Special Feature

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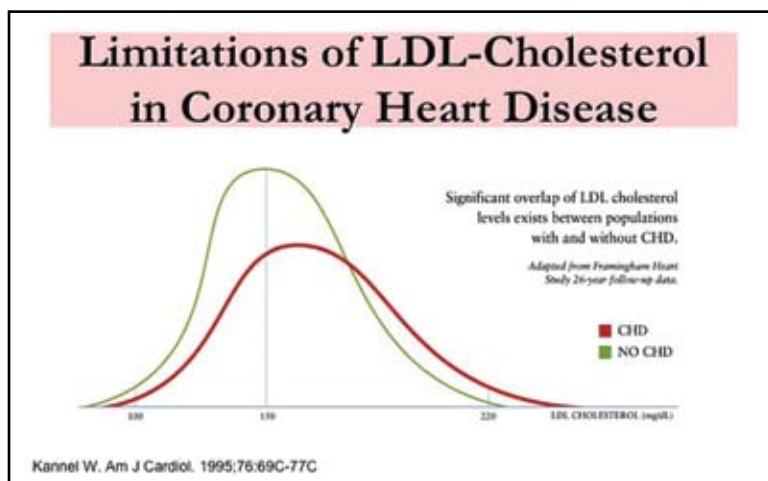*Los Angeles, CA*

Advanced Lipoprotein Testing

Hyperlipidemia (dyslipoproteinemia), smoking and hypertension, are the most easily modifiable risk factors leading to atherosclerosis and coronary artery disease (CAD). Prevention of CAD starts with identifying people at risk and providing individualized treatment directed at their specific problem. Traditional LDL concentration testing (LDL-C) may miss up to 50% of people who will have a coronary artery related event or even death.

It is with this background that I will discuss Advanced Lipoprotein Testing and its role in risk assessment and subsequent management of dyslipidemia. Any tool that would enable healthcare providers, other than those who practice lipidology, to more accurately identify those individuals that would be missed by traditional lipid testing might significantly improve the ability to impact cardiovascular morbidity and mortality.

Limitations of LDL-Cholesterol in Coronary Heart Disease

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

Kannel W. Am J Cardiol. 1995;76:69C-77C

Classically, healthcare providers were and are trained to use the lipid profile composed of Total Cholesterol (TC), HDL-C, LDL-C, and triglycerides to ascertain risk but the majority still use LDL-C as a target for treatment. Current data suggests that there are significant limitations with relying on traditional lipid concentration testing, such as LDL-C, especially in those with cardiometabolic risk (CMR). CMR risk factors are good indicators of one's overall risk of developing heart disease and Type 2 diabetes mellitus. CMR risk factors include obesity, hypertension, hyperglycemia, dyslipidemia, chronic inflammation, physical inactivity, smoking, and one's age, race, gender, and family history. Data from the

26-year follow-up in the Framingham Heart Study has demonstrated significant overlap of LDL-C concentrations in populations with and without CAD (Figure). Eighty percent of the patient population with myocardial infarctions had similar LDL-C levels as those who did not have a myocardial infarction. Recently, the American Diabetes Association and American College of Cardiology released a joint consensus statement on lipoprotein management in patients with CMR.[1] The statement advises that in such patients with moderately high, high, and very high risk, all pharmacological decisions should be guided by quantification of atherogenic lipoproteins, over 90% of which are LDL particles, using measured apolipoprotein B (apoB) or the equally informative, but with limitations, LDL-P (particle number measured via nuclear spectroscopy) to assess risk and serve as the goal of therapy.

All lipids, including sterols, are hydrophobic molecules. As such, they are trafficked within lipoproteins: chylomicrons, VLDL, IDL, LDL, and HDL particles. HDL particles, which are usually nonatherogenic, have as their main apolipoprotein two to four molecules of apoA-I. All of the remaining particles, which are potentially atherogenic when present in excess quantities, are enwrapped with a single molecule of ApoB. NCEP ATP-III recommends calculating the non-HDL cholesterol value as a lipid concentration surrogate of apoB when the TG are ≥ 200 mg/dL. Approximately 90% of all the circulating apoB particles are LDL particles (LDL-P) which have a half-life of 2–3 days. By simple diffusion, the apoB particles can move through the endothelium in the intima of the artery wall as long as their diameter does not exceed 70 nm. This excludes larger chylomicrons and VLDLs. The apoB lipoproteins, after being modified or oxidized are then internalized by macrophages creating foam cells which are the hallmark of atherosclerosis. Data from multiple trials demonstrate that particle concentration measurements (apoB and LDL-P) remained the most significant and independent predictor of hard cardiovascular endpoints compared to lipid concentration parameters including non-HDL-C. In a nutshell, it is the number of atherogenic apoB (LDL-P) particles and not how much cholesterol that is within the

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particles that matter most.

I tell all my patients that "it is the number of cars that cause a traffic jam on a highway not the number of people in the cars." For example, consider a person with moderate risk who has met NCEP ATP-III guidelines and has a LDL-C of 110mg/dL on a routine lipid panel. How do I know that there are not 110 cars with one person

> *I tell all my patients that "it is the number of cars that cause a traffic jam on a highway not the number of people in the cars."*

driving or two big buses with 55 people? The answer is that I do not know with any degree of certainty unless I quantitate particles using apoB or LDL-P. Traditional lipid concentration testing measures the number of passengers and lipoprotein testing measures the number of cars. Current data shows that it is particle number, not particle size or lipid concentration, which drives the lipoprotein particle into the arterial wall.

Although a comprehensive review of each of the methodologies to perform lipoprotein testing is beyond the scope of this paper, I will give a brief overview of

the different technologies: The Vertical Auto Profile (VAP) test by Atherotec is performed using Density Gradient Ultracentrifugation to separate the particles and then standard cholesterol assays are performed to measure particle cholesterol concentrations. LDL phenotypes are reported but the actual lipoprotein diameters are not. ApoB levels are not measured but calculated using an "in-house" formula, not yet published, based on non- HDL-C and particle size. Berkeley Heart Labs uses gradient gel electrophoresis to separate lipoproteins by sizes. Berkeley does provide apoB and ultra–ApoB (LDL ApoB) levels as quantification measures. HDL particle sizes are reported but apoA-I is not. NMR spectroscopy is performed by LipoScience Corporation. By subjecting plasma (which needs no alteration by any reagent) to magnetic waves, lipoproteins can be sized and enumerated. VLDL, IDL, LDL, and HDL sub-particle concentrations are reported.

Reference:

1. Brunzell J, Davidson M, Furberg C, et al. Lipoprotein Management in Patients With Cardiometabolic Risk: Consensus statement from the American Diabetes Association and the American College of Cardiology Foundation. *Diabetes Care.* 31: 811-822.

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loss and, in addition, have some beneficial long-term effects compared to the low fat diets. Their data also demonstrate that an increasing improvement in some biomarkers over 24 months such as HDL-C, CRP and adiponectin, and in diabetic subjects glucose and insulin levels, despite the gradual increase in weight after its nadir at about 6 months, suggests that a diet with a healthful composition has benefits beyond weight reduction. Finally, the fact that the calorie deficit achieved in all diet groups was similar suggests that a low carb, non-calorie restricted diet may be preferable for those who will not follow a calorie-restricted dietary regimen.

Reference:

1. Shai I, Schwarzfuchs D, Henkin Y, et al. Dietary Intervention Randomized Controlled Trial (DIRECT) Group. Weight loss with a low-carbohydrate, Mediterranean, or low-fat diet. *N Engl J Med.* 2008;17;359: 229-41.