Lipoprotein(a) and Cardiovascular Disease

Lipoprotein(a), a unique and relatively pervasive lipoprotein abnormality, is an independent risk factor for, and causal agent in, cardiovascular disease. It is estimated that 1 in 5 patients, or 63 million Americans, are affected by this atherogenic lipoprotein. Treatment includes clinically based therapies aimed at managing known risk factors and dramatically lowering LDL cholesterol.

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Cardiovascular disease (CVD) is the leading cause of death in the United States. CVD-related diseases affect 83.6 million people in the US and are responsible for almost 800,000 deaths annually.[1] The myriad underlying causes for these disorders range from inadequate lifestyle management to genetic abnormalities. One genetically determined abnormality is lipoprotein(a), or Lp(a).[2-4]

It is estimated that 25% of the US population has elevated Lp(a) levels (> 30 mg/dL) that are clinically significant.[5] Lp(a) is recognized as an independent risk factor for CVD, stroke, retinal artery occlusions, and restenosis of vein grafts.[2-5]

Regardless of practice type, clinicians at some point in their career will see a "vasculopath." Many of these patients have undiagnosed familial hypercholesterolemia, which affects 1 in 200 to 300 patients in the US and manifests with LDL cholesterol (LDL-C) levels ≥ 190 mg/dL.[6-8] Other patients may have CVD with relatively "normal" traditional lipids, more aggressive premature disease, and/or progressive disease despite "usual therapy."

As clinical lipid specialists working both in cardiology and endocrinology, the authors find the lack of evaluation for additional abnormalities in high-risk patients to be quite disturbing. The patient most commonly seen with the Lp(a) abnormality is one with CVD onset approximately one decade earlier than expected, along with a family history of premature CVD or closure of recently placed stents. Unfortunately, this may result in disease in the second or third decade for men and third or fourth decade for women.

Of course, CVD can leave patients with less productive lives and increase the burden to the health care system and to society. A positive outcome of identification of this apolipoprotein abnormality is that it may prompt evaluation of other family members prior to the inception of vascular disease. When it is identified in the asymptomatic, disease-free patient, aggressive risk reduction—in the form of lifestyle management and medication—may delay or prevent disease onset.

IDENTIFICATION OF THE PROBLEM

Office visits seldom include a thorough and complete patient history. A "good" family history should include first-degree relatives. Time-constrained practitioners may take a rudimentary family history of immediate relatives when a pedigree of the patient would be more appropriate.

Pedigree assessment offers a more specific picture of disease in families and identifies prevalence and incidence. Busy clinicians could have patients use an online resource to generate their own family pedigree. Or, as in most practices, a medical assistant or other appropriate office staff could initiate the process in the chart.

Patients with premature or advanced disease and significant family history need further investigation. A suspect history would include multiple family members with disease earlier in life than expected and perhaps early cardiovascular death. The personal history of the patient may include

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multiple cardiovascular incidents despite therapeutic intervention; despite taking lipid-lowering and/or antiplatelet therapy, the patient will present with progressive disease. Often, disease manifests in multiple areas of the vasculature or as restenosis of previous interventions.

GENETICS

Lp(a) results from a genetic variation of the apolipoprotein(a) (LPA) locus on chromosome 6q27. Lp(a) is comprised of an apolipoprotein(b) (apoB)–containing LDL molecule that is bonded to LPA. LPA is structurally similar to plasminogen, the precursor for plasmin that degrades fibrin in blood clots. Due to this similarity, LPA can competitively inhibit plasmin activity and thereby increase risk for thrombosis.[4,9]

PHYSICAL EXAMINATION

Patients with very elevated LDL-C levels in whom Lp(a) is also high may present with other outward stigmata of dyslipidemia. Visualization of the eye may reveal evidence of severe dyslipidemia with arcus cornea. This arcus can present as unilateral, bilateral, inferior, superior, or mixed and is representative of the buildup of cholesterol that cannot be removed from the body by normal means. Further examination may reveal tendon xanthomas, which are also representative of a genetic cholesterol disorder—in most cases, familial hypercholesterolemia.[7]

LABORATORY WORKUP

In patients who are known or suspected to be at high risk for CVD, the laboratory workup should include a fasting lipid panel, with Lp(a) and apoB; a comprehensive metabolic profile to establish renal and liver function (as therapeutic interventions utilize these organs for metabolism); and a fasting glucose measurement to rule out occult diabetes, which enhances risk factors. Thyroid function is also assessed, secondary to its deleterious effects on lipid metabolism.

Lp(a) results must be interpreted in the context of ethnicity; significance will vary. For example, both the African-American and Asian populations have been found to have high levels of Lp(a), but these are generally felt to be less atherogenic in African Americans. No major differences have been identified for other populations. It is, however, important to note that those patients with nephropathies and elevated Lp(a) carry a higher risk for coronary artery disease.

Lp(a) levels will remain relatively steady throughout life, negating the need for routine monitoring once a patient's levels have been established. The exception is postmenopausal women, in whom Lp(a) levels may increase due to changes in estrogen. It is prudent to assess Lp(a) in women both pre- and postmenopause, based on data from the Women's Health Study.[10]

DIAGNOSIS AND TREATMENT

Elevated Lp(a), which is found in 25% to 35% of the population, is diagnosed at a level > 30 mg/dL, regardless of sex.[4,9] In conjunction with known disease, elevated Lp(a) is sufficient to warrant consideration of very aggressive treatment. In these circumstances, the provider may consider a target LDL-C level ≤ 70 mg/dL.[6,7,11] In primary prevention, clinicians should consider lowering this threshold. Levels that may have been considered appropriate in a low- or moderate-risk patient (≤ 160 mg/dL and ≤ 130 mg/dL, respectively) may be reduced to ≤ 130 mg/dL and ≤ 100 mg/dL, respectively.[6,11]

There is no peer-reviewed evidence with regard to lifestyle management (exercise and diet) for reduction of Lp(a). However, it is reasonable to recommend that high-risk patients adopt healthier regimens.

Management of elevated Lp(a) includes consideration of pharmacologic intervention. Since Lp(a) is prothrombotic, all patients without contraindications should at least be taking low-dose (81-mg) aspirin. Those with evidence of thrombotic events may need lifetime antiplatelet therapy.[12] Statin therapy has mixed and minimal effects on Lp(a), although it remains the mainstay of treatment due to its effects on LDL-C and other lipoproteins.[13] Although long-term data are lacking, there is some anecdotal evidence of improvement with fibrate therapy. However, it is not recommended for treatment of elevated Lp(a).[14]

Nicotinic acid has had the longest and most robust history for reduction of Lp(a).[9,12] However, recent studies examining combination therapy with statins and nicotinic acid have yielded discouraging results—and in some cases have suggested negative outcomes with this combination.[15,16] High doses (4-5 g for immediate release and 2-3 g for sustained release) of nicotinic acid are necessary to produce beneficial results on Lp(a) or other lipid abnormalities (eg, elevated triglycerides, low HDL cholesterol).[17] Use of OTC nicotinic acid

is not recommended, since these products are considered dietary supplements and regulated as such, raising the potential for untoward adverse effects and/or the possibility that little to no active ingredient is present.[18-20]

Results from the Women's Health Study and the Heart and Estrogen/progestin Replacement Study suggested that estrogen might be an effective therapy. In one analysis, women with elevated Lp(a) derived greater potential cardioprotective effects from hormone replacement therapy (HRT) than those with lower Lp(a), and the researchers noted a "significant interaction" between baseline Lp(a), HRT treatment, and CVD risk. However, use of HRT is not approved for treatment of vascular risk today, due to the potential for adverse effects.[10,21]

A novel therapy, in the form of PCSK9 inhibition, has been shown to reduce LDL-C significantly; reduction in Lp(a) was also observed. The FDA recently approved two PCSK9 inhibitors (alirocumab and evolocumab) for use, although the primary indication is for further reduction in LDL-C on top of the maximally tolerated dose of statin therapy, not for reduction of Lp(a).[22,23]

Apheresis has been shown to have positive effects in reducing ongoing vascular events in select patient populations. It is approved by the FDA for treatment of refractory LDL-C, mostly in patients with familial hypercholesterolemia, but it is not indicated for treatment of elevated Lp(a). However, since Lp(a) tracks with LDL-C, it is also removed during the process; about a 50% reduction in Lp(a) levels has been noted, although levels rebound posttreatment. To date, reimbursement issues remain in the absence of an FDA indication and due to the paucity of treatment centers in the US.[24,25]

Follow-up. The therapies mentioned require routine evaluation to assess tolerability and safety, as recommended in the prescribing information. Patients with known CVD should undergo an appropriate cardiac workup annually to evaluate for occult progression of disease. Patients require further evaluation of related cardiovascular risk factors and adherence with medication regimens. For primary prevention patients, annual follow-up is also recommended to assess for any changes in health status, lifestyle, or medication adherence.

CONCLUSION

The average health care provider frequently performs the standard evaluation of a patient at risk for, or with, CVD. However, a subset of this population may be at increased cardiovascular risk due to Lp(a), a common genetic risk factor that can be responsible for premature or progressive CVD. Because of the aggressive nature of this disorder and the young age at which it influences the development of vascular disease, health care providers must be more vigilant about looking beyond the obvious in patients with familial hypercholesterolemia or family history of premature CVD.

Patients with progressive disease must be more thoroughly evaluated; there are already more than 63 million persons with elevated Lp(a) in the US—and many more undiagnosed—who may benefit from aggressive care. Underdiagnosis has been associated with decreased quality and productivity in the work environment, decreased quality of life, increased use of health dollars, and possibly early loss of life.

While the test for Lp(a) is readily available, the cost may not be covered by insurance and therefore may be passed on to the patient. It would behoove health care professionals to lobby for coverage as a means to reduce the prevalence of CVD, the number one cause of mortality in the US. **CR**

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