



## Lipid screening: Is measuring cholesterol enough?

**I**n the September-October 1992 issue of the *Cleveland Clinic Journal of Medicine*, Olin and colleagues<sup>1</sup> prospectively identified lipid and lipoprotein abnormalities in 125 consecutive patients with symptomatic atherosclerosis of the lower extremities. Their meticulously performed study has yielded scientifically interesting data with important clinical ramifications. Most notably, one third of their patients had a total serum cholesterol less than 200 mg/dL, a "desirable" value. However, when a complete lipoprotein profile was performed, 87% of the total group had abnormal lipoprotein profiles. The authors point out that if standard screening recommendations of the National Cholesterol Education Program (NCEP) had been followed, a substantial proportion of patients with abnormal lipoprotein profiles would not have been identified. Many of these patients are at risk because of low levels of high-density lipoprotein cholesterol (HDL-C).

In 1988, the expert panel published the results of its deliberations.<sup>2</sup> These NCEP guidelines recommended that all adults over age 20 undergo a measurement of total serum cholesterol. A value less than 200 mg/dL was considered desirable, and the test would be repeated in 5 years. If the value was greater than 200 mg/dL, a lipoprotein analysis was recommended, and treatment would be guided by the level of the low-density lipoprotein cholesterol (LDL-C). An LDL-C below 130 mg/dL would not require further treatment.

An LDL-C between 130 and 159 mg/dL was considered somewhat elevated, and dietary treatment was recommended. An LDL-C greater than or equal to 160 mg/dL was considered abnormal, and it conferred a high risk of cardiovascular events. A patient with such an elevated level would be treated more aggressively, first with diet and then with medication, if necessary.

The risk of death from cardiovascular disease increases in a parabolic fashion with increases in the level of total serum cholesterol. The inflection point for this curve occurs at a value of approximately 200 mg/dL, after which the rate of death from cardiovascular events rises more steeply with increases in total serum cholesterol.<sup>3,4</sup> This observation is one of the major reasons for the NCEP panel's choice of 200 mg/dL as the cutoff point for screening the *general population*. However, these guidelines may not be stringent enough for subsets of the population, such as those with documented atherosclerosis.

The study by Olin and colleagues suggests that patients with intermittent claudication have an exceedingly high prevalence of lipoprotein abnormalities, even when total serum cholesterol is in a "desirable" range. The stigmata of atherosclerosis—ie, intermittent claudication, transient ischemic attacks, angina, and renovascular hypertension—likely select out a group of patients in whom routine screening is not adequate. In the study by Olin et al, almost half the patients had HDL-C levels below the normal range. A low HDL-C is becoming increasingly recognized as a major risk factor for progression of atherosclerosis and appears to be at least as important as an elevated LDL-C. In the Framingham study,<sup>5</sup> the HDL-C level was inversely related to the risk of developing myocardial infarction, especially in women. This effect of low

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HDL-C levels persists even in people with a total cholesterol below 200 mg/dL. More recently, in the Physicians Health Study,<sup>6</sup> a reduced HDL-C was the most potent predictor for cardiovascular events, even more so than an elevation in apoprotein B (the major lipoprotein of LDL-C). In the Olin study, a low HDL-C was more common in patients with coexistent coronary artery disease. In summary, a low HDL-C is common in patients with atherosclerotic vascular disease and puts these patients at increased risk for cardiovascular events. Because therapeutic elevations in HDL-C are associated with reduced progression and even regression of atherosclerotic lesions, it seems justifiable to be more aggressive in screening for this abnormality.<sup>7-11</sup>

Arguably, even a "complete" lipoprotein profile (total cholesterol, HDL-C, LDL-C, and triglycerides) may not be definitive in some subsets of our patient population. Two recent publications have implied that 25% of patients with myocardial infarction before age 60 are at risk because of elevated lipoprotein (a).<sup>12,13</sup> Lipoprotein (a) is a lipoprotein identical to LDL-C except for its association with an unusual apoprotein, apoprotein (a). This apoprotein has recently been cloned and the protein has been characterized: it is now known to be composed of multiple repeats (up to 22) of a protein sequence identical to the "kringle" region of plasminogen.<sup>14,15</sup> The striking similarity between this subunit of lipoprotein (a) and the kringle region of plasminogen has led some to propose that the marked atherogenicity of this particle may be due to its antagonism of endogenous thrombolysis. Proponents of this theory argue that this would have the effect of allowing thrombus to be incorporated into plaque and may even be partly responsible for acute thrombosis of a diseased vessel.<sup>16</sup> It is also possible that the unusual apoprotein associated with this lipoprotein enhances its incorporation into cellular or extracellular components of the atherosclerotic plaque.

The normal range of lipoprotein (a) in the general population is between 5 and 10 mg/dL; levels above this are associated with an increased risk of coronary artery disease.<sup>17,18</sup> Identification of this lipoprotein abnormality is important because these are patients at high risk of premature cardiovascular events who should receive aggressive risk-factor modification. Also, therapy for this disorder is potentially different from standard approaches to hypercholesterolemia in that only nicotinic acid (and, possibly, antioxidant therapy) appears to be effective in reducing plasma values.<sup>19,20</sup>

It is becoming increasingly clear that hypercholesterolemia induces an endothelial injury or alteration that initiates atherogenesis. Oxidized LDL-C plays a major role in the initiation and propagation of this process.<sup>21</sup> The endothelium is now thought to elaborate specific adhesion proteins for monocytes, in response to minimally modified or oxidized LDL-C.<sup>22,23</sup> This lipoprotein also induces the expression of monocyte chemotactic proteins by the endothelium and vascular smooth muscle.<sup>24</sup> This response to the injurious lipoprotein causes monocytes to adhere to and penetrate the vessel wall. Once there, the monocytes become activated, and these tissue macrophages are capable of imbibing and oxidizing more lipoprotein, to initiate a self-propagating process. Oxidized LDL-C also interferes with the vasodilator and antiplatelet properties of the endothelium.<sup>25,26</sup> Its immunogenicity may further amplify the inflammatory response. Recent reports suggest there could be differences between patients in their tendency to oxidize lipoprotein. Diabetics and smokers may be at increased risk.<sup>27-30</sup> A greater tendency of one patient to oxidize lipoproteins may explain the great variation in the extent of disease in individuals with equivalent elevations of LDL-C. In the future, assays for plasma lipid peroxides may become routine.<sup>31</sup>

To conclude, Olin and colleagues have suggested that patients with peripheral arterial occlusive disease represent a subset of patients in which routine screening for lipid abnormalities may not be sufficient. It does appear that there are subsets of patients at greater risk who deserve more aggressive screening and therapy. The Cleveland Clinic approach reflects an increasing trend among lipidologists to screen patients more intensively and to treat lipid abnormalities more aggressively, with attention to both LDL-C and HDL-C, as well as other possible lipoprotein abnormalities.

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#### REFERENCES

1. Olin JW, Cressman MD, Young RJ, Hoogwerf B, Weinstein CE. Relationship of lipid, lipoprotein abnormalities, and lower extremity arteriosclerosis obliterans. *Cleve Clin J Med* 1992; 59: 491-497.
2. Report of the National Cholesterol Education Program Expert Panel on detection, evaluation, and treatment of high blood cholesterol in adults. *Arch Intern Med* 1988; 148:36-39.
3. Martin MJ, Hulley SB, Browner WS, Kuller LH, Wentworth D.

- Serum cholesterol, blood pressure, and mortality: implications from a cohort of 361,662 men. *Lancet* 1986; 2:933-936.
4. Stamler J, Wentworth D, Neaton JD. Is relationship between serum cholesterol and risk of premature death from coronary heart disease continuous and graded? Findings in 356,222 primary screenees of the Multiple Risk Factor Intervention Trial (MRFIT). *JAMA* 1986; 256:2823-2828.
  5. Abbot RD, Wilson PWF, Kennel WB, Castelli WP. High density lipoprotein cholesterol, total cholesterol screening, and myocardial infarction: The Framingham study. *Arteriosclerosis* 1988; 8:207-211.
  6. 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* 1991; 325:373-381.
  7. Brown G, Albers JJ, Fisher LD, et al. Regression of coronary artery disease as a result of intensive lipid-lowering therapy in men with high levels of apolipoprotein B. *N Engl J Med* 1990; 323:1289-1298.
  8. Levy RI, Brensike JF, Epstein SE, et al. The influence of changes in lipid values induced by cholestyramine and diet on progression of coronary artery disease: results of the NHLBI Type II Coronary Intervention Study. *Circulation* 1984; 69:325-337.
  9. Nikkilä EA, Viikinkoski P, Valle M, Frick MH. Prevention of progression of coronary atherosclerosis by treatment of hyperlipidemia: a seven year prospective angiographic study. *Br Med J* 1984; 289:220-223.
  10. Arntzenius AC. Regression of atherosclerosis: benefit can be expected from low LDL-C and high HDL-C levels. *Acta Cardiol* 1991; 46:431-438.
  11. Badimon JJ, Badimon L, Fuster V. Regression of atherosclerotic lesions by high density lipoprotein plasma fraction in the cholesterol-fed rabbit. *J Clin Invest* 1990; 85:1234-1241.
  12. Rosengren A, Wilhelmsen L, Eriksson E, Risberg B, Wedel H. Lipoprotein (a) and coronary heart disease: a prospective case-control study in a general population sample of middle aged men. *Br Med J* 1990; 301:1248-1251.
  13. Rhoads GG, Dahlen G, Berg K, Morton NE, Dannenberg AL. Lp(a) lipoprotein as a risk factor for myocardial infarction. *JAMA* 1986; 256:2540-2544.
  14. McLean JW, Tomlinson JE, Kuang W-J, et al. cDNA sequence of human apolipoprotein(a) is homologous to plasminogen. *Nature* 1987; 330:132-137.
  15. Eaton DL, Fless GM, Kohr WJ, et al. Partial amino acid sequence of apolipoprotein(a) shows that it is homologous to plasminogen. *Proc Natl Acad Sci USA* 1987; 84:3224-3228.
  16. MBewu AD, Durrington PN. Lipoprotein (a): structure, properties and possible involvement in thrombogenesis and atherogenesis. *Atherosclerosis* 1990; 85:1-14.
  17. Murai A, Miyahara T, Fujimoto N, Matsuda M, Kameyama M. Lp(a) lipoprotein as a risk factor for coronary heart disease and cerebral infarction. *Atherosclerosis* 1986; 59:199-204.
  18. Armstrong VW, Cremer P, Everle E, et al. The association between serum Lp(a) concentrations and angiographically assessed coronary atherosclerosis. *Atherosclerosis* 1986; 62:249-257.
  19. Carlson LA, Hamsten A, Asplund A. Pronounced lowering of serum levels of lipoprotein Lp(a) in hyperlipidaemic subjects treated with nicotinic acid. *J Intern Med* 1989; 226:271-276.
  20. Gurakar A, Hoeg JM, Kostner G, Papadopoulos NM, Brewer HB. Levels of lipoprotein Lp(a) decline with neomycin and niacin treatment. *Atherosclerosis* 1985; 57:293-301.
  21. Steinberg D, Parthasarathy S, Carew TE, Khoo JD, Witztum JL. Beyond cholesterol: modifications of low density lipoprotein that increase its atherogenicity. *N Engl J Med* 1989; 320:915-924.
  22. Berliner JA, Territo MC, Sevanian A, et al. Minimally modified low density lipoprotein stimulates monocyte endothelial interactions. *J Clin Invest* 1990; 85:1260-1266.
  23. Drake TA, Hannai K, Fei H, Lavi S, Berliner JA. Minimally oxidized LDL induces tissue factor expression in cultured human endothelial cells. *Am J Pathol* 1991; 138:601-607.
  24. Cushing SD, Berliner JA, Valente AJ, et al. Minimally modified low density lipoprotein induces monocyte chemotactic protein 1 in human endothelial cells and smooth muscle cells. *Proc Natl Acad Sci USA* 1990; 87:5134-5138.
  25. Andrews HE, Bruckdorfer KR, Dunn RC, Jacobs M. Low-density lipoproteins inhibit endothelium-dependent relaxation in rabbit aorta. *Nature* 1987; 327:237-239.
  26. Chin JH, Azhar S, Hoffman BB. Inactivation of endothelial derived relaxing factor by oxidized lipoproteins. *J Clin Invest* 1992; 89:10-18.
  27. Scheffler E, Huber L, Frübis J, Schulz I, Ziegler R, Dresel HA. Alteration of plasma low density lipoprotein from smokers. *Atherosclerosis* 1990; 82:261-265.
  28. Lyons TJ. Oxidized low density lipoproteins: a role in the pathogenesis of atherosclerosis in diabetes? *Diabetic Med* 1991; 8:411-419.
  29. Morel DW, Chisolm GM. Antioxidant treatment of diabetic rats inhibits lipoprotein oxidation and cytotoxicity. *J Lipid Res* 1989; 30:1827-1834.
  30. Avogaro P, Bon GB, Cassalato G. Presence of a modified low density lipoprotein in humans. *Arteriosclerosis* 1988; 8:79-87.
  31. Harats D, Ben-Naim M, Dabach Y, et al. Effect of vitamin C and E supplementation on susceptibility of plasma lipoproteins to peroxidation induced by acute smoking. *Atherosclerosis* 1990; 85:47-54.