Déjà Vu All Over Again

Running title: Ockene; Déjà vu all over again

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Current guidelines recommend the use of standard lipid measures, including the total/high-density lipoprotein cholesterol ratio, inexpensive and readily available, for routine cardiovascular disease risk assessment. Other studies and consensus panels, however, have suggested that the number of circulating atherogenic particles (and apo-B as a surrogate) provide better risk prediction than standard lipid measures. Tests such as the Vertical Auto Profile (VAP) (Atherotech, Birmingham, Alabama) which determines the cholesterol content of VLDL, LDL, and HDL subclasses, and patterns of LDL size; and nuclear magnetic resonance (NMR) spectroscopy, which determines the sizes and concentrations of lipoprotein particles, have been described as improving the predictive power of lipid measurements. At times there has been intense debate in the literature over the relative merits of these tests vs. the standard lipid profile. The clinical popularity of lipid subfractionation and particle number and size measurements varies widely, but it is not uncommon to have patients specifically ask for these tests, and multiple websites suggest that if your physician is not knowledgeable about such studies he or she is simply not to be thought of as keeping up with the times.

The data however do not consistently support the additional value of these studies when added to standard lipid profile measurement. Ingelsson and colleagues utilized data from the Framingham Heart Study to assess the incremental utility of apolipoproteins over traditional lipids for CHD prediction. They followed 3322 middle-aged participants, (53% women), for a median of 15 years. The primary outcome measure was incidence of first CHD event, including myocardial infarction, angina pectoris, coronary insufficiency, or coronary heart disease death. In both men and women, models using the apo B:apo A\textsubscript{1} ratio demonstrated performance characteristics comparable with but not better than that for other lipid ratios. The apo B:apo A\textsubscript{1}
ratio did not improve prediction of CHD risk in a model containing all components of the Framingham risk score including total cholesterol:HDL-C.  

The added value of NMR spectroscopic measurement of lipoprotein particle number and size was studied by Mora and colleagues in 27,673 initially healthy women in the Women’s Health Study followed up for incident cardiovascular disease over an 11-year period. Hazard ratios for NMR-measured lipoprotein particle concentration were comparable but not superior to standard lipids. Essentially no reclassification improvement was found with the addition of LDL particle concentration or apolipoprotein B100 to a model that already included the total/HDL cholesterol ratio and nonlipid risk factors. Even though LDL NMR particle concentration performed well for CVD risk prediction and was similar in risk to apolipoprotein B100, neither measurement was better than the total/HDL cholesterol ratio that is readily obtained from a standard lipid panel.

The paper by Parish and colleagues in this issue of Circulation adds importantly to this debate. In contrast to the observational studies described above, the authors utilize data from the MRC/BHF Heart Protection Study (HPS), a blinded, randomized trial of statin and antioxidant therapy in over 20,000 high-risk men and women with an average 5.3 year follow-up, during which time more than 5000 vascular events occurred, permitting separate evaluations of associations of lipoprotein subclasses with coronary and other cardiac events, ischemic strokes and revascularization procedures. The predictive power of standard cholesterol fractions was compared with measurements of apolipoproteins B and A1 and lipoprotein particles assessed by nuclear magnetic resonance, as well as subclass levels. The various measures were all strongly correlated and had similar predictive value for major vascular events, and LDL subclasses provided little additional information. Likewise, the particle distribution measures did not add
The totality of the evidence from these and other studies does not support measurement of apolipoproteins and particle subclasses as adding meaningfully to our ability to predict risk of atherosclerotic disease. But perhaps more importantly, we need to recognize that our hunt for progressively finer discriminatory tools for risk assessment is a misplaced effort. The underlying assumption is that we have difficulty recognizing who is at risk. This is not the case. We know how to recognize those at risk for atherosclerotic disease. It used to be said that many myocardial infarctions occur in people without abnormalities of traditional risk factors. This is a myth. Pooling data from the Chicago Heart Association Detection Project in Industry, the Framingham Heart Study, and the Multiple Risk Factor Intervention Trial demonstrated that for fatal CHD (a total of 20,995 deaths), exposure to at least 1 clinically elevated major risk factor ranged from 87% to 100%. Risk factors were here defined as a total cholesterol of at least 240 mg/dL, systolic blood pressure of at least 140 mm Hg, diastolic blood pressure of at least 90 mm Hg, cigarette smoking, and clinical diabetes, an analysis that did not even utilize LDL, HDL, or TC/HDL ratio. Our greatest problem is delivering appropriate risk factor modification to those where the risk is obvious; it is useful to seek better discrimination of risk in those at the margins, but it is not where our greatest effort should be focused.

In 1965 Fredrickson and Lees described “A System for Phenotyping Hyperlipoproteinemia”, in which they replaced ultracentrifugation with the much more accessible electrophoretic analysis, and described a taxonomy for the classification of hyperlipidemia. They noted that each of the described types tended to respond better to specifically targeted therapeutic approaches. Ten years later, however, Fredrickson published another paper in this journal now entitled "It’s Time to Be Practical".
decade, Fredrickson noted that a technique that worked well for categorizing familial hyperlipidemias did not separate individuals nearly as well when extended to larger populations containing a high proportion of more moderate abnormalities. Two of his conclusions are as appropriate today as they were 37 years ago:

- “…the majority of patients with hyperlipidemia can be detected, sorted and managed by lipid analyses alone.”
- “…the conversion of lipid concentrations to patterns of hyperlipoproteinemia offers the clearest view of physiological mechanisms and metabolic derangements alike. Nevertheless, there are practical limits to obtaining this illumination….”

The analysis of lipid subfractions and NMR lipid particle analysis is important in improving our understanding of lipid physiology. But as was the case with the Fredrickson classification, it is time to be practical. The present study adds to a body of evidence demonstrating that it is not necessary to go beyond standard lipid analyses in defining their contribution to cardiovascular risk. Additional studies add cost and do not add to clinical utility.

The "Choosing Wisely" campaign has emphasized the importance of controlling health care costs by avoiding additional screening tests that have not been shown to be useful for improving health. As an example, the cost to my institution for a standard 3-component lipid profile with LDL calculation is $5.79. Adding a direct LDL (automatically done when triglycerides are >350 mg/dl) brings the cost to $7.72. A lipoprotein subfractionation by ultracentrifugation costs $58.38, and NMR particle number and size determination adds an additional $72.96.

A physician can, in quite a short interval of time, easily categorize a patient's risk. That component of risk related to lipids is also easily assessed with inexpensive and well-standardized
measurements. Our greatest effort must be directed towards the overall reduction of cardiovascular risk: behavior change with regard to smoking, obesity, unhealthy diet, inadequate physical activity, and psychosocial factors such as stress and depression; greater attention to the health of our children and the facilitation of healthy behavior throughout the life course; prescription of appropriate medication for hyperlipidemia and hypertension with attendant emphasis on medication adherence; and systematic public health and societal strategies that support beneficial change. The tools we have available to define cardiovascular risk are quite adequate to the task; we now need to improve their utilization so as to further reduce the population burden of cardiovascular disease.

**Conflict of Interest Disclosures:** None

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