Review

The LDL to HDL Cholesterol Ratio as a Valuable Tool to Evaluate Coronary Heart Disease Risk

Maria Luz Fernandez, PhD, and Densie Webb, PhD, RD

Department of Nutritional Sciences, University of Connecticut, Storrs, Connecticut (M.L.F.), Health and Nutrition Communications, Austin, Texas (D.W.)

Key words: LDL cholesterol, HDL cholesterol LDL-C/HDL-C ratio, cardiovascular disease risk, apolipoprotein B, apolipoprotein A-I

The current National Cholesterol Education Program Adult Treatment Panel III guidelines recommend specific target levels of LDL cholesterol (LDL-C) and HDL cholesterol (HDL-C) for determining cardiovascular disease (CVD) risk and evaluating the effectiveness of lipid-lowering therapies. 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 CVD 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. Because it will take time before apolipoprotein terminology is recognized by the general public and recommended by the NCEP Adult Treatment panel to evaluate risk, it may be more efficacious to continue adhering to the already familiar and proven measurements of the LDL-C/HDL-C ratio. The following review provides evidence that the LDL-C/HDL-C ratio continues to be a valuable and standard tool to evaluate CVD risk in all populations.

Key teaching points:

- The NCEP recommends target levels for both LDL cholesterol and HDL cholesterol to assess risk for heart disease
- The LDL-C/HDL-C ratio provides key information regarding coronary heart disease risk
- Several epidemiological and clinical studies have found that the LDL-C/HDL-C ratio is an excellent monitor for effectiveness of lipid lowering therapies
- The LDL-C/HDL-C is a better predictor for risk of heart disease than LDL-C alone
- The LDL-C/HDL-C reflects the two way traffic of cholesterol entering and leaving the arterial intima

Introduction

Controversy exists regarding what is the best method for identifying those who are at increased risk for coronary heart disease. Some experts have proposed C-reactive protein (CRP), a marker for inflammation, as a screening tool for prediction of cardiovascular disease (CVD). Several epidemiological studies have shown positive associations between CRP levels and the incidence of cardiovascular disease [1–5] although recent studies have questioned the validity of the connection [6,7]. However, The current National Cholesterol Education Program (NCEP) guidelines recommend specific target levels of LDL and HDL cholesterol for determining CVD risk and evaluating effectiveness of lipid-lowering therapies [8]. It is interesting to note that recent studies have found the level of apolipoprotein (apo) B and the ratio of the lipoproteins apo B/apol A-I to be the most accurate predictors of risk and the best measurements for evaluating treatment [9–13]. Because each atherogenic particle contains one molecule of apoB, levels of apo B are a direct measurement of the number of potentially atherogenic particles including very low density lipoprotein (VLDL), intermediate density lipoprotein (IDL) and LDL [14]. Similarly, the concentration of apo A-I reflects the number of antiatherogenic HDL particles and not just the concentration of cholesterol

Address reprint requests to: Maria Luz Fernandez, PhD, University of Connecticut, Dept. Nutritional Sciences, 3624 Horsebarn Road Ext., U-17, Storrs, CT 06269. E-mail: maria-luz.fernandez@uconn.edu

Abbreviations: Apo = apolipoprotein, CRP = C reactive protein, CVD = cardiovascular disease, HDL-C = HDL cholesterol, LDL-C = LDL cholesterol, MI = myocardial infarction, NCPE = National Cholesterol Education Program.

Journal of the American College of Nutrition, Vol. 27 No. 1, 1–5 (2008)
Published by the American College of Nutrition

carried by this lipoprotein. In other words the number of atherogenic versus non-atherogenic lipoproteins transported in blood provides a more comprehensive evaluation of cardiovascular disease risk.

Traditional cholesterol measurements tend to be most accurate at predicting risk for those at the lower and higher ends of the risk spectrum. These measurements are less helpful for the majority of people whose risk falls somewhere in between [15]. The Thirty-Person/Ten-Country Panel recently concluded that the apo B/apo A1 ratio is superior to conventional cholesterol measurements in patients without symptomatic vascular disease or diabetes to evaluate the lipoprotein-related risk of vascular disease [12]. The panel also recommended that apo B be included in all guidelines as an indicator of cardiovascular risk. Both the INTERHEART [10] and the AMORIS [16] studies, show a strong, direct relation between a high apoB/apoA-1 ratio and an increased risk for fatal and acute myocardial infarction (MI).

While the apo B/apo A I ratio is rapidly gaining favor as the most accurate measurement the question remains if the improved ability to predict risk, justifies the increased cost of widespread apolipoprotein screening and whether the substitution of apolipoprotein-centered measurements to cholesterol-centered measurements would serve to help or simply to confuse both patients and health professionals.

Problems in Changing from Lipoprotein Cholesterol to Apolipoproteins

From a practical standpoint, questions have been raised as to how readily a change in standards for assessing risk would be accepted by patients as well as physicians in general practice including cardiology, diabetology, neurology and other specialties [17]. The measurement of LDL cholesterol (LDL-C) and HDL cholesterol (HDL-C) is part of the standard blood lipid profile while determination of circulating apolipoproteins is not. Additional testing must be ordered by the physician and the additional cost carried by the patient. Major insurance carriers consider that testing for apoB is experimental and not a routine measurement and therefore will not reimburse the expense [18]. Insurance companies are unlikely to cover costs of apo B and apo A1 testing as long as it is not part of the NCEP guidelines, but the guidelines are unlikely to focus on apolipoproteins until testing and reimbursement are readily available and affordable for patients.

Aside from the added expense, the implementation of apolipoprotein testing presents some general public education problems. While cholesterol is a household word, apo B and apo A-I are not. Dr. Ole Faergeman of the National Heart and Lung Institute in London has argued that it would be difficult to educate the public in "apolipoproteinology" [17] and supports the idea that the wisest action should be to maintain cholesterol measurements as the focus for patients. Dr. Margo Denke from the University of Texas Health Science Center in San Antonio, who coauthored the latest US NCEP guidelines also argues against moving to apolipoprotein measurements. Her rationale is based on the enormous amount of time, effort and money that have been spent educating health professionals and the public regarding cholesterol terminology. Replacing cholesterol with apo B or a ratio of apo B/apo A-I, would result in further confusion [19]. Moreover, substituting apo B for LDL-C would be difficult at this point, since the central principle of the NCEP guidelines is to use new knowledge to build on existing guidelines, not to replace them with guidelines based on new concepts. However, the path of least resistance in terms of cholesterol education may not be the best path to take in terms of improving detection and treatment of cardiovascular disease.

A more tenable option that has been proven to be an accurate predictor of cardiovascular risk is the LDL-C/HDL-C ratio, which can be obtained from a standard lipid profile and is more accurate than LDL-C or HDL-C alone [20]. Changes in ratios have been shown to be better indicators of successful CHD risk reduction than changes in absolute levels of lipids or lipoproteins [21,22]. Moreover, while not perfect, measurements of apo B and apo A-I tend to reflect the levels of LDL-C and HDL-C [23].

Evidence for the Predictive Value of LDL-C/HDL-C Ratios

Several large epidemiological and clinical studies have found the LDL-C/HDL-C ratio to be an excellent predictor of CHD risk and an excellent monitor for the effectiveness of lipid-lowering therapies [20,22,24–26].

In the Helsinki Study, a 5-year clinical trial of more than 4,000 middle-aged men with elevated lipids, the LDL-C/HDL-C ratio had more prognostic value than LDL-C or HDL-C alone [20]. The ratio was especially accurate at predicting risk among those who also had elevated triglyceride levels. It was found that by using the LDL-C/HDL-C ratio along with fasting triglyceride concentration, it was possible to identify a subgroup that was able to achieve over 70% reduction in CHD risk with gemfibrozil (a lipid-lowering agent). The findings suggest that relatively simple laboratory measurements can be used to identify a small group of people that is most likely to benefit from long-term drug intervention.

The PROSPER trial, a retrospective analysis of 6,000 patients, found that the ratio of LDL-C/HDL-C was the most powerful measure of cardiovascular disease risk in elderly people [27]. The researchers also concluded that changes in LDL-C/HDL-C ratio as a result of statin treatment appeared to account for the beneficial effects of therapy and suggested that statin therapy could usefully be targeted to those with an LDL-C/HDL-C ratio >3.3.

The PROCAM Study, which included almost 11,000 men aged 36 to 65 years who were studied for 4 to 14 years,

found a continuous and graded relationship between the LDL-C/HDL-C ratio and CVD mortality [24]. Coronary deaths spiked when the LDL-C/HDL-C ratio reached between 3.7 and 4.3. In the Physicians' Health Study, which involved almost 15,000 men ages 40 to 84 years, a 1-unit increase in the LDL-C/HDL-C ratio was associated with a 53% increase in risk of MI [25]. In the Boston Area Health Study, which analyzed a group of men and women less than 76 years of age with no prior history of CVD but who had experienced a first MI, a 1-unit increase in the LDL-C/HDL-C ratio was associated with a 75% increase in risk of MI [28]. In addition, comparison of individual LDL-C/HDL-C ratios from subjects in the Framingham Study clearly indicates that the ratios are significantly more robust predictors of CVD than the individual levels of LDL-C or HDL-C [22].

The Effect of Dietary Cholesterol on the LDL-C/HDL-C Ratio

The effects of dietary cholesterol on blood lipid can be used as an example to illustrate why LDL-C/HDL-C is a better predictor of CVD than LDL-C alone. Numerous studies have shown that the LDL-C/HDL-C ratio is not affected by dietary cholesterol [29,30]. However, earlier studies evaluating the impact of dietary cholesterol on serum cholesterol focused on total cholesterol as the primary marker for risk, and dietary cholesterol was, at the time, believed to have an impact on this marker. Subsequent studies focused on plasma LDL-C concentrations as is reflected in the ATP III Guidelines, and limitations on dietary cholesterol are a part of the recommendations for diet and lifestyle changes designed to reduce risk [8].

Feeding studies have demonstrated that dietary cholesterol increases both LDL and HDL cholesterol, with little change in the LDL-C/HDL-C ratio. On average, the LDL-C/HDL-C ratio is predicted to increase 0.01 unit per 100 milligrams/day increase in dietary cholesterol, an amount unlikely to impact cardiovascular disease risk [31]. In fact, studies have found that including as many as 3 eggs per day (about 640 milligrams of cholesterol) raised both LDL-C and HDL-C in those individuals classified as hyper-responders. In addition, no significant increases in cholesterol carried by these lipoproteins was observed in hypo-responders resulting in all cases in a non-significant effect on the LDL-C/HDL-C ratio [29,30]. Moreover, studies show that when LDL-C increases as a result of eating eggs, the LDL particles are generally large and less atherogenic [32,33]. A significant decrease in the small LDL particles, associated with increased risk for CVD [34], has also been observed [35].

Conclusions

Though apo B levels and apo B/apo A1 ratios appear to be the most accurate predictors of CHD, the question remains whether the potential improvement in risk prediction over that provided by currently available lipid measurements justifies the additional costs of substituting apolipoprotein determinations for the current measurements of lipoprotein cholesterol [36]. Another issue is whether the difference is enough to warrant major changes in the framework of existing cholesterol guidelines for assessing risk determining the best treatment plan and monitoring progress. Existing guidelines (ATP III) for detecting cardiovascular disease risk and treating patients focus on plasma LDL-C concentrations as the primary clinical target and these guidelines are followed by most physicians in patient care. While the current literature supports the use of apoB/apo A-I ratio as the most accurate predictor of CVD risk, it may not be the most practical. In contrast, numerous reports show LDL-C/HDL-C to be a more accurate predictor of risk than LDL-C alone and currently is the most practical approach available.

An LDL-C/HDL-C ratio point for initiating lipid-lowering therapy should be determined. The current NCEP guidelines recommend levels of LDL and HDL that represent a ratio of about 2.5 [8]. Current research suggests risk of death from cardiovascular disease begins to increase significantly around a ratio of 3.3–3.7 [24].

Until questions regarding the practicality of utilizing apoliprotein measurements as predictors of CVD risk can be answered, guidelines should incorporate LDL-C/HDL-C ratios for determining whether to initiate therapy and for monitoring progress. The existing focus on LDL-C as the primary culprit in atherogenesis may divert attention from the more efficient lipid profile of LDL-C/HDL-C. The LDL-C/HDL-C ratio reflects the two-way traffic of cholesterol entering and leaving the arterial intima in a way that the individual levels of LDL-C and HDL-C do not [22].

REFERENCES

1. Lardus O, Knetsch AM, Blleumink GS, Deckers KW, Hofman A, Stricker BJ, Witteman JC: C-reactive protein and risk of heart failure. The Rotterdam Study. Am Heart J 152:514–520, 2006.
2. Tuomisto K, Jousilahti P, Sundvall, J, Pajunen P, Salomaa V: C-reactive protein, interleukin-6 and tumor necrosis factor alpha as predictors of incident coronary and cardiovascular events and total mortality. A population-based, prospective study. Thromb Haemost 95:511–518, 2006.
3. Aguilar D, Fisher MR, O'Connor CM, Dunne MW, Muhlestein JB, Yao L, Gupta S, Benner RJ, Cook TD, Edwards D, Pfeffer MA: Investigators in the Weekly Intervention with Zithromax for Atherosclerosis and its Related Disorder study. Am Heart J 152:298–304, 2006.
4. de Ferranti S, Rifai N: C-reactive protein and cardiovascular disese: a review of risk prediction and interventions. Clin Chim Acta 328:1–15, 2002.
5. Best LG, Zhang Y, Lee ET, Yeh JL, Cowan L, Palmieri V, Roman M, Devereuz RB, Fabsitz RR, Tracy RP, Robbins D, Davidson M, Ahmed A, Howard BV: C-reactive protein as a predictor of cardiovascular risk in a population with a high prevalence of diabetes: the Strong Heart Study. Circulation 112:1289–1295, 2005.

6. Wilson PW, Nam BH, Pencina M, D'Agostino RB SR, Benjamin EJ, O'Donnell CJ: C-reactive protein and risk of cardiovascular disease in men and women from the Framingham Heart Study. Arch Intern Med 165:2473–2478, 2005.
7. Kuller LH, Grandits G, Cohen JD, Neaton JD, Prineas R; for the Multiple Risk Factor Intervention Trial Research Group: Lipoprotein particles, insulin, adiponectin, C-reactive protein and risk of coronary heart disease among men with metabolic syndrome. Atherosclerosis 195:122–128, 2006.
8. Adult Treatment Panel III: Executive summary of the third report of the national cholesterol education program (NCEP) expert panel on detection evaluation, and treatment of high blood cholesterol in adults. J Am Med Assoc 285:2486–2497, 2001.
9. Marcovina S, Packard CJ: Measurement and meaning of apolipoprotein AI and apolipoprotein B plasma levels. J Intern Med 259:437–446, 2006.
10. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, McQueen M, Budaj A, Pais P, Varigos J, Sisheng L: Effect of potentially modifiable risk factors associated with myocardial infarctin in 52 countries (the INTERHEART study): case-control study. Lancet 364:937–952, 2004.
11. Meisinger C, Loewel H, Mraz W, Koenig W: Prognostic value of apolipoprotein B and A-I in the prediction of myocardial infarction in middle-aged men and women: results from the MONICA/KORA Augsburg cohort study. Eur Heart J 26:271–278, 2005.
12. Barter PJ, Ballantyne CM, Carmena R, Cabezas MC, Chapman MJ, Couture P, De Graaf, J, Durrington PN, Faergeman O, Frohlich J, Furberg CD, Gagne C, Haffner SM, Humphries SE, Jungner I, Krauss RM, Kwiterovich P, Marcovina S, Packard CJ, Pearson TA, Reddy KS, Rosenson R, Sarrafzadegan N, Sniderman AD, Stalenhoef AF, Stein E, Talmud PJ, Tonkin AM, Walldius G, Williams KMS: Apo B versus cholesterol in estimating cardiovascular risk and in guiding therapy: report of the thirty-person/ten-country panel. J Intern Med 259:247–258, 2006.
13. Kim HK, Chang SA, Choi EK, Kim YJ, Kim HS, Sohn DW, Oh BH, Lee MM, Park YB, Choi YS: Association between plasma lipids, and apoliproteins and coronary artery disease: a cross-sectional study in a low-risk Korean population. Int J Cardiol 101:435–440, 2005.
14. Walldius G, Junger N: The apo B/apoA-I ratio: a strong, new risk factor for cardiovascular disease and a target for lipid-lowering therapy - a review of evidence. J Int Med 259:493–519, 2006.
15. Gotto AM, Whitney E, Stein EA, Shapiro DR, Clearfield M, Weis S, Jou JY, Langendorfer A, Beere PA, Watson DJ, Downs JR, de Cani JS: Relation between baseline and on-treatment lipid parameters and first acute major coronary events in the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/Tex CAPS). Circulation 101:477–484, 2000.
16. Walldius G, Jungner I, Holme I, Aastvelt AH, Kolar W, Steiner E: High apolipoprotein B, low apolipoprotein A-I, and improvement in the prediction of fatal myocardial infarction (AMORIS study): a prospective study. Lancet 358:2026–2033, 2001.
17. Faergeman O: Introduction: Apolipoproteins and guidelines for prevention of cardiovascular disease. J Intern Med 259:434–436, 2006.
18. Blue Cross Blue Shield: Apolipoprotein B Testing for the Diagnosis and Management of Cardiovascular Disease. Medical Policy Reference Manual. Blue Cross of Idaho, 2005.
19. Denke MA: Weighing in before the fight: low-density lipoprotein cholesterol and non-high-density lipoprotein cholesterol versus apolipoprotein B as the best predictor for coronary heart disease and the best measure of therapy. Circulation 112:3368–3370, 2005.
20. Manninen V, Tenkanen L, Koskinen P, Huttunen JK, Manttari M, Heinonen OP, Frick MH: Joint effects of serum triglyceride and LDL cholesterol and HDL cholesterol concentrations on coronary heart disease risk in the Helsinki Heart Study. Implications for treatment. Circulation 85:37–45, 1992.
21. Natarajan S, Glick H, Criqui M, Horowitz D, Lipsitz SR, Kinosian B: Cholesterol measures to identify and treat individuals at risk for coronary heart disease. Am J Prev Med 25:50–57, 2003.
22. Kannel WB: Risk stratification of dyslipidemia: Insights from the Framingham Study. Curr Med Chem Cardiovasc Hematol Agents 3:187–193, 2005.
23. Walldius G, Jungner I: Rationale for using apoliprotein B and apolipoprotein A-1 as indicators of cardiac risk and as targets for lipid-lowering therapy. Eur Heart J 26:210–212, 2005.
24. Cullen P, Schulte H, Assmann G: The Munster Heart Study (PROCAM) Total Mortality in Middle-Aged Men is increased at low total and LDL cholesterol concentrations in smokers but not in nonsmokers. Circulation 96:2128–2136, 1997.
25. Stampfer MJ, Sacks FM, Salvini S, Willett WC, Hennekens CH: A prospective study of cholesterol apolipoproteins and the risk of myocardial infarction. N Engl J Med 325:373–381, 1991.
26. Gaziano JM, Hennekens, CH, O'Donnell CJ, Breslow JL, Buring JE: Fasting triglycerides, high-density lipoprotein, and risk of myocardial infarction. Circulation 96:2520–2525, 1997.
27. Packard CJ, Ford I, Robertson M, Shepherd J, Blauw GJ, Murphy MB, Bollen EL, Buckley BM, Cobbs SM, Gaw A, Hyland M, Jukema JW, Kamper AM, Macfarlane PW, Perry IJ, Stott DJ, Sweeney BJ, Twomey C, Westendorp RG; PROSPER Study Group: Plasma lipoproteins and apolipoproteins as predictors of cardiovascular risk and treatment benefit in the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER). Circulation 112:3058–3065, 2005.
28. Gaziano JM, Hennekens, CH, O'Donnell CJ, Breslow JL, Buring JE: Fasting triglycerides, high-density lipoprotein, and risk of myocardial infarction. Circulation 96:2520–2525, 1997.
29. Greene CM, Zern TL, Wood RJ, Shrestha S, Aggarwal D, Sharman MJ, Volek JS, Fernandez ML: Maintenance of the LDL cholesterol:HDL cholesterol ratio in an elderly population given a dietary cholesterol challenge. J Nutr 135:2793–2798, 2005.
30. Herron KJ, Vega-Lopez S, Conde K, Ramjiganesh T, Roy S, Shachter N, Fernandez ML: Pre-menopausal women classified as hypo-or hyper-responders, do not alter their LDL/HDL ratio following a high dietary cholesterol challenge. J Am Coll Nutr 21:250–258, 2002.
31. McNamara DJ: The impact of egg limitations on coronary heart disease risk: Do the numbers add up? J Am Coll Nutr 19:540S–548S, 2000.
32. Fernandez ML: Dietary cholesterol provided by eggs and plasma lipoproteins in healthy populations. Curr Opin Clin Nutr Metab Care 9:8–12, 2006.
33. Herron KL, Lofgren IE, Sharman M, Volek JS, Fernandez ML: High intake of cholesterol results in less atherogenic low-density lipoprotein particles in men and women independent of response classification. Metabolism 53:823–830, 2004.

34. Austin MA, Breslow JL, Hennekens CH, Buring JE, Willett WC, Krauss RM: Low-density lipoprotein subclass patterns and risk of myocardial infarction. JAMA 260:1917–1921, 1988.
35. Greene CM, Waters D, Clark RM, Contois JH, Fernandez ML: Plasma LDL and HDL characteristics and carotenoid content are positively influenced by egg consumption in an elderly population. Nutr Metab (Lond) 3:6, 2006.
36. Pischon T, Girman CJ, Sacks FM, Rifai N, Stampfer MJ, Rimm EB: Non-high-density lipoprotein cholesterol and apolipoprotein B in the prediction of coronary heart disease in men. Circulation 112:3375–3383, 2005.

Received January 2, 2007; Accepted March 2, 2007.