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EDITORIAL COMMENT

Measurement of Lipoprotein(a)

A Once in a Lifetime Opportunity*

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Lipoprotein(a), or Lp(a), is an apolipoprotein (apo) B-containing lipoprotein particle similar in lipid composition to low-density lipoproteins but characterized by the presence of a carbohydrate-rich protein, termed apo(a), covalently linked to apoB. Apo(a) is characterized by a marked size heterogeneity, which gives origin to >40 apo(a) isoforms.[1] Circulating plasma Lp(a) levels are inversely correlated to the size of apo(a), and both apo(a) size and Lp(a) concentration are primarily determined by the *LPA* gene locus encoding apo(a). Epidemiological and Mendelian randomization studies have provided strong support for a causal role of elevated Lp(a) in the development of atherosclerotic cardiovascular disease (ASCVD), rendering Lp(a) the most prevalent form of inherited dyslipidemia.[1] Measurement of Lp(a) levels is predominantly performed by immunoassays using antibodies specific to apo(a). However, the variable mass of apo(a) does not allow apo(a) in the samples and in the assay calibrator to achieve the same degree of immunoreactivity per particle. Therefore, samples with apo(a) sizes smaller than the predominant sizes present in the calibrator will be underestimated, whereas larger apo(a) sizes will be overestimated.[1] To minimize the inaccuracy generated by the difference between apo(a) size in the samples and in the assay calibrator, immunoassays have been developed based on 5 independent calibrators, with Lp(a) levels ranging from low to high and containing predominant isoforms ranging from large to small. This approach reduces the difference in immunoreactivity between the samples and the assay calibrator resulting in more accurate and comparable Lp(a) values.[1] To reflect the number of Lp(a) particles, these assays are calibrated in nmol/L. However, as historically done, many assays are still reporting Lp(a) values in mg/dL of total Lp(a) mass, rendering the interpretation of Lp(a) data more difficult for clinicians.[1]

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It is within this context that Trinder et al,[2] in this issue of the *Journal*, report results of their study aimed at investigating the stability of longitudinal measurements of Lp(a) and the association between variation in Lp(a) levels and incident coronary artery disease (CAD). Additionally, the authors evaluated whether statin therapy results in significant changes in Lp(a) concentration. To address these questions, the investigators examined the correlation between baseline and first follow-up measurements of Lp(a) among 16,017 unrelated participants in the UK Biobank. Lp(a) measurements were performed by a turbidimetric method shown to minimize the impact of apo(a) size heterogeneity and whose Lp(a) values are reported in nmol/L. Moreover, the authors assessed the association between changes in plasma Lp(a) molar concentration and incident CAD (n = 15,432) in survival analyses. In brief, they found that baseline and follow-up Lp(a) molar concentrations were significantly correlated over a median of 4.42 years. This correlation was stable across all measured time points: <3, 3-4, 4-5, and >5 years. The investigators found no association between statin use and changes in Lp(a) molar concentration when

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baseline values were <70 nmol/L. However, statin use was associated with a modest but statistically significant increase in Lp(a) among individuals with baseline levels ≥70 nmol/L. Follow-up Lp(a) molar concentration was significantly associated with risk of incident CAD. However, the difference between follow-up and baseline Lp(a) values was not significantly associated with incident CAD before or after adjustment for the follow-up concentration of Lp(a).

There are a few important considerations to take into account when interpreting these results. First, statin exposure was only characterized dichotomously, but, as acknowledged by the authors, the impact of statin therapy on Lp(a) concentration may be dependent on the specific drug, dose, potency, and baseline Lp(a) level. Additionally, the UK Biobank enrolled participants free of clinical cardiovascular disease at entry. Thus, the generally modest variation in Lp(a) measurements observed in this study does not necessarily translate to individuals in secondary prevention, where fluctuations in Lp(a) are likely to be more pronounced. Also, patients with manifest ASCVD more frequently use high-intensity statin therapy and more commonly have elevated baseline Lp(a) levels, both of which may accentuate measurement variability.

ARE REPEAT MEASURES OF Lp(a) REPRODUCIBLE?

Taken together, the results of this study indicate that the molar concentration of Lp(a) appears reasonably stable, regardless of statin use, suggesting that longitudinal measurements of Lp(a) are not needed for ASCVD assessment in the context of primary prevention. National and international professional society guidelines have recommended measuring Lp(a) in select populations, while some have recommended that Lp(a) be measured at least once in the general population.[3-6] The finding of this study, confirming that plasma Lp(a) concentrations are generally stable, support that a once in a lifetime measurement may reliably allow patients and clinicians to determine whether Lp(a)-related risk is present.

ARE CURRENT Lp(a) ASSAYS ADEQUATE FOR CLINICAL INTERPRETATION OF RISK THRESHOLD?

The methodological problems related to the measurements of Lp(a) and the existence of 2 different units to report the results may cast doubt about implementation of Lp(a) screening in the general population before assay standardization. However, considering that in primary prevention, clinicians only need to determine whether Lp(a) levels are within the normal range or are elevated to the point that Lp(a)-related risk is present, all current analytical methods, particularly those based on a 5-point calibration approach as used in this paper, appear to be well-suited to assess ASCVD risk in the general population.

HOW SHOULD CLINICIANS MANAGE Lp(a) IN mg/dL VS nmol/L?

The International Federation of Clinical Chemistry Standardization Group is actively working on the global standardization of Lp(a) methods with the expression of Lp(a) concentration in SI units.[7] Therefore, when standardization is implemented in the near future, Lp(a) concentration will only be expressed in nmol/L and harmonization of results among methods is expected. Until this is achieved, clinicians should interpret Lp(a) results in primary prevention using the currently proposed, method-specific Lp(a) threshold of 50 mg/dL or 100 nmol/L.[3-6]

WHAT LEVEL OF ACCURACY WILL BE REQUIRED FOR Lp(a) LEVELS AROUND THE THRESHOLD IN CLINICAL TRIALS?

At present, there are no specific interventions to lower Lp(a). However, novel drugs able to specifically and potently lower Lp(a) are in different phases of clinical trials, and the Lp(a) HORIZON (Assessing the Impact of Lipoprotein (a) Lowering With TQJ230 on Major Cardiovascular Events in Patients With CVD (Lp(a); NCT04023552) phase III cardiovascular outcome trial is well underway. The Lp(a) threshold for enrollment in this trial is 70 mg/dL or 150 nmol/L. Therefore, in addition to method standardization, a global method certification system should be implemented to verify that methods are able to provide a high level of accuracy and precision around the Lp(a) treatment threshold to ensure that patients are not undertreated or overtreated with Lp(a)-lowering drugs.

WHAT IS EXPECTED FROM CLINICAL TRIALS?

In addition to providing conclusive evidence that lowering Lp(a) improves cardiovascular outcomes, other important information is expected to be garnered from these intervention studies. Sound evidence has been provided that the risk conferred by elevated Lp(a) strictly depends on its plasma concentrations, with individuals with the most severely

elevated Lp(a) being at greatest risk of CVD.[8] Therefore, instead of relying on a single threshold, results from these large intervention studies are expected to provide a more nuanced definition of the graded impact of elevated Lp(a) on CVD risk and to evaluate whether the same categories of Lp(a) levels for risk classification are applicable to populations of different ancestries.

CONCLUSIONS

Potentially, >1.5 billion individuals worldwide have Lp(a) concentrations associated with increased ASCVD risk. This alone should serve as an appeal for universal Lp(a) screening, performed once in a lifetime, to be implemented as soon as possible.

We thank the authors of the present study for providing new data that constitute a sound basis in support of general screening of Lp(a) and for giving us the opportunity to clarify important clinical issues related to Lp(a) measurements.

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REFERENCES

1. Marcovina SM, Albers JJ. Lipoprotein(a) measurements for clinical application. *J Lipid Res*. 2016;57:526–537.

2. Trinder M, Paruchuri K, Haidermota S, et al. Repeat measures of lipoprotein(a) molar concentration and cardiovascular risk. *J Am Coll Cardiol*. 2022;79(7):617–628.

3. Cegla J, Neely RDG, France G, et al. Heart UK consensus statement on Lipoprotein(a): a call to action. *Atherosclerosis*. 2019;291:62–70.

4. Wilson DP, Jacobson TA, Jones PH, et al. Use of Lipoprotein(a) in clinical practice: a biomarker whose time has come. A scientific statement from the National Lipid Association. *J Clin Lipidol*. 2019;13:374–392.

5. Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS guidelines for the management of dyslipidemias: lipid modification to reduce cardiovascular risk: the Task Force for the Management of Dyslipidemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS). *Eur Heart J*. 2020;41:111–188.

6. Pearson GJ, Thanassoulis G, Anderson TJ, et al. 2021 Canadian Cardiovascular Society guidelines for the management of dyslipidemia for the prevention of cardiovascular disease in adults. *Can J Cardiol*. 2021;37:1129–1150.

7. Cobbaert CM, Althaus H, Begcevic Brkovic I, et al. Toward an SI-traceable reference measurement system for seven apolipoproteins using bottom-up quantitative proteomics: conceptual approach enabled by cross-disciplinary/cross-sector collaboration. *Clin Chem*. 2021;67:478–489.

8. Kamstrup PR, Tybjaerg-Hansen A, Steffensen R, Nordestgaard BG. Genetically elevated lipoprotein(a) and increased risk of myocardial infarction. *JAMA*. 2009;301:2331–2339.

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