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Lipoprotein(a): Why is it important?

Selected patients may need to use niacin alone or in combination with a statin to lower elevated Lp(a) levels and reduce cardiovascular disease risk.

ABSTRACT: Elevated lipoprotein(a) is an independent risk factor for cardiovascular disease, particularly in individuals with elevated low-density-lipoprotein cholesterol. Candidates for lipoprotein(a) screening include patients with familial hypercholesterolemia, those with personal or family history of premature cardiovascular disease, or those with recurrent cardiovascular events despite treatment with statins. While niacin is the most effective pharmalogical agent for lowering Lp(a) levels, the initial step should be to decrease risk due to Lp(a) by lowering LDL-C below 2.0 mmol/L with a statin.

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Although lipoprotein(a) or Lp(a) was discovered 50 years ago, its role in cardiovascular disease (CVD) still challenges both basic scientists and clinicians. Elevated Lp(a) is an independent risk factor for atherosclerotic coronary artery disease (CAD) and stroke, particularly in those with high low-density-lipoprotein cholesterol (LDL-C) or non-high-density-lipoprotein cholesterol (non-HDL-C) levels.[1,2] The association of elevated Lp(a) with an increased risk of cardiovascular mortality and morbidity suggests that lowering Lp(a) using the therapeutic options available may be beneficial.

Lp(a) and cardiovascular disease

Lp(a) consists of an LDL particle attached to apolipoprotein(a) or apo(a)—a distinct protein responsible for the functional properties of Lp(a).[1,2] The presence of apo(a) increases the density of Lp(a) compared with LDL-C, and reduces its affinity for the LDL receptor. Lp(a) also promotes thrombosis by interfering with the fibrinolytic pathway.[3,4] There is considerable heterogeneity in the size and molecular weight of apo(a), both of which are determined by the *LPA* gene.[1-4]

Several studies have found an independent and continuous association between Lp(a) and CVD,[1,2] while others indicate that the risk is markedly greater at the extreme levels of Lp(a).[5,6] The size of Lp(a) modulates CAD risk, with the smaller apo(a) isoforms associated more strongly with risk of CAD.[1-4] Polymorphism in the *LPA* gene also influences Lp(a) levels and increases the risk of myocardial infarction, with some common variants of the *LPA* gene being associated with a more than 50% risk of heart disease.[7] Lp(a) is found in a wide range of plasma concentrations (from 20 mg/L to more than 2000 mg/L), with almost 20% of individuals at the extreme levels.[1-4]

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Even though elevated Lp(a) is a known CAD risk factor, the clinical utility of using elevated Lp(a) as a prognostic factor in secondary prevention is not fully established. This may be because clinical studies undertaken to date lack consistency in patient selection, doses and duration of treatment, and methods used for measuring Lp(a).[8]

Testing and treatment options

Nordestgaard and colleagues[2] recommend that Lp(a) should be measured in patients with:

- Familial hypercholesterolemia.
- Strong family history of CVD.
- Personal history of premature CVD.
- Recurrent CVD despite statin treatment.
- Inadequate response to statins.

Repeat measurement is indicated only in individuals treated for high Lp(a).

Unlike elevated LDL-C, elevated Lp(a) is resistant to both lifestyle modification and statin treatment. Statins decrease Lp(a) only modestly.[9] In patients with familial hypercholesterolemia, statins have been shown to reduce Lp(a) by 17% to 22%.[10] The only treatment that effectively lowers Lp(a) in a dose-response manner is niacin alone or in combination with a statin.[1,2] Lowering appears to be greater at extreme Lp(a) levels, with several studies showing that niacin reduces Lp(a) by up to 40%.[1,2] Niacin also has other beneficial effects, such as reducing LDL-C and triglycerides, and raising HDL-C.[1,2]

Other agents that have a minor effect on Lp(a) (lowering levels by less than 10%) are aspirin, estrogen, thyroxine replacement, fish oil, and calcium antagonists.[2]

Lipoprotein apheresis is the most effective way to lower Lp(a).[1-4,9] Mipomersen, an antisense oligonucleotide,[1,2] is a new agent that lowers both Lp(a) and LDL by inhibiting synthesis of apolipoprotein B. The protein convertase subtilisin/kexin-type 9 (PCSK9) inhibitor and cholesterol ester transfer protein (CETP) inhibitor are two other compounds that reduce Lp(a) by 40% and 17%, respectively, but they are currently undergoing phase 3 clinical trials.[1]

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Even though niacin reduces Lp(a) by 40%, the National Cholesterol Education Program (NCEP) Adult Treatment Panel III says it is unclear if this niacin-induced reduction in Lp(a) decreases risk of CAD.[11] In patients with elevated Lp(a) in the presence of elevated LDL-C, the first LDL-C step should be to lower the level.[11] Several studies have shown that Lp(a)-associated cardiovascular risk is markedly decreased in patients with LDL-C levels below 2.0 mmol/L.[12,13] Consequently, the following treatment approaches are indicated:

- If the Lp(a) level is greater than 300 mg/L (above the 75th percentile in most populations) the patient should be treated with a maximally tolerated dose of statin and/or other LDL-lowering medications to achieve a reduction in LDL-C below 2.0 mmol/L.
- If LDL remains between 2.0 and 2.6 mmol/L, the addition of niacin should be considered, up to 2 g daily.
- If LDL remains equal to or greater than 4.1 mmol/L, or if the patient has progressive CAD, LDL-C apheresis should be considered.

Recently, Bruckert and colleagues[14] published a meta-analysis on the use of niacin in patients with elevated Lp(a) that supported the following recommendations:

- After elevated LDL-C levels have been reduced, elevated Lp(a) levels should be reduced.
- Elevated Lp(a) levels should be reduced in patients at intermediate or high risk of CVD, even if they do not have diabetes or established CVD.
- Combination therapy with a statin and niacin should be used in patients with Lp(a) greater than 500 mg/L, and in those with familial hypercholesterolemia, those with a family history of premature CVD and high Lp(a), those with premature CVD, and those with recurrent CVD and resistance to statins.

Selected patients should be screened and treated. While niacin is the most effective pharmacological agent, the first step for lowering Lp(a) should be to lower LDL-C below 2.0 mmol/L with a statin.

Conclusions

Epidemiological and genetic studies have identified elevated lipoprotein(a) as an independent risk factor for cardiovascular disease. Elevated Lp(a) levels promote atherosclerosis and thrombosis. Selected patients should be screened and treated. While niacin is the most effective pharmacological agent, the first step for lowering Lp(a) should be to lower LDL-C below 2.0 mmol/L with a statin.

Competing interests

None declared.

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