Artículo de Revisión

Targeting Lipoprotein(a) to reduce residual risk in high risk atherosclerotic cardiovascular disease patients.

Enfocando en la Lipoproteína(a) para reducir el riesgo residual en enfermedad cardiovascular aterosclerótica de alto riesgo.

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ABSTRACT

Abnormal lipoprotein(a) [Lp(a)] levels are associated with an elevated risk of cardiovascular events. Lp(a) has been used to risk stratify primary prevention patients, and more recently, it has been identified as a marker of residual risk in secondary prevention patients. Treatment for these patients is limited to LDL lowering therapies and optimizing lifestyle changes. Novel nucleic acid therapies that target Lp(a) production, including antisense oligonucleotide (pelacarsen) and small-interfering RNA (olpasiran), are safe and markedly lower Lp(a) levels. Phase 3 trials, HORIZON and OCEAN(a), are currently studying if significant reduction in Lp(a) with these drugs will lower major adverse cardiovascular events in patients with atherosclerotic cardiovascular disease (ASCVD).

Palabras clave:
Lipoproteína(a) – riesgo residual – prevención secundaria – oligonucleótidos antisentido – moléculas pequeñas de interferencia RNA

Enfocando en la Lipoproteína(a) para reducir el riesgo residual en enfermedad cardiovascular aterosclerótica de alto riesgo.

RESUMEN

Los niveles anormales de lipoproteína (a) (Lp(a)) están asociados a un elevado riesgo de padecer eventos cardiovasculares. La Lp(a) ha sido utilizada para estratificar el riesgo en pacientes en prevención primaria, y más recientemente, ha sido identificada como un marcador de riesgo residual en prevención secundaria. El tratamiento de estos pacientes está limitado a las terapias de descenso del cLDL y a la optimización de los cambios en el estilo de vida. Nuevas terapias de ácidos nucleicos enfocadas en la producción de Lp(a), incluyendo los oligonucleótidos antisentidos (pelacarsen) y las moléculas pequeñas de interferencia RNA (Olpasiran) son seguras y disminuyen marcadamente Lp(a). Estudios en fase 3, HORIZON y OCEAN(a), están actualmente estudiando si una significativa reducción de Lp(a) con estas drogas podría disminuir los eventos adversos cardiovasculares en pacientes con enfermedad cardiovascular aterosclerótica (ECVA).

CASE PRESENTATION

Mr. Sonic presented in 2009 as a 36-year-old male. He was diagnosed with dyslipidemia in high school. He has no symptoms. He eats a diet of lean protein and vegetables. He exercises aerobically five days a week for 45 minutes. He is a prior smoker with a family history of stroke. He brings his recent lipid panel: total cholesterol 252 mg/dL, triglycerides 64 mg/dL, HDL 53 mg/dL, LDL 186 mg/dL, and lipoprotein (a) 117 mg/dL. He was started on atorvastatin 80mg. Six months later his LDL was not at goal, and he was started on ezetimibe 10mg q day. To be continued…

INTRODUCTION

Elevated lipoprotein(a) [Lp(a)] is a known independent risk factor for developing cardiovascular disease. Lp(a) is considered a risk enhancer in primary prevention and a residual risk factor in secondary prevention[1,2,3,4]. With multiple targeted Lp(a) lowering therapies currently in development, there has been a resurgence of interest in Lp(a), specifically in the secondary prevention realm. Trials are currently underway to investigate if marked reductions in Lp(a) levels with nucleic acid therapies will significantly decrease future major adverse events in patients with established high risk atherosclerotic cardiovascular disease

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(ASCVD) and high Lp(a) levels. The objectives of this review article are to:

1) Discuss the evidence for Lp(a) as a target for risk reduction.
2) Consider the various indications for measuring Lp(a).
3) Review current and future potential Lp(a) treatment options.

BACKGROUND ON LP(A)

Lp(a) is a low-density lipoprotein (LDL) with an added apolipoprotein(a) attached to the apolipoprotein(b) component of the LDL particle via a disulfide bridge. Levels are not impacted significantly by lifestyle, including diet and exercise[5]. Certain non-genetic factors have been found to alter levels, including hypothyroidism/hyperthyroidism, pregnancy, nephrotic syndrome, dialysis, and several autoimmune diseases[6,7,8,9,10]. However, levels of Lp(a) are primarily determined by the LPA gene and are less influenced by non-genetic factors[11,12,13]. In a recent study on over 15,000 participants, there was a strong correlation between baseline and follow-up Lp(a) measurements over a median of 4.42 years, suggesting it is consistent over time in most people and can be considered a "once in a lifetime" measurement[14,15].

Lp(a) levels are skewed in the population. Most people have Lp(a) levels less than 50mg/dL; however, 20% of the population has elevated Lpa(a) levels >50mg/dL[16]. In 2022, the EAS consensus panel classified levels <30mg/dL as "low risk," and levels >50 mg/dL "high risk;" the risk for patients with intermediate levels ranging from 31-50mg/dL is less certain[17,18]. This risk estimate can be further adjusted if other risk factors are also considered[18]. Lp(a) levels have been shown to vary depending on race and sex. Black participants are more likely to have higher concentrations of Lp(a) compared to white, south Asian, or Chinese participants, and females tend to have higher concentrations compare to men[19]. Despite differences in median levels between races, elevated Lp(a) has been shown to be an independent risk factor in all racial groups[19,20].

MEASURING LP(A)

The challenge of accurately measuring Lp(a) is due to the complexity of the LPA gene that codes the apo(a) protein and the various genetic regulatory mechanisms[21,22]. The apo(a) protein "tail" consists of a chain of five cysteine-rich domains known as kringles. The apo (a) gene has ten repeats of the fourth domain (kringle IV); these repeats are called subtypes (IV_1-IV_{10}). The second subtype (IV2) has 1-40 possible repeats, making it highly heterogeneous with many different isoforms of various sizes of Lp(a)[22]. This is important because the size of apo(a) is associated with the concentration[23]. For example, a patient with lower KIV_2 repeat number tends to have a higher particle number compared to a patient with a higher KVI_2 repeat number[24].

There are two major problems affecting the accuracy of Lp(a) results and interpretation. The first is related to the size variability of apo(a), which leads to overestimations and underestimations in measurement of Lp(a) because different assays are calibrated for different Lp(a) isoforms[25]. This makes it challenging to accurately compare values from different assays. As a solution, there are now commercially available assays with a large range of calibrated Lp(a) isoforms which can be standardized against approved, gold standard reference material[26,27].

The second problem is that there are two different units for reporting Lp(a): mg/dL and nmol/L. Currently, the preferred reporting unit for Lp(a) is nmol/L because it more accurately reflects the number of Lp(a) particles; if this is not possible, it is recommended to report the units from the assay that was used rather than attempting conversion[17]. There have been suggestions to multiple the value in mg/dL by 2-2.5 to estimate the value in nmol/L; however, there have not been any agreed upon conversion formulas to convert between these units, so this is not recommended[18,28].

PATHOGENIC MECHANISMS

The mechanisms responsible for the pathogenicity of Lp(a) for atherosclerotic disease and vascular events is not well understood, but has been attributed to its pro-thrombotic, pro-atherosclerotic, and pro-inflammatory properties.

The apo(a) tail has structural homology with plasminogen, and Lp(a) has been found to assist with wound healing and reduce bleeding, especially during childbirth[29]. While this has its evolutionary benefits, it is postulated that abnormally high levels could pathologically impair thrombolysis. The key pro-thrombotic mechanisms of Lp(a) studied *in vitro* included inhibition of the fibrinolytic system by competitively inhibiting plasmin generation and increasing tissue-factor-mediated thrombosis[30,31,32,33]. However, the pro-thrombotic contribution of Lp(a) *in vivo* is questionable and remains controversial because most clinical data is confounded by atherosclerosis[34]. In a study using Lp(a) lowering therapy with a nucleic acid injectable drug, pelacarsen, there was no change in measurements of fibrinolysis, including clot lysis times and coagulation biomarkers, suggesting that more data is needed to fully understand if thrombosis is truly a key pathogenic feature of Lpa(a)[35].

Lp(a) deposits in the arterial intima and binds to macrophages via high affinity receptors to promote foam cell formation and the initial stages of atherosclerosis[36]. Evidence from immunostaining of human coronary and carotid atherosclerotic lesions shows that Lp(a) is present in every stage of atherogenesis, from early superficial lesions to unstable plaque[37]. Given that Lp(a) is composed of an LDL particle, its shared atherogenic risk with LDL is expected, but when compared on an equimolar level, Lp(a) is more atherogenic than LDL[38]. This has been attributed to its pro-inflammatory effects from the apo(a) tail because it is the preferred carrier of oxidized phospholipids[39,40]. Lp(a) and oxidized phospholipids associated with apo(a) and apo (B) are strongly correlated with multivessel coronary disease, as well as major adverse cardiovascular events

(MACE) at 4-year follow-up in a statin treated patient population with a relatively low average baseline LDL of 83 mg/dL[41]. Additional pro-inflammatory effects of Lp(a) include increase IL-8 macrophage expression and increase monocyte cytokine release[42,43].

CLINICAL EVIDENCE THAT LP(A) MEDIATES CARDIOVASCULAR DISEASE

Coronary artery disease and myocardial infarcts

There is a linear association between elevated Lp(a) and MACE. In a study from 2009, it was found in three independent studies in Denmark, that the risk of myocardial infarct increased with increasing concentration of Lp(a)[44]. A metanalysis of 36 prospective studies showed an association with Lp(a) concentration and risk for MI, cardiovascular death, and ischemic stroke[45]. The same association was not found with Lp(a) concentration and nonvascular death[45]. These results were adjusted for systolic BP, smoking, history of DM, BMI and total cholesterol with minimal change in results. In a more recent 2022 UK study on 460,506 participants over a median of 11.2 years, primary and secondary ASCVD patients who had an Lp(a) ≥ 150 nmol/L were found to have a significantly higher risk of atherosclerotic events including myocardial infarct, revascularization, and ischemic stroke[17]. There was a minimal change in risk when adjusting for HTN, DM, smoking, total cholesterol, and prior cardiac disease.

Aortic stenosis

Abnormal levels of Lp(a) are associated with an increased risk of developing aortic stenosis and the LPA gene is associated with a risk of developing aortic valve stenosis[46,47]. In a 2019 study, elevated Lp(a) (>50mg/dL) was an independent risk factor for aortic stenosis after adjustments for age, sex, LDL, and concomitant CAD[48,49]. Increased calcification activity, including a faster progression of calcium scores, has been found in patients with elevated Lp(a)[48]. Additionally, there is a faster progression to hemodynamic significant aortic stenosis needing aortic valve replacement in patients with abnormal Lp(a)[48]. Lp(a) should be considered in patients with premature aortic stenosis with no other causes of early valvular calcification, such as bicuspid valves, rheumatologic disorders, or chronic kidney disease. In the future, there is potential for utilizing Lp(a) as a marker to help determine shorter echo surveillance duration and as a treatment target in aortic stenosis patients with abnormal Lp(a)[50].

Peripheral arterial disease

There is a strong association between Lp(a) and PAD. In a genetics study that looked at DNA sequences (approximately 32 million DNA sequence variants) in over 30,000 patients with PAD, there were 19 loci identified to have an association with PAD. Out of these 19 loci, which included the LDLR and LPL loci, the LPA gene was found to be the strongest predictor of PAD[51]. In a recent study in 2022 on patients undergoing peripheral artery disease endovascular therapy, elevated Lp(a) was independently associated with adverse cardiovascular and limb events even in patients on statin therapy[52].

WHO TO MEASURE LP(A)?

Recommendations on who to consider a measurement of Lp(a) vary across different guidelines and organizations. The 2018 AHA/ACC cholesterol guidelines recommend checking Lp(a) in primary prevention patients who are intermediate risk and patients with a family history of premature CAD[1]. The guidelines consider Lp(a) a risk enhancer for primary prevention if levels are >50mg/dL or >125 nmol/L, and these patients should be considered for statin therapy[1].

Over the past couple of years, the indication for Lp(a) measurement has broadened. The NLA statement in 2019 includes patients with suspected familial hypercholesterolemia (FH) and patients who are high risk considering PCSK9 monoclonal antibody inhibitor initiation[53]. The ESC/EAS guidelines in 2020, as well as the CCS, have extended this further to recommend universal screening in all adults[54,55].

Identifying patients with high Lp(a) is useful in cascade screening for genetic lipid disorders. Both FH and abnormal Lp(a) result in premature cardiovascular disease. A study from 2022, directly compared these two traits and the risk of MI[56]. The results showed that patients who carried a clinical diagnosis of FH had a similar risk to patients with Lp(a) of 70 mg/dL or greater. This varied depending on which scoring system was used. Over 15% of the population has Lp(a) levels greater than 70mg/dL; therefore, the population risk of abnormal Lp(a) is likely higher than FH[57]. Lp(a) is transmitted in an autosomal dominant fashion, making it a 50% chance of finding a first degree relative with the diagnosis through cascade screening[58]. If lifestyle changes and treatment options are implemented early in these relatives, it could significantly impact the younger generation's future.

CASE PRESENTATION (CONTINUED)

In December 2022, Mr. Sonic is now 49 years old and presents to the Emergency Department with acute decompensated congestive heart failure. He was last seen in lipid clinic in 2011. He reported being compliant with his statin and ezetimibe. Echo showed severely reduced EF. Left heart catheterization revealed multivessel disease, and a cardiac MRI showed evidence of a large infarct. What should be considered for his lipid therapy now?

AVAILABLE TREATMENT OPTIONS FOR PATIENTS WITH ELEVATED LP(A)

Unfortunately, current available lipid therapies have not shown a significant lowering of Lp(a) with reduction in cardiovascular events. Niacin reduces Lp(a) values by up to 38%[59,60]. However, in two large clinical trials, HPS2-THRIVE and AIM HIGH, niacin therapy did not decrease

the incidence of cardiovascular disease events[61,62]. Statins have been found to slightly increase Lp(a), but still reduce the incidence of cardiovascular disease, regardless of Lp(a) level[63]. While there appears to be an overall benefit for these patients to be on statin therapy, a significant risk for recurrent events remains. In a metanalysis of seven randomized controlled trials, patients with elevated Lp(a) on statin therapy had an independent, linear relationship with cardiovascular disease and continued to have significant risk of cardiovascular disease independent of risk factors including age, LDL-C, HDL-C, and diabetes[2].

Lipoprotein apheresis reduces Lp(a) by as much as 75% with each treatment[44]. In trials conducted in Germany, it was found to reduce risk 75-95%[45]. Unfortunately, it is cumbersome, expensive, and often given weekly to biweekly. Also, questions arise about whether the derived benefit is predominantly from the many lipoproteins that are reduced, since it is not targeted specifically for Lp(a) lowering[46]. Lipoprotein apheresis remains an option, albeit unappealing, for patients with recurrent ASCVD events despite optimal lipid lowering.

Finally, PCSK9 monoclonal antibody inhibitors also modestly reduce Lp(a). In the FOURNIER trial, there was a median reduction in Lp(a) of 26.9% in patients on evolocumab and a median reduction of 36 nmol/L (16%) in the highest quartile[4]. In the ODYSSEY outcomes trial, there was a similar reduction in Lp(a) levels with alirocumab[3]. Mendelian randomization analysis estimated that the risk reduction from lowering 38 mg/dL of LDL is equivalent to 101 mg/dL of Lp(a)[64]. Another similar study showed a lower target of Lp(a) at 65.7 mg/dL[65]. In the FOURNIER trial, there was only a 36 nmol/L (approximately 16 mg/dL) reduction in Lp(a) levels, which is significantly lower than what was estimated in the two Mendelian randomization analyses. Furthermore, patients with an abnormal Lp(a) level in FOURNIER trial ranged from 125 nmol/L to over 500 nmol/L. This small reduction in Lp(a) seems unlikely to have any clinical significance in patients with a very high Lp(a) level.

In both post-hoc analyses of PCSK9 monoclonal antibody inhibitors, patients in the highest quartiles of Lp(a) levels had a reduction in outcomes compared to those with lower Lp(a), suggesting a benefit to using a PCSK9 monoclonal antibody inhibitor in this higher risk patient population with significantly elevated Lp(a). These drugs are not approved or currently recommended for Lp(a) lowering. However, Lp(a) can be a useful marker for patients and providers to consider when weighing decisions regarding alirocumab and evolocumab initiation.

LP(A) AS A MARKER FOR RESIDUAL RISK

CASE PRESENTATION (CONTINUED)

Mr. Sonic was started on a PCSK9 monoclonal antibody inhibitor. His recent LDL is now 44 mg/dL. He is planning to undergo CABG soon. While it is reassuring to see his LDL significantly lowered, what about his Lp(a)? In his current state, is he still at increased risk of future events, despite revascularization and low LDL?

Post-CAGB patients with high Lp(a) have been found to have a threefold risk of vein graft occlusion at one year follow-up[66]. Lp(a) is predictive of recurrent events in statin treated patients[67]. In a study from 2014, post-CABG patients with Lp(a) level greater than 30mg/dL were at a greater risk for cardiovascular death, non-fatal MI, hospitalization for unstable angina or repeat revascularization within 15 years after CABG, regardless of statin use[68]. In a study on the Copenhagen General Population with median follow of 7.4 years, MACE was higher at a Lp(a) level >50mg/dL, even with LDL-C levels <70mg/dL[17]. This was consistent with analysis from the JUPITER trial which showed higher Lp(a) levels were associated with residual risk of cardiovascular disease, even with low LDL (median 54 mg/dL)[63]. Overall, these data suggest that patients with elevated Lp(a) are at increased risk of repeated cardiovascular events despite being on lipid lower therapy.

NOVEL THERAPIES TO TARGET LP(A)

Three nucleic acid therapies have been developed to treat elevated Lp(a). Pelacarsen is a hepatocyte directed antisense oligonucleotide targeting the mRNA from the LPA gene[69]. Olpasiran and SLN360 are small interfering RNA therapies that disrupts expression of LPA by degrading apolipoprotein (a) mRNA, which in turn inhibits translation of the apo(a) protein in the hepatocyte[70]. Early studies of these drugs have shown a marked reduction in Lp(a) levels.

The HORIZON phase 2 trial showed dose-dependent reductions in patients with elevated Lp(a) and established CVD. Specifically, Lp(a) was lowered by 35-72% when pelacarsen was given every 4 weeks, and as high as 80% if given weekly[69]. The most common adverse events were mild injection site reactions. Enrollment for the phase 3 trial is completed with results expected in 2025. The inclusion criteria were Lp(a) ≥ 70mg/dL with established ASCVD (MI, CVA, PAD). The primary end point of the study is cardiovascular death, nonfatal MI, nonfatal stroke, and urgent coronary revascularization.

The OCEAN(a) phase 2 trials with olpasiran showed an equally impressive reduction with a longer duration between injections (12 weeks). There was a decrease of greater than 90% from baseline Lp(a) at most doses every 12-24 weeks[70]. Adverse events were similar across all groups, and the most common adverse event was injection-site reactions. The phase 3 OCEAN(a) trial is a double-blind, randomized, placebo-controlled multicenter study to assess the impact of olpasiran on major cardiovascular events and is currently enrolling patients.

Phase 1 trials for SLN360 showed a decrease of Lp(a) by up to 98%[71,72]. SLN360 showed a sustained reduction of levels lasting up to 150 days[72]. There have been no major safety concerns in the early phases of this agent and a phase 2 trial is underway currently.

The patient population for the HORIZON and OCEAN(a) phase 3 trials is high risk ASCVD patients. For both trials, the inclusion and exclusion criteria do not have a LDL-C goal

for enrollment. There is no exclusion for most of the novel LDL lowering therapies including statins, ezetimibe, PCSK9 monoclonal antibody inhibitors, and/or bempedoic acid. These trials will assess whether marked Lp(a) reduction can improve residual risk and decrease adverse cardiovascular events in secondary prevention patients.

CONCLUSION

Lp(a) is an important risk marker for cardiovascular disease and can guide treatment decisions in both primary and secondary prevention. Measurement of Lp(a) should be considered in patients with premature ASCVD, a family history of premature ASCVD, a family history of elevated Lp(a), recurrent cardiovascular events despite statins, LDL-C not at target despite treatment, FH, and premature calcific aortic stenosis. Additionally, there is strong evidence to support universal screening. Maximizing preventive care remains the cornerstone of treatment for these patients. This includes LDL-C lowering, blood pressure control, glucose management, diet, exercise, and tobacco cessation; practitioners should also consider referral to a lipid specialist and clinical trials. Novel nucleic acid therapies can safely and effectively reduce Lp(a). While awaiting the outcome data from these trials, treatment for high risk ASCVD patients with elevated Lp(a) remains limited and challenging

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