CRL Insurer Services

CAN LIPOPROTEIN(A) TESTING IMPROVE RISK INSIGHTS FOR INDIVIDUAL LIFE INSURANCE APPLICANTS?

A 2024 CRL White Paper for Life Underwriting

Summary: *CRL now offers a test for Lipoprotein(a), an independent cardiovascular risk factor. Data from a CRL study investigating Lp(a) in a life insurance population demonstrates the utility of testing applicants for Lp(a), including select targeted at-risk populations, given there was no or limited correlation of Lp(a) to lipid, NTproBNP, and HbA1c levels, BMI, smoking status, and hypertension history.*

Lipoprotein(a), abbreviated Lp(a), is a lipid component that is currently receiving attention from researchers and clinicians as an independent cardiovascular (CV) risk factor, adding to the known risk associated with low-density lipoprotein (LDL). This paper summarizes current Lp(a) research and details a CRL study evaluating Lp(a) in a life insurance population.

The Lp(a) particle consists of an apolipoprotein(a) [apo(a)] molecule tightly bonded to an LDL-like particle consisting of an apolipoprotein B (apoB) molecule and associated cholesterol. Both creation and catabolism of the Lp(a) particle likely occur in the liver by pathways independent of LDL and triglyceride metabolism.[1] The cholesterol in Lp(a) is typically already included in the LDL cholesterol (LDL-C) measurement (along with that in intermediate density lipoproteins) because LDL-C is usually not measured directly but derived from the Friedewald formula (LDL Chol = total Chol - HDL Chol - Trig/5). However, Lp(a) CV morbidity and mortality appears greater than can be explained by the relatively small additional amount of cholesterol present. If not measured directly, Lp(a) cholesterol can also be estimated (and subtracted from LDL-C if desired) by multiplying Lp(a) mass (mg/dL) x .3.[2]

Lp(a) levels are largely (as high as 90%) under the control of a single gene (LPA) with little dietary or environmental influence. Levels are not impacted by statin treatment or other currently available lipid treatments.[3] Some studies suggests that statins may actually increase Lp(a) levels.[3] Niacin has been shown to decrease Lp(a) in a dose-dependent manner by approximately 30-40% on average, but only 18% in those with the highest levels of Lp(a)[4].

While there are currently no FDA-approved medications specially targeting Lp(a), such drugs are currently in late-stage clinical trials. One drug based on siRNA, Olpasiran, demonstrated up to a 95% reduction in Lp(a) levels[5]. Another siRNA drug, Zerlasiran, lowered Lp(a) levels by 90% in a phase 2 trial.[6] Studies suggest that absolute reductions in Lp(a) levels of 60 to 100 mg/dL would be the therapeutic equivalent of reducing LDL-C by 38.7 mg/dL (1 mmol/L) [5].

Accurate measurement of Lp(a) is a critical issue both for research and for clinical/insurance use. Lp(a) comes in isoforms with a wide range of sizes largely based on the number of repeats of the apo(a) peptide sequences. Research has shown that CV risk is either unchanged by Lp(a) isoform size, or smaller isoforms may actually have greater CV risk.[7] Measuring the concentration of particles (regardless of particle size) expressed as nmol/L may be the preferred measure for risk assessment but currently most FDA approved tests in the US report as a measure of mass concentration of the Lp(a) particles in mg/dL.

The concentration of Lp(a) is typically measured by use of polyclonal antibodies directed at the apo(a) component. However, different apo(a) isoforms with variable numbers of repeats may have variable amounts of antibody binding. This result is then converted to a mg/dL result by use of a proprietary calibrator function based on prior testing of a small number of individuals potentially introducing additional inaccuracy. An estimate of the cholesterol and apoB mass of the Lp(a) particle must be included by the calibrator function but this may also vary and is not actually measured. A 2022 review of this issue found wide variation in reported Lp(a) mass concentration (mg/dL) between available tests and no consistent conversion factor that mediates between mass concentration in mg/dL and particle concentration in nmol/L.[8] Because conversion back to nmol/L (which may be the better risk predictor) is problematic and almost all US results are reported in mg/dL, this paper will generally use this mass concentration converting back and forth only as needed using an averaged conversion factor of mg/dL x 2.42 = nmol/L[8], unless another factor is provided in an article. Of note, a major supplier of Lp(a) tests to laboratories expresses results as mg/dL in the US product brochure without mention of nmol/L. In its UK literature for the identically named test, it enthusiastically embraces reporting as nmol/L indicating repeatedly that is the superior measure of risk.

Approximately 20-25% of people worldwide have high levels of Lp(a) (>50ng/dL), which is the cutoff specified by the American College of Cardiology / American Heart Association to be risk-enhancing for CVD.[9] Lp(a) levels vary by race and sex with African ancestry being associated with 3 times higher median levels based on differences in isoform size and genetics.[1] How this impacts risk is still uncertain.

Following are Lp(a) percentiles for the US population adapted from Marcovina[10] in nmol/L and converted to mg/dL dividing by 2.42:

Lp(a) levels for percentiles in nmol/L & then converted to mg/dL for White, Black and Japanese Americans

	50th	**80th**	**90th**	**95th**	**99th**	**99.5th**
Whites	20/8	100/41	154/64	209/86	320/132	360/148
Blacks	74/31	148/61	199/82	234/96	368/151	407/168
Japanese	19/8	49/20	75/31	103/42	194/80	237/97

The mechanism by which Lp(a) increases CV risk is an area of active research. The LPA gene (present only in primates and old-world monkeys) appears to have evolved from a duplication of the plasminogen gene (which existed earlier). One possible effect of Lp(a) would be to impair fibrinolysis (has a prothrombic effect) but alternative explanations such as enhanced ability relative to LDL to penetrate artery walls and create plaque or a unique vascular inflammatory effect or some combination is also under consideration.

Risk associated with increasing Lp(a) levels follows a log-linear curve with low and similar CV risk present for the 70-80% of individuals with lowest values and progressively increasing risk for

values above that. The main risk is CAD but aortic stenosis appears to be increased as well with less certainty about stroke risk. Little or no increased risk for non-cardiovascular mortality is present. Risk associated with small isoforms may be higher than for large isoforms, but such division does not appear to impact overall CV or all-cause mortality risk.

In reviewing the literature on Lp(a), Langsted showed a CV mortality HR of 1.16 per 50 mg/dL (105 nmol/L) increase in Lp(a) with an all-cause mortality HR of 1.05 for each 50 mg/dL increase based on measured Lp(a) in a Danish population.[11]

Patel, using UK Biobank data, showed a HR for incidence of CV disease (not mortality) of 1.11 per 50 nmol increase in Lp(a) concentration.[12] This might translate into a HR for CV disease of approximately 1.3 per 50 mg/dL increase with a similar HR for CV mortality but a much lower increase in all-cause HR on the order of 1.1 per 50 mg/dL increase in Lp(a).

Shiyovich, using the Mass General Brigham registry of those with CV disease, compared those with Lp(a) below 200 nmol/L (93.5 mg/dL) to those at or above 200 nmol/L, finding an adjusted HR of 1.33 for CV events with a HR of 1.39 for CV death and a HR of 1.10 for all-cause mortality.[13]

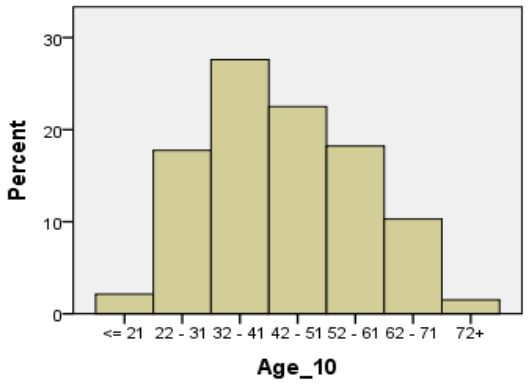
Wong, using data from the HIM-HIGH trial of those with established ASCVD, showed a HR of 1.27 for CV events for between those with Lp(a) values <15 mg/dl and those with values 50 to 70 mg/dL, approximating a 50 mg/dL difference.[14]

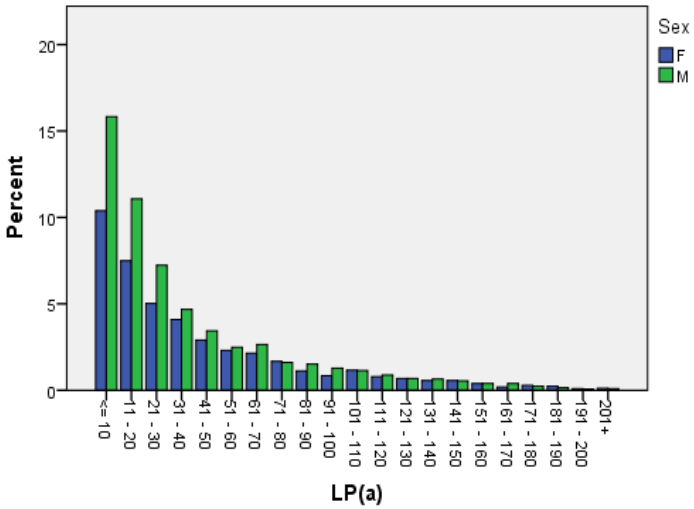
Amiri did a systematic review of Lp(a) articles with mortality outcome in 2023 and was able to use 7 articles which provided data that could be converted into the amount of increased risk per 50 mg/dL increase in Lp(a). Risk increase ranged from a hazard ratio of .80 to 1.59 with overall combined HR of 1.05 for all-cause mortality per 50 mg dL increase in Lp(a).[15]

CRL Lp(a) Life Insurance Study

To explore the findings from studies mentioned above, CRL investigated Lp(a) in a life insurance applicant population. A total of 4,304 insurance applicant samples were tested for Lp(a) at CRL using the Roche LPA2 Tina-quant Lipoprotein (a) Gen.2 test during December 2023 on a convenience block of tested insurance applicants ranging in age from 17 to 85 years. Additional history and laboratory results for those applicants along with BMI were available.

Distribution of tested applicants by 10-year bands of age and of Lp(a) results by each 10 mg/dL band split by sex are presented below:



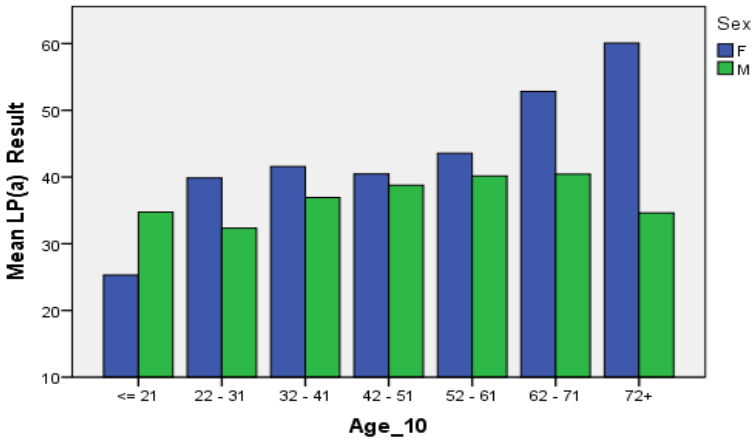


Lp(a) values ranged from 0 (undetectable) to 227 mg/dL with a mean of 40 and a median of 24. The data is highly skewed to the right, like the studies detailed above.

The 50th percentile (median) was 24 mg/dL, 80th was 66 mg/dL, 90th was 102 mg/dL, and the 99th was 210 mg/dL. The median is 20% higher (24 vs. 20 mg/dL) than that shown by Marcovina[16] (for a white population). The 80th, 90th, and 99th percentiles show progressively higher values (66 vs 41, 102 vs 64, and 210 vs 132 mg/dL) than seen by Marcovina. Whether the populations are different (at least some black applicants with higher values would be expected in the insurance pool), the tests are different, or the conversion from nmol/L to mg/dL produces different results or a combination of factors is unclear.

Lp(a) values for applicants at CRL were compared to lipid, NTproBNP, and HbA1c levels, BMI, smoking status, and hypertension history finding either no or very limited correlations.

Female values were found to be slightly higher than for males but more prominently so at older ages as shown to the right consistent with a similar pattern noted in the Kronenberg[5] review. That review also referenced Lp(a) reductions up to 25% seen during hormone replacement therapy making a hormonal effect likely.



A firm foundation for how to use Lp(a) in risk assessment is in progress. Data do show that high Lp(a) levels are associated with increased CV risk for both those at moderate and high pre-existing CV risk based on history or other findings. Focused clinical screening of patients with high CV risk or those with inadequate response to statin therapy may soon have value because therapies to dramatically reduce Lp(a) levels will soon be available.

Screening Lp(a) in select targeted at-risk populations for life insurance risk selection appears to be of value. Based on the applicant testing at CRL, 28% of results would exceed 50 mg/dL with 10% exceeding 100 mg/dL. The test may identify some applicants who would not be eligible for a (better than residual standard) preferred class. It may also serve as a "tiebreaker" in cases where an applicant is close to lipids thresholds perhaps qualifying him or her for Preferred classifications. This is in line with recent recommendations by the European Atherosclerotic Society that adults be tested at least once for Lp(a) and that this assessment may help make treatment decisions regarding modifiable risk factors such as high cholesterol or high blood pressure[17]. Lp(a) testing may also have value in assessing risk for applicants with existing CV disease, but the likely number whose risk category moves up or down is unknown. It is reasonable to expect that test standardization and a better understanding of how to ascertain individual risk will improve substantially as drug therapy to reduce Lp(a) levels comes into use.

CRL will continue to evaluate Lp(a) testing for general screening and use for selected applicants to improve risk insights. As with all CRL research, we are available to partner with insurers on such efforts.

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