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Clinical Lipidology Roundtable Discussion

What's next for lipoprotein(a)? A national lipid association report from an expert panel discussion

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This is an exciting time in the lipoprotein(a) (Lp(a)) field. Attention to this important lipoprotein and potent cardiovascular risk marker is transitioning from the purview of the specialist to that of the general practitioner. Its clinical adoption as an important test is increasing in momentum. There is evidence that Lp(a) contributes to the pathology of atherothrombotic disease, aortic valve stenosis, and childhood ischemic strokes. Three large, Phase 3, randomized, cardiovascular outcomes trials in which Lp(a) is specifically and substantially lowered by mRNA-directed therapies in secondary prevention settings are in progress and will start to report results as early as 2025. Regardless of outcomes, there remain many unanswered questions about Lp(a), ranging from fundamental unknowns about Lp(a) biology, to the complexity of its measurement, optimal screening strategies, and clinical management in individuals with high Lp(a) levels both with and without overt cardiovascular disease. Accordingly, The National Lipid Association (NLA) convened an Expert Discussion involving clinicians and fundamental researchers to identify knowledge gaps in our understanding of Lp(a) biology and pathogenicity and to discuss approaches in the management of elevated Lp(a) in different clinical settings. (183 words)

The purpose of this National Lipid Association (NLA)-hosted Expert Discussion was to bring together a group of clinicians (from the areas of Lipidology, Cardiology, Endocrinology, Primary Care) and fundamental researchers to identify unmet needs in the Lp(a) field. The list of attendees and their affiliations is found at the end of this document. Participants volunteered their time to attend this important meeting and did not receive compensation for participation. Discussion topics ranged from raising awareness of Lp(a) as an important risk marker/potential therapeutic target, and technical aspects of Lp(a) measurement and optimal screening strategies, identification of gaps in our understanding of the metabolism and pathobiology of Lp(a). We also discussed management concerns in secondary, primary and primordial prevention, clinical management of individuals with elevated Lp(a), and considerations for elevated Lp(a) in the pediatric population. The robust exchange of ideas around these key discussion points is summarized below.

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RAISING AWARENESS of Lp(a) THROUGH EDUCATION OF KEY STAKEHOLDERS

The group identified key stakeholders: patients, medical professionals from related disciplines and multiple fields including cardiology, endocrinology, and primary care practitioners as well as the general public. Other key stakeholders will include foundational and implementation science colleagues, medical association leadership and guideline authors, as well as health system and payer/insurance company administrators. There is a need for educational materials – written in lay language for this purpose – that should focus on key topics to guide patient-provider discussions including: (i) why should Lp(a) be measured, and (ii) what action can be taken when a high level of Lp(a) level is found. The delivery of this information may take the form of live conferences, webinars, podcasts, and printed educational materials.

Key Educational Messages for Clinicians:

- Elevated Lp(a) is a prevalent heritable risk factor for CVD including atherosclerosis, ischemic strokes, and aortic valve stenosis.
- Lp(a) is a unique lipoprotein with proinflammatory, proatherosclerotic, and possibly prothrombotic properties.
- Lp(a)-attributable residual risk for CVD can be managed currently, even as we await the results of Lp(a) Phase 3 randomized clinical trials (RCT) to assess the cardiovascular benefit of targeted Lp(a) lowering (Lp(a)HORIZON [NCT04023552], OCEAN(a) [NCT05581303], and ACCLAIM-Lp(a) [NCT06292013]). This includes management of baseline cardiovascular disease (CVD) risk through lifestyle changes and optimal management of CVD risk factors including low-density lipoprotein-cholesterol (LDL-C). Specific guidelines in this regard are outlined in the 2019 NLA Scientific Statement on Lp(a)[1] and in the 2022 European Atherosclerosis Society (EAS) Consensus Statement on Lp(a).[2]
- Lp(a) should be measured at least once in all adults and incorporated into routine clinical practice, a point included in the recent focused update to the NLA 2019 Scientific Statement.

Education for patients: This is critical to allow productive discussions between patients and their physicians. Online and printable education documents have to be created for all reading levels and languages and to include optimized graphics. The NLA has been an important resource for clinicians and the general public and has a useful platform for education through both existing courses and additional courses designed to explore novel concepts; meeting updates; scientific publications; and direct-to-clinician information, as well as patient website portals like the Foundation of the NLA patient education site (www.learnyourlipids.com).

Lp(a) MEASUREMENT

The intrinsic complexity of Lp(a) represents a challenge in our ability to convey clearly its role to clinicians and to patients. In order to increase frequency of Lp(a) measurement, however, it was recognized that clinicians require a basic understanding of Lp(a) and its contribution to CVD risk, as well as knowledge of how to manage patients with elevated levels of Lp(a). In this regard, there was strong agreement that a major impediment to ordering an Lp(a) test is the lack of a specific therapy to lower Lp(a). However, it was further agreed that there are other similar examples of potent risk markers that are not targets of therapy (e.g. coronary artery calcium scoring).

There was general agreement by participants that Lp(a) should be routinely tested, at least once in all adults. The units for measurement at this time are either in nmol/L or in mg/dL, and these units cannot reliably be interconverted. Harmonization of measurement methods, including units, is ongoing in the US and Europe. These issues should not, however, dissuade clinicians from measuring Lp(a), and they should use the units of measurement they receive to assist in clinical decision-making. Currently available assays, despite lack of harmonization, are adequate to assign Lp(a)-attributable risk.

Lipid specialists' perspectives

At this time, the frequency of Lp(a) testing in the population is very low, both in North America and Europe. Expert discussions are an excellent venue to focus on important scientific and clinical questions and ultimately lead to consistent recommendations for screening. Prior scientific statements (NLA and EAS mentioned above) are useful documents for clinical reference and need to be updated regularly (a focused update to the 2019 NLA statement on Lp(a) was recently completed[14]). Clear recommendations for management of Lp(a) in both primary and secondary prevention are needed and are expected to evolve as evidence from targeted Lp(a) lowering trials becomes available. In addition to measuring Lp(a) and other lipid risk factors, complementary testing approaches such as coronary imaging, when available, remain important; clarity is needed with respect to impact when there is concordance between risk tools, versus when there is discordance between risk markers (e.g. high Lp(a) but no coronary artery calcification on computed tomography).

There are differences in published screening recommendations from the U.S. compared to Europe and Canada. American Heart Association/American College of Cardiology/Multisociety guidelines[3] and the NLA Scientific Statement[1] do not recommend universal screening of Lp(a), but do suggest that elevated Lp(a) be considered as a risk-enhancing factor. Additionally, specific ways to incorporate Lp(a) into clinical care are outlined for primary and secondary prevention. More recently, both the Canadian Cardiovascular So-

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ciety[4] and the European Atherosclerosis Society,[2] and now the NLA endorse universal screening of Lp(a) at least once in adults.[14]

The group generally agreed that universal screening of Lp(a) should be recommended, but there was acknowledgement about the associated challenges. It was also acknowledged that universal screening should be considered as aspirational until there is broader acceptance of the concept over time. In the interim, strong recommendations for targeted screening validate the importance of Lp(a) testing for proactive clinicians.

The group discussed ways to streamline Lp(a) screening. For example, the group discussed measurement of Lp(a) coincident with LDL-C screening as in the Canadian Cardiovascular Society guidelines[4] where Lp(a) measurement in every adult is recommended with the first lipid profile. However, it was recognized that a patchwork health record like the ones typically seen in the U.S. where there is no single public health system does add to the complexity of identifying the first lipid profile.

The Danish experience represents a model of care where Lp(a) measurement is performed for individuals suspected of ischemic events. These patients are referred to a specialized lab for genetic testing for FH and other lipid disorders where Lp(a) is measured. Despite this important targeted approach, it is limited because it does not allow general practitioners to order Lp(a) directly, introducing an unnecessary barrier to care.

Expertise in implementation science was represented within the group, and discussion centered around ways to leverage the electronic health record (EHR). There are already many prompts, so the infrastructure is already present, though there is significant "prompt fatigue/overload"; health systems may balk at adding another until there is strong consensus in guidelines for universal Lp(a) measurement until there is strong consensus in guidelines for universal Lp(a) measurement or evidence that such interventions are effective. At that point, it would be expected that a prompt would be efficient, analogous to current prompts for one-time HIV or Hepatitis C testing. Similar to other screening tests with EHR prompts, supportive text and education on Lp(a) would be necessary to enable fully informed patient-clinician discussions and agreement on testing. In the meantime, it is reasonable to include Lp(a) testing as part of order sets in specific conditions (e.g. aortic valve replacement for calcific aortic valve stenosis).

OUTSTANDING QUESTIONS ABOUT Lp(a) – Fundamental Knowledge

There are many outstanding questions related to Lp(a) metabolism (production and clearance of the particle) and how it exerts its pathogenic effects in the vasculature. It was recognized that a challenge to accelerating fundamental research on Lp(a) is the relatively small number of scientists working in this area. This was attributed, in part, to challenges in obtaining research funding from government agencies.

It was recognized that lack of mechanistic information about Lp(a) also reflects the absence of good animal models.

Some of the questions regarding the metabolism and pathophysiology of Lp(a) that require further research are summarized below:

1) **How is Lp(a) produced and assembled by the liver?**
It appears that apo(a) and apolipoprotein B-100 associate non-covalently inside the cell and that the disulfide bond forms extracellularly.[5] The nature of the intracellular lipoprotein particle containing apolipoprotein(a) (apo(a)) is not fully characterized – is it more VLDL- or LDL-like? It is not clear whether all of the apo(a) becomes bound to apoB-100 to form Lp(a), although levels of free apo(a) in plasma are very low. Is free apo(a) cleared rapidly or does it become associated extracellularly with circulating LDL or VLDL? This raises the possibility that targeting the apo(a)-apoB interaction might increase the amount of free apo(a), which would have unknown consequences.
2) **How is Lp(a) cleared from the circulation?**
It has been speculated that there are a variety of hepatocyte receptors that can clear Lp(a) under different metabolic conditions including, for example, the LDL receptor (LDL-R). As of this time, there is no clear mechanism to enhance Lp(a) clearance. Notably, at present, all therapeutic strategies for specifically lowering Lp(a) are aimed at reducing apo (a) synthesis.
3) **Other unknown aspects of Lp(a) metabolism**
Results from in vivo stable isotope metabolic studies have been inconsistent. Mechanistic studies to corroborate these observations (such as recycling of Lp(a) components after uptake, and exchange of apo(a) between lipoprotein particles in plasma) are incomplete.
A consistent observation has been an inverse correlation between the levels of Lp(a) and plasma triglycerides (TG).[6] Pharmacological inhibition of cholesteryl ester transfer protein (CETP) lowers Lp(a) as well as non-HDL-cholesterol and triglycerides (TG), and so the inverse relationship between Lp(a) and TG levels remains unexplained. Whether Lp(a) levels are affected post-prandially is also unclear.
Indeed, several classes of drugs lower Lp(a) levels, although Lp(a) is not the primary target of treatment.[7] Lomitapide and mipomersen reduce apoB synthesis which appears to explain their effect on Lp(a) levels. PCSK9 inhibitors also lower Lp(a), although the mechanism is unclear since effects on both Lp(a) biosynthesis and clearance have been documented. The mechanism by which CETP inhibitors lower Lp(a) is unknown.[6]
4) **What is the role of the kidney in determining plasma Lp(a) levels?**
In patients with advanced chronic kidney disease, especially when there is proteinuria, Lp(a) levels are in-

creased. The exact mechanism is unknown but may result from increased hepatic synthesis.[8]

5) **How does Lp(a) mediate its pathogenic effects?**
   a) The proatherosclerotic effects of Lp(a) likely reflect the preferential accumulation of pro-inflammatory oxidized phospholipids on Lp(a).[9] Although the contribution of Lp(a) to different stages of atherosclerotic plaque development remains unclear, there are compelling data from Mendelian randomization studies as well as coronary imaging data that strongly suggest a role for Lp(a) in the initial phases of atherosclerosis.[10] The potential ability of Lp(a) to promote prothrombotic events in the arterial system may have a role in precipitating events.[11] This includes potential effects of Lp(a) on injured endothelium, blood clot properties and platelet function. Lp(a) may also lead to increased vulnerable plaque features. This could also give the appearance of a potential prothrombotic link: is Lp(a) affecting thrombosis per se or does it favor the formation of a vulnerable plaque that ruptures and causes a thrombotic event? Notably, the former could explain the association between Lp(a) and ischemic stroke in childhood, an event that occurs in the absence of atherosclerosis.
   b) Although the precise mechanisms are unclear, genetic and clinical studies both affirm the strong causal link between Lp(a) and the incidence and progression of aortic valve stenosis (AVS).[9] Whether specific Lp(a) lowering will decrease AVS progression remains to be determined, although the design of clinical trials to address this question is challenging since the optimal timing of intervention, likely critical, is unknown. Due to the lack of therapies to prevent AVS progression, this represents an important unmet clinical need.

The group agreed that we need to figure out how Lp(a) contributes to disease. This, in turn, will open up doors to new strategies to increase the armamentarium of therapeutic options, both for lowering Lp(a) and interfering with its pathogenic effects. It is not entirely clear at this time what features of elevated Lp(a) increase ASCVD and AVS risk since there is variable susceptibility of disease between individuals with high Lp(a). We cannot make progress on addressing these questions until we understand better the fundamentals of Lp(a) biology.

OUTSTANDING QUESTIONS ABOUT Lp(a) – Clinical

1) Does targeted lowering of Lp(a) reduce ASCVD event risk in a secondary prevention population? This is the most time sensitive clinical question, and it is being addressed by multiple ongoing multinational Phase 3 RCT's. If negative results are observed in these trials, it might indicate that elevated Lp(a) merely serves as a marker for disease.
2) If its benefit in secondary prevention can be established, this will raise questions about targeted lowering of Lp(a) in the subclinical atherosclerosis population? And how early can/should Lp(a) lowering be considered?
3) How much Lp(a) lowering is required to see a beneficial effect? Alternatively, can it be established that there is an achieved Lp(a) level below which risk for ASCVD events is reduced?
4) Does Lp(a) have a physiological role that could lead to unexpected effects of Lp(a) lowering? Is there such thing as a level of Lp(a) that is "too low"?
5) Will therapeutic Lp(a) lowering cause hyperglycemia or incident type 2 diabetes mellitus? If so, what is the mechanism?
6) What is the conclusive pathogenic mechanism of Lp(a), and what are the modifiers of Lp(a) risk? Are there protective mitigating factors? The answers could lead to protective interventions beyond established care, such as aspirin or anti-inflammatory agents.
7) Is there sufficient variability in Lp(a) levels within an individual to warrant repeated measurements? One recent study using a high-quality Lp(a) assay revealed up to 20 % variability in Lp(a) levels within healthy individuals.[12] Repeated measurements may be required when an individual's level is close to a cutpoint (75 – 125 nmol/L or 30 – 50 mg/dL). Other times to consider repeat testing may be in the context of clinical changes (e.g. after menopause or other hormonal changes, if proteinuria/kidney or liver disease develops, after initiation of PCSK9 inhibitor).
8) How much is Lp(a) contributing to LDL-C in patients with extreme Lp(a) elevation? What are the relative contributions to disease of LDL and Lp(a) in these patients? What about the role of other disease risk factors?

CLINICAL MANAGEMENT OF INDIVIDUALS WITH ELEVATED Lp(a)

As we move towards its more widespread clinical adoption, Lp(a) cannot be divorced from ongoing trends in clinical medicine. Rigorous implementation science methods can be used to translate knowledge to clinical practice. We can marshal existing and emerging resources – such as EHR and artificial intelligence (AI) technology and the different skills that our students and trainees are learning – to screen populations more effectively.

One of the many challenges faced by clinicians and researchers in the field is the limited databases that explore the contribution of Lp(a) to risk in the full clinical context including individual and population variability within our country and around the globe, and the interplay with social determinants of health and population genetic variation. Widespread testing of Lp(a) would enable broader, more complete databases to inform the science, but that is not likely to happen until the evidence informs its widespread adoption. Ultimately, this may have to proceed in stepwise fashion: researchers may first have to establish local/regional

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registries and report on their experience with cascade screening of Lp(a) to generate interest across the clinical spectrum.

We also discussed the difficulties in obtaining Lp(a) levels in different parts of the US. Some participants shared examples of health systems that did not offer testing in-house but incurred added costs by sending samples to centralized testing centers; often, the Lp(a) result comes back 3 – 4 days after the rest of the lipid panel, significantly decreasing any momentum towards using the Lp(a) value. In other cases, Lp(a) testing is not offered at all. The clinicians in the group could all report examples of insurance denials after Lp(a) levels were ordered. As a result, clinicians were required to spend additional time appealing the lack of covering of a test that is recommended by national guidelines. Obviously, payors are stakeholders in the rollout of widespread Lp(a) testing and they will have to be included in future discussions that address universal and targeted screening programs.

The University of California at San Diego (UCSD) example was discussed as an example of the efficiency of the EHR. Their clinicians are given a choice to either select lipid panel, or lipid panel with Lp(a). Lp(a) testing is also incorporated into the pre-TAVR (transcatheter aortic valve replacement) order set. As a consequence, the Lp(a) testing rate increased to the point where essentially everyone who was getting a TAVR at UCSD had their Lp(a) measured. It was recognized by the group, however, that institutions elsewhere may not be as amenable to these approaches.

From a primary care perspective, major considerations for Lp(a) testing can be grouped into three buckets. One is cost, another is clinical decision support, and a third is education.

Cost: As described above, a major stumbling block in primary care occurs when a requisitioned Lp(a) test is not covered by the insurer. This can occur because an incorrect diagnostic code was used, or the insurer considers this as an "experimental" test. Agreement on the utility of universal screening will enable testing to occur without these stumbling blocks that frustrate clinicians and patients, and impact clinician-patient relationships.

Clinical Decision Support: The discussion suggested that generalists are reluctant to over-test, over-diagnose and over-treat which may account for an unwillingness to measure Lp(a) at this time. This may reflect, in large part, anxiety over not knowing what to do with the information. In this regard, having robust clinical decision support tools will be very helpful. These tools should be designed to make sense of the information and to help clinicians decide how to best manage patients. All this needs to be incorporated at the primary care level to avoid a log jam of specialist referrals.

Education: Expert associations like the NLA and others have established algorithms for management of Lp(a) based on available information, but more clear directions for care will be provided upon completion of the NLA Scientific Statement update and the reporting on the results of the ongoing RCT's. Such tools should be created with EHR-adoption in mind to improve ease of use and clinical uptake.

LIPOPROTEIN(a) IN THE PEDIATRIC POPULATION

There was consensus in the group that more studies of Lp(a) in the pediatric population need to be performed, particularly on the relationship between elevated Lp(a) and pediatric stroke.[13] The literature in this area is old and based on relatively small cohorts. Given the rarity of this condition, registries are needed and clinicians who care for individuals who have suffered childhood stroke should be encouraged to gather more information about these patients.

Lp(a) can be measured as early as age 5 to estimate lifetime risk for ASCVD and aortic stenosis as part of a universal screening program. This could be done at the same time as the lipid profile (between ages 9–11 years old), as recommended by the American Association of Pediatrics (AAP) and the AHA. Early identification can be incorporated into long-term ASCVD risk planning, especially in families with premature disease. Pediatricians and/or pediatric lipid specialists would need to be equipped to counsel families where children have either extreme or less extreme Lp(a) elevations.

At present, there are no recommendations for universal pediatric Lp(a) measurement. As new therapies are approved, their use in children will be considered for those who have suffered Lp(a)-associated stroke and for those with a family history of very premature ASCVD. We expect that there will be a significant gap in time from FDA approval in adults of Lp(a) therapeutics based upon RCT outcomes, to availability of these drugs for at-risk children.

CONCLUDING REMARKS

Results of large prospective clinical trials that specifically and significantly reduce Lp(a) in the secondary prevention population are ongoing. The results of the Lp(a)HORIZON trial using pelacarsen (the first of the RNA interfering drugs under investigation) is scheduled to report in 2025. The results will demonstrate, for the first time, whether specifically lowering Lp(a) will reduce cardiovascular endpoints in a secondary prevention setting. As we eagerly await these results, discussions are intensifying around all aspects of Lp(a), from fundamental understanding of this enigmatic lipoprotein to basic clinical management. This NLA Expert Discussion (November 2023) brought together a variety of stakeholders to explore unmet needs/outstanding questions in the Lp(a) field. We look forward to future gatherings where specific data can be reviewed and debated, and where we can broaden our perspectives further. This holistic approach will be necessary to employ going forward as clinical interest in Lp(a) grows.

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Author contribution statement

M.L.K and M.B.B. contributed to writing of the original draft, and review and editing; D.S. contributed to review and editing.

Use of AI and AI-assisted-technologies

These have not been used in the writing process.

Ethical statement

Not applicable (is not a research study)

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Marlys L. Koschinsky: Writing – review & editing, Writing – original draft, Project administration, Conceptualization. **Daniel E. Soffer:** Writing – review & editing, Writing – original draft, Project administration, Conceptualization. **Michael B. Boffa:** Writing – review & editing, Writing – original draft.

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