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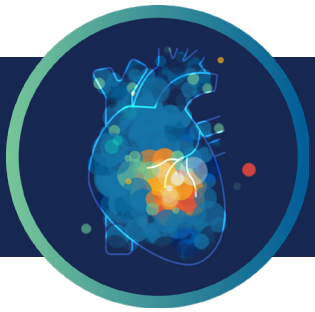
EXPERT INSIGHTS: Q&A WITH DR. PABLO CORRAL



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Given the rising tide of evidence demonstrating that elevated Lp(a) is an independent predictor of adverse cardiovascular events, should it now be incorporated into validated cardiovascular risk scores?

Absolutely - according to different estimates, 20% of the population has high levels of Lp(a), so it is crucial to incorporate this determination in cardiovascular risk scores. Lp(a) is an ApoB lipoprotein with multiple deleterious characteristics; it is not only proatherogenic but also has prothrombotic and proinflammatory effects. Therefore, based on the high prevalence and adverse cardiovascular effects, I believe that it is mandatory to incorporate the Lp(a) value in validated cardiovascular risk scores.

Do you agree with the Lp(a) cut-off level of ≥75 nmol/L (or ≥ 30 mg/dL) used for inclusion into this Phase 1 trial of lepodisiran in individuals with no history of cardiovascular disease?

One of the main goals of phase 1 studies is to evaluate safety, so in my opinion the Lp(a) level is not very important in this phase.

Since the evidence shows that the risk starts at these levels I think those cut-off levels are fine for a phase 1 trial.

Given that the mechanism underlying the observed long-term effects of lepodisiran remain incompletely understood, are you concerned that the highest dose tested in this Phase 1 study (608 mg) attenuated the Lp(a) concentration to below the lower limit of quantification for over 8 months?

Certainly, safety is one of the main topics to follow in this phase. Given our limited understanding of the Lp(a) function, attempting the 'elimination' of Lp(a) could lead to unexpected consequences. On the other hand, researchers should focus on the effects observed on elevated levels of aminotransaminases and creatine kinase, and also notable is the increase in C-reactive protein levels in 14 patients.

Do you think an annual vaccine-like shot of an Lp(a)-lowering medication to lower cardiovascular risk would be an attractive proposition in the future?

Certainly, adherence is one of the main obstacles when facing asymptomatic risk factors such as dyslipidemia. New technologies such as antisense oligonucleotides have shown improved adherence, making an annual vaccine-like injection a very attractive option.

Knowing that traditional lifestyle modifications are ineffective for lowering Lp(a), what do you tell your patients in clinic about managing their cardiovascular risk?

The first recommendation is to keep the rest of the cardiovascular risk factors under control and a healthy lifestyle is the basis for improving cardiometabolic health. Regarding Lp(a), it is important to explain in detail the genetic origin of this disorder and evaluate/review other family members, and explain this condition to the patient in detail. For pharmacological interventions, consider the use of aspirin (supported by some evidence) and incorporate statins along with other lipid lowering therapies if cardiovascular risk is high.