LIPOPROTEIN(a) IN YOUTH

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ABSTRACT

Lipoprotein (a) [Lp(a)] represents a class of lipoproteins with structural similarity to low-density lipoprotein (LDL). In adults, Lp(a) has been shown to be an independent risk factor in the development of atherosclerotic cardiovascular diseases (ASCVD) and calcific aortic valve disease (CAVD). Outcomes in youth are limited by the paucity of data but several studies suggest that it is a risk factor for arterial ischemic stroke (AIS). The usual pitfalls of extrapolating from adult data may be *less* problematic for Lp(a) given that the gene is fully expressed at a very young age and high levels in childhood are associated with elevated levels in adulthood, irrespective of pubertal development or lifestyle changes. Universal screening for elevated lipoprotein (a) is controversial, with some groups recommending universal screening and others advocating for selective screening. Regardless of strategy, screening is warranted given that the gene for Lp(a) is inherited as an autosomal co-dominant trait and is one the most heritable disorders in humans. We will review recent guideline-based evidence for Lp(a), the distribution and interpretation of the Lp(a) measurement, and pharmaceutical therapies to reduce Lp(a). We will also summarize the available evidence and recommendations regarding the detection and treatment of youth with elevated Lp(a). Although the relative merits of screening and treating Lp(a) in youth may be debatable, it is clear that youth who enter adulthood with the lowest possible burden of risk factors will have a much lower risk of developing ASCVD in adulthood.

INTRODUCTION

Just over a decade ago, there was little consensus about whether or not Lp(a), a highly atherogenic lipoprotein, was an independent ASCVD risk factor. Much of the discordance was attributable to both biologic and analytical problems, including the unparalleled structural variability, racial/ethnic variations, difficulty defining 'normal' levels, and lack of consensus with respect to measurement methodology. The wider availability of improved methods for measuring Lp(a) coupled with data from observational studies of large diverse populations, genome-wide association studies (GWAS), and large Mendelian randomization studies leave little doubt that in adults, Lp(a) is an independent risk factor for ASCVD including coronary heart disease (CHD), ischemic stroke, peripheral arterial disease, and calcific aortic valve disease (CAVD) (1-9). Data suggest that Lp(a) is the strongest independent genetic risk factor for both myocardial infarction (MI)

and aortic stenosis (10), and inversely correlated with life expectancy (11).

In many ways, Lp(a) is more atherogenic than low density lipoprotein cholesterol (LDL-C) because of its pro-inflammatory and antifibrinolytic properties (12). The bulk of available data show that Lp(a) is predictive of ASCVD events independent of the LDL-C level (13); the lifetime risk of ASCVD increases with higher Lp(a) levels independent of the LDL-C level.

Although fewer studies have focused on Lp(a) in youth, data in the pediatric population suggests that it augments the risk of future ASCVD and is a risk factor for arterial ischemic stroke (AIS) including recurrent events. Recently, data from YFS (Cardiovascular Risk in Young Finns) and the BHS (Bogalusa Heart Study) showed adults with early onset ASCVD were more likely to have Lp(a) ≥ 30 mg/dL at 9-24 years of age, with a hazard ratio of 2.0 in YFS and 2.5 in BHS (14). Like familial hypercholesterolemia (FH), Lp(a) is a highly hereditable disorder and although the genes for these two lipid disorders are not linked, when they occur jointly and/or in combination with other common risk factors such as diabetes and hypertension, they markedly accelerate the development of premature ASCVD, underscoring the importance of cascade screening and reverse cascade screening in families (15-17).

EPIDEMIOLOGY AND GENETICS

The distribution and prevalence of elevated Lp(a) levels in the population are based on data from well-known epidemiologic studies including the Copenhagen General Population Study (18), Epic-Norfolk (19), and the Multi-Ethnic Study of Atherosclerosis (20). In children, initial data came from the 3rd National Health Nutrition and Examination Survey (NHANES), which characterized Lp(a) levels in 4-19 year-old youth (21). Since then multiple studies have evaluated Lp(a) levels in youth (22) and newborns (23) The percentile distributions and prevalence of Lp(a) > 30 mg/dL in youth aged 4–19 years from the NHANES survey is shown in Figure 1. To better understand the choice of cut points in youth and adults, the distribution of Lp(a) in the Danish adult population from the Copenhagen study is shown in Figure 2.

Ethnic group	Age (yrs)	Lipoprotein(a) (mg/dL)						N
		Percentile					Percent > 30 (mg/dL)	
		5	10	50	90	95		
Nonhispanic white								
	4–5	0	0	7	38	62	15.0	214
	6–11	0	0	12	48	65	18.8	304
	12–15	0	0	10	48	56	20.2	187
	16–19	0	0	9	53	62	25.8	149
Nonhispanic black								
	4–5	2	6	31	75	94	52.5*	303
	6–11	1	5	32	76	100	53.3*	574
	12–15	0	5	33	77	95	56.4*	358
	16–19	1	6	31	69	76	54.6*	307
Mexican American								
	4–5	0	0	5	30	48	8.2	309
	6–11	0	0	9	45	62	21.0	376
	12–15	0	0	9	48	58	20.1	272
	16–19	0	0	8	36	52	11.4	232

* Indicates unadjusted statistically significant difference in levels of Lp(a) > 30 mg/dl between black and white children, and between black and Mexican American children in the same age group. Significance level was set at < 0.05.

Figure 1. The percentiles distributions and prevalence of Lp(a) > 30 mg/dL in youth aged 4–19 years from the NHANES study (Ref 24).

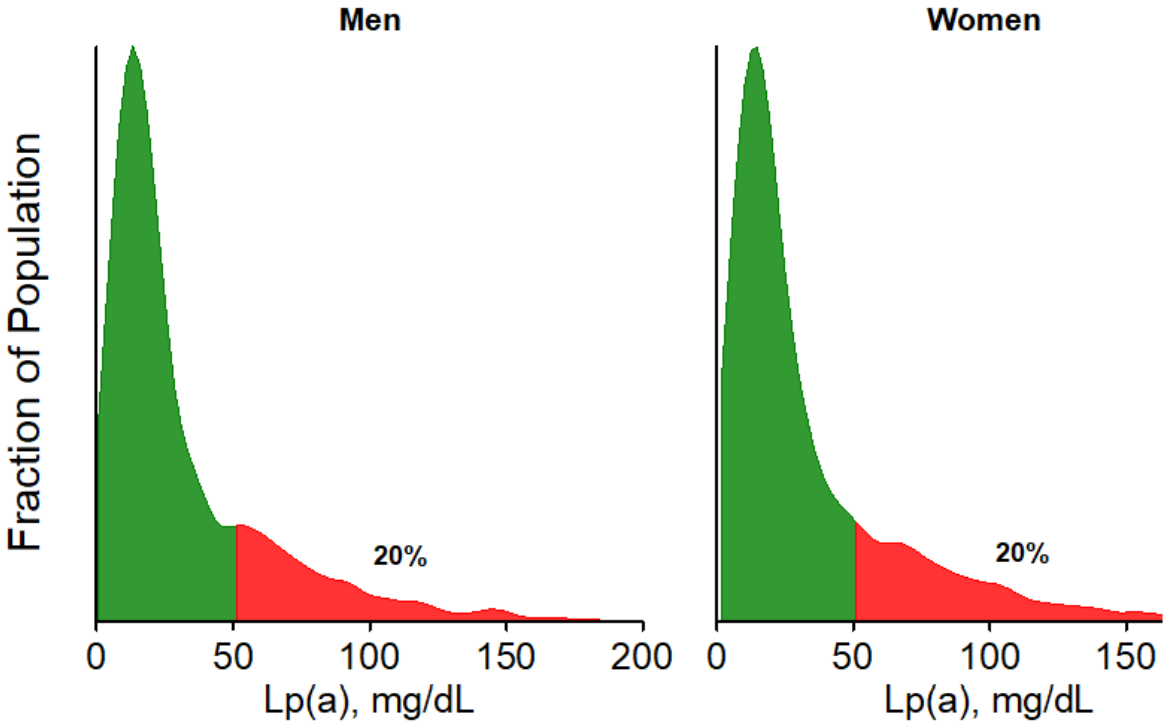

Fig 2. Distributions of Lp(a) levels in ~3000 men and 3000 women in the Copenhagen General Population Study from Ref. 21.

The distribution is highly skewed towards low levels and varies with gender. A threshold value of 50 mg/dL corresponding to values > 80th percentile in a predominately Caucasian population have been proposed by the European Atherosclerosis Society/European Society of Cardiology (EAS/ESC) (24) and the National Lipid Association guideline statement but these values are not used in all guidelines. Many laboratories across the U.S. consider values > 30 mg/dL as abnormal, which may arguably be more appropriate since this is a value above which excess ASCVD risk begins to accrue (25).

Significant variability in Lp(a) levels exists among different races and ethnicities (see NHANES data in Figure 1); higher rates of elevated Lp(a) in Black children have been demonstrated compared to White children (26). In adults, the median (inter-quartile range) values for White adults in the Copenhagen study were 12 mg/dL (5-32 mg/dL), while in Hispanic adults the mean was 19 mg/dL (8–43 mg/dL), and in Black adults it was 39 mg/dL (19–69 mg/dL) (18). The UK Biobank study found that the median value of Lp(a) was the lowest in Chinese individuals (16 nmol/L) slightly higher in Whites and South Asians (19 and 31 nmol/L respectively) and the highest in Black individuals (75 nmol/L) (4).

Overall, the concentration of Lp(a) *can vary up to a 1000-fold among individuals* and up to ~3-fold higher levels are reported in Black populations compared to White populations (2, 27, 28). This can be compared to the extremes of LDL-C where there is approximately a 5-fold difference between individuals with normal values versus those with familial hypercholesterolemia (FH). Lipoprotein (a) and LDL-C levels in children can also vary throughout the year and in the setting of

infection. Gidding et al studied the combined biologic and analytic variation in Lp(a) and other lipid levels measured 4 times over a one year period when children were healthy as well as within a week after acute infections in 63 adolescents (29). The 50th percentile for variability in children's Lp(a) was 19%, but 5% of children had up to 40% variability in Lp(a) over the one year period. For LDL-C, less variability overall was noted (25% variability for the 50th and 95th percentile). No significant differences were observed for lipids after acute infections, except for a statistically significant drop in HDL-C and apo A-I.

The gene encoding apo(a) is inherited as an autosomal co-dominant trait and is one of the most heritable disorders in humans with estimates of 0.51 to 0.98 for the total Lp(a) level (30-32), accounting for the strong association with parental ASCVD (31, 32). By some estimates, up to 90% of the variation in the Lp(a) level is attributed to genetic expression (30). A child inherits one allele from each parent; as a result, most individuals produce two distinct Lp(a) isoforms differing with respect to both structure and concentration.

When an evaluated Lp(a) is found in an individual of any age, it is vitally important to emphasize this strong genetic inheritance pattern and facilitate screening of family members. Zawacki et al in fact noted that a family history of early-onset ASCVD correlated better with an elevated Lp(a) level in a child (>50 mg/dL) than an elevated LDL-C level (>190 mg/dL) (16). This is similar to findings from the LIPIGEN (Lipid Transport Disorders Italian Genetic Network) pediatric group (33). Cascade screening (parent to child) as well as reverse cascade screening (child to parent) has a high yield for detecting new cases. In the SAFEHEART (Spanish Familial Hypercholesterolemia Cohort) study, Ellis et al showed that in individuals with both FH and an elevated Lp(a), 1 new case of elevated Lp(a) was detected for every 2.4 individuals screened; index cases with FH who did not have an elevated Lp(a) level detected 1 individual for every 5.8 individuals screened (15). In Australia, a cascade screening program for FH and high Lp(a) found a new case of FH for every 1.5 relatives tested, a new case of high Lp(a) and FH for every 2.1 relatives tested, and a new case of isolated high Lp(a) in every 3.0 relatives tested (17). Youth with FH and a family history of premature ASCVD (defined as onset of ASCVD in male relatives ≤ 50 years and females ≤ 60 years), were 3 times more likely to have an elevated Lp(a) level (≥ 50 mg/dL) than those with late onset ASCVD (16). The Family Heart Foundation (www.thefhfoundation.org) and the National Lipid Association (www.lipid.org) provide a number of resources for patients and clinicians to facilitate a better understanding and identification of affected family members.

When screening for elevated lipoprotein (a), biochemical testing, as opposed to genetic testing, is generally performed (see testing discussion below in Interpretation of Lp(a) Levels). In contrast, FH can be diagnosed either by biochemical measurement of LDL-C or through genetic testing.

INTERPRETATION OF Lp(a) LEVELS

The unparalleled polymorphism in the apo(a) gene gives rise to the vast diversity of levels among individuals and ethnicities. This polymorphism is the result of a varying number of repeats of one of the kringle domains (tri-looped structures depicted in Figure 3) resulting in ~55 different isoforms of apo(a) ranging from 300 – 800 kDa. It is this structural heterogeneity that has also led to interassay variability, lack of standardization, and consequently much difficulty correlating and reconciling differences in reported outcomes (34, 35) . The serum Lp(a) level is inversely related to the size of the apo(a) protein i.e., individuals with small apo(a) isoforms have high serum Lp(a) levels while individuals with large apo(a) isoforms have low serum Lp(a) levels. As noted

above, the size of the apo(a) isoforms is inherited, with an individual having two distinct apo(a) isoforms derived from apo(a) genes from their mother and father. This results in individuals having two different size Lp(a) particles in the serum.

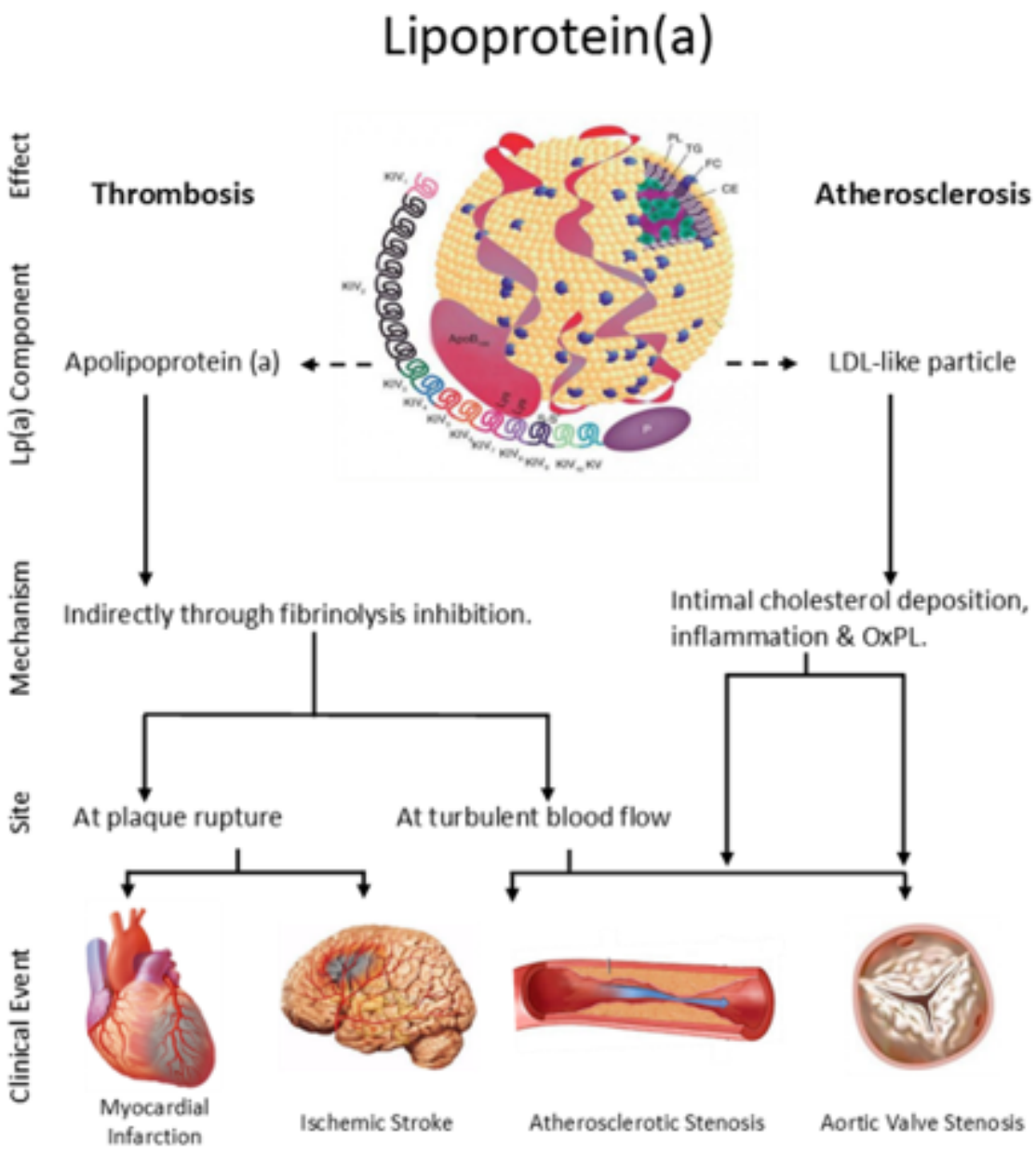

Fig 3. Structure of lipoprotein(a) depicting the apo(a) protein with repeating KIV domains linked through a S-S bond to apoB100. TG=triglycerides, CE=cholesterol ester, FC=free cholesterol, PL=phospholipid (from Ref 1).

There are also multiple methods to measure Lp(a) (36), reported as either the molecular weight (mass concentration) in mg/dL or the particle (molar) concentration (nmol/L), and these measures are not interconvertible. The molecular weight of the Lp(a) particle includes all components shown in the Lp(a) structure in Fig. 3, namely the apo(a) protein, the LDL-like particle (including the protein portion which accounts for roughly one-third of the particle mass), the associated particle lipids (free cholesterol, triglycerides, phospholipids), and carbohydrate moieties. As noted above, there is substantial variation in the molecular weight due to the variability in the two apo(a) isoforms each person expresses. Additionally, the size of the apo(a) isoform, i.e., small versus large, has been proposed as a key determinant of the atherogenic characteristics (37). Although much of the literature discussing population distribution of values and/or the attributable ASCVD risk references report Lp(a) values in mg/dL, a value strongly influenced by the apo(a) size, it has been suggested that measuring the number of Lp(a) particles (nmol/L) is preferred, in part because Lp(a) reference material is standardized in nmol/L and independent of isoform size (1). This approach was affirmed in a landmark study by Gudbjartsson et al showing that in a large Icelandic population, the association of Lp(a) with CHD was highly correlated with the molar concentration rather than the type pf of apo(a) isoform (38). In the past, a conversion factor of 2.85 for small apo(a) isoforms and 1.85 for large apo(a) isoforms with a mean of 2.4 nmol/L per 1 mg has been used. However, since individuals can express two distinct apo(a) isoforms, this conversion estimate can be inaccurate and is not generally recommended. Like the measurement of apoB100 (the protein portion of the LDL particle), neither assay is affected by whether or not the individual was fasting since they measure lipoprotein mass or molar levels do not vary with food intake.

In a standard lipid profile, the *cholesterol carried by Lp(a)*, i.e., Lp(a)-C, is included in the LDL-C and non-HDL-C measurement. A simplified way to think of this is to imagine lipoproteins as "buckets" that carry cholesterol and triglyceride. The Lp(a) measurement itself is the number of "buckets" whereas the cholesterol carried by this "bucket" is included in the LDL-C measurement. Correction factors have been proposed to estimate the contribution of Lp(a)-C to the calculated LDL-C value based on the Dahlen equation, but these are rarely used or reported in the literature (36). With the development of drugs designed to specifically lower Lp(a) and Lp(a)-C knowledge of the true LDL-C and Lp(a)-C levels may assume greater importance (39).

Methods are being developed to measure Lp(a) cholesterol levels (40); these methods indicate that calculating the cholesterol in Lp(a) using equations may not be accurate. The EAS consensus panel recommended to avoid routine correction of LDL-C by subtracting 30% of the Lp(a) mass measurement till we have more data on the Lp(a) cholesterol content (13).

DEVELOPMENTAL AND DYNAMIC CHANGES IN Lp(a)

Lp(a) is detectable in the serum of newborn infants; gestational age but not birth weight seems to affect newborn levels (21, 41, 42). Lp(a) levels in umbilical cord blood correlated strongly with measurements on neonatal venous blood, which had moderate correlations with levels at 2 months and 15 months of age. Most significantly, Lp(a) levels at birth greater than the 90th percentile predicted lipoprotein (a) > 42mg/dL at 15 months (43). This is consistent with previous studies of Lp(a) showing full expression of the gene product in the first (44) and second (45) years

of life, a pattern strikingly different from other lipoproteins.. In fact, no other lipoprotein level seems to track as perfectly to adulthood as Lp(a). The highly hereditable trait is reflected by a close correlation with the Lp(a) level and the number of grandparents the child has with a history of CHD (46). However, some studies suggest there is variability in Lp(a) measurements in childhood; one study of children referred to a pediatric lipid clinic showed 22% of children who were on no lipid lowering therapy had an increase in Lp(a) in adulthood. Among children prescribed statin monotherapy or statin/ezetimibe in combination, 43% and 9% of children had higher Lp(a) in adulthood respectively (22). Analysis of the YFS cohort showed that most individuals with Lp(a) ≥ 30mg/dL at any point continued to have high Lp(a) (47), indicating that the clinical impact of variability in Lp(a) during childhood may not be clinically significant.

Lp(a) is produced by the liver, but the clearance pathways are not well understood. The clearance of Lp(a) is not predominantly regulated by the LDL receptor and therefore lowering LDL-C levels with statins or ezetimibe does not lower Lp(a) levels. The kidney appears to play an important role in Lp(a) clearance as renal disease is associated with increased Lp(a) levels. The levels of Lp(a) appear to be regulated primarily by the rate of production of Lp(a). Renal disease may increase levels while severe liver disease may result in lower Lp(a) levels (1). Recently, high endogenous levels or therapeutic administration of human growth hormone were linked to increased serum Lp(a) levels, which may explain the association between childhood human growth hormone treatment and higher risk of ASCVD (48).

SCREENING FOR ELEVATED Lp(a)

Expert opinions on screening strategies for elevated Lp(a) differ. The National Lipid Association recommends a selective screening strategy which is summarized in Table 1 (1). The European Atherosclerosis Society recommends universal screening in adulthood and a selective screening strategy for youth (13). The American College of Cardiology and the American Heart Association do not have official screening guidelines for Lp(a) (49). Canadian guidelines (50) and the European Society of Cardiology (13) advise universal screening for Lp(a) in adulthood. The 2011 Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents suggested testing Lp(a) in children with ischemic or hemorrhagic stroke, or with a family history of ASCVD not explained by classical risk factors (51). However, it should be noted that since the time of their publication the knowledge regarding Lp(a) as a risk factor has been considerably strengthened - data which was incorporated into the NLA statement.

The main argument against universal Lp(a) testing in adults or children is that to date, no clinical trials have been able to show benefit from treatment aimed at lowering Lp(a) (52). However, such data are expected to be forthcoming with the release of drugs that specifically target Lp(a). Thanassoulis argues that “although there is no targeted therapy for Lp(a) lowering yet, to properly care for our cardiovascular patients requires knowledge of Lp(a). Individuals with high Lp(a) have a higher burden of atherogenic lipoproteins and are therefore at higher cardiovascular risk, which can only be detected by Lp(a) measurement. These individuals can obtain significant benefit from more aggressive lifestyle modifications and the maintenance of optimal risk factors throughout life.” This is similar to advice from Zawacki et al (16) who noted that “reverse-cascade screening of children with FH and high Lp(a) represents two opportunities for potentially life-saving diagnosis and treatment for family members” providing “an opportunity to intervene at an earlier age for both children and their adult relatives.” In summarizing key points, the NLA guidelines noted that “Even in the absence of an approved Lp(a)-lowering medication, in youth found to have an elevated level of Lp(a), it is important to

emphasize early and lifelong adoption of a heart-healthy lifestyle by the child and family members, especially with respect to smoking avoidance or cessation, given the thrombotic risk attributable to Lp(a)" (1).

Table 1. NLA Recommendations (from Ref 1)
Clinically suspected or genetically confirmed FH.
A family history of first-degree relatives with premature ASCVD (<55 years of age in men, <65 years of age in women).
An unknown cause of ischemic stroke.
A parent or sibling found to have an elevated Lp(a).

All recommendations were Class IIb (weak) and were based on limited data (Level C-LD)

Some professional societies have also suggested levels be measured in those whose LDL-C levels fails to decrease as predicted following statin therapy, and individuals with a history of coronary artery restenosis or recurrent ASCVD not explained by other risk factors (53-55).

RELATIONSHIP WITH STROKE IN YOUTH

The most extensive data on the impact of Lp(a) in youth come from pediatric stroke studies. Although the evidence for Lp(a) as a stroke risk factor is not as robust as the relationship with CHD, in part likely due to the more heterogeneous etiology for stroke, i.e., both ischemic (large and small artery), hemorrhagic, and embolic, several meta-analyses concluded that an elevated Lp(a) level is a risk factor for incident stroke in adults (8, 56-58) as well as a large prospective, observational study demonstrating that Lp(a) levels were independently associated with large artery stroke, odds ratio (OR) of 1.48 per unit $\log_{10}$ Lp(a) increase and recurrent cerebrovascular events (58). Tsimikas suggests that the etiology and relationship of Lp(a) with stroke is age dependent, with the more purely antifibrinolytic properties predominating in children and also noting that children with strokes frequently have other exacerbating diseases including congenital heart disease, coagulation disorders, or chronic inflammatory conditions. By contrast, the proinflammatory effects and proatherogenic effects of Lp(a) predominate in adults. Boffa and Koschinsky note that associations of genetic risk factors for thrombosis in children are less contaminated by acquired risk factors such as smoking as in the adult population and may therefore more accurately represent the thrombotic risk of Lp(a) (13, 59, 60).

The recommendation of the 2011 Expert Panel (51) included Lp(a) in lipid screening focused on youth with an ischemic or hemorrhagic stroke. This built on the 2008 pediatric stroke guidelines; although not specifically classified as a risk factor that warranted screening, Lp(a) was listed as one of the hypercoagulable abnormalities that may cause stroke (61). Sultan et al included observational studies of imaging-confirmed AIS where lipid levels, including Lp(a), were available (62). Race/ethnicity were not specified; and the majority of studies were from Germany and the United Kingdom. There was a strong, positive association of AIS with Lp(a) (odds ratio [OR] 4.24 (confidence interval [CI] 2.94 – 6.11)). Kenet et al reported a pooled OR 6.53 (CI 4.46 – 9.55) for elevated Lp(a) in cases of AIS (63). A third case-control study in predominately white U.S. children only found a positive association of a Lp(a) >90th percentile using race-specific cut points with recurrent AIS but the effect

was large - OR 14.0 (CI 1.0 – 184, p=0.05)., OR 14.0, but with a substantially larger CI 1.0 – 184 but P=0.05. This effect was correlated with a small apo(a) isoform size below 10th percentile (OR 12.8 (1.61 – 101), P=0.02) (64). An important consideration in these studies is that Lp(a) levels were measured in many cases after the initiation of anticoagulation therapy, which likely included aspirin, the latter which has been reported to reduce Lp(a).

While venous thromboembolism (VTE) is rare in children and the majority of events are due to central venous line-related thrombotic events or underlying medical conditions (i.e., congenital heart disease, infection, cancer, prematurity), several studies reported an increased risk of VTE with an elevated Lp(a) level (65, 66). However, this has not been supported in larger adult studies (13). As is the case in many studies of the impact of childhood risk factors, long-term studies linking elevated levels of Lp(a) to adult-onset ASCVD-related events are limited.

LIFESTYLE CHANGES TO LOWER Lp(a)

As Lp(a) levels are dominated by genetic influence, conventional wisdom has been that diet has little impact (53). Paradoxically, multiple studies have reported that a low-fat diet and low-fat-high-carbohydrate diets significantly *increase* Lp(a) in adults (67-69). More limited studies have demonstrated similar findings in youth. Brandstatter et al measured Lp(a) mass and the apo(a) isoform size before and after a 3-week hypocaloric diet and exercise in obese children (67). With a 6.6% decrease in body weight, they observed a ~20% decrease in Lp(a) levels, which was comparable to the declines seen for LDL-C and triglycerides. The decline in Lp(a) was greater in youth with higher baseline levels of Lp(a). Studies of a diet enriched in plant sterols (70) failed to significantly change Lp(a) levels. Data on lipoprotein (a) levels in low carbohydrate diets are mixed, with one study showing a low glycemic index diet did not change Lp(a) levels (71) and another study showing a decrease in Lp(a) with a low carbohydrate diet (72). It is unclear if weight loss or diet composition is the primary factor. Importantly, a healthy diet, exercise, avoidance of tobacco (including secondhand smoke exposure), and maintaining a healthy body weight are fundamental in minimizing the acquisition of additional risk factors that compound the atherogenic effect of an elevated Lp(a) level.

PHARMACEUTICAL INTERVENTIONS TO LOWER Lp(a)

Currently, there are no Food and Drug Administration (FDA) approved medications for targeted lowering of Lp(a) in adults or children. Previously niacin, which has been shown to lower Lp(a) levels, was commonly used in adults with elevated Lp(a) but failed to prevent ASCVD events in two clinical outcome trials, the Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides and Impact on Global Health Outcomes (AIM-HIGH) (73) and the Second Heart Protection Study (HPS-2 THRIVE) (74). Although proprotein convertase subtilisin/kexin 9 inhibitors (PCSK9i) are not indicated for targeted treatment of Lp(a), studies show significant reductions. For example, the FOURIER study found that adults with the highest Lp(a) levels had greater reductions in Lp(a) with their use and greater risk reduction (75). Only one clinical trial of this class of drugs has included adolescents, all of whom had homozygous FH. In this population evolocumab was safe and effective (76).

Statin therapy has been the foundation treatment to reduce LDL-C and to lower the risk of ASCVD events but it does not seem to reduce Lp(a) mass appreciably and in fact may actually increase levels of Lp(a) (77). Despite this trend, statins remain the mainstay of pharmaceutical therapy to reduce ASCVD risk in both children and adults. Statin therapy in children with high Lp(a) remains controversial, with very limited data to guide clinical decision making. Generally speaking, statin therapy is not recommended for children whose sole risk factor is an elevated Lp(a) level, but as in adults, it is the first-line therapy to reduce LDL-C in youth with a high risk of developing premature ASCVD as adults (51) and it should be considered when a child has elevated LDL-C and Lp(a), particularly with a family history of premature ASCVD or other ASCVD risk factors (51). A 20-year study using pravastatin in children affirmed both the long-term safety and efficacy of this approach in 214 youth with FH (78).

In addition to the effects of PCSK9i and niacin, mipomersen, lomitapide, and cholesterol-ester-transfer protein inhibitors have also been shown to decrease Lp(a) concentrations (79-81). Antisense oligonucleotides to apo(a) mRNA are in development (80, 82) and, in the future, may play a role in treatment of elevated Lp(a) in children (83). While bempedoic acid lowers LDL-C, it has a minimal impact on the Lp(a) level (2.4% elevation) (84). The effect of the various pharmaceuticals on Lp(a) levels is shown in Table 2. Finally, lipoprotein apheresis, which removes all apoB-containing lipoproteins including LDL-C and Lp(a), can be used but is generally reserved for youth with extremely high short-term risk of ASCVD events such as those with homozygous FH (85, 86).

Table 2. Effect of Lipid Lowering Drugs on Lp(a) Levels

Statins	No Effect or slight increase
Ezetimibe	No Effect or slight increase
Fibrates	No Effect
Bempedoic Acid	Minimal Effect
Niacin	Decrease 15-25%. Greatest decrease in patients with highest Lp(a) levels
PCSK9 Inhibitors	Decrease 20-30%
Estrogen	Decrease 20-35%
Mipomersen*	Decrease 25-30%
Lomitapide*	Decrease 15-20%
CETP Inhibitors**	Decrease ~ 25%
Apo (a) antisense**	Decrease > 75%

*Only approved for the treatment of Homozygous FH; **not currently available

CONCLUSIONS

Future investigations of the relationship of Lp(a) and ASCVD risk will require large and ethnically diverse populations as well as uniformity and standardization of Lp(a) measurement. As is the case in most pediatric outcome studies, sample size is problematic. However, the usual pitfalls of extrapolating from adult data may be *less* problematic for Lp(a) given that the gene is fully expressed at a young age. Clearly in cases of AIS and strong family history of ASCVD, measurement of Lp(a) is warranted. Whether or not youth with markedly elevated Lp(a) levels should be treated with lipid-lowering medications (i.e., statins) remains controversial.

At a minimum, encouraging avoidance of acquired ASCVD risk factors is a critical component of the health care we can provide children and their parents. Emphasis should be placed on teaching youth about the importance of lifelong tobacco avoidance. The role of maintaining a healthy body weight and daily physical activity is critical in helping reduce the additional inflammatory risk attributable to obesity and insulin resistance, problems which are exacerbated by the development of added risk factors (low HDL-C, type 2 diabetes, and hypertension). In young women with an elevated Lp(a) level, issues surrounding the potential thrombotic risk of oral contraceptives should also be addressed and attention given to choosing a formulation with the lowest risk (87).

Given that a child's medical history is often forgotten with time, it is essential that youth appreciate and articulate the importance of Lp(a) as a risk factor to their future health care providers and be aware that their children may acquire this risk factor. While the relative merits of screening and treating Lp(a) in the pediatric population may be debatable, what is irrefutable is that youth who enter adulthood with the lowest possible burden of ASCVD risk will have a much lower risk of developing ASCVD than those with multiple risk factors, including elevated Lp(a).

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