced Cholesterol Testing
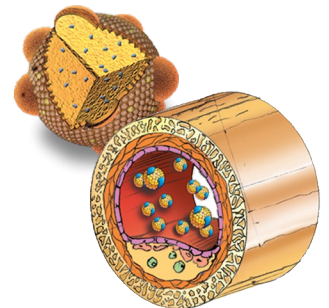
A Basic Understanding

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The Center for Cholesterol Management
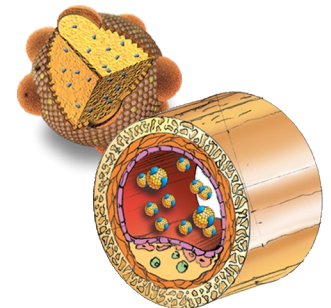
Los Angeles, California

www.lipidcenter.com

Objective

- **Come to terms with the limitations of traditional lipids alone**

Burden of Heart Disease

- **Heart disease, stroke and other cardiovascular diseases are the No. 1 killer of Americans**

- **Over 2,600 Americans die of cardiovascular disease each day.[1]**

- **US heart disease prevalence is projected to double in the next century. [2]**

- **Over 125 million lipid panels are done annually in U.S.[1]**
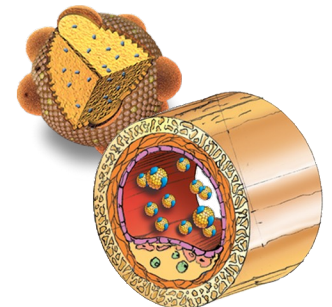
1 Burden of Heart Disease and Stroke in the United States from Steps to a Healthier US. US Department of Health and Human Services, 2003.
2 ACC /AHA Guidelines, 2001; NHLBI Chart Book 2000; and adapted from Foot et al; JACC 2000.
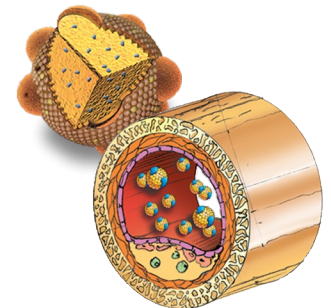
LIPID TESTING

Routine Lipid Testing is recommended to begin for all adults >20 years old

Dyslipidemia is usually an asymptomatic condition and early recognition and treatment improves prognosis
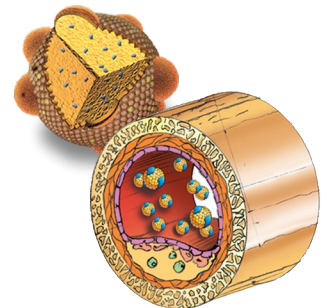
Major Risk Factors for CAD

- Smoking

- Age

- Hypertension (High Blood Pressure)

- Diabetes

- High Cholesterol

Dyslipidemia

- **High Cholesterol is the most prevalent and important modifiable risk factor for Atherosclerosis affecting one in two U.S. adults**

- **Proper Treatment reduces the risk of MI, Cardiac Death, Stroke, Revascularization Procedures, and PVD by 25-50%**

Why the Interest in Cholesterol?

MRFIT: Age Adjusted CHD Death Rate and Serum Cholesterol in 361,662 U.S. Men

6 year CHD death rate per 1,000 men

~ 50% of CHD

Serum cholesterol mg/dL (mostly LDL-C)
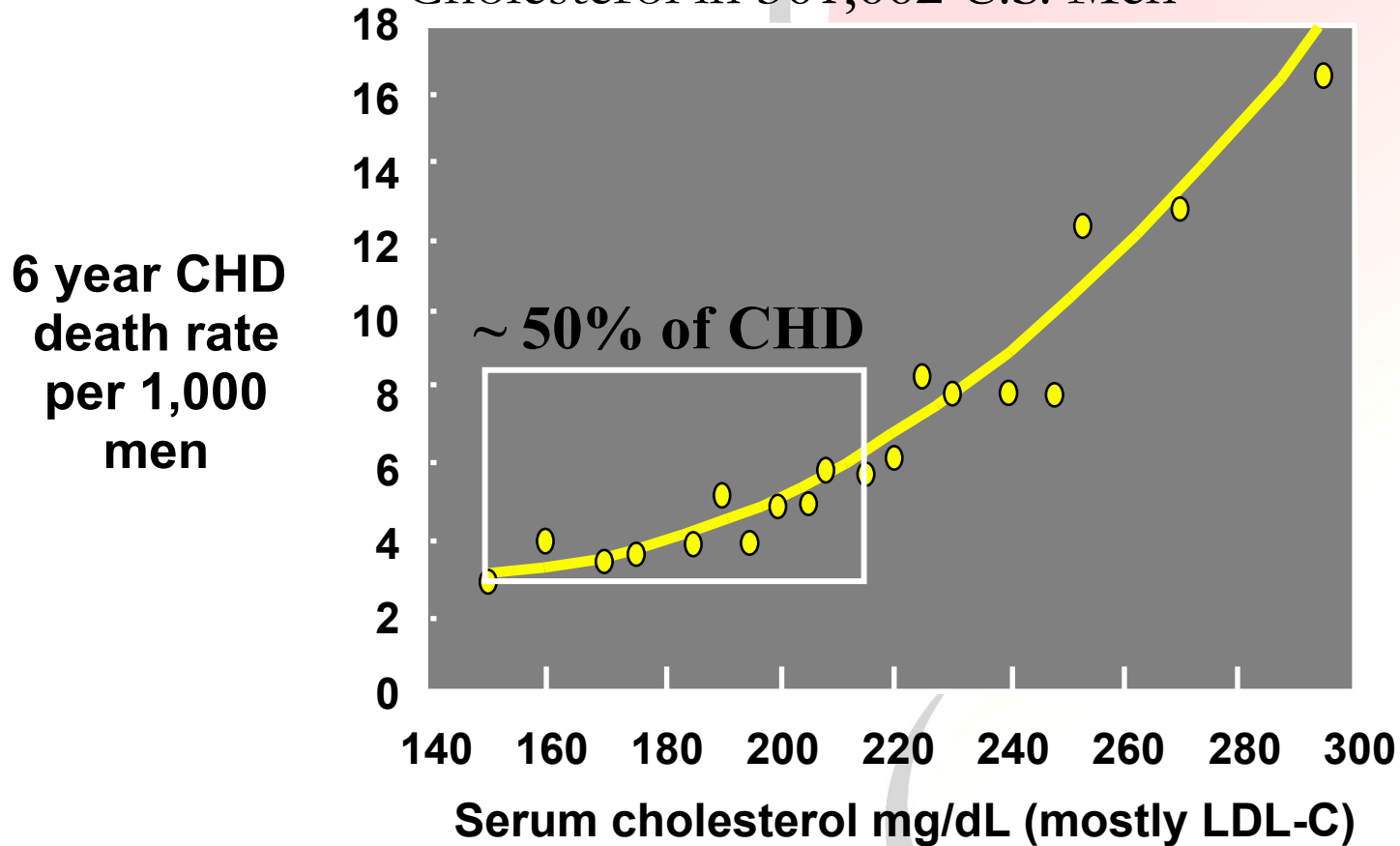
Is What You're Looking at Enough?

Significant overlap of LDL cholesterol levels exists between populations with and without CHD.

Adapted from Framingham Heart Study 26-year follow-up data.

■ CHD
■ NO CHD

LDL CHOLESTEROL (mg/dL)

100   150   220

Kannel W. Am J Cardiol. 1995;76:69C-77C
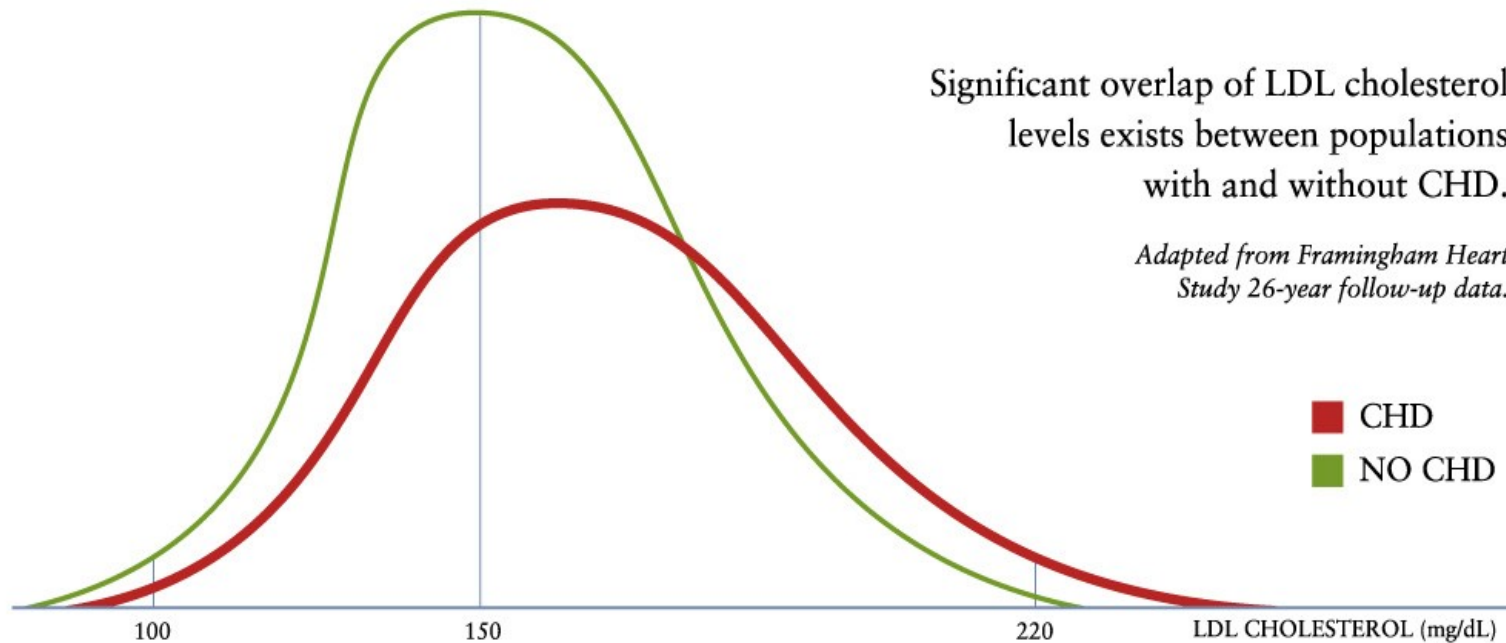
Cholesterol and Heart Disease

- Cholesterol is an oily, waxy substance that can contribute to heart disease

- At first, physicians measured total cholesterol to determine heart disease risk

- Identified "bad" cholesterol (LDL-C) and "good" cholesterol (HDL-C)

Doctors now know that approximately 50% of people who have had heart attacks had "normal" cholesterol!

Equally Important Questions

- **Is LDL-C the best measure of LDL-related CVD risk?**

- **Is LDL-C the best target of LDL-lowering therapy?**

Traditional lipids alone are not <u>identifying</u> everyone at lipid-related risk for heart disease and do not provide the best information to <u>manage</u> that risk optimally.

Limitations of Cholesterol

"It is now generally recognized that although traditional risk factors are reasonably good at predicting excess risk above the baseline for particular populations, they allow clinicians to predict only approximately 50% to 60 % of the variation in absolute risk in individual patients. **Therefore, factors that enhance predictive ability in an** additive fashion over traditional risk factors **would have considerable clinical usefulness, allowing better decisions to be made regarding the use of proven preventive therapies."**

D.J. Rader, MD
Lipid Disorders
Textbook of Cardiovascular
Medicine

Lipid Disorders. Textbook of Cardiovascular Medicine - Second Edition (Topol, EJ editor) 2002, Lippincott Williams & Wilkins, Philadelphia. pp 65.

LDL-P: The Number of Lipoprotein Particles

Measuring the number of lipoprotein particles provides additional information that allows clinicians to identify everyone at lipid-related risk for CHD and miss no one.

The Cause of Heart Disease

- Think of lipoproteins as cars along a highway and the passengers in the cars as cholesterol.

- No matter how much cholesterol is being carried by these lipoproteins, it is the number of and size of these lipoproteins that contribute to heart disease.
- You can be at increased risk for heart disease even if you have normal cholesterol levels.
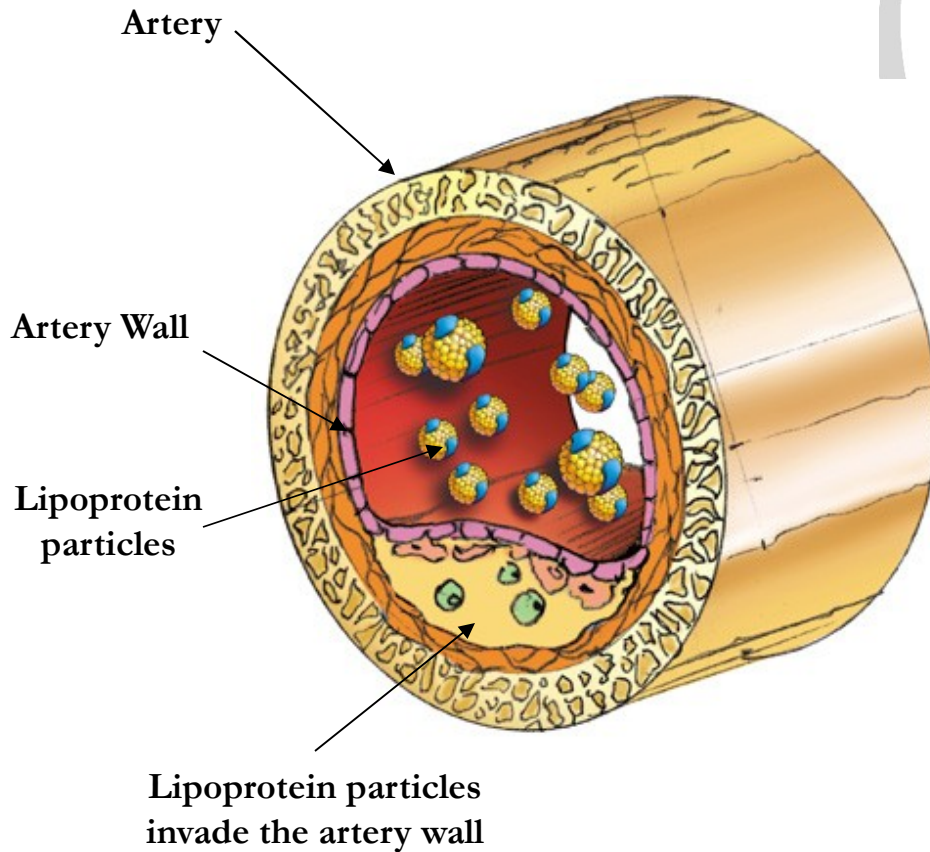
What are Lipoprotein Particles?

Lipoprotein particle shell

Inner core full of cholesterol and triglycerides
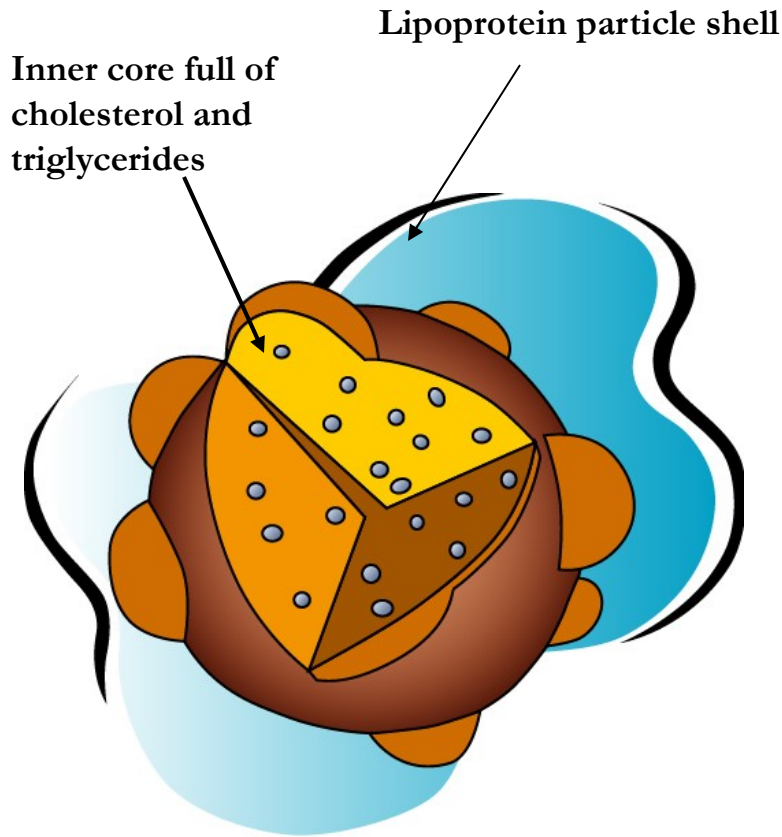
- Lipoprotein particles have two parts
  - Inner core region of cholesterol and triglyceride
  - An outer shell

- Particles in the blood that carry cholesterol
  - LDL
  - HDL
  - VLDL

The Cause of Heart Disease

Artery

Artery Wall

Lipoprotein
particles

Lipoprotein particles
invade the artery wall

- **Lipoprotein particles move into the artery wall**

- **These particles build up in a person's arteries**
  - **Heart Attacks**
  - **Stroke**
  - **Death**

- **An increased number of LDL particles (LDL-P) means an increased risk of heart disease**

Low-Density Lipoproteins:
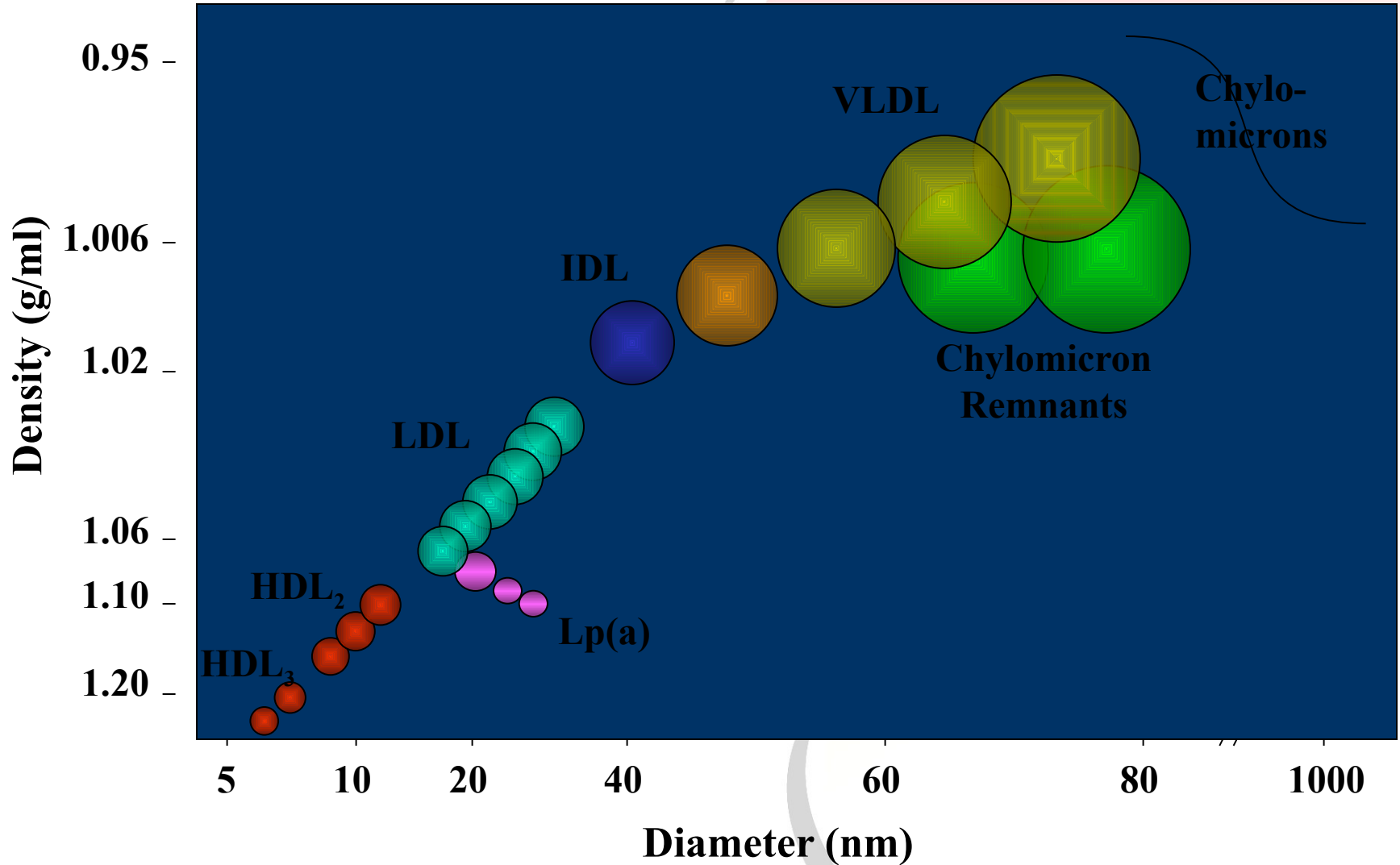## *The Causal Agents in Atherosclerosis*
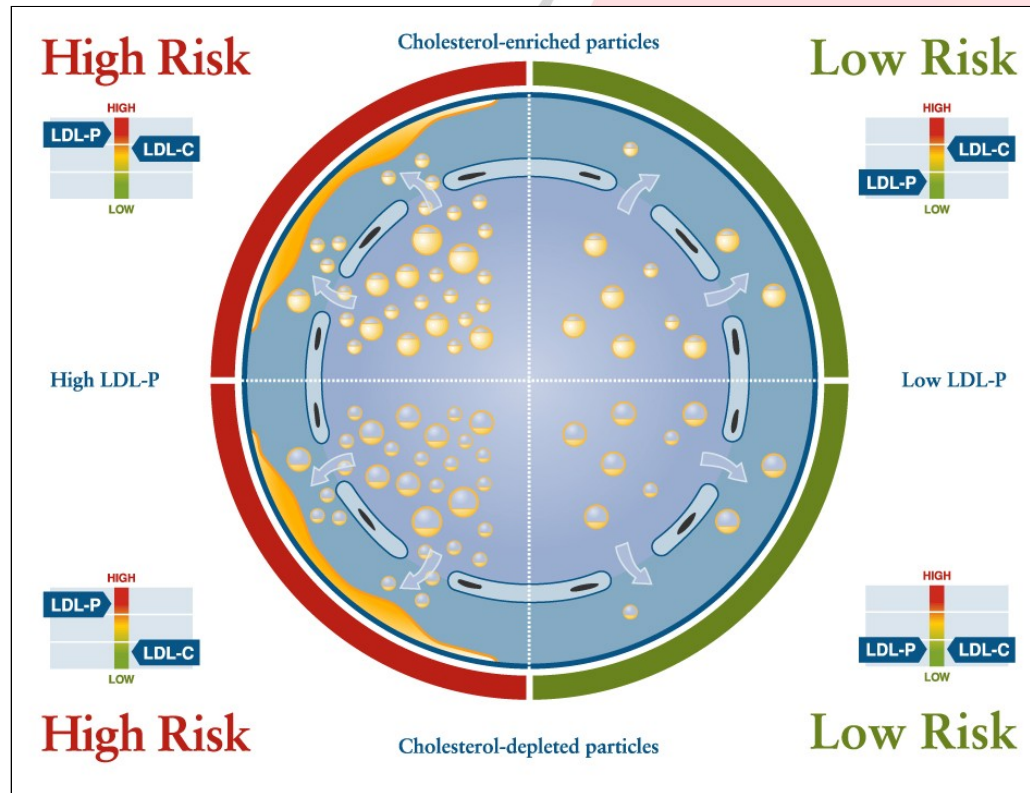

LDL Particles: The Process of Atherosclerosis

Penetration　　**Modification**　　**Plaque Formation**

Weissburg PL, Rudd JHF. In: Topol EJ, ed. *Textbook Cardiovasc Med* 2nd Ed 2002.
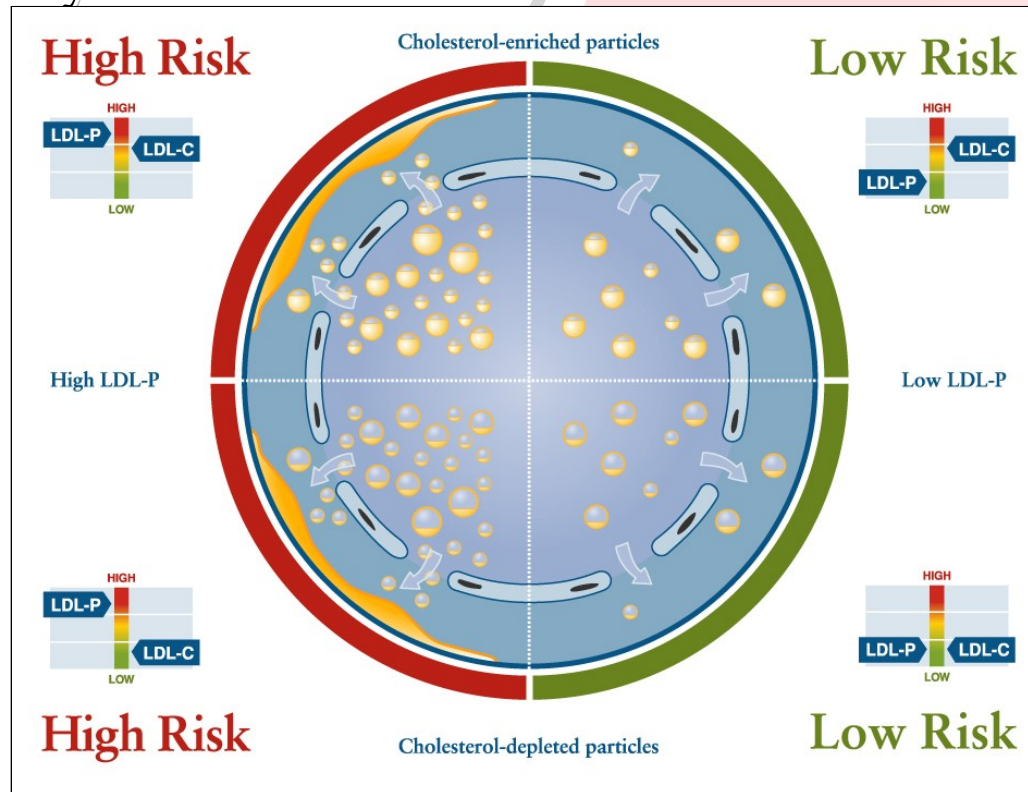
Lipoprotein Subclasses

LDL-C is Not a Reliable Predictor of LDL-P

Particles contain cholesterol, but LDL-C is not a reliable predictor of LDL-P due to the variability of particle size and cholesterol content.[6]

6 Otvos JD, Jayarajah E, Cromwell, WC. AJC 2002;90(8A):22i-29i
Original Artwork courtesy of LipoScience, Inc. Used with permission.

Increased Numbers of LDL Particles (LDL-P) are Significantly Associated with Increased CHD Risk

Only the *NMR LipoProfile* test provides both *traditional lipid values* and the number of atherogenic *lipoprotein particles* to better identify and manage everyone at risk for lipid-related CHD.

7 Cromwell et al. Curr Athero Reports 2004;6:381-387.
8 Kuller et al. Arterioscler Thromb Biol 2002, 22:1175-1180.
9 Mackey et al. Am J Cardiol 2002; 90(8A):71i-76i.

LDL Particle Number Has Been Repeatedly Shown to be Superior to LDL Cholesterol

Study	CHD Status	CHD Endpoint	NMR Particle Number Associations*
Cardiovascular Health Study Arterioscler Thromb Vasc Biol. 2002.	Primary Prevention	Incident MI or Angina	Increase in Total LDL-P Increase in Small LDL-P
Women's Health Study Circulation 2002.	Primary Prevention	Incident MI, CHD Death, Stroke	Increase in Total LDL-P Increase in Small LDL-P
Healthy Women's Study Am J Cardiol 2002.	Primary Prevention	EBCT Coronary Calcium Score	Increase in Total LDL-P Increase in Small LDL-P Increase in Large VLDL-P
Veterans Affairs HDL Intervention Trial (VA-HIT) Am Heart Assoc 2002. Circulation 2006.	Secondary Prevention	Nonfatal MI or CHD Death	Increase in Total LDL-P Decrease in Total HDL-P
Pravastatin Limitation of Atherosclerosis in Coronary Arteries (PLAC-I) Am J Cardiol 2002.	Secondary Prevention	Angiographic Minimal Lumen Diameter	Increase in Total LDL-P Increase in Small LDL-P Decrease in Large HDL-P
Framingham Offspring Study Am Heart Assoc 2004.	Secondary Prevention	Incident MI, Stroke, Claudication, Angina	Increase in Total LDL-P Increase in Small LDL-P

* Significant and independent in multivariate models adjusted for lipids

LDL and HDL Particle Numbers Predict Coronary Events in the Veterans Affairs HDL Intervention Trial (VA-HIT)
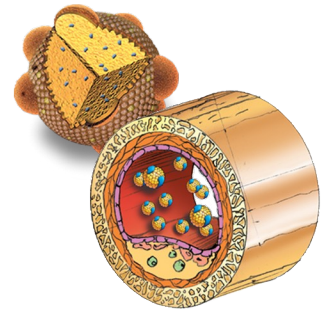
STUDY BACKGROUND:

The Original VA-HIT trial was conducted to determine if incresing low HDL-C would decrease CHD events. A group of 2,531 men with CHD, low HDL-C (31.5mg/dl) and low LDL-C(111mg/dl) was studied, with treatment of either the fibric acid, Gemfibrozil (1.2 g/d) or placebo.

Gemfibrozil treatment resulted in a 22% decrease in nonfatal MI + CHD death and 31% decrease in stoke. Gemfibrozil induced a 6 % increase in HDL-C, 31% decrease in triglycerides, and no change in LDL-C. Only HDL-C was a significant independent predictor of CHD events among on-trial lipid/apolipoprotein variables. However, changes in levels of HDL-C and other lipids could account for <25 % of the drug benefit.

OBJECTIVE:

Determine if some of the benefit of gemfibrozil is due to favorable changes in lipoprotein particle subclass levels or size distributions that are not reflected by conventional lipid or apolipoprotein measurements
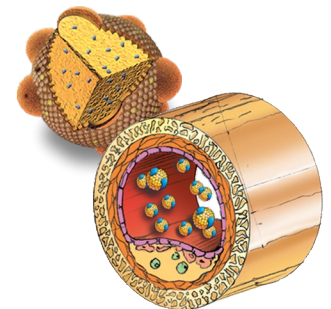
Conclusion:

In this nested case-control sub-study of VA-HIT, NMR measured HDL and LDL particle numbers were significant independent predictors of incident CHD events, whereas levels of HDL and LDL cholesterol (or apolipoproteins A-1 and B) were not……

LDP-P was 2-3 times more strongly related to CHD events than LDL-C
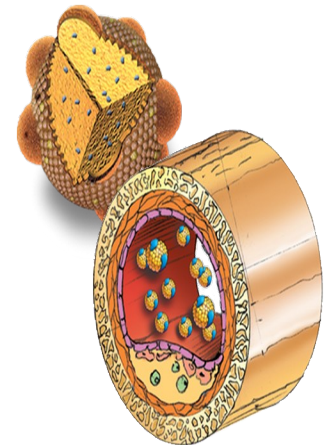
Heart Health and Diabetes

People with Diabetes are at increased risk for heart disease.

People with Diabetes are as likely to have a heart attack as someone who has already had one.

Two out of three people with diabetes die from a heart-related illness.

Key Terms to Understand

- **LDL– Low Density Lipoprotein. People with diabetes are likely to have small dense LDL particles, which means an increased risk of heart disease.**

- **LDL-C – A calculation of the amount of cholesterol carried by an unknown number of lipoprotein particles.**

- **LDL-P - A direct measurement of the number of lipoproteins that carry "bad" cholesterol to your arteries**

The more particles you have carrying cholesterol, the higher your risk.

LDL-C and LDL-P are both <u>very</u> <u>important</u> for patients with diabetes.

Patients with Diabetes Are at Increased Risk

- **Diabetic Dyslipidemia can lead to heart attack or stroke.**
  - Tend to have fewer HDL particles that tend to be small, to help clear cholesterol from the body
  - Tend to have an excessive amount of small, dense LDL particles which increases risk

- **Knowing how many lipoprotein particles is important - Cholesterol cannot tell you the whole story**

What Can You Do?
Talk to your Doctor About….

- Lifestyle changes
  - Diet and Exercise
  - Stop smoking
- Medications
  - Statins
  - Fibrates
  - Niacin
  - Cholesterol Absorption Inhibitors
- Additional Testing

# The Impact of Supplements on Lipid Levels: What really works

Red Yeast Rice

- **Active Ingredient is Monacolin K which is identical to Lovastatin…..inhibits HMG-CoA Reductase**

- **No-Longer Available Proprietary Chinese Red Yeast Rice (Cholestin) does lower TG and LDL cholesterol**

- **In US, Cholestin contains only Flavones from Citrus, Geraniol, and Fish Oil…no evidence it alters lipids**

Guggul (Guggulipid)

- Active ingredient in the resin of Commiphora Mukul tree in India/Pakistan

- Gum Resin has been used in traditional Indian Medicine for 2000 years

- All non-placebo controlled trials in Indian population and the only one US double-blind randomized trial

- High rate of Hypersensitivity rashes (9%) in US study

In US Study, Guggulipids did not lower LDL-C…in fact actually increased LDL-C in the majority of treated patients
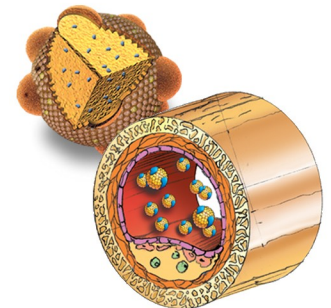
Policicosanol

- Isolated from Sugarcane Wax….Cuban Sugarcane is most widely available product in 40 countries
- Until recently, all studies conducted by single Cuban Research Group….shown to reduce LDL-C 24% using 5-40 mg dose
- In 2006, 3 groups (2 US and 1 German) published trials and found no effect on LDL-C at 10-80 mg/day
- Cannot be recommended for treatment of Hyperlipidemia

The NMR LipoProfile Test

- The only test that directly measures lipoprotein particles
- Your doctor can make treatment decisions based on your results and assess your response to medications

- The most important item to look at on the report is the LDL particle number
- Once you know the number of LDL particles, it is important to know their size, particularly if you have a relatively high number of these lipoprotein particles
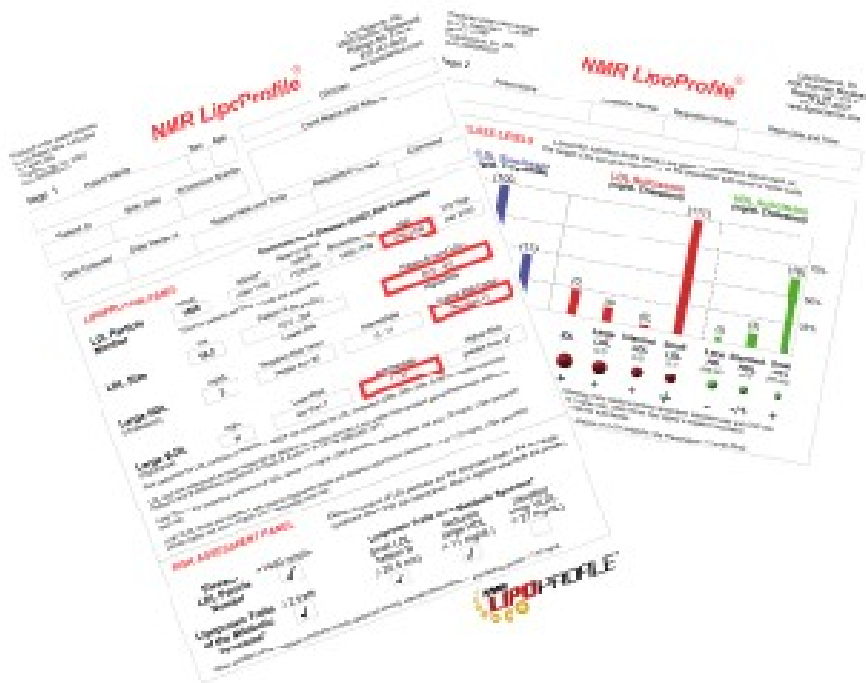
In Summary

- **Dyslipidemia affects one in two U.S. adults**
- **Lipoprotein particles are the vehicles that carry cholesterol, and are the cause of coronary heart disease**
- **Patients with diabetes tend to have small, dense lipoprotein particles – leading to increased risk of heart disease**
- **To manage your level of risk, monitor the number of LDL particles, particularly the small ones, along with your cholesterol**