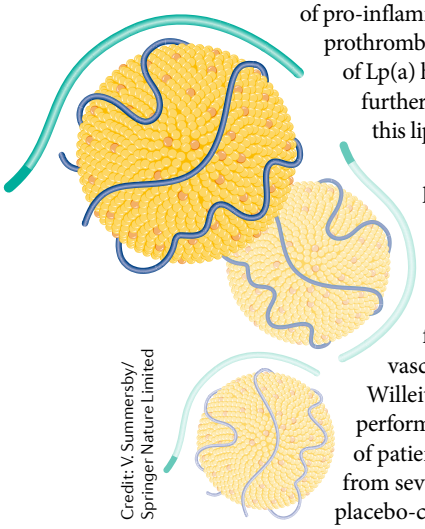
DYSLIPIDAEMIA

# Lipoprotein(a) is an independent predictor of CVD

> The results also provide a rationale to further explore Lp(a)-lowering strategies to reduce the risk of CVD in patients receiving statins

In the general population, high levels of lipoprotein(a), also known as Lp(a), are associated with an increased risk of cardiovascular disease (CVD). According to a new study published in *The Lancet*, elevated levels of Lp(a) also predict future cardiovascular events in patients receiving statin therapy.

A substantial number of patients treated with statins for the primary or secondary prevention of CVD can still experience cardiovascular events even if the target level of plasma LDL cholesterol (LDL-C) has been achieved. "Several possibilities could explain this residual risk of CVD," says Robert Hegele (Robarts Research Institute, Canada), who was not involved in the study. "Any research that can assign this residual risk to other target variables would help guide future intervention studies, and Lp(a) is a particularly interesting target," he adds. Lp(a), an LDL-like particle composed of an apolipoprotein(a) bound to an apolipoprotein B, is known to be pro-atherogenic and has been the focus of several studies. In the past few years, additional evidence of pro-inflammatory and prothrombotic properties of Lp(a) have increased further the interest in this lipoprotein.



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To assess the predictive value of Lp(a) levels, both at baseline and with statin treatment, for future cardiovascular events, Willeit and colleagues performed a meta-analysis of patient-level data from seven randomized, placebo-controlled, statin outcomes trials including 29,069 patients (14,536 allocated to receive statin therapy). The combined end point was the occurrence of fatal or nonfatal coronary heart disease, stroke, or any revascularization procedure at 3 years of follow-up.

Strengths of this meta-analysis include its design, which was well-powered to assess the risk of CVD in patients with Lp(a) levels ≥50 mg/dl, the high number of cardiovascular events recorded and the variety of patients included, such as patients in primary or secondary prevention of CVD, patients with diabetes mellitus and patients with high LDL-C levels, which is representative of the broad population of patients who are prescribed statin therapy.

Baseline Lp(a) levels of 30–50 mg/dl (approximately 11% of the study patients) and ≥50 mg/dl (14% of the study patients) were associated with an 11% (HR 1.11, 95% CI 1.00–1.22) and 31% (HR 1.31, 95% CI 1.08–1.58) increased risk of cardiovascular events, respectively, compared with baseline levels of <15 mg/dl. Statin therapy reduced plasma LDL-C levels by 39% from baseline, but did not significantly change plasma Lp(a) levels. Therefore, Lp(a) levels with statin therapy had a similar association with the risk of CVD to baseline concentrations of Lp(a): patients with Lp(a) levels ≥50 mg/dl had a 43% increased risk of cardiovascular events compared with patients with Lp(a) levels <15 mg/dl (HR 1.43, 95% CI 1.15–1.76).

The analysis also showed that high Lp(a) concentrations in plasma were associated more strongly with an elevated risk of CVD in patients receiving statins than in patients receiving placebo: compared with Lp(a) levels <50 mg/dl, Lp(a) levels ≥50 mg/dl were associated with a 48% (HR 1.48, 95% CI 1.23–1.78) and 23% (HR 1.23, 95% CI 1.04–1.45) increased risk of cardiovascular events in the groups treated with statins and placebo, respectively. Therefore, when the risk of CVD attributable to elevated LDL-C levels is reduced, the plasma level of Lp(a) becomes a strong indicator of the residual risk of CVD.

"This study dissects out the impact of increasing Lp(a) levels on cardiovascular risk, and emphasizes that Lp(a) is an independent risk predictor for CVD," comments Hegele. The results also provide a rationale to further explore Lp(a)-lowering strategies to reduce the risk of CVD in patients receiving statins. To date, no drug to reduce circulating Lp(a) levels has been approved for clinical use. In phase I and phase II trials, targeting *LPA* with antisense oligonucleotides reduced plasma Lp(a) levels by >90%. Future randomized clinical trials on the effect of these agents on cardiovascular outcomes will inform on the contribution of Lp(a) to the residual risk of CVD.

"Measuring Lp(a) levels could also be helpful clinically in risk prediction and patient stratification; it would be worthwhile to check Lp(a) levels in a patient who has suffered an event but has no traditional risk factors to explain it," concludes Hegele.

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**ORIGINAL ARTICLE** Willeit, P. et al. Baseline and on-statin treatment lipoprotein(a) levels for prediction of cardiovascular events: individual patient-data meta-analysis of statin outcome trials. *Lancet* **392**, 1311–1320 (2018)
**FURTHER READING** Nordestgaard, B. G. et al. Advances in lipid-lowering therapy through gene-silencing technologies. *Nat. Rev. Cardiol.* **15**, 261–272 (2018)