

Beyond Routine Cholesterol Testing: The Role of LDL Particle Size Assessment

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Cholesterol testing is an integral part of the global risk assessment promoted by the National Cholesterol Education Program (NCEP) ATP-3 guideline for clinicians. For the majority of patients, such routine cholesterol testing and risk assessment will provide a fairly unequivocal determination of those needing pharmacological treatment. However, for borderline cases, clinicians have looked to a variety of new tests to further stratify risk. One such new test is LDL particle size. The rationale for the use of this test and suggestions for how clinical management may be altered are reviewed below.

The NCEP ATP-3 identifies LDL as the primary target of treatment not only because it has been shown to be predictive of clinical events and angiographic disease progression but also because of ease of measurement and low cost. The LDL value reported to clinicians is the summed contribution

in mg of LDL particles in a deciliter of plasma. LDL particles are, however, heterogeneous in size, density, and composition. A growing body of evidence suggests that LDL particles that are small and

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dense are more atherogenic than those which are large and “fluffy.”¹ Thus, two patients with the same LDL measurement in mg/dl may have differing levels of cardiovascular risk depending on the relative proportions of small, dense and large, fluffy particles.

An increase in the proportion of small, dense LDL may increase risk for any given level of LDL. This increased risk may be due in part to increased deposition in the sub-endothelial space where plaque forms. It may be due also to increased uptake by macrophages and increased susceptibility to oxidation, both early steps in atherogenesis. It may be due in part to decreased clearance because of reduced affinity

for the LDL receptor².

Observational and epidemiological studies suggest those having a predominance of small, dense particles may have an increase in risk up to 300 percent greater than those having a predominance of large and fluffy LDL particles. This observed increase in risk forms the basis of the rationale in using particle size as an adjunct to the standard proven means of risk assessment.

Small, dense LDL may be measured directly by various means. Berkeley HeartLab, Inc. (www.bhinc.com) offers an LDL gradient gel electrophoresis; LipoScience, Inc. (www.lipoprofile.com) offers a nuclear magnetic resonance (NMR) method; and Athertec, Inc. (www.thevaptest.com) has their vertical auto profile

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(VAP) test. All measure small, dense LDL and thus may identify patients as belonging to LDL subclass “phenotype B.” Phenotype B is terminology used to describe the LDL pattern in which small,

dense LDL predominate. It is seen more commonly in diabetic patients and those with established coronary artery disease (CAD).

Small, dense LDL may also be identified in some situations by routine cholesterol testing. Small, dense LDL particles are found in association with high triglycerides (TG) and low HDL. When TG, in a 12-hour fasting specimen, are increased in the serum, it is usually a result of increased VLDL (very low density lipoprotein). Under these conditions, TG are transferred from VLDL to LDL in exchange for cholesterol ester by CETP (cholesterol ester transfer protein). These TG enriched, cholesterol ester depleted LDL particles are then acted upon by hepatic lipase which cleaves out the TG leaving cholesterol ester depleted LDL particles. The depleted LDL particles are physically smaller and because of the resultant relative increase in protein also denser. The association of TG with small, dense LDL suggests a possible means of establishing the presence of predominant small, dense LDL by use of TG measurement. Indeed,

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such an association exists and proves helpful in determining those for whom the test may best be applied.

Austin has shown that those with TG above 140 have small, dense LDL and may be classified as LDL phenotype B on the basis of TG alone³. Consequently, a separate test of LDL particle size to identify individuals at increased risk from small, dense LDL would be generally unnecessary for these individuals. TG may also be used to track response to treatment because the approaches which lower TG also convert small, dense LDL to large, fluffy, less atherogenic LDL. Thus, weight loss, exercise, niacin, and fibrates which, independently, have been shown to reduce TG, also convert small, dense LDL to larger, fluffy LDL.

Individuals with TG below 70 do not have small, dense LDL. It would not be necessary to measure LDL particle size in these individuals. For individuals with TG between 70 and 140, TG cannot be used to predict those with small, dense LDL and a test of LDL particle size may be useful.

As a class, statin drugs do not change particle size appreciably. Thus, once patients achieve their NCEP LDL targets on statin treatment, if they also need pharmacological treatment of TG to achieve NCEP TG target (<150), then a test of LDL particle size would not be needed. If the TG were between 70 and 140 and the individual was a CAD risk equivalent, or had established CAD and, more so, if he or she had progressing CAD, consideration may be given to

measuring LDL particle size before the addition of niacin or fibric acid derivatives. The higher risk of combination therapy may suggest documenting the need for a second agent, especially if the lipid profile was already normalized by NCEP guideline criteria.

In summary, the measurement of LDL particle size may be of benefit for cardiovascular risk stratification as an adjunct to routine cholesterol testing and global risk assessment for selected populations. Identification of small, dense LDL may alter pharmacological management. TG may be used to identify the majority of individuals with small, dense LDL. Individuals with TG between 70 and 140 may require a direct measurement of particle size to establish the presence of small, dense LDL.

Please see CDPHP resource coordination policy “LDL Particle Size 1370/20.000404” for coverage guidelines for particle size testing.

1. Gardner CD, Fortmann SP, Krauss RM. Small low density lipoprotein particles are associated with the incidence of coronary artery disease in men and women. *JAMA* 1996; 276:875-881.
2. Lamarche F, Tchernof A, Moorjani S, et al. Small, dense low-density lipoprotein particles as a predictor of the risk of ischemic heart disease in men. *Circulation*. 1997;95:69-75.
3. Austin MA, King MC, Vranizan KM, Krauss RM. Atherogenic lipoprotein phenotype. A proposed genetic marker for coronary heart disease risk. *Circulation*. 1990;82:495-506.

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