Current Atherosclerosis Reports (2023) 25:299–307
https://doi.org/10.1007/s11883-023-01102-5

Lipoprotein (a): Does It Play a Role in Pediatric Ischemic Stroke and Thrombosis?

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Accepted: 12 April 2023 / Published online: 9 May 2023

Abstract

Purpose of Review The goal of this paper is to describe the current understanding of lipoprotein (a) (Lp(a)), clinical practice guidelines, and the potential pathophysiological mechanisms that appear to increase the risk of cardiovascular and thromboembolic events, specifically within the pediatric population.

Recent Findings The proatherogenic and pro-thrombotic properties of Lp(a) may increase the risk of atherothrombotic disease. In adults, atherosclerotic plaques increase thrombotic risk, but antifibrinolytic and proinflammatory properties appear to have an important role in children. Although it is not well established in neonates, recent studies indicate the risk of incident thrombosis and ischemic stroke are approximately fourfold higher in children with elevated Lp(a) which also increases their risk of recurrent events. Despite this higher risk, Pediatric Lp(a) screening guidelines continue to vary among different medical societies and countries. The inconsistency is likely related to inconclusive evidence outside of observational studies and the lack of specific therapies for children with elevated levels.

Summary Additional research is needed to improve understanding of the pro-thrombotic mechanisms of Lp(a), appropriate screening guidelines for Lp(a) in the pediatric population, and to elucidate the short and long term effects of elevated Lp(a) on the risk of pediatric thrombosis and stroke.

Keywords Lipoprotein (a) · Pediatric stroke · Thrombosis · Ischemic stroke

Introduction

Lipoprotein (a) (Lp(a)) is a complex lipoprotein particle believed to have proatherogenic and pro-thrombotic properties. The enigmatic nature and structure of Lp(a) has been attributed to its pathologic roles in atherogenesis, inflammation, and coagulation. In adults, there is significant evidence supporting a causal relationship between high Lp(a) plasma levels, particularly small Lp(a) isoforms, and atherosclerotic cardiovascular disease (ASCVD) [1–3]. Historically, elevated Lp(a) has also been considered a risk factor for venous thromboembolism (VTE) [4], however one of the largest prospective studies failed to confirm a causal relationship [5].

In children, the pathogenic role of Lp(a) is more bewildering. Although atherosclerosis is not considered a risk factor for pediatric thromboembolic events, emerging evidence has shown elevated Lp(a) levels to be a risk factor in children with stroke [6, 7] and venous thrombosis [8, 9]. Due to the rarity of pediatric stroke, these relationships have not been studied as extensively as Lp(a) and adult ASCVD, but the mechanism of Lp(a)'s role in pediatric thrombosis continues to be investigated.

Despite extensive laboratory and clinical research, recommendations about screening and management of elevated levels remains controversial in adults. Not surprisingly, less is known about its role in pediatric stroke and thrombosis, which is the basis of controversies regarding screening guidelines and management of children with elevated levels. This review will summarize the current understanding of Lp(a)'s structure and function and its proposed role in stroke and

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thrombosis with emphasis on the pediatric population. The author is aware of the lack of supportive evidence of such a role in children, but based on review of the current literature, recommendations will be provided for Lp(a) screening and treatment during childhood.

Lipoprotein (a) Structure and Function

Lp(a) is an apolipoprotein B100 (apoB) containing a LDL-like molecule covalently bound to apolipoprotein(a) (apo(a)). The Lp(a) gene (*LPA*) that codes for apo(a) evolved from the plasminogen gene (*PLA*) [3, 10] and accounts for 90% of variations in Lp(a) plasma levels [11]. Hence, apo(a) shares many similarities with plasminogen. It contains a variable number of kringle IV domains (KIV domains 1–10) analogous to KIV of plasminogen, one kringle V (KV) similar to plasminogen KV, and like plasminogen, a proteolytic like domain. Apo(a) polymorphism consists of a variable number of KIV-2 repeats (up to 40) that translates into an apo(a) protein with highly variable molecular weights, resulting in differences of Lp(a) levels among individuals and populations when measured in mg/dL [12].

Due to its structural resemblance to low-density lipoprotein (LDL), the apoB component of Lp(a) is thought to be proatherosclerotic while apo(a) is proposed to have antifibrinolytic activity given its homology with plasminogen and lack of catalytic activity [13]. At the same time, atherogenesis appears to be intimately related to the role of Lp(a) in inflammation and its similarity to plasminogen. Lp(a) competes with plasminogen for fibrin-binding sites but since it lacks catalytic activity, less plasmin is released and consequently less clot lysis (hypo-fibrinolysis). Additionally, Lp(a) associates not only to fibrin but also to proteoglycans on the arterial wall contributing to plaque deposition. Oxidized Lp(a) triggers inflammatory response of endothelial cells and uptake by foam cells. In addition, Lp(a) is believed to promote proliferation of smooth muscle cells, all of which contribute to atherogenesis. Lp(a) may also contribute to venous thrombosis and atherothrombosis by increasing endothelial cell plasminogen activator inhibitor-1 (PAI-1) expression and decreasing tissue factor pathway inhibitor activity (TFPI) [14] together with possibly inducing platelet aggregation [15].

Although evidence from *in vitro* studies [16–23] and animal models [24] have shown evidence of antifibrinolytic effect, ex vivo clot lysis times were not impacted when Lp(a) was lowered [25]. Adult observational studies have struggled to support antifibrinolytic activity as a pathogenic mechanism for Lp(a) [5] except in cases with extremely high ($>99^{th}$ percentile) levels of Lp(a) [26]. In contrast to observations in adults, there is one study in North American children looking at the relationship of elevated Lp(a), small isoform of apo(a), and the risk of arterial ischemic stroke (AIS). In this study, fibrinolytic studies did show the antifibrinolytic effect of Lp(a). The authors measured the euglobulin lysis time (ELT) using the automated euglobulin clot lysis assay (ECLA). A statistically significant, but weak correlation was found between ELT and both elevated Lp(a) levels (longer ELT in children with levels $>90^{th}$ percentile) and apo(a) size (longer ELT in children with predominant apo(a) isoforms less than 25^{th} percentile of normative values) [27•].

In a review of a prospective multicenter study involving stroke patients under 60 years, Tsimikas proposes that Lp(a) pathogenesis may use alternate mechanisms depending on an individual's age. For example, Lp(a)-related thrombotic occlusions in older adults likely occur through a proatherogenic etiology due to the LDL-like nature of Lp(a) in combination with additional risk factors. In contrast, the antifibrinolytic mechanism of Lp(a) may play a larger role in pediatric strokes. Instead of developing atherogenic plaques, fibrinolytic pathways are continually disrupted overtime. This damage can become amplified in children with secondary risk factors and may explain the occurrence of recurrent ischemic events. Young adults may also be more prone to the pro-inflammatory mechanisms of Lp(a) especially in individuals with genetically elevated Lp(a). These risk factors may combine with the antifibrinolytic properties of apo(a) and put this age category at an increased risk for non-atherogenic ischemic events [28••]. Recent findings from a nested case–control study, support the idea that the pathophysiological etiology of Lp(a) becomes more proatherogenic with age. In particular, the study provides confirmation that atherosclerosis is rare in pediatric strokes with a frequency of less than 2% in individuals under 20 and steadily increases to 42.5% by 50 years of age [29•].

Lp(a) and Risk for Pediatric Arterial Ischemic Stroke and Venous Thromboembolism

Over the last few years, several observational studies have been performed on the association between elevated Lp(a) and risk of pediatric stroke and VTE. These studies have many limitations including sample size, sample population (single ethnic group), study design, and most importantly, a lack of standardized Lp(a) measurements (e.g., measurement unit discrepancies, differences in normal reference values). Current review of published data suggests some association of Lp(a) and pediatric stroke and VTE, but it also points out why this remains a controversy.

Perinatal Stroke

Perinatal ischemic strokes involve cerebral arterial or venous infarctions within the first 28 days of life with an incidence rate of 24.6 per 100,000 live births according to a recent

meta-analysis of hospital and published literature [30]. Perinatal arterial infarctions are subdivided into neonatal arterial ischemic stroke (NAIS) with diagnosis by the 28th day of life, and arterial presumed perinatal ischemic stroke (APPIS) which are thought to have occurred before the 28th day of life, but in whom the diagnosis is delayed until 4–6 months of age. Venous infarctions occur less often, but are termed periventricular venous infarction (PVI) with presentation later in infancy and evidence of stroke in utero. Risk of perinatal AIS has been attributed to maternal, placental, and neonatal risk factors, but the cause remains unknown in many cases and the role of thrombophilia in perinatal stroke is still controversial.

Studies have found the frequency of prothrombotic risk factors to be as low as 15% [31] and as high as 68% [32] in NAIS. Despite these reports, large population-based controlled studies on prothrombotic risk factors and perinatal stroke are lacking especially related to elevations in Lp(a). Publications include case reports with Lp(a) evaluation only at stroke diagnosis [33, 34] and a small cross-sectional study ($N=35$) where only 4 APPIS patients had elevated Lp(a) in addition to heterozygous MTHFR mutations [35]. Only two case–control studies have been performed in this age group (Table 1A). In the first study, Gunther and colleagues focused on NAIS patients and showed almost a fivefold increase in neonates with Lp(a) > 30 mg/dL [32]. However, a second study published more recently used their control population to determine Lp(a) reference ranges instead of 30 mg/dL. When their control population was compared to mean Lp(a) levels in perinatal stroke types (PVI, AIS (NAIS + APPIS)), no significant difference in Lp(a) was observed between groups [41].

Childhood Arterial Ischemic Stroke

In comparison to perinatal ischemic stroke, childhood AIS (> 29 days-18 years) is less common with incidence rates between 1.3–1.6 per 100,000 children per year [31, 36]. Although it has a lower incidence rate, more evidence exists on risk factors for childhood AIS compared to perinatal strokes. In general, the pathogenesis of childhood AIS has been associated with one or more of the following risk factors: arteriopathies, cardioembolic / cardiopulmonary diseases, inflammatory disorders, genetic mutations, connective tissue disorders, and hematologic disorders (thrombophilia and sickle cell disease). A recent epidemiological study involving Canadian neonates and children showed that thrombophilia was present in one third of the AIS patients (516 tested children) with Factor V Leiden, Lp(a), and activated protein C resistance (APCR) abnormalities being the most predominant findings [31]. However, among the thrombophilia risk factors already associated with increased risk of AIS, the role of Lp(a) and incident arterial stroke remains controversial.

The relationship between elevated Lp(a) and childhood AIS is described in multiple studies (Table 1B). Elevated Lp(a) > 30 mg/dL was positively associated with a history of AIS in pediatric patients compared to controls in 2 case control studies ([OR: 7.2, 95% CI (3.8–13.8), $P<0.0001$] [38]; [OR: 2.5, 95% CI (1.1–6.2), $P<0.05$] [37]) and 1 case control sub-study of pediatric patients with ischemic stroke associated with cardiac disease [OR: 4.3 (1.3–14.4), $P=0.03$] [39]. Additionally, two meta-analyses of first childhood AIS found the odds of elevated Lp(a) greater among cases compared to controls ([OR: 6.5, 95% CI (4.5–9.6] [6]; [OR: 4.2, 95% CI (2.9–6.1)] [42]). In contrast, a publication by Goldenberg and authors [27•] found no association between elevated Lp(a) and incident AIS (all stroke subtypes) when using previously published 75th and 90th Lp(a) race-percentiles [43] instead of Lp(a) > 30 mg/dL as a cut-off. Similarly, he found no association with small isoform apo(a) < 10th and < 25th and risk of incident AIS. When odds of incident stroke for Lp(a) > 75th and 90th percentiles were narrowed down to only isolated idiopathic cases, the odds increased to 2.53 and 3.43, but never reached statistical significance [27•].

Cerebral Sinus Vein Thrombosis and Venous Thromboembolism

Similar to AIS, CSVT and VTE are more frequent in neonates (14.5/10,000 annually) compared to children, with an annual incidence of 0.05–0.07 per 10,000 children [40, 44]. Several observational studies have pointed out the presence of multiple risk factors in children with thrombotic complications. For example, CSVT is commonly associated with infections of the head and neck (e.g., otitis media, mastoiditis, and meningoencephalitis) and modifiable risk factors such as iron deficiency anemia, fever, and dehydration. Central venous lines (CVLs), chronic inflammatory conditions, childhood malignancies, and certain prothrombotic medications are also reported as additional risk factors for VTE. Therefore, even though the presence of an inherited thrombophilia is considered an additional risk factor for pediatric CSVT/VTE, the findings of most of these studies are limited by a lack of statistical power.

The limited studies published on Lp(a) assessing the risk of childhood CSVT or VTE are described in Table 1C. In a prospective multicenter study with equally matched cases and controls, Lp(a) levels were significantly different than controls [median: 19.0, range 1–170; median: 4.4, range 0–125; $P<0.001$, respectively]. Odds of any VTE in children with Lp(a) > 30 mg/dL were 7 times greater in cases than controls, but statistical significance of the Wald χ^2 test were not reported [8]. A second German case control study

Table 1 Incident stroke/thrombosis studies by thrombotic event type

Reference	Population; Study Type	Cases	Controls	Cases Lp(a) (mg/dL) (Median, (range))	Controls Lp(a) (mg/dL) (Median, (range))	P-value	# Elevated Lp(a) Cases/ # Cases Tested	# Elevated Lp(a) Controls/ # Controls Tested	OR (95% CI), P-value	Limitations
(A) Perinatal/Neonatal Ischemic Stroke Studies										
Gunther et al. [31]	Germany; Case Control	NAIS = 91	182	8.6 (0–120)	3.6 (0–104)	NR	20/91	10/182	4.8 (2.2–10.9), < 0.001	• Not generalizable to other racial/ethnic groups
Curtis et al. [35]	Canada; Case Control	PVI = 55 AIS(NAIS + APPIS) = 80	77	PVI: 0.24; 0.04 (0.0–0.7) ^ AIS: 0.24; 0.04 (0.0–0.9) ^	0.23; 0.04,(0.0–0.7) ^	0.989	NR	NR	NR	• Controls used as cut-off reference instead of 30 mg/dl
(B) Childhood AIS Studies										
Nowak-Göttl [36]	Germany; Case Control	AIS = 148	296	21 (0–162)	5 (0–115)	< 0.001	39/148	14/296	7.2 (3.8–13.8), < 0.0001	• Not generalizable to other racial/ethnic groups
Strater [37]	Germany; Case Control	AIS = 38	100	NR	NR	NR	7/38	5/100	4.3 (1.3–14.4), 0.03	• Only evaluated ischemic strokes with cardiac etiology • Small sample size tested for Lp(a)
Teber [38]	Turkey; Case Control	AIS = 52	78	11.8 (1.9–140)	6.02 (0.6–76.8)	< 0.05	14/52	10/78	2.5 (1.1–6.2), < 0.05	• Small sample size • Not generalizable to other racial/ethnic groups
Kenet [6]	Meta-Analysis	AIS = 1526 CSVT = 238	2799	NR	NR	NR	AIS: 163/616 CSVT & AIS: 207/722	AIS Controls: 39/578 AIS & CSVT Controls: 56/727	AIS: 6.5 (4.5–9.6) AIS & CSVT: 6.3 (4.5–8.7)	• CSVT could not be assessed alone • Lp(a) testing not done in most studies
Goldenberg [26]	United States; Case Control	AIS = 43	127	7.5 (0.4–108)	8.5 (0.08–117.5)	0.62	7/43 † 3/43 ‡	19/127 † 7/127 ‡	1.5 (0.6–3.6), 0.36 † 1.3 (0.3–5.2), 0.49 ‡	• Lp(a) and incident AIS not comparable to other studies since Lp(a) race-percentiles utilized
Sultan [39]	Meta-Analysis	AIS = 341	729	NR	NR	NR	90/341	57/729	4.2 (2.9–6.1)	• Not all studies reported Lp(a) testing
(C) Childhood VTE and CSVT Studies										
Nowak-Göttl [8]	Germany; Case Control	VTE/CSVT = 186	186	19 (1–170)	4.4 (0–125)	< 0.001	78/186	19/186	7.2 (3.7–14.5)	• Wald χ^2 results not reported for prevalence differences
Heller [40]	Germany; Case Control	CSVT = 149	149	NR	NR	NR	44/106	17/149	7.2 (3.7–14.2), < 0.05	• Only 71% of cases had Lp(a) testing done (106/149)
Young [9]	Meta-Analysis	VTE = 589	1441	NR	NR	NR	NR	NR	4.5 (3.3–6.2)	• Studies included in Lp(a) meta-analysis not documented

^: mean; standard error (95% CI); †: > 75th percentile; ‡: > 90th percentile

Lp(a) Lipoprotein (a); *OR* Odds ratio; *NR* Not reported; *NAIS* Neonatal arterial ischemic stroke; *PVI* Periventricular venous infarction; *APPIS* Arterial presumed perinatal ischemic stroke; *AIS* Arterial ischemic stroke; *CSVT* Cerebral sinus vein thrombosis; *VTE* Venous thromboembolism

focused on patients with a history of CSVT and elevated Lp(a). Although this study only tested Lp(a) in 71% of cases and did not include other VTEs, the odds were almost identical to the previous study and statistical significance was confirmed [OR: 7.2, 95% CI (3.7–14.2), $P < 0.05$] [45]. A meta-analysis conducted by Young and colleagues analyzed 8 studies of VTE in individuals < 20 years old, and included 589 incident cases compared to 1441 controls. The odds of elevated Lp(a) were almost 5 times greater in incident cases than controls [OR: 4.5, 95% CI (3.3–6.2)], but the authors did not describe which studies were included in the Lp(a) meta-analysis and the prevalence of elevated Lp(a) in the population was not reported [9]. A second meta-analysis conducted by Kenet and colleagues summarized AIS and CSVT studies, but they were unable to perform a meta-analysis on CSVT alone since only 1 CSVT case control study was identified [6].

In recently published studies, design flaws provide incomplete details on the relationship between Lp(a) and CSVT/VTE. For instance, in a cross-sectional study of Indian children with AIS ($n = 57$) and CSVT ($n = 7$), three patients had elevated Lp(a) levels, but the type of stroke was not reported [46]. Another cross-sectional study looked at inherited thrombophilic risk factors among 29 Turkish CSVT patients and elevated Lp(a) was the second most common trait after factor V Leiden mutation with a prevalence of 13.8% [47]. In contrast to the older case control and meta-analyses studies, a prospective cohort of incident VTE (only deep venous thrombosis cases) in pediatric patients with CVL reported no association with any prothrombotic conditions including elevated Lp(a) [48]. Similarly, another prospective cohort study ($n = 131$) was conducted in patients with at least one prothrombotic defect at time of acute lymphoblastic leukemia diagnosis. Of the patients included in the study, 20/125 patients had elevated Lp(a) at enrollment, but only one patient developed symptomatic thromboembolism [OR: 0.91, 95% CI (0.82 - 1.01); $p = 0.092$] [49].

Recurrent AIS/VTE

In regards to the risk of recurrence for patients with perinatal ischemic stroke and elevated Lp(a), Lehman and colleagues reported 6 instances of recurrence (2.8%; 3 venous, 2 arterial, 1 arterial & venous) after a median follow-up of 3.17 years in 215 cases of incident perinatal ischemic stroke. No significant difference was observed between recurrent strokes with elevated Lp(a) levels compared to those with elevated Lp(a) levels and no recurrence (2/6 vs. 33/176; $p = 0.1525$, respectively) [50]. Similarly, for VTE, no increased risk for recurrent VTE was observed in the meta-analysis of 6 observational studies (135 recurrences/1020 without recurrence; [OR: 0.81 (0.49–1.36); $p = 0.51$]) [9].

In a review done by the Vascular Effects of Infection in Pediatric Stroke group (VIPS) on the risk of recurrent childhood AIS, the cumulative rate of stroke recurrence was 6.8% one month following incident stroke and 12% after one year of follow-up despite most children being on antithrombotic treatment. The highest risk for recurrence was found in children with cerebral arteriopathies although thrombophilia was not analyzed [51].

Regarding Lp(a), in the prospective cohort portion of the study by Goldenberg and colleagues, 7/43 patients had a recurrent AIS within a median of 0.4 months (0.25–34 months). In the same population, the odds of recurrent AIS in patients with Lp(a) > 75th percentile was not statistically significant [OR: 3.75, 95% CI (0.66–21.3); $P = 0.15$]. However, in the group with Lp(a) > 90th percentile, odds of stroke recurrence were 14 times greater than no recurrence [OR: 14.0, 95% CI: (1.0–184); $P = 0.05$] and small apo(a) isoform ($< 10^{th}$ percentile) was a significant risk factor for recurrent childhood AIS [OR: 12.8, 95% CI (1.61–101); $p = 0.02$] [27•]. In comparison, two studies review elevated Lp(a) with risk of AIS recurrence based on data from the international, multicenter IPSS registry. In the first study, out of 237 AIS patients with initial Lp(a) testing, 48 (20.3%) had an Lp(a) > 30 mg/dL and 5.6% of patients had a recurrent AIS or transient ischemic attack, but correlation to Lp(a) levels at initial event was not assessed [52]. In a second review of the IPSS database, 115/580 tested patients, had an elevated Lp(a) at initial AIS. The presence of an elevated Lp(a) > 30 mg/dL was associated with higher risk of recurrent stroke [HR: 2.3, 95% CI (1.3–4.1)] with a median time to recurrence of 3.1 months (0.1–136 months) [53••].

Pediatric Lp(a) Screening

Even though there is clear evidence of Lp(a) increasing ASCVD risk in adults, there are still differences in guidelines between organizations about timing and Lp(a) levels that require intervention. In the pediatric population clinicians face similar problems and subsequently, there is high variability in clinical practice.

Clinical Practice

The only study assessing current Lp(a) clinical practices on a larger scale is a cross-sectional review of data from the IPSS registry conducted by Sultan and colleagues. As evidenced by this study, testing of Lp(a) in pediatric AIS remains an uncommon practice as only 25% of patients had lipid or Lp(a) testing recorded. When children with Lp(a) testing were compared to those without Lp(a) testing: children (5–11 years) and adolescents (12–18 years) were

more likely to have Lp(a) testing than infants [(OR 1.8, 95% CI (1.3–2.5), $p < 0.0001$); (OR 2.2, 95% CI (1.7–3.0), $p < 0.0001$), respectively], testing was less likely to be recorded in black compared to white children [OR 0.4, 95% CI (0.3–0.6), $p < 0.0001$], and children in the United States with Hispanic ethnicity were 2 times more likely to have testing recorded than non-Hispanics [OR 2.2, 95% CI (1.4–3.4), $p = 0.001$]. Interestingly, the study showed increased odds of Lp(a) testing reported in children with recurrent thrombotic events compared to those without recurrent events [OR 2.7, 95% CI (1.8–4.0), $p < 0.0001$] [54].

Current Guidelines

Recommendations for pediatric Lp(a) screening vary between different scientific advisory committees but continue to expand as evidence increases on the relationship between pediatric stroke and VTE with elevated Lp(a). Levels of Lp(a) are dominated by genetic influence, reaching adult levels by age 2–5 years old. Measurement of Lp(a) in children > 2 years with any type of stroke or a family history of unusual cardiovascular disease (CVD) was suggested in 2011 by the National Heart, Lung, and Blood Institute (NHLBI) [55]. Delayed *LPA* gene expression observed in a study by Rifai and colleagues [56] supported the postponement of Lp(a) testing in younger children. The National Lipid Association (NLA) added to the NHLBI recommendations: the testing of children with a family history of hypercholesterolemia [57], a first-degree relative with elevated Lp(a), and/or an ischemic stroke of unknown etiology [58•]. In 2019, a joint statement by the American Heart Association (AHA) and the American Stroke Association (ASA) on the treatment of neonatal and pediatric strokes did not suggest Lp(a) testing in the initial stroke work-up, but advised for it to be included in cases of cryptogenic stroke [7]. In contrast, the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS) recommend all adults have Lp(a) testing at least once during their life time, but their youth testing guidelines only discussed Lp(a) testing for children with family or personal history of ASCVD events and/or a hypercholesterolemia diagnosis [59].

Conclusions and Future Recommendations

Despite much progress in the research of Lp(a) as a risk factor for pediatric stroke and VTE, we still have major challenges in achieving uniform guidelines for screening children and young adults.

One major problem is the lack of standardization on how Lp(a) should be measured. Given the high variability of molecular weight between Lp(a) isoforms and recent data showing importance of apo(a) isoform size, current NLA guidance recommends switching from laboratory assays that measure mass concentrations (mg/dL) to those that measure particle concentrations (nmol/L) [58•]. However, this may not be feasible to adopt in general clinical practices unless commercial laboratories modify their tests to conform to these guidelines.

This recommendation adds another challenge: establishing cutoff levels/ranges that warrant intervention. The majority of studies conducted over the past 20 years have referenced a value of Lp(a) > 30 mg/dL as a threshold. This was based on percentiles from a study of German children [8]. However, the latest European Atherosclerosis Society Consensus Statement [60] suggests that the association of Lp(a) levels and ASCVD risk is continuous without evidence of a threshold. Acceptance of this concept and preferentially measuring Lp(a) particle number (nmol/L) would move us away from relying upon the Lp(a) > 30 mg/dL 'cutoff' value. Other alternatives to a predetermined abnormal Lp(a) value include the use of race specific-percentiles for cohort studies [27•] or utilizing Lp(a) levels from the control population in case–control investigations [41]. Standardization of Lp(a) measurement methods would provide solid data regarding Lp(a) as a risk factor for pediatric stroke and VTE and answer the question if children should be universally screened. At our center, only patients with stroke or VTE (not associated with central lines) undergo a thrombophilia workup that includes measurement of Lp(a) (mg/dL).

One of the biggest hesitations for testing Lp(a) in childhood is the lack of treatment options. In adults, while lifestyle changes are considered beneficial in decreasing the ASCVD risk, they have minimal effect on Lp(a) levels (not surprising given its strong genetic determination). Nevertheless, lifestyle changes are encouraged since they have the potential of optimizing other ASCVD risk factors. In addition, efforts to develop targeted Lp(a) lowering therapies are ongoing since statins have no beneficial effects on Lp(a) levels [61]. In children, as of this review, documented treatments have been limited to evidence from 2 case studies. Both studies involved AIS in 11 year olds with no other medical history except elevated Lp(a) levels at diagnosis. One patient received acetylsalicylic acid and nicotinic acid with a successful decrease in Lp(a) levels from 269 nmol/L to 48 nmol/L (normal: < 75 nmol/L) and no evidence of recurrent stroke/thrombosis [62]. The Lp(a) level in the second case was 131 mg/dL (normal: ≤ 30 mg/dL) and treated with acetylsalicylic acid and verapamil, but a recurrent stroke was observed 6 days later. Lipoprotein apheresis was utilized in this case without another stroke recurrence after 18 months of follow-up [63]. It is worth mentioning the role of acetylsalicylic acid reported in adult studies, not only in lowering Lp(a) levels but also decreasing the ASCVD events risk specifically in carriers of a particular apo(a) isoform. Acetylsalicylic acid is used as an antiplatelet agent in children

with congenital cardiovascular disorders and many pediatric stroke patients. Given Lp(a)'s antifibrinolytic properties together with its proposed ability to induce platelet aggregation [15], acetylsalicylic acid is another therapeutic option to consider for secondary stroke or VTE prevention in children with elevated Lp(a) levels.

As outlined in this review, much research is still needed to clarify the true extent of elevated Lp(a) levels on the risk of ASCVD and VTE, particularly in the pediatric population. The development of new clotting assays for measurement of thrombin generation and fibrinolysis is another path of investigation to aid in this research. This would not be limited to the fibrinolytic pathway, but also provide insight on thrombus formation, thrombin generation, and the effect of Lp(a) on the coagulation activation pathway. In addition, there is a clear need for prospective cohort studies in children using standardized Lp(a) measurements to further define ranges associated with increased risk of stroke and VTE. These larger studies would provide a better understanding into the effectiveness of novel treatments in reducing Lp(a) levels and its correlation with reducing stroke and VTE risk.

Declarations

Conflict of Interest The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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• Of importance
•• Of major importance

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