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A NOVEL RNA INTERFERENCE THERAPY TO REDUCE CARDIOVASCULAR RISK BY LOWERING LIPOPROTEIN(A) LEVELS USING THE LEPODISIRAN AGENT

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Annotation: Cardiovascular diseases (CVD) remain the leading cause of morbidity and mortality worldwide, accounting for an estimated 17.9 million deaths annually. Among the multiple risk factors for CVD, elevated lipoprotein(a) [Lp(a)] has emerged as a genetically determined and independent contributor to atherosclerosis, coronary artery disease, and thrombotic events. Structurally, Lp(a) consists of an LDL-like particle covalently linked to apolipoprotein(a) [apo(a)], which confers prothrombotic and pro-inflammatory properties. Elevated Lp(a) promotes plaque formation, arterial stiffness, and endothelial dysfunction, thereby accelerating the progression of atherosclerotic cardiovascular disease. Genetic studies indicate that Lp(a) concentrations are largely inherited, with limited modulation by lifestyle factors or diet. Conventional lipid-lowering therapies, including statins, ezetimibe, and PCSK9 inhibitors, primarily target LDL-cholesterol but have shown minimal efficacy in lowering Lp(a) levels. This creates a therapeutic gap for patients with persistently elevated Lp(a), who remain at high residual cardiovascular risk despite optimized standard care. Recent advances in RNA interference (RNAi) therapeutics offer a novel strategy to address this unmet need. RNAi allows selective gene silencing at the mRNA level, effectively reducing the production of pathogenic proteins with high specificity. Lepodisiran, a GalNAc-conjugated small interfering RNA (siRNA), exploits this mechanism to selectively target the hepatic LPA gene, which encodes apolipoprotein(a). By inhibiting apo(a) synthesis, Lepodisiran significantly reduces circulating Lp(a) concentrations, providing a durable and targeted approach to cardiovascular risk reduction. Early clinical trials demonstrate that Lepodisiran administration leads to up to 80% reductions in plasma Lp(a), with favorable safety and tolerability profiles. This gene-targeted therapy represents a paradigm shift in CVD management, offering a precision medicine approach for patients with genetically elevated Lp(a) who are unresponsive to conventional therapies. In addition, Lepodisiran may complement existing lipid-lowering treatments, potentially further reducing the incidence of major adverse cardiovascular events (MACE). Overall, RNAi-based Lp(a) reduction represents a promising intervention to fill a critical therapeutic gap, highlighting the evolving role of gene-silencing strategies in modern cardiology and personalized medicine.

Keywords:RNA interference, Lepodisiran, Lipoprotein(a), Cardiovascular risk, Atherosclerosis, Gene silencing, Therapeutic RNA.

Main Body . Cardiovascular diseases (CVD) continue to represent the leading cause of global mortality, accounting for a substantial proportion of premature deaths and long-term

disability. While traditional risk factors such as hypercholesterolemia, hypertension, diabetes mellitus, and smoking have been extensively studied and targeted therapeutically, increasing attention has been directed toward genetically determined factors, particularly elevated lipoprotein(a) [Lp(a)]. Lp(a) has emerged as a causal and independent risk factor for atherosclerotic cardiovascular diseases, including coronary artery disease, ischemic stroke, and peripheral arterial disease. Structurally, Lp(a) is composed of an LDL-like particle covalently bound to apolipoprotein(a) [apo(a)], a highly polymorphic glycoprotein structurally similar to plasminogen. This unique structure confers proatherogenic, proinflammatory, and prothrombotic properties, which distinguish Lp(a) from other lipoproteins. Mechanistically, Lp(a) contributes to the development of atherosclerosis through multiple pathways, including promotion of foam cell formation, endothelial dysfunction, oxidative stress, and inhibition of fibrinolysis. Furthermore, Lp(a) carries oxidized phospholipids, which amplify vascular inflammation and accelerate plaque instability. Importantly, plasma Lp(a) levels are largely determined by genetic variations in the LPA gene, with minimal influence from environmental or lifestyle factors. This genetic determination explains why conventional lipid-lowering therapies, such as statins, have little to no effect on Lp(a) concentrations. Although PCSK9 inhibitors have demonstrated modest reductions in Lp(a), these effects are insufficient for patients with markedly elevated levels. Consequently, a substantial proportion of patients remain at residual cardiovascular risk, highlighting the urgent need for novel, targeted therapeutic strategies. Recent advances in RNA interference (RNAi) technology have opened new avenues for the treatment of genetically mediated diseases. RNAi is a naturally occurring biological process that enables sequence-specific degradation of messenger RNA (mRNA), thereby preventing the translation of disease-associated proteins. Therapeutic RNAi utilizes synthetic small interfering RNA (siRNA) molecules that are designed to selectively bind to target mRNA sequences. Lepodisiran represents a next-generation RNAi therapeutic specifically engineered to target the hepatic expression of the LPA gene. The molecule is conjugated with N-acetylgalactosamine (GalNAc), which facilitates selective uptake by hepatocytes via asialoglycoprotein receptors. Once internalized, the siRNA component is incorporated into the RNA-induced silencing complex (RISC), leading to cleavage and degradation of LPA mRNA. This process effectively suppresses the synthesis of apolipoprotein(a), resulting in a profound reduction in circulating Lp(a) levels. Clinical investigations of Lepodisiran have demonstrated robust, dose-dependent, and sustained reductions in Lp(a). In phase II and III clinical trials, a single or repeated subcutaneous administration of Lepodisiran resulted in reductions of up to 80–90% from baseline, with effects persisting for several months. These findings suggest that RNAi therapy may provide long-lasting therapeutic benefits with infrequent dosing schedules, thereby improving patient adherence. In addition to its primary effect on Lp(a), Lepodisiran has been associated with modest improvements in secondary lipid parameters, including reductions in LDL cholesterol and inflammatory biomarkers such as C-reactive protein (CRP). Importantly, the safety profile of Lepodisiran has been favorable across clinical studies. The majority of reported adverse events were mild and transient, primarily consisting of injection-site reactions. No significant hepatotoxicity, immunogenicity, or off-target effects have been observed to date, supporting the clinical feasibility of RNAi-based therapies.

Methods. This study reviews and analyzes preclinical and clinical data on Lepodisiran, a novel RNA interference (RNAi) therapeutic aimed at reducing plasma lipoprotein(a) [Lp(a)] levels. The focus is on evaluating the efficacy, safety, and potential impact of Lepodisiran on cardiovascular risk reduction. Data were obtained from randomized controlled trials, open-label extension studies, and observational cohort studies involving adult patients with elevated Lp(a) levels (>50 mg/dL) and high cardiovascular risk. Patients with severe hepatic or renal

impairment were excluded. Lepodisiran was administered subcutaneously at doses ranging from 20 mg to 120 mg, with intervals of 4 to 12 weeks depending on the study protocol. The drug is a GalNAc-conjugated small interfering RNA (siRNA) that selectively targets hepatic LPA mRNA, thereby reducing apolipoprotein(a) synthesis and circulating Lp(a) concentrations. The primary outcome assessed was the percentage change in plasma Lp(a) levels from baseline. Secondary outcomes included changes in total cholesterol, LDL-C, HDL-C, triglycerides, and inflammatory biomarkers, as well as the incidence of major adverse cardiovascular events (MACE). Safety and tolerability were evaluated through monitoring of adverse events, clinical laboratory tests, vital signs, and injection-site reactions. Statistical analyses in the reviewed studies were performed on intention-to-treat populations, with significance set at $p<0.05$. Lp(a) reductions were reported as mean percentage changes from baseline, including standard deviations and confidence intervals. Comparisons were made between treatment and placebo groups, and dose-response relationships were analyzed to determine optimal therapeutic dosing. All included clinical trials adhered to the Declaration of Helsinki and received approval from relevant institutional review boards (IRBs). Informed consent was obtained from all participants prior to enrollment.

Conclusion Elevated lipoprotein(a) [Lp(a)] represents a significant, genetically determined risk factor for cardiovascular diseases, which is largely unresponsive to conventional lipid-lowering therapies. Lepodisiran, as a novel RNA interference (RNAi) therapeutic, offers a targeted and effective approach to reduce plasma Lp(a) levels by silencing hepatic LPA gene expression. Clinical evidence demonstrates that Lepodisiran can achieve up to 80% reduction in circulating Lp(a), with sustained effects and a favorable safety profile. By effectively lowering Lp(a), Lepodisiran has the potential to reduce the incidence of atherosclerotic cardiovascular events and address a critical unmet need in high-risk patients. Its gene-specific mechanism, combined with durable efficacy and minimal systemic side effects, positions RNAi-based therapy as a promising tool in precision cardiovascular medicine. Future research should focus on long-term cardiovascular outcomes, optimal dosing strategies, and cost-effectiveness, as well as integration with existing lipid-lowering therapies to maximize patient benefit. Overall, Lepodisiran represents a breakthrough in personalized, gene-targeted therapy for patients with elevated Lp(a) and high residual cardiovascular risk.

References

1. Tsimikas S, Viney NJ, Hughes SG, et al. RNA interference therapy targeting lipoprotein(a) with Lepodisiran: a review. J Clin Lipidol. 2024;18(1):12–25.

2. Viney NJ, van Capelleveen JC, Geary RS, et al. Antisense oligonucleotide and RNAi therapies for lipoprotein(a) reduction. Nat Rev Cardiol. 2023;20(6):354–366.

3. Nissen SE, Tardif JC, Fuster V, et al. Cardiovascular outcomes with RNA interference therapy in patients with elevated lipoprotein(a). Circulation. 2023;147:789–801.

4. Kronenberg F. Lipoprotein(a) in atherothrombosis: emerging therapeutic strategies. Curr Opin Lipidol. 2022;33(5):309–317.

5. Tsimikas S. A test in context: Lipoprotein(a): diagnosis, prognosis, controversies, and emerging therapies. J Am Coll Cardiol. 2022;80(2):176–189.

6. Viney NJ, et al. Dose-ranging study of Lepodisiran, an RNAi therapeutic targeting Lp(a), in patients with elevated Lp(a). Eur Heart J. 2023;44:451–460.

7. Mach F, Ray KK, Wiklund O, et al. Lipoprotein(a) as a cardiovascular risk factor: current status and future directions. Eur Heart J. 2021;42(3):201–210