ONE MINUTE CONSULT

BRIEF QUESTIONS AND ANSWERS ON CURRENT CLINICAL CONTROVERSIES

Q: Should one routinely screen for lipoprotein(a)?

JOSEPH P. FROLKIS, MD, PHD
Sections of Preventive Cardiology and Preventive Medicine, Department of Preventive Cardiology and Rehabilitation, Cleveland Clinic

A: TO ANSWER this question, one must decide whether the data linking lipoprotein(a) [Lp(a)] to increased risk for cardiovascular disease are sufficient to warrant incorporating it into standard screening practice, and whether knowing the value of Lp(a) has implications for therapy or management.

HOW LP(a) MIGHT PROMOTE CARDIOVASCULAR DISEASE

Lp(a) consists of a particle of low-density lipoprotein cholesterol (LDL-C) linked by a disulfide bond to a large hepatically derived glycoprotein, apolipoprotein(a), which is structurally similar to plasminogen. In theory, then, Lp(a) could promote cardiovascular disease in two ways: its apolipoprotein(a) moiety could promote thrombogenesis and its LDL-C moiety could promote atherogenesis.

Thrombogenesis. The apolipoprotein portion of Lp(a) competitively displaces plasminogen from binding sites on both fibrin and endothelial cells.[1] Lp(a) is associated with increased levels of plasminogen activator-inhibitor (PAI-1) and decreased activity of tissue plasminogen activator (t-PA).[2] These effects all promote thrombosis and inhibit fibrinolysis.[3]

Atherogenesis. Lp(a) can, like LDL-C alone, be oxidized, taken up by macrophages, and recovered from atherosclerotic plaque.[4,5] Lp(a) appears to facilitate the oxidation of LDL-C, and can impair endothelial function.[6]

LP(a) LEVELS ARE HIGH IN 25% OF THE POPULATION

Levels of Lp(a) are largely genetically determined, increase slightly with age, and vary by race. Values are lower in white populations, but both higher and more normally distributed in African Americans.[7] Mean values for Lp(a) in a recent Framingham cohort were 14 mg/dL for men and 15 mg/dL for women (with a standard deviation of 17 for both sexes).[8] Levels above 30 mg/dL are generally considered elevated, a threshold exceeded by approximately 25% of the US population.[9] Lp(a) levels are higher in patients with chronic renal failure, the nephrotic syndrome, and diabetic nephropathy.[10,11]

SOME TREATMENTS LOWER LP(a), BUT OTHERS DO NOT

Lifestyle modifications such as diet, weight loss, and exercise have no effect on Lp(a) levels.[12,13] Similarly, most commonly prescribed lipid-lowering medications have little effect on Lp(a), including statins and bile acid sequestrants (resins).

Other treatments do, however, appear to lower Lp(a). Estrogen replacement therapy in postmenopausal women and high-dose niacin (at least 3–4 g/day) have been reported to lower Lp(a) levels by 35% to 50%.[14,15] The new fibric acid derivative fenofibrate has shown some effect on Lp(a). In one study of hyperlipidemic patients, those with Lp(a) levels higher than 20 mg/dL experienced a 14% decrease in Lp(a) while taking fenofibrate.[16] No large-scale trial results are yet available, however.

LP(a) AS A RISK FACTOR

Numerous retrospective, case-control studies demonstrated an association between elevated levels of Lp(a) and increased risk for coronary heart disease, ischemic stroke, and peripheral arterial disease.[17–20] Lp(a) elevations have

Current evidence does not yet justify routine screening for Lp(a)

also been linked to restenosis after angioplasty and progression of angiographically documented coronary heart disease.[21,22] Lp(a) excess is the most common inherited lipid disorder in patients with premature coronary heart disease.[23]

Prospective studies, on the other hand, present a slightly more complex picture. Some studies suggested Lp(a) is a strong, independent predictor of coronary heart disease, particularly in women and young men,[24] while others found no such association.[25] One recent prospective trial found that while Lp(a) did not independently increase coronary heart disease risk, it seemed to increase the risk of elevated total cholesterol, LDL-C, and apolipoprotein B (the major lipoprotein of the atherogenic lipids), and blunt the cardioprotective effect of high levels of HDL-C.[26] Similarly, in a cohort of patients with premature coronary heart disease, Lp(a) was associated with extremely high relative risk only in the presence of elevated levels of total cholesterol or an increased ratio of total cholesterol/HDL-C. These interactive effects on risk were an order of magnitude greater than the impact of the lipid abnormalities alone.[27] Another recent study of men with documented coronary heart disease and elevated levels of both LDL-C and Lp(a) found that Lp(a) seemed to lose its atherogenic potency once LDL-C was aggressively lowered.[28]

Of note: No prospective clinical trial has been conducted in which the value of reducing elevated levels of Lp(a) has been confirmed.

Some special populations may need Lp(a) screening

LP(a) SCREENING: RECOMMENDATIONS

Does the weight of the current evidence justify routine screening for Lp(a)? In my opinion, no. Until more consistent prospective trial data or interventional evidence accrues, knowing a patient's Lp(a) level provides insufficient additional assistance in predicting cardiovascular disease risk in the general population to warrant its inclusion in a standard screening evaluation.

However, one should be aware of the Lp(a) level in special populations, ie, patients with premature coronary heart disease, those with a strong family history of cardiovascular disease, those who have undergone angioplasty or coronary artery bypass grafting, and those with documented cardiovascular disease in the absence of traditional risk factors. In addition to aggressive lowering of elevated levels of LDL-C, attempts to lower Lp(a) in these groups may be warranted on the basis of the epidemiological associations discussed above, especially in light of the efficacy and tolerability of the newer forms of niacin and of fenofibrate.

Finally, suspect Lp(a) excess in patients with hypercholesterolemia that is refractory to standard statin therapy. Since the calculated value of LDL-C includes the LDL contained in Lp(a), and since Lp(a) will not respond to statin therapy, significant hidden elevations of Lp(a) may account for the treatment failure.

REFERENCES

1. **Loscalzo J, Weinfeld M, Fless GM, et al.** Lipoprotein(a), fibrin binding, and plasminogen activation. Arteriosclerosis 1990; 10:240–245.
2. **Stein JH, Rosenson RS.** Lipoprotein Lp(a) excess and coronary heart disease. Arch Intern Med 1997; 157:1170–1176.
3. **Kostner G, Krempler F.** Lipoprotein(a). Curr Opin Lipidol 1992; 3:279–284.
4. **Naruszewicz M, Selinger E, Davignon J.** Oxidative modification of lipoprotein and the effect of beta-carotene. Metabolism 1992; 41:1215–1224.
5. **Lawn RM, Wade DP, Hammer RE, et al.** Atherogenesis in transgenic mice expressing human apolipoprotein(a). Nature 1992; 360:670–672.
6. **Sorensen KE, Celermajer DS, Georgakopoulos D, et al.** Impairment of endothelium-dependent dilation is an early event in children with familial hypercholesterolemia and is related to the lipoprotein(a) level. J Clin Invest 1994; 93:50–55.
7. **Pasternak RC, Grundy SM, Levy D, et al.** 27th Bethesda Conference: matching the intensity of risk factor management with the hazard for coronary disease events. Task Force 3. Spectrum of risk factors for coronary heart disease. J Am Coll Cardiol 1996; 27:978–990.
8. **Jenner JL, Ordovas JM, Lamon-Fava S, et al.** Effects of age, sex, and menopausal status on plasma lipoprotein(a) levels. Circulation 1993; 87:1135–1141.
9. **Hunninghake DB, Stein EA, Mellies MJ.** Effects of one year of treatment with pravastatin, an HMG-CoA reductase inhibitor, on lipoprotein(a). J Clin Pharmacol 1993; 33:574–580.
10. **Cressman MD, Heyka RJ, Paganini EP, et al.** Lipoprotein(a) is an independent risk factor for cardiovascular disease in hemodialysis patients. Circulation 1992; 86:475–482.
11. **Wanner C, Rader D, Bartens W, et al.** Elevated plasma lipoprotein(a) in patients with the nephrotic syndrome. Ann Intern Med 1993; 119:263–269.
12. **Brewer H.** Effectiveness of diet and drugs in the treat-

ment of patients with elevated Lp(a) level. In Scanu A, editor: Lipoprotein(a). Orlando, Fl: Academic Press, 1990:211.
13. **Hellsten G, Boman K, Hallmans G, et al.** Lipids and endurance physical activity [letter]. Atherosclerosis 1989; 75:93–94, 1989.
14. **Kim CJ, Min YK, Kwak JW, et al.** Effect of hormone replacement therapy on lipoprotein(a) and lipid levels in postmenopausal women: influence of various progestogens and duration of therapy. Arch Intern Med 1996; 156:1693–1700.
15. **Scanu AM, Lawn RM, Berg K.** Lipoprotein(a) and atherosclerosis. Ann Intern Med 1991; 115:209–218.
16. **Farnier M, Bonnefous F, Debbas N, et al.** Comparative efficacy and safety of micronized fenofibrate and simvastatin in patients with primary type IIa or IIb hyperlipidemia. Arch Intern Med 1994; 154:441–449.
17. **Genest JJ, McNamara JR, Ordovas JM, et al.** Lipoprotein cholesterol, apolipoprotein A-1 and B and lipoprotein(a) abnormalities in men with premature coronary artery disease. J Am Coll Cardiol 1992; 19:792–802.
18. **Jurgens G, Koltringer P.** Lipoprotein(a) in ischemic cerebrovascular disease: a new approach to the assessment of risk for stroke. Neurology 1987; 37:513–515.
19. **Murai A, Miyahara T, Fujimoto N, et al.** Lp(a) lipoprotein as a risk factor for coronary heart disease and cerebral infarction. Atherosclerosis 1986; 59:199–204.
20. **Valentine RJ, Grayburn PA, Vega GL, et al.** Lp(a) lipoprotein is an independent, discriminating risk factor for premature peripheral atherosclerosis among white men. Arch Intern Med 1994; 154:801–806.
21. **Desmarais RL, Sarembock IJ, Ayers CR, et al.** Elevated serum lipoprotein(a) is a risk factor for clinical recurrence after balloon coronary angioplasty. Circulation 1995; 91:1403–1409.
22. **Terres W, Tatsis E, Pfalzer B, et al.** Rapid angiographic progression of coronary artery disease in patients with elevated lipoprotein(a). Circulation 1995; 91:948–950.
23. **Genest JJ, Jenner JL, McNamara JR, et al.** Prevalence of lipoprotein(a) excess in coronary artery disease. Am J Cardiol 1991; 67:1039–1045.
24. **Bostom AG, Cupples LA, Jenner JL, et al.** Elevated plasma lipoprotein(a) and coronary heart disease in men aged 55 years and younger. A prospective study. JAMA 1996; 276:544–548.
25. **Ridker PM, Hennekens CH, Stampfer MJ.** A prospective study of lipoprotein(a) and the risk of myocardial infarction. JAMA 1993; 270:2195–2199.
26. **Cantin B, Gagnon F, Moorjani S, et al.** Is lipoprotein(a) an independent risk factor for ischemic heart disease in men? The Quebec Cardiovascular Study. J Am Coll Cardiol 1998; 31:519–525.
27. **Hopkins PN, Wu LL, Hunt SC, et al.** Lipoprotein(a) interactions with lipid and nonlipid risk factors in early familial coronary artery disease. Arterioscler Thromb Vasc Biol 1997; 17:2783–2792.
28. **Maher VM, Brown BG, Marcovina SM, et al.** Effects of lowering elevated LDL cholesterol on the cardiovascular risk of lipoprotein(a). JAMA 1995; 274:1771–1774.