Current and Emerging Treatment Options for Elevated Levels of Lipoprotein(a)

Elevations in Lp(a) have been implicated as an independent risk factor for major adverse cardiovascular events (MACE). Given the lack of approved medications that specifically target Lp(a) lowering, at the time of writing, clinicians focus intensively on managing all other risk factors for heart attack and stroke to improve patients' cardiovascular outcomes.

Statins might increase Lp(a) concentrations.
In recent years, several reviews and meta-analyses have shown that statin therapy is often associated with an overall increase in Lp(a) levels. In a retrospective cohort study, using a health database and 221 participating hospitals in China, researchers conducted a to examine the impact of statin use on Lp(a) concentrations. Patients were matched 1:1 for statin vs non-statin users; hazard ratios were calculated on Lp(a) changes based on the statin usage cohorts. (Feng, 2023) Participants were matched across groups according to their age, comorbidity history, sex, and duration of follow-up time. After adjusting for age, LDL-C, comorbidity history, HDL-C, APO-A, APO-B, and the change of LDL-C, statin use was associated with increased concentrations of Lp(a) (HR = 1.47 and the 95% CI: 1.43 to 1.50). When patients had comorbidities, statin use was associated with a lower increase in Lp(a) concentrations as compared with patients who did not have comorbidities. (Feng, 2023) Fluvastatin and simvastatin increased Lp(a) concentrations less than atorvastatin, while pravastatin increased Lp(a) concentrations more than atorvastatin. (Feng, 2023) These findings might help explain why patients still carry an increased CV risk despite maximally tolerated statin therapy.

PCSK9 inhibitors help lower Lp(a) concentrations in addition to LDL-C
Secondary analysis of the FOURIER and ODYSSEY trials indicated that reductions in risk for CVD, PAD, and venous thromboembolic events were associated with Lp(a) concentrations and treatment with evolocumab and alirocumab, respectively. Evolocumab significantly reduced Lp(a) concentrations at 48 weeks by a median of 26.9% (IQR: 6.2%-46.7%). (O'Donoghue, 2019) At 48 weeks, there were also positive associations between the percent change in Lp(a) and LDL-C levels. Evolocumab reduced the risk of coronary heart disease death, MI, or urgent revascularization by 23% (HR, 0.77; 95% CI, 0.67-0.88) in patients with a baseline Lp(a) >median 37 nmol/L (range 13-165 nmol/L). (O'Donoghue, 2019) The authors of this study concluded that patients with higher baseline Lp(a) concentrations experienced greater absolute reductions in Lp(a) and tended to benefit slightly more in terms of coronary risk reduction from PCSK9 inhibition. (O'Donoghue, 2019) Bittner et al. (2020) examined the effect of the PCSK9 inhibitor, alirocumab, on LDL-C and Lp(a) levels and their impact on MACE and found that baseline Lp(a) concentrations were 21.2 mg/dl (median; IQR: 6.7-59.6 mg/dl) and were predictive of MACE (as were LDL-C levels). Alirocumab reduced Lp(a) by 5.0 mg/dl, corrected LDL-C by 51.1 mg/dl, and reduced the risk of MACE (HR: 0.85; 95% CI: 0.78 to 0.93). Furthermore, a 1 mg/dl reduction in Lp(a) with alirocumab was associated with an HR of 0.994 (95% CI: 0.990 to 0.999; p = 0.0081. In the ORION-1 trial involving another PCSK9 inhibitor, investigators observed that 90% of participants in the 300 mg dose group, dosed twice, exhibited a 26% median decrease in Lp(a) concentrations at day 180. (Katsiki, 2023) Furthermore, this effect was observed regardless of whether patients had diabetes as a comorbidity. In the ORION-9 trial, inclisiran's effects were tested on patients with heterozygous familial hypercholesterolemia. On day 540, Lp(a) concentrations were decreased by 13.5% in this patient population. (Katsiki, 2023) At this time, none of the PCSK9 inhibitors have an explicit indication on their label for reducing Lp(a) concentrations.

Lipoprotein apheresis lowers LDL-C and Lp(a) concentrations
This technique is approved for removing lipoproteins from the blood. Itis usually indicated when patients have familial hypercholesterolemia (FH) and LDL-C levels >300 mg/dl, or for patients with FH, high CVD risk, and an LDL-C >200 mg/dl, or patients with progressive CVD and Lp(a) levels >60 mg/dl. (Feingold, 2023) Typically, apheresis can result in LDL-C and Lp(a) reductions of 50-75%. (Feingold, 2023) Triglyceride and HDL-C levels decrease but return to baseline by 24 hours. However, apheresis can be time-consuming and expensive, and patients may find it hard to locate treatment centers that provide the technique. (Feingold, 2023)

Molecules in development for Lp(a) lowering
Results of a phase 2 study examining the impact of pelacarsen on Lp(a) concentrations were published in 2020. Tsimikas et al. conducted a randomized, double-blind, placebo-controlled, dose-ranging trial in 286 patients with established CVD and Lp(a) concentrations of at least 60 mg/dl (150 nmol/L). Pelacarsen is an antisense oligonucleotide directed at the liver and administered subcutaneously. This therapy inhibits the production of apolipoprotein(a) in the liver to reduce Lp(a) concentrations. The primary endpoint was the percent change in Lp(a) level from baseline to month 6 of exposure. Patients received 20, 40, or 60 mg monthly, or 20 mg every two weeks or 20 mg of pelacarsen weekly. Lp(a) concentrations were reduced in a dose-adjusted fashion such that mean percent decreases of 35% were observed with a dose of 20 mg every 4 weeks, 56% at 40 mg every 4 weeks, 58% at 20 mg every 2 weeks, 72% at 60 mg every 4 weeks, and 80% at 20 mg every week, as compared with 6% with placebo (P values for the comparison with placebo ranged from 0.003 to <0.001). (Tsimikas, 2020) Platelet counts, liver and renal measures, and influenza-like symptoms did not differ between placebo and drug groups. The most common adverse event was injection site reactions.

Currently, this agent will be administered on a monthly basis and is being studied in a phase 3 trial termed HORIZON, which has just completed enrollment. (Ionis Press Release, 2022)

Olpasiran is also being studied as a small interfering RNA that reduces lipoprotein synthesis. Similar to pelacarsen, the results of the phase 2 study were recently published. Patients with a history of ASCVD, PAD, or atherosclerotic cerebrovascular disease were randomly assigned to receive one of four doses every 12 weeks: 10 mg, 75 mg, 225 mg, or 225 mg every 24 weeks. (O'Donoghue, 2022) The median concentration of Lp(a) at baseline was 260.3 nmol/L, while LDL-C was 67.5 mg. Placebo-adjusted mean percent decreases in Lp(a) concentrations were as follows at week 36: 10 mg and -70.5%, 75 mg and -97.4%, 225 mg and -101.1%, and with 225 mg given every 24 weeks, a decrease of -100.5% was observed (P<0.001 for all comparisons with baseline). (O'Donoghue, 2022) Thus, in patients with pre-existing disease, olpasiran was effective in lowering Lp(a) concentrations. Results from the off-treatment extension period show that patients previously dosed with ≥75 mg of olpasiran sustained a ~40%-50% placebo-adjusted percent reduction in Lp(a) nearly a year after the last dose. (Amgen Press Release, 2023) This agent is also currently in phase 3 trials.

Results from a phase I, single-dose trial of lepodisiran, another siRNA designed to disrupt apolipoprotein(a), have also been published. Nissen et al. (2023) tested doses of 4 mg, 12 mg, 32 mg, 96 mg, 304 mg, or 608 mg administered subcutaneously in 48 adults without CVD and who had Lp(a) concentrations of 75 nmol/L or greater (≥ 30 mg/dl). The primary outcome was the safety and tolerability of lepodisiran. The secondary outcome was plasma levels of lepodisiran 168 days after administration and changes in fasting Lp(a) concentrations through 48 weeks. At 48 weeks, the median change in Lp(a) concentrations was a decrease of 94% (IQR: -94% - -85%) in the 608 mg dose group. Maximal median changes for Lp(a) levels were -41% for the 4 mg group, -59% for 12 mg, -76% for the 32 mg group, -90% for the 96 mg group, -96% for the 304 mg dose, and -97% for the 608 mg group. (Nissen, 2023) Thus, early study results demonstrate long-lasting reductions in Lp(a) levels with lepodisiran.

An additional therapy, zerlasiran, a siRNA, is also being investigated for its effects on Lp(a) concentrations. In a safety and tolerability study, investigators examined the impact of zerlasiran on lowering serum concentrations of Lp(a) in patients with stable ASCVD and Lp(a) levels > 150 nmol/L. (Nissen, 2024) Participants were randomized to receive placebo or the following single doses of zerlasiran: 300 mg, 600 mg, or two doses of placebo, 200 mg, every four weeks, or 300 mg or 450 mg every nine weeks. Mean baseline concentrations of Lp(a) in patients who received multiple doses were 288 nmol/L (IQR: 199-352). After two doses, maximal median changes in Lp(a) concentration were 19 (IQR, −17 to 28) nmol/L for the placebo group, −258 (IQR, −289 to −188) nmol/L for the 200 mg group, −310 (IQR, −368 to −274) nmol/L for the 300 mg group, and −242 (IQR, −343 to −182) nmol/L for the 450 mg group. (Nissen, 2024) The maximal change in Lp(a) concentration for a single dose was a decrease of 30% for the 300 mg group. The following maximal median percent changes were also observed 201 days following administration: placebo, 7% (IQR, −4% to 21%); for 200 mg, −97% (IQR, −98% to −95%); for 300 mg, −98% (IQR, −99% to −97%); and for the 450 mg group −99% (IQR, −99% to −98%). Thus, even with only two doses, this therapy can effectively lower Lp(a) serum concentrations in patients. In a summary piece about another study, writers noted that zerlasiran was delivered subcutaneously at doses of 300 mg every 16 or 24 weeks and 450 mg every 24 weeks to patients with a median baseline Lp(a) level of around 215 nmol/L. (Klein, 2024) Results released early from this phase 2 study showed that both dosage groups experienced a median reduction in Lp(a) of 90% or more by week 36. No serious safety concerns were reported to date in either Nissen 2023 or Klein 2024.

To date, muvalaplin is the first oral therapy in trials to test its safety and efficacy in lowering serum concentrations of Lp(a). (Nicholls, 2023) A randomized, double-blind, parallel-design, single-site, phase 1 study examined the impact of a single ascending or a multiple ascending dose paradigm for 14 days in patients who had Lp(a) levels of 30 mg/dl or greater. Doses ranged from 30 mg to 800 mg with a half-life ranging from 70-414 hours. Maximum placebo-adjusted Lp(a) reduction was 63%-65%, resulting in plasma levels <50 mg/dL in 93% of participants. Similar effects were seen at daily doses of 100 mg or more. This therapy was not associated with tolerability concerns or clinically significant adverse events. (Nicholls, 2023)

Conclusion: Currently, there are no medications that are FDA approved to lower serum concentrations of Lp(a), an independent risk factor for cardiovascular disease. However, multiple therapeutic agents are under investigation and in various phases of clinical trials that are being examined for their efficacy and safety in reducing serum Lp(a) concentrations. The majority of these therapies are administered subcutaneously, and one of them is an oral therapy. To date, all therapies look promising in lowering Lp(a) concentrations, even over the long term. Additionally, some of these trials will also likely investigate the effect of MACE risk reduction in concert with Lp(a) lowering efficacy. These therapies hold promise for further reducing the risk of future adverse CV events in patients.

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