

Lipoprotein(a) in prevention: from an index result to family care

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For many years, a lipoprotein(a) (Lp[a]) test result was treated as a laboratory finding only relevant to the person in whom it had been measured, which is an increasingly inadequate view. Lp(a) is a largely inherited, apolipoprotein B (apoB)-containing particle whose level is usually stable throughout adult life and causally linked to atherosclerotic cardiovascular disease (ASCVD).^{1,2} Therefore, a high Lp(a) value has 2 clinical meanings: it refines the index patient's lifetime risk and signals that there may be other individuals in the family with a similarly high exposure. This second meaning poses a practical question facing clinicians: when an index patient has a high Lp(a) level, which adult first-degree relatives (FDRs) should be invited for testing, and what should follow if their Lp(a) level is high? Rather than assigning the index result to relatives, clinicians should perhaps use it to identify families in which a measurement result of one member can help refine risk assessment and guide prevention.

First, cascade assessment can only begin with a confirmed Lp(a) test result in the index patient. Direct Lp(a) testing, rather than inference from

routine clinical information, is therefore the necessary starting point. In SCAPIS (Swedish Cardiopulmonary BioImage Study), a population-based trial, self-reported clinical characteristics discriminated poorly for elevated Lp(a) levels (area under the receiver operating characteristic curve, 0.54); in the same cohort, adding Lp(a) measurements to the European Society of Cardiology/European Atherosclerosis Society assessment increased lipid-lowering treatment eligibility from 11.3% to 19.6%.³ The EPIC (European Prospective Investigation of Cancer)-Norfolk cohort study likewise showed that Lp(a) contributed to the 20-year cardiovascular event risk alongside low-density lipoprotein cholesterol (LDL-C) and high-sensitivity C-reactive protein.⁴ These findings support a single-time measurement in adult life, particularly when a low short-term score could otherwise defer a preventive discussion in a person with substantial lifetime exposure. Because the Lp(a) level in adults is largely stable over time, a single timely result, rather than serial testing, is usually enough to shape preventive priorities.

Kindborg et al⁵ extended previous evidence of familial Lp(a) concordance by showing that the index patient's Lp(a) result also carries clinically useful information about cardiovascular risk in FDRs. The investigators linked 41 304 individuals with a routine Lp(a) level determination to 61 715 FDRs without Lp(a) measurement. By the age of 65 years, the cumulative incidence of major adverse cardiovascular events (MACEs) in the FDRs rose from 6.2% when the index Lp(a) was below the 50th percentile to 8.1% when it was at or above the 95th percentile; adjusted MACE risk was approximately 30% higher once the index Lp(a) exceeded the 80th percentile.⁵ The familial signal was especially marked at the severe end of the distribution range: the FDRs of the index individuals with Lp(a) levels at or above the 95th percentile were 14.4 times more likely to have Lp(a) at or above the 95th percentile themselves than the FDRs of the index patients with levels below the 50th percentile.⁵ The 53% concordance for the Lp(a) level at or above the 80th percentile in the related-pair analysis shows both the value and the limit of the index result: it identifies a family in which high Lp(a) level is enriched, but it cannot establish the concentration of any individual relative. An elevated index result should therefore prompt direct Lp(a) measurement in adult FDRs, and not serve as a surrogate for it.⁵⁻⁷

These findings support a family-wide offer of single-time Lp(a) testing, but not a fixed order based on relationship type. Concordance was similar in parent–child and sibling pairs, so the study provides no evidence that one of these groups should routinely be approached first.⁵ A single-center real-world study found that family history of coronary artery disease was the recorded indication for only 12 (0.4%) of 2822 Lp(a) level measurements.⁸

If practical constraints require a staged approach, clinical timing is more useful than kinship: testing should be arranged promptly when a relative has premature ASCVD or is at a primary-prevention treatment decision point, while ensuring that younger adult relatives are not deferred indefinitely because their 10-year risk is low. The index result identifies the family to be screened; the relative's own clinical situation determines when testing will have the greatest immediate value.

Once family testing has established the relative's own Lp(a) level, management should be organized around that person's disease status and modifiable risk. A low Lp(a) concentration returns the focus to conventional risk assessment. An elevated concentration should prompt a structured review of whether ASCVD is already present, whether LDL-C or apoB, blood pressure, glycaemia, smoking, and kidney disease are adequately addressed, and whether the person is at a point at which preventive treatment is being decided. In a relative with established ASCVD, particularly when the disease is premature, a high Lp(a) level identifies additional residual risk and reinforces the need for intensive secondary prevention. In primary prevention, it should act as a risk enhancer: it may move an uncertain decision toward earlier statin-based LDL-C lowering or a lower LDL-C or apoB target when overall risk warrants it.⁹ A low 10-year score should not dismiss a high Lp(a) result in a younger adult, because the purpose is to reduce cumulative exposure to modifiable risk over the following decades.

Statins remain foundational even if the Lp(a) level itself changes little or rises modestly with this treatment. Proprotein convertase subtilisin/kexin type 9 inhibitors and lipoprotein apheresis may lower the Lp(a) concentration but they are used for their established indications or in selected patients with progressive disease.¹ Therefore, current management reduces the modifiable risk that accompanies high Lp(a) values, but no outcome-proven strategy yet targets Lp(a) itself.¹

This therapeutic gap explains the current interest in Lp(a)-lowering therapies. Obicetrapib, an oral cholesteryl ester transfer protein inhibitor, lowered LDL-C, apoB, and Lp(a) levels in a pooled analysis of 2356 high-risk patients, with a placebo-adjusted Lp(a) level reduction of 37.3%.¹⁰ RNA-based agents, including pelacarsen, olpasiran, lepodisiran, and zerlasiran, have produced much larger reductions in phase 2 trials; the reported time-averaged reductions with lepodisiran and zerlasiran exceeded 80%.¹¹⁻¹⁴ Oral muvalaplin, which interferes with Lp(a) particle formation, reduced the Lp(a) level by 70% to 85.8%, depending on the assay.¹⁵ While Lp(a) assays are available on clinical laboratory analytical platforms, further

work is required to ensure all assays utilized in clinical trials are traceable to the World Health Organization/International Federation of Clinical Chemistry and Laboratory Medicine reference material.¹⁶ The need for assay standardization is further highlighted by the impact of apoA isoforms on measurement of circulating Lp(a) concentration.¹⁷

These reductions are biologically compelling, but the studies differ in drug class, assay, duration, and population, and none has yet shown that lowering the Lp(a) level prevents cardiovascular events.^{1,2} Whether these biochemical effects translate into fewer events, and in which patients, is now the decisive question for outcome trials. Until these data are available, the clinical task is clear: use a high index Lp(a) result to identify adult relatives for direct testing, and use each relative's own result to intensify proven prevention.

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