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Recurrent stroke: the role of thrombophilia in a large international pediatric stroke population

Gabrielle deVeber,[1]* Fenella Kirkham,[2,3]* Kelsey Shannon,[1] Leonardo Brandão,[1] Ronald Sträter,[4] Gili Kenet,[5] Hartmut Clausnizer,[6] Mahendranath Moharir,[1] Martina Kausch,[6] Rand Askalan,[1] Daune MacGregor,[1] Monika Stoll,[7] Antje Torge,[6] Nomazulu Dlamini,[1] Vijeja Ganesan,[2] Mara Prengler,[2] Jaspal Singh[3] and Ulrike Nowak-Göttl[4,6]

[1]The Hospital for Sick Children, Toronto, Canada; [2]Developmental Neurosciences Programme, UCL Great Ormond Street Institute of Child Health, London, UK; [3]University Hospital Southampton, UK; [4]Department of Paediatric Haematology/Oncology, University of Münster, Münster, Germany; [5]Pediatric Coagulation Service, National Hemophilia Centre and Institute of Thrombosis and Hemostasis Sheba Medical Center, Tel-Hashomer, Israel; [6]Institute of Clinical Chemistry, University Hospital Kiel-Lübeck, Kiel, Germany and [7]Department of Genetic Epidemiology, University of Münster, Münster, Germany

**GdeV and FK contributed equally to this work.*

ABSTRACT

Risk factors for arterial ischemic stroke in children include vasculopathy and prothrombotic risk factors but their relative importance to recurrent stroke is uncertain. Data on recurrent stroke from databases held in Canada (Toronto), Germany (Kiel-Lübeck/Münster), and the UK (London/Southampton) were pooled. Data were available from 894 patients aged 1 month to 18 years at first stroke (median age, 6 years) with a median follow-up of 35 months. Among these 894 patients, 160 (17.9%) had a recurrence between 1 day and 136 months after the first stroke (median, 3.1 months). Among 288 children with vasculopathy, recurrence was significantly more common [hazard ratio (HR) 2.5, 95% confidence interval (95% CI) 1.92-3.5] compared to the rate in children without vasculopathy. Adjusting for vasculopathy, isolated antithrombin deficiency (HR 3.9; 95% CI: 1.4-10.9), isolated elevated lipoprotein (a) (HR 2.3; 95% CI: 1.3-4.1), and the presence of more than one prothrombotic risk factor (HR 1.9; 95% CI: 1.12-3.2) were independently associated with an increased risk of recurrence. Recurrence rates calculated per 100 person-years were 10 (95% CI: 3-24) for antithrombin deficiency, 6 (95% CI: 4-9) for elevated lipoprotein (a), and 13 (95% CI: 7-20) for the presence of more than one prothrombotic risk factor. Identifying children at increased risk of a second stroke is important in order to intensify measures aimed at preventing such recurrences.

Correspondence:

ULRIKE NOWAK-GÖTTL
leagottl@uksh.de

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Introduction

Published estimates of the annual incidence of arterial ischemic stroke (AIS) in children range from 1.2 to 8 per 100,000 children.[1-5] Prior diagnoses in children with symptomatic AIS are common and include cardiac disorders, hematologic conditions (sickle cell anemia, prothrombotic disorders), collagen tissue diseases, metabolic disorders, other chronic diseases, and acute illnesses.[6-8] Childhood infections, including *Varicella zoster* virus, have been shown to be associated with an increased risk of AIS, with routine vaccination being protective against AIS.[9,10] In addition, the presence of prothrombotic risk factors has been found in small case series and case control studies to be associated with ischemic stroke in children and this association has been confirmed by a meta-analysis.[11] This is in contrast to perinatal stroke, in which recent studies have not shown an association with thrombophilia[12] and recurrence is relatively rare.[13,14]

In children, stroke recurrence is common and associated with significant morbidity and mortality. Five-year recurrence rates are estimated to be between 6-20%, with rates as high as 66% in certain subgroups.[15-20] Several studies have identified vasculopathy, in particular moyamoya, as an important factor in predicting recurrent stroke.[8,15,20] There are some early data to suggest that prothrombotic states may also enhance the risk of recurrence, but many of these studies are limited by size and scope.[7,11,15,16,21] We therefore conducted an international cohort study to investigate the relevance of prothrombotic risk factors, as well as underlying stroke subtypes, to a second stroke in pediatric patients.

Methods

Study population, design, and endpoints

The present study is a multicenter cohort study to assess the rate of symptomatic stroke recurrence per 100 person-years following a first AIS. The core protocol was developed by the German collaborative group and was adopted by centers in Toronto and the UK; data were pooled across these sites to determine whether the data were generalizable and to increase the statistical power for analysis of the secondary study objective, i.e. the time to recurrence. From January 1990 to January 2016, consecutively admitted in- and out-patients from each study site, i.e. Canada (Toronto: single-center registry), Germany (Kiel-Lübeck/Münster: multicenter national registry: patients newly enrolled after 2002), and the UK (London/Southampton: two-center registry) were enrolled and pooled in the pediatric stroke database located in Germany. Consecutive patients with a first symptomatic AIS were recruited whether or not prothrombotic risk factors were present and recurrence was ascertained during follow up in survivors. Patients referred from other tertiary centers were excluded. Neonates <1 month of age and children with sickle cell anemia were not enrolled in the present dataset, as recurrence rates and risk factors differ markedly in these subjects from those in other subtypes of childhood AIS. After enrollment, children with moyamoya, and those with congenital homozygous protein C or antithrombin deficiency were excluded, since recurrence risk and therapy differ substantially from those in the remaining study cohort. In addition, we excluded children in whom thrombophilia screening was not performed and those lost to follow up.

The first AIS was confirmed by standard imaging methods, i.e. magnetic resonance imaging and computed tomography.[15,16] AIS was defined as an acute-onset neurological deficit with an acute focal infarct in a corresponding arterial vascular territory.

Recurrence was defined as clinically symptomatic AIS events which presented as acute focal neurological deficits with infarction in a vascular distribution on neuroimaging and which began more than 24 h following the onset of the first stroke. The fixed study end date for the last follow up was January 1, 2017. The number of patients with recurrence, and type of antithrombotic (antiplatelet or anticoagulant) therapy administered prior to recurrence were recorded. The proportion of deaths following stroke recurrence was also recorded. Following discontinuation of antithrombotic treatment, asymptomatic pediatric patients were followed up every few months for the first year and at more prolonged intervals thereafter (at least yearly). All patients were seen at least once for a follow-up evaluation by a pediatric neurologist. Transient ischemic attacks, defined as acute-onset neurological deficits lasting <24 h and with no associated infarct on repeat neuroimaging, were excluded from the study endpoint, as were 'silent' recurrent strokes noted on follow-up imaging without clinical manifestations.

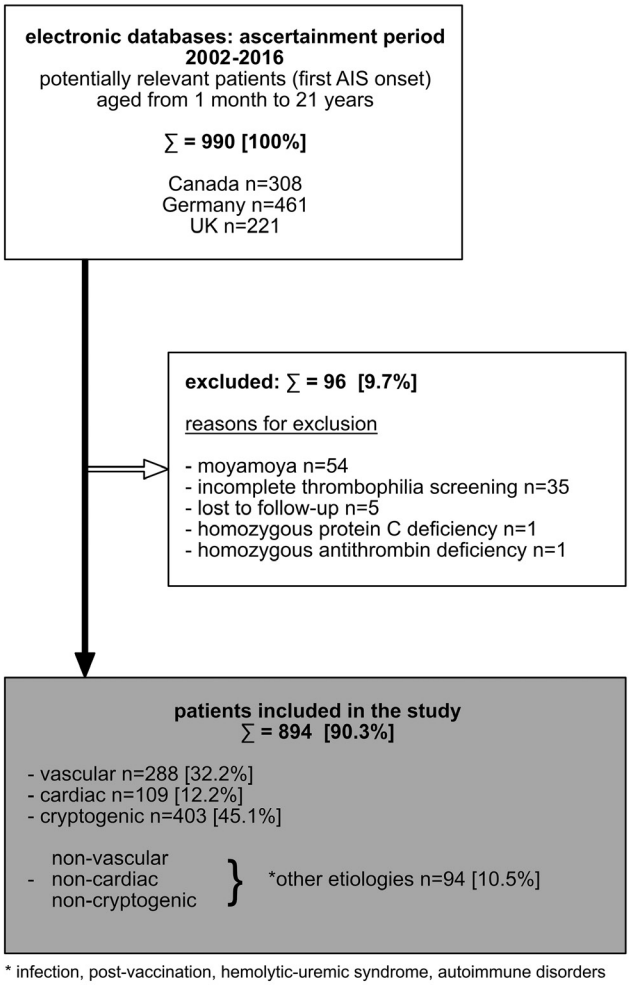
Ethics

This study was performed in accordance with the ethical standards laid down in the updated version of the 1964 Declaration of Helsinki and was either approved or the requirement for approval was waived, by Research Ethics Boards at the Hospital for Sick Children, Toronto, the Great Ormond Street Hospital, (and UK National Health Service), and the University of Münster.

Details of the stroke subtypes,[11,22] treatment modalities,[21-25] laboratory work-up[26-28] and statistical methods applied[29,30] are summarized in the *Online Supplement.*

Results

From January 1990 to January 2016, a total of 990 in- and out-patients consecutively reviewed at the study sites from Canada (n=308), Germany (n=461), and the UK (n=221), aged >1 month and without sickle cell anemia were enrolled and pooled in the pediatric stroke database located in Germany. After enrollment, we excluded 54 children with moyamoya, two patients with either congenital homozygous protein C or homozygous antithrom-



* infection, post-vaccination, hemolytic-uremic syndrome, autoimmune disorders

Figure 1. Flow chart of patients' distribution through the study. AIS: arterial ischemic stroke.

bin deficiency, five children who were lost to follow up and 35 children in whom thrombophilia screening was not performed (Figure 1). We therefore studied 894 consecutively recruited children aged 1 month to ≤18 years who survived a first episode of AIS (Figure 1, Table 1) and were followed for a median (minimum-maximum) duration of 35 (1-256) months. These patients' clinical characteristics are summarized in Table 1. In total, 160 children (17.9%) experienced a recurrent AIS at a median time from the initial stroke of 3.1 months (minimum-maximum: 0.1-136). Of the 160 children who had a second AIS, 15 (9.4%) died at the time of the second stroke. The overall recurrence rate, with the 95% confidence interval (95% CI), calculated per 100 person-years was 5 (95% CI: 4-6) with a yearly incidence of 0.05%.

Data on antithrombotic prophylaxis prior to a second AIS, i.e. anticoagulation with low molecular weight heparin or a vitamin K antagonist or antiplatelet therapy (with acetylsalicylic acid or clopidogrel), were available for a subgroup of 122 out of the 160 cases on an exploratory basis: antithrombotic prophylaxis was administered independently of the presence or absence of thrombophilia (P=0.89) or different stroke subtypes (P=0.2). In children with vasculopathy prior to the second AIS, 34 of 72 index patients were on antiplatelet agents (acetylsalicylic acid alone), 19 were being treated with low molecular weight heparin, and one child developed a second stroke while taking a vitamin K antagonist. In patients without vasculopathy 15 out of 50 children were on acetylsalicylic acid, in two cases combined with clopidogrel, seven were being treated with low molecular weight heparin and three were on oral anticoagulation with a vitamin K antagonist. Forty-four of the 122 patients did not receive anticoagulation or antiplatelet therapy prior to a second AIS (vasculopathy group n=19; non-vasculopathy group n=25; P=0.05).

Vascular territory of the second arterial ischemic stroke

In the majority of cases (75%) the same vascular territory was involved as in the first AIS. The anterior circulation was involved in 62.5% of cases and the posterior circulation in the other 37.5%.

Stroke subtypes

Stroke subtypes are presented in Figure 1 and Table 1. Of the 894 incident pediatric stroke cases, 288 (32.2%) had vasculopathy. The sub-classification of the types of vascular stroke is shown in the *Online Supplement*. Imaging-confirmed recurrent stroke occurred in 160/880 enrolled children, for (i) cardiac disease 23/109 (21.1%), (ii) vasculopathy 82/284 (28.9%), for (iii) cryptogenic 41/401 (10.2%) and for (iv) other stroke types 14/78 (17.9%). Recurrent AIS was significantly more frequent in patients with vasculopathy (HR 2.5, 95% CI: 1.92-3.5; P<0.001) than in patients with cryptogenic stroke. Calculated per 100 person-years in those with vasculopathy, the recurrence rate was 8 (95% CI: 6-10) with a yearly incidence rate of 7.7%. The time to recurrence, calculated as the probability of AIS-free survival, comparing pediatric AIS patients with and without vasculopathy, is depicted in Figure 2 (log rank P-value <0.001). No statistically signifi-

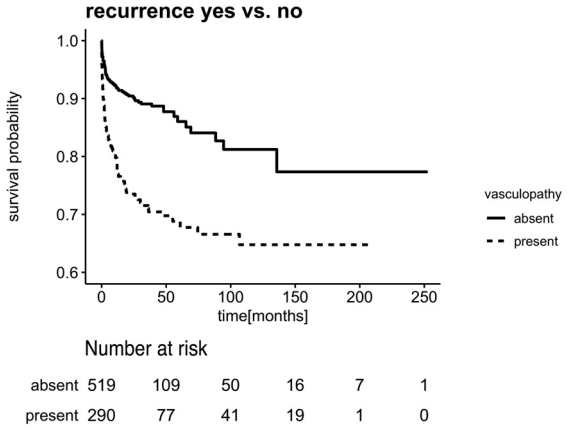


Figure 2. Arterial ischemic stroke-free survival in children with vasculopathy compared with that in the remaining children with a normal arterial examination (P<0.001). Two additional patients suffering from cardiac disease, autoimmune disorder along with short vessel stenosis are included.

Table 1. Clinical characteristics of the 894 children with a first arterial ischemic stroke studied for stroke recurrence.

Characteristics at first stroke onset	Canada number (%)	Germany number (%)	UK number (%)	Total number (%)
Ethnicity	**294 (100.0)**	**379 (100.0)**	**221 (100.0)**	**894 (100.0)**
Caucasian	166 (56.5)	377 (99.5)	190 (86.0)	733 (81.2)
Black	17 (05.8)	-	4 (2.0)	
Asian	44 (15.0)	-	27 (12.2)	
First nations/Aboriginal	2 (0.70)	-	-	
Central/South American	5 (01.7)	-	-	
Mixed ethnicity	9 (03.1)	2 (0.95)	-	
Unknown	51 (17.3)			
Median age, years [min-max]	4.8 [0.1-17.7)	7.1 [0.2 -18]	4.5 [0.1-16.7]	6 (0.1-21]
Male	183 (59.4)	203 (54.7)	125 (56.5)	511 (56.8)
Children with a first cryptogenic AIS	43 (14.6)	264 (69.5)	96 (43.4)	403 (45.1)
Children with a first vascular stroke	89 (30.3)	86 (22.7)	113 (51.1)	288 (32.2)
Children with a first cardiac stroke	92 (31.3)	8 (2.1)	9 (4.1)	109 (12.2)
Children with a recurrent AIS	76 (25.9)	27 (7.1)	57 (25.8)	160 (17.9)
Patients on treatment prior to second AIS	54 (71.1)	17 (63.0)[#]	30 (52.6)	101 (63.1)

[#]Cohort data previously published in part.[25]

Table 2. Univariable analysis: association between prothrombotic risk factors and a second stroke. A single prothrombotic disorder was detected in 269 children.

Risk factor	AIS first onset: numbers with abnormal test /numbers tested (%)	AIS recurrence: numbers with abnormal test /numbers tested (%)	Chi-squared *P*-value
	Reference: no thrombophilia		
Fasting Lp(a) >30 mg/dL	115/580 (19.8)	23/115 (20.0)	0.04
Fibrinogen	43/787 (5.5)	13/43 (30.2)	0.04
Fasting homocysteine	16/708 (2.3)	7/16 (43.8)	0.01
Antithrombin-deficiency	23/750 (3.1)	7/23 (30.4)	0.15
Protein C deficiency	26/778 (3.3)	5/26 (19.2)	0.9
Protein S deficiency	28/708 (4.0)	7/28 (28.0)	0.2
Factor 5 at rs6025	71/726 (9.8)	8/71 (11.3)	0.17
Factor 2 at rs1799963	21/631 (3.3)	3/21 (15.0)	0.84
Combined defects	88/848 (10.4)	23/88 (26.1)	0.04

AIS: arterial ischemic stroke; Lp: lipoprotein

cant association was found between recurrent AIS and the remaining stroke subgroups: cardiac stroke (HR 1.15, 95% CI: 0.7-2.0; *P*=0.61); non-vascular/non-cardiac/non-idiopathic (HR 1.01, 95% CI: 0.5-2.0; *P*=0.95).

Prothrombotic risk factors

Results derived from univariable analyses are shown in Table 2. A single prothrombotic disorder was detected in 269 children, whereas more than one prothrombotic risk factor was diagnosed in 88 cases. Heterozygous antithrombin deficiency, high lipoprotein (a) [Lp(a)], high fibrinogen, high fasting homocysteine and the presence of more than one prothrombotic disorder were associated with recurrence. Of the 7/23 patients with heterozygous antithrombin deficiency who experienced a recurrent stroke, none was on unfractionated heparin or vitamin K antagonist treatment: four were prescribed acetylsalicylic acid at the time of recurrence, one patient was on low molecular weight heparin, while two subjects were taking no prophylaxis immediately prior to the recurrent stroke (non-compliance was not excluded). In six of 23 (26%) patients with combined defects and a second stroke, the factor 5 mutation at rs6025 was involved. Interestingly, however, the factor 2 mutation at rs1799963 did not play a role in children with combined defects.

Examination of the roles of different stroke subtypes and prothrombotic risk factors, using multivariable Cox proportional hazards regression of variables with a *P*-value ≤0.15 in the univariable analyses, adjusted for age, gender and study center, demonstrated that the presence of vasculopathy (HR 2.5), antithrombin deficiency (HR 3.9), elevated Lp(a) (HR 2.3) and the presence of more than one prothrombotic risk factor (HR 1.9) were independently associated with an increased risk of recurrent stroke (Table 3). The time to recurrence, i.e. recurrence-free survival comparing pediatric AIS patients with elevated Lp(a) to those with normal Lp(a) levels is illustrated in Figure 3 (log rank *P*-value <0.039). Recurrence rates calculated per 100 person-years were 10 (95% CI: 3-24) for antithrombin deficiency, yearly incidence rate 0.1%, 6 (95% CI: 4-9) for elevated Lp(a), yearly incidence rate 0.13%, and 13 (95% CI: 7-20) for the presence of more than one prothrombotic risk factor, yearly incidence rate 0.13%. Exposure time of the children was 2437 years for those with antithrombin deficiency, 1938 years for those with elevated Lp(a) and 2887 years for patients with more than one prothrombitic risk factor. Kaplan-Meier survival curves for children with multiple thrombophilic factors and for those with normal thrombophilic status are illustrated in *Online Supplementary Figure S1*.

Table 3. Risk contribution to a second arterial ischemic stroke adjusted for age at onset, gender and study center (Cox proportional hazards model).

Risk factor	Hazard ratio	95% confidence interval
Stroke subtypes		
Reference: cryptogenic stroke		
Vascular stroke	2.5	1.92-3.5
Cardiac stroke	1.15	0.7-2.0
Non-vascular, non-cardiac non-cryptogenic	1.01	0.5-2.0
Thrombophilia		
Reference: no thrombophilia		
Fasting Lp(a) >30 mg/dL	2.3	1.3-4.1
Fibrinogen	0.9	0.3-2.8
Fasting homocysteine	3.6	0.8-15.8
Heterozygous antithrombin-deficiency	3.9	1.4-10.9
Protein C deficiency	1.3	0.3-5.5
Protein S deficiency	2.2	0.5-9.8
Factor 5 at rs6025	0.7	0.23-1.91
Factor 2 at rs1799963	1.8	0.4-7.8
Combined prothrombotic risk factors	1.9	1.12-3.2

AIS: arterial ischemic stroke; Lp: lipoprotein

Based on data from the Caucasian pediatric population, the number-needed-to-screen to detect one patient with elevated Lp(a) was 10 and that to detect children with more than one prothrombotic abnormality was 20.

Discussion

In our study cohort of 894 Canadian, English and German

pediatric stroke patients > 1 month of age, a second AIS event was diagnosed in 17.9% of patients within a median period of 3.1 months after the first stroke. In this international cohort of children who had had a stroke we found that the presence of more than one prothrombotic risk factor was associated with AIS recurrence. Specifically, as demonstrated recently in children with recurrent deep venous thrombosis and thromboembolic stroke, heterozygous antithrombin deficiency is a major risk factor for second AIS events.[31] In addition, data presented here confirm an increased risk for recurrent stroke events in the subgroup of patients with an underlying vasculopathy.[15,22,32-35]

The rates of recurrent cerebral thrombo-embolic events vary widely across published studies. Differences are likely related to: (i) the variable inclusion of neonates, known to have a very low rate of recurrence; (ii) the ethnicity of the patients enrolled and other variables in the patient populations; (iii) the definitions of recurrence; and (iv) the duration of follow up. Some studies mix transient ischemic attacks and recurrent stroke in reporting the recurrence risk.[14-20] Adverse outcomes resulting from recurrent AIS are certainly more ominous than those for a transient ischemic attack alone, with a mortality rate after second AIS of 9.4% in our patients. Keeping in mind differences in patient populations, underlying diseases as well as treatment modalities applied, and assuming that inclusion of transient ischemic attacks would approximately double the recurrence risk,[16] the recurrence rate reported by us for AIS alone is within the lower rate of approximately 20% reported by other authors.[14-20] It is possible that our lower rate of recurrence reflects the use of standardized treatment protocols and institutional pediatric stroke programs in our centers. Specialized stroke care is likely to lower the rate of recurrence through experienced selection of patients for antiplatelet/anticoagulant treatment and more consistent use of any preventative treatment.

With respect to the inherited prothrombotic risk factors investigated, multivariable analysis provided evidence that the presence of vasculopathy, heterozygous antithrombin deficiency, increased Lp(a) and more than one cause of thrombophilia are risk factors for recurrent ischemic stroke in pediatric patients.[14,36-38] The numbers needed to screen to detect one patient each with elevated Lp(a) or combined thrombophilic abnormalities in the present cohort were 10 and 20, respectively. The benefit of recognizing an underlying thrombophilic condition, as well as the numbers need to screen to detect a carrier at risk, should be balanced against clinical impact, cost and potential insurance implications. In contrast to the literature on recurrent venous thromboembolism in a similar population of children, as well as an association with first AIS onset,[11,38] the presence of isolated mutations in factor 5 at rs6025, factor 2 at rs1799963, protein C- and protein S were not individually significantly associated with recurrent AIS in this multicenter cohort. Despite the recurrence rate of 17.9% (160/894 patients), our study may have been underpowered to find these associations. Alternatively, these factors may have been more aggressively treated with antithrombotic treatment, reducing the risk of recurrence in affected patients. Importantly, combinations of prothrombotic risk factors, including the factor 5 mutation at rs6025, in 26% of cases were associated with recurrence, emphasizing the importance of comprehensive investigation and appropriate management.

Our study has several limitations. First, the long duration of the study means that many children were enrolled more than a decade ago, when the selection of treatments may have been different from that currently recommended. While this long duration provided us with the opportunity to monitor children for longer-term recurrent AIS, our inclusion of some children with only a brief follow-up duration, as short as 1 month, could also have resulted in our underestimating recurrence risk, and our rate of recurrence should therefore be viewed as a minimum estimate. Secondly, the proportions of children with vascular, cardiac or cryptogenic stroke varied across countries, likely representing either differences in assignment of patients to categories (e.g. inclusion or exclusion of occlusion alone as 'vasculopathy') or different referral patterns to the centers (Toronto, London/Southampton and Kiel-Lübeck/Münster) in the three countries. Thirdly, we were unable to include pediatric stroke drug therapy as a main focus of this study since recommendations on antithrombotic and antiplatelet agents for children with stroke are derived from non-randomized pediatric trials and small case series with a low level of evidence, without adjustment for treatable prothrombotic risk factors such as heterozygous antithrombin deficiency[21-25] or routine drug monitoring to detect resistance to acetylsalicylic acid or non-drug compliance. Finally, the thrombophilia testing was done over time and in three different laboratory settings. However, since laboratory parameters were investigated with standard laboratory techniques and assays and were only classified as abnormal when (i) abnormal on a repeat test and (ii) confirmed by family studies or the identification of an underlying gene mutation,[26-28] it is likely that our results are reliable.

In summary, recurrent AIS is relatively frequent, and is associated with significant mortality. Risk is enhanced in children who have vasculopathy, even when moyamoya is excluded, and in those with certain isolated thrombophilic risk factors or more than one prothrombotic disorder. The results of this study emphasize the value of pooling individual patients' data across geographic regions. Future studies should seek to validate our findings in additional cohorts of children with a first AIS with stroke subtypes clearly defined according to new pediatric stroke classifications, such as CASCADE.[39,40] Of note, our finding that recurrence of childhood AIS is comparable across European and North American centers supports the feasibility of multinational recruitment strategies to provide sufficient power to ran-

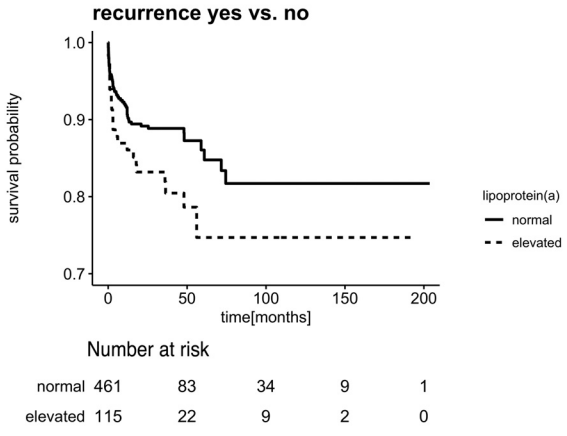


Figure 3. Arterial ischemic stroke-free survival in children with elevated lipoprotein (a) compared with that in the remaining children with normal lipoprotein (a) levels (*P*=0.039).

domized treatment studies, which could include the development of stroke recurrence prediction models. Such studies should be focused on prevention of recurrent stroke in subpopulations of pediatric patients with the highest risks of recurrent AIS. In addition, from the data reported here, prediction models could be derived combining non-moyamoya vasculopathy with the presence of multiple thrombophilic risk factors of interest. On the background of regional differences with respect to prevalence rates of thrombophilic risk factors across study populations, the numbers need to screen to detect carriers at risk will allow investigators to power future pediatric stroke trials adequately. It is important to keep in mind, however, that (i) antithrombotic and/or antiplatelet therapy may also have a significant impact on the risk of AIS recurrence in children, and (ii) up to now, due to the lack of randomized controlled trials, pediatric stroke treatment modalities are recommended on the basis of low-level evidence.[21-25] Further efforts must be made to address the latter issue, as well.

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