

## NON-HDL CHOLESTEROL: MEASUREMENT, INTERPRETATION, AND SIGNIFICANCE\*

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### ABSTRACT

The reduction of cardiovascular risk by lowering low-density lipoprotein cholesterol (LDL-C) levels is well documented, and LDL-C remains the main target of lipid-lowering therapy. However, not all patients with coronary heart disease have elevated LDL-C levels. There is growing recognition that non-high-density lipoprotein cholesterol (HDL-C) also strongly relates to cardiovascular risk. Non-HDL-C can be calculated by subtracting HDL-C from total cholesterol, and encompasses all cholesterol present in potentially atherogenic lipoprotein particles (very low density-lipoproteins, remnants, intermediate-density lipoproteins, LDL, and lipoprotein[a]). Non-HDL-C may be a particularly important measure in certain populations, such as patients with diabetes, in whom dyslipidemia is characterized by low HDL-C levels and elevated triglycerides. Non-HDL-C has been shown to correlate with coronary artery disease severity and progression as well as predict cardiovascular morbidity and mortality.

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Many people who develop coronary heart disease have low-density lipoprotein cholesterol (LDL-C) levels that are normal or only mildly elevated, but have low high-density lipoprotein cholesterol (HDL-C) levels and/or high triglycerides (TG). Focusing exclusively on LDL-C as an indicator of risk in these individuals may not accurately detect many high-risk patients. Whereas LDL-C remains the main target of lipid-lowering therapy, non-HDL-C has been designated a secondary target of therapy among individuals with hypertriglyceridemia by the National Cholesterol Education Program's (NCEP) Expert Panel.<sup>1,2</sup> In the following paragraphs, we will define non-HDL-C and review its relationship to coronary atherosclerosis and coronary events.

### INTERPRETING THE LIPID PROFILE

A standard lipid profile consists of total cholesterol (TC), HDL-C, and TGs. The laboratory also generally reports a value for LDL-C that may have been calculated by the Friedewald formula or directly measured.

Lipid data are more difficult to interpret than standard chemistries for several reasons. First, cholesterol and TGs are not in solution like electrolytes and other chemistries. Rather, cholesterol and TGs are transported in a variety of lipoprotein particles containing cholesterol and TGs, but in very different proportions. Although HDL/HDL-C and LDL/LDL-C are frequently used interchangeably, it is very important to make a distinction between the cholesterol content of any given particle and the particle itself.

The spectrum of lipoprotein particles in circulation is very large. These differ by density and size, ranging from small HDL particles to very large chylomicron particles. Each particle has a hydrophobic core composed of TGs and cholesterol ester and a hydrophilic surface containing phospholipids, cholesterol, and,

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most importantly, the apolipoprotein(s) which determine(s) the metabolic fate of the particle. The relative proportion of cholesterol and TG vary significantly by particle. For example, chylomicron particles and very low-density lipoprotein (VLDL) particles have a small proportion of cholesterol and a high percentage of TGs, whereas LDL particles have a large percentage of cholesterol and small percentage of TGs. The clinician has the difficult task to infer lipoprotein particle physiology and pathophysiology from concentrations of cholesterol and TGs reported by the clinical laboratory.

### LOOKING BEYOND STANDARD LDL-C MEASURES

The vast majority of laboratories calculate LDL-C using the Friedewald equation:  $TC - HDL-C - TG/5 = LDL-C$ . The component of the equation, "TGs divided by 5," actually represents an approximation of the cholesterol content of VLDL particles—one that is correct only when the proband is fasting, the TG value is less than 400 mg/dL, and the particle composition is normal. It is important to remember that the Friedewald calculation includes lipoprotein(a) and also intermediate-density lipoprotein cholesterol (IDL-C) in the LDL-C fraction.

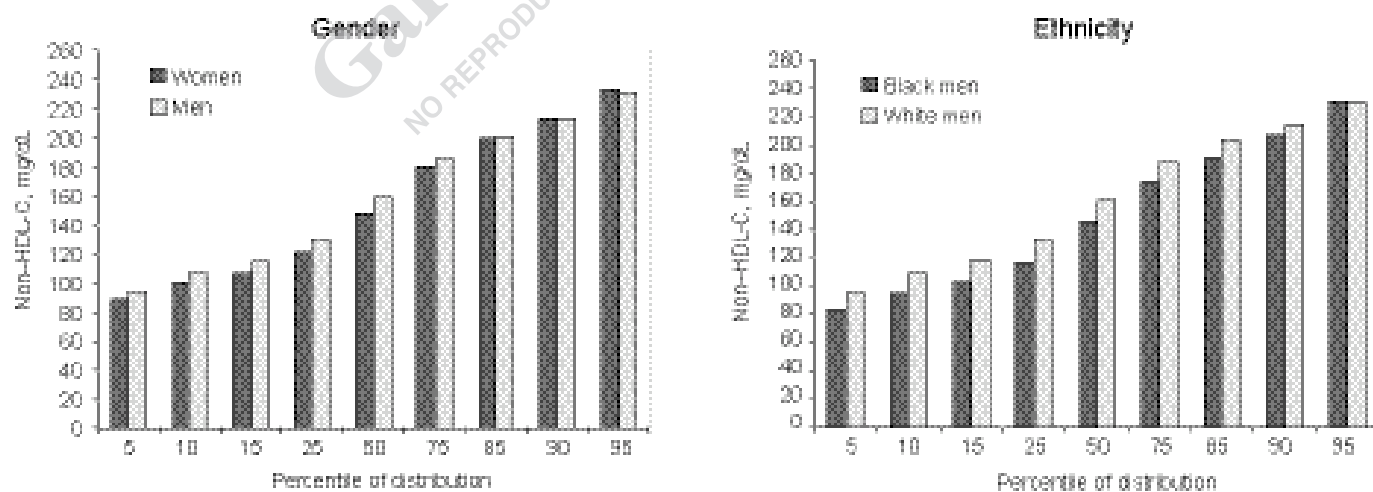
It is now clear that LDL is not the only potentially atherogenic lipoprotein, but that other apoprotein

B—containing particles, such as VLDL, VLDL remnants, chylomicron remnants, and IDL—are also potentially atherogenic. Thus, a better summary measure of the overall atherogenicity of a patient's serum is needed. Apoprotein B is such a measure, but is not widely available in commercial laboratories.

A measure that can be easily calculated by clinicians in any location is non-HDL-C. This value is calculated by subtracting HDL-C from TC, both of which are measured directly. The non-HDL-C calculation does not assume normal lipoprotein composition, does not require a fasting specimen, and reflects the sum of serum cholesterol carried by all of the potentially atherogenic lipoproteins—LDL, VLDL, IDL, and remnant lipoproteins.

Investigators from the Third National Health and Nutrition Examination Survey have published national reference values for non-HDL-C (Figure). Gardner et al determined serum levels of non-HDL-C and sociodemographic characteristics for 3618 black, 3528 Mexican American, and 6043 white women and men, aged older than 25 years.<sup>3</sup> Non-HDL-C concentrations were higher in men than in women in the younger age categories, a finding likely explained by the fact that women are known to have higher HDL-C than men. In the 55- to 64-year-old age category, however, non-HDL-C levels began to rise in women, a change likely related to hor-

Figure. Non-HDL-C Distribution



HDL-C = high-density lipoprotein cholesterol.

Data from Gardner et al.<sup>3</sup>

monal changes at the time of menopause. The study also found that non-HDL-C concentrations were highest among people aged 55 to 64 years, and higher among Mexican American and white women and men than black women and men. Lower education levels were associated with higher non-HDL-C concentrations.<sup>3</sup>

### NON-HDL-C CONCENTRATION AND CARDIOVASCULAR RISK

Mounting evidence suggests that a relationship exists between non-HDL-C and atherosclerosis, even in very young individuals. An autopsy investigation of young people who died from noncardiovascular causes showed that non-HDL-C was associated with the presence of fatty streaks and raised lesions in the coronary arteries. The study showed a very strong graded relationship between the extent of atherosclerosis and the level of HDL-C and non-HDL-C.<sup>4</sup>

A relationship between coronary artery disease progression and non-HDL-C was demonstrated more than 15 years ago in a multivariate logistic regression analysis of data from the Cholesterol Lowering Atherosclerosis Study, a randomized, placebo-controlled trial of colestipol plus niacin therapy in men with previous coronary bypass surgery.<sup>5</sup> In this multivariate analysis, non-HDL-C appeared to be the best predictor of overall change in extent of coronary disease among men who were not using cholesterol-lowering medications.

The Lipid Research Clinics Follow-up Study sought to determine whether non-HDL-C was predictive of cardiovascular disease (CVD) mortality in patients aged 40 to 64 years who were free of CVD at baseline.<sup>6</sup> In men, the predictive value of LDL-C and non-HDL-C was similar whereas non-HDL-C appeared to be a stronger predictor among women.

This author investigated the role of non-HDL-C in a secondary prevention population of subjects in the Bypass/Angioplasty Revascularization Investigation, a randomized trial of percutaneous transluminal coronary angioplasty versus coronary artery bypass graft in individuals with multivessel coronary artery disease. Whereas previous studies demonstrated the predictive value of non-HDL-C in individuals free of CVD, this study sought to validate the use of non-HDL-C as a predictor of outcome

among patients with established coronary disease. At 5 years, non-HDL-C was an important independent predictor of nonfatal myocardial infarction and angina, even following adjustments for demographics and many clinical characteristics known to influence outcomes in this patient population. Neither HDL-C nor LDL-C were predictive of outcome. TG values were predictive of nonfatal myocardial infarction but not angina pectoris.

### NON-HDL-C AND DIABETES

Cardiovascular disease is currently the primary cause of morbidity and mortality in patients with diabetes. Heart disease and stroke account for approximately 65% of deaths in people with diabetes. Adults with diabetes have heart disease death rates approximately 2 to 4 times higher than adults without diabetes.<sup>7</sup> Given these facts, it is particularly important to accurately identify and address CVD risk in this population.

There is increasing evidence that non-HDL-C may be a more powerful predictor of coronary heart disease mortality and nonfatal coronary events than LDL-C in people with diabetes. The Strong Heart Study<sup>8</sup> was a population-based study of CVD and its risk factors in American Indians, who are at increased risk of diabetes. Those who have diabetes also have a greatly increased risk of CVD.<sup>9</sup> Using data collected during this prospective study, Lu et al evaluated the ability of non-HDL-C and individual lipoprotein indicators to predict CVD in 2108 study subjects diagnosed with diabetes.<sup>10</sup> Univariate comparisons of base-

**Table LDL-C and Non-HDL-C Treatment Targets**

	LDL-C, mg/dL	Non-HDL-C, mg/dL
High risk (20%)	<100	<130
<i>optional for very high risk</i>	(optional: <70)	(optional: <100)
Moderate risk (2 risk factors, <20%)	<130	<160
<i>optional for moderately high risk</i>	(optional: <100)	(optional: <130)
Low risk (0–1 risk factor)	<160	<190

HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol. Data from Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report<sup>1</sup> and Grundy et al.<sup>2</sup>

line CVD risk factors revealed that study subjects reported to have increasing non-HDL-C concentrations had significant, curvilinear relationships with CVD and chronic heart disease risk ( $P < .001$ ). Although the confidence intervals (CI) were overlapping, hazard ratios (HR) for non-HDL-C were higher than those for either LDL-C or TGs for prediction of cardiovascular outcomes in men and women, with an HR of 2.23 (95% CI, 1.41–3.43) in men and an HR of 1.80 (95% CI, 1.32–2.46) in women. In women, non-HDL-C was an even stronger predictor than the TC:HDL-C ratio.

## CONCLUSIONS

Taken together, these studies provide convincing evidence that non-HDL-C is a strong predictor of cardiovascular risk in a variety of populations: individuals of all ages, women and men, persons with and without diabetes, and in individuals with and without documented CVD. Moreover, non-HDL-C predicts atherosclerosis progression over as little as 2 years of follow-up, as well as cardiovascular events and mortality over the long term. A direct comparison of the prognostic value of LDL-C and non-HDL-C is difficult when LDL-C is calculated rather than directly measured, because LDL-C values cannot be calculated in precisely those individuals who have greater concentrations of potentially atherogenic TG-rich lipoproteins. Thus, direct comparisons between LDL-C and non-HDL-C may actually under-represent the value of the non-HDL-C measure.

The NCEP Adult Treatment Panel III established LDL-C as the primary target of therapy. Non-HDL-C is a secondary treatment target in individuals who have TGs of at least 200 mg/dL. Guideline cut-points for non-HDL-C, shown in the Table, are set at 30 mg/dL higher than for LDL-C for every risk category.

Given the mounting evidence that non-HDL-C is a strong predictor of cardiovascular risk and patient outcomes, laboratories should be encouraged to routinely report this value as part of every lipid profile,

and clinicians should routinely consider this laboratory value as part of their comprehensive approach to preventing or delaying CVD in their patients with hypertriglyceridemia.

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