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Correlation between Metabolic Syndrome and Cardiovascular Disease Risk: A Longstanding Question

What happens when one does a 15-year retrospective study on individuals with normal fasting glucose? In 2008, a group of Italian researchers published the results of such a study in *Atherosclerosis*. Subjects (687 of them, between the ages of 35 and 75 years) were followed for 15 years. The researchers registered all cardio and cerebro-vascular events and mortality. Primary endpoint was the incidence of cardiovascular (CV) events, including new cases of angina, acute myocardial infarction, and stroke (fatal or non-fatal). Secondary endpoints were total and cardiovascular mortality. The individual incidences of myocardial infarction, stroke, and angina pectoris, were also considered as components of the composite primary endpoint. The findings of this study indicate that metabolic syndrome is predictive of CV events regardless of the presence of impaired fasting glucose (IFG) or diabetes mellitus. REF #1

A Variety of Perspectives on Biomarkers

Controversy exists about the best method for identifying those with increased risk for coronary heart disease. Dr. Maria Luz Fernandez, from the Department of Nutritional Sciences at the University of Connecticut, has written recently about the LDL to HDL cholesterol ratio as a valuable tool to evaluate coronary heart disease risk. While there is a growing consensus that levels of apolipoprotein (apo) B and the ratio of apo B/apo A-I are more accurate predictors of cardiovascular disease risk, the question has been raised as to whether it is realistic to expect patients and health professionals to switch from cholesterol-based guidelines to apolipoprotein-based guidelines, and Dr. Fernandez suggests that because it will take time before apolipoprotein terminology is recognized by the general public, it may be more efficacious to continue adhering to the already familiar and proven measurements of the LDL-C/HDL-C ratio. REF #2

From his own experience, Dr. Bland describes a study involving biomarker measurement performed by his own research group and published in 2008. He also discusses a very recent article by Dr. Jay Heinecke, of the University of Washington, and his associate, Dr. Baohai Shao. In this article titled “HDL, Lipid Peroxidation, and Atherosclerosis,” which was published in the *Journal of Lipid Research*, the authors state, “Paradoxically, native LDL fails to exert potentially atherogenic effects in vitro, suggesting that it must be modified to promote vascular disease. Indeed, many lines of evidence support the LDL oxidation hypothesis, which suggests that oxidative damage to LDL is one important mechanism for rendering lipoproteins atherogenic.” REF #3-4

The Dallas Heart Study is a population-based, probability sample of 6101 subjects in Dallas County that was designed to study early stages of cardiovascular disease. Researchers from the University of Texas Southwestern Medical Center in Dallas

recently published an article in *Clinical Chemistry* that aimed to characterize the association of lipoprotein-associated phospholipase A2 (Lp-PLA2) with coronary and aortic atherosclerosis. Lp-LPA2 mass and activity were measured in 2171 subjects 30-65 years old who were participants in the Dallas Heart Study. The association of Lp-PLA2 levels with 3 atherosclerosis phenotypes was examined: coronary artery calcium (CAC) measured by electron-beam computed tomography, and abdominal aortic plaque (AAP) and aortic wall thickness (AWT) measured by magnetic resonance imaging. The findings of this study suggest that if Lp-PLA2 independently influences clinical events, it does so by promoting atherosclerotic plaque instability rather than by stimulating atherogenesis. REF #5

The role of low high-density lipoprotein cholesterol (HDL-C) in coronary heart disease (CHD) development has been widely accepted, but the role of hypertriglyceridemia remains controversial. Recent analyses demonstrate that hypertriglyceridemia is an independent predictor of CHD and may be a stronger risk factor among women than among men. A study published in 2009 in the *American Heart Journal* examined the prognostic utility of the triglyceride/high-density lipoprotein (TG/HDL-C) ratio, a marker for insulin resistance and small dense low-density lipoprotein particles. The study participants included 544 women without prior myocardial infarction or coronary revascularization who were referred for clinically indicated coronary angiography and enrolled in the Women's Ischemia Syndrome Evaluation (WISE). Data from this study suggest that among women with suspected ischemia, the TG/HDL-C ratio is a powerful independent predictor of all-cause mortality and cardiovascular events. REF #6

The Omega-3 Index: A New (and Cholesterol-Independent) Biomarker for CHD?
Dr. Bland discusses the research of Dr. William S. Harris, of the Mid America Heart Institute of Saint Luke's Hospital at the University of Missouri-KC School of Medicine. Dr. Harris and his associates conducted clinical and laboratory experiments to generate data necessary for the validation of the Omega-3 Index as a CHD risk factor. The results of these experiments suggested that the Omega-3 Index was inversely associated with risk for CHD mortality. Dr. Harris and his colleagues concluded that the Omega-3 Index may represent a novel, physiologically relevant, easily modified, independent, and graded risk factor for death from CHD that could have significant clinical utility. REF #7

Establishing Criteria for Diagnosing Metabolic Syndrome: Confusion, Controversy, and Endless Debates
The metabolic syndrome is a constellation of interrelated metabolic risk factors that appear to directly promote the development of diabetes and cardiovascular disease. Controversy—possibly stemming from confusion between the syndrome and obesity—exists about the definition of the metabolic syndrome and whether or not it meets the criteria of a syndrome. The purpose of establishing criteria for diagnosing metabolic syndrome is to find individuals who are at increased risk of diabetes and cardiovascular diseases and who require specific therapy, including diet and exercise. Japanese researcher, Dr. Eiji Oda, published a review paper in *Hypertension Research* in 2007 that discusses the metabolic syndrome as a concept of adipose tissue disease. Dr. Oda states that the syndrome may be an adipose tissue disease different from obesity, and in that

case, it would be characterized by inflammation clinically detected through systemic inflammatory markers such as high-sensitivity C-reactive protein and insulin resistance reflecting histological changes in adipose tissue. REF #8

Clinician/Researcher of the Month

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Ralph LaForge is a physiologist and board-certified lipid specialist. He is the Managing Director of the Duke Lipid Disorder Physician Education Program at Duke University Medical Center. He is faculty for the National Lipid Association Lipid Clinic Training Program, and he has written over 300 papers on the topic of therapeutic lifestyle changes and CVD prevention.

Mr. La Forge is an expert in the area of therapeutic lifestyle management. Dr. Bland and Mr. La Forge discuss his experience and publications, but also get into areas such clinical trials on statin drugs and controversies surrounding data interpretation. Mr. La Forge provides a review of the current biomarkers for coronary heart disease, and his thoughts about future directions. REF #9-12

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