Lepodisiran Moves the Needle on Lipoprotein(a)

by Cliff Dominy PhD

A multinational clinical trial has reported that lepodisiran, a new gene silencing drug, can reduce lipoprotein(a) levels by up to 93.9% compared to placebo [1,2].

Lipoprotein(a), or Lp(a), is recognized as one of the most atherogenic risk factors identified in humans, with no drugs available to lower it - until now.

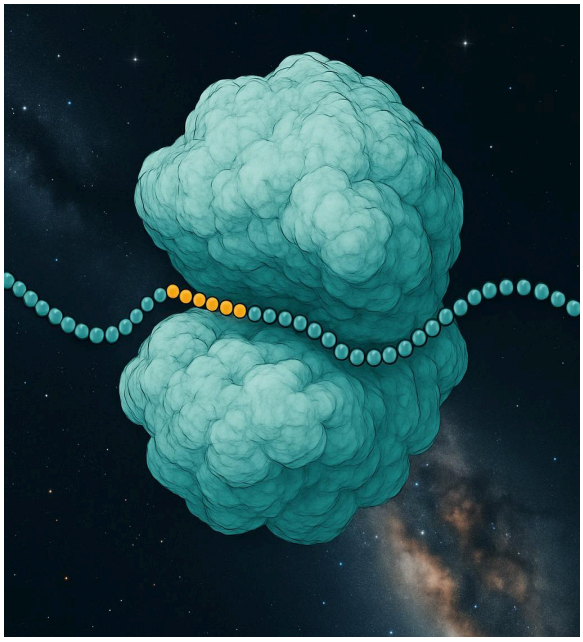
Researchers based in the US and Australia found that lepodisiran, a small interfering RNA molecule, effectively lowers Lp(a) concentrations in adults with dangerously elevated levels.

The ALPACA trial, funded by Eli Lilly (NYSE: LLY), involved 320 participants across 66 centers in 10 countries [2].

The study, published in May 2025 in the *New England Journal of Medicine,* investigated the safety and efficacy of subcutaneous lepodisiran at varying doses in lowering Lp(a) - a highly atherogenic protein that is dangerously elevated in 20% of humans.

Trial participants were adults, aged 40 years or older, with a serum Lp(a) of at least 175 nmol per liter. Exclusion criteria included recent cardiovascular events, moderate-to-severe heart failure, impaired kidney function, and elevated liver enzymes. Participants were randomly divided to receive either placebo or lepodisiran at doses of 16 mg, 96 mg, or 400 mg at baseline and again six months later.

The ALPACA primary outcome was the percent change from baseline in serum Lp(a) concentration from day 60 to day 180, compared to the placebo group. Secondary outcomes included percent change in Lp(a) across other time periods (day 240-360, day 30-180, day 30-360) and changes in other cardiovascular risk factors - apolipoprotein B and C-reactive protein.



The results showed statistically significant reductions in Lp(a) levels across all lepodisiran dose groups compared to placebo. Specifically, Lp(a) concentrations were 40.8% lower in the 16-mg dose group, 75.2% lower for the 96-mg dose, and 93.9% lower in the 400-mg group. The study also found dose-dependent reductions in

apolipoprotein B concentrations, but not the inflammatory risk marker C-reactive protein.

Adverse events were generally mild, with injection-site reactions being most commonly reported (12%). Serious adverse events occurred in 11% of participants, but none were attributed to lepodisiran or placebo by the investigators.

The ALPACA trial demonstrates that lepodisiran is effective in reducing Lp(a) concentrations, with a favorable safety profile.

A larger phase 3 trial (NCT06292013) is currently underway, which will include a more diverse participant base and explore the efficacy of other doses of lepodisiran. The investigators will also be able to measure clinical outcome data, ie cardiovascular death, in the longer study.

Cardiovascular disease remains the world's leading cause of death, and addressing Lp(a) could benefit millions.

It's early days of course, but there is hope that Lp(a) - the worst actor on the cardiovascular stage - may soon face a curtain call. If so, humanity will surely applaud.

References

1. Nissen SE, Linnebjerg H, Shen X, et al. Lepodisiran, an Extended-Duration Short Interfering RNA Targeting Lipoprotein(a): A Randomized Dose-Ascending Clinical Trial. *JAMA*. 2023;330(21):2075-2083.
2. Nissen SE, Ni W, Shen X, et al. Lepodisiran - A Long-Duration Small Interfering RNA Targeting Lipoprotein(a). *N Engl J Med*. 2025;392(17):1673-1683.