

# Aspirin Versus Low-Dose Low-Molecular-Weight Heparin: Antithrombotic Therapy in Pediatric Ischemic Stroke Patients

## A Prospective Follow-Up Study

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**Background and Purpose**—We sought to compare different antithrombotic secondary treatments (mainly medium-dose aspirin with low-dose low-molecular-weight heparin [LMWH]) in pediatric patients with a first ischemic stroke onset with regard to the risk of stroke recurrence.

**Methods**—The population comprised 135 consecutively recruited children aged  $\geq 6$  months to  $\leq 18$  years with a first episode of ischemic stroke (idiopathic,  $n=79$ ; cardiac,  $n=15$ ; vascular,  $n=30$ ; infectious,  $n=11$ ). The stroke patients enrolled received prophylactic antithrombotic therapy (aspirin,  $n=49$ ; LMWH,  $n=86$ ) in a nonrandomized fashion and were prospectively followed up for a median (range) of 36 (8 to 48) months. The study end point was recurrent stroke.

**Results**—Recurrent ischemic stroke was diagnosed at a median (range) of 5 (2 to 13) months after the first stroke onset in 13 of the 135 children (9.6%) receiving antithrombotic therapy. In the majority of cases (84.6%) the same vascular territory was involved. No significant difference was found with respect to the antithrombotic medication used ( $P=0.76$ , Fisher's exact test). No major drug-related side effects were observed.

**Conclusions**—This prospective multicenter follow-up study has provided evidence that low-dose LMWH is not superior to aspirin and vice versa in preventing recurrent stroke in white pediatric stroke patients. However, further adequately sized randomized trials are required to obtain reliable information on safety and efficacy with respect to the antithrombotic medications used. (*Stroke*. 2001;32:2554-2558.)

**Key Words:** aspirin ■ heparin ■ risk factors ■ stroke, ischemic, pediatric ■ stroke, recurrent

Pediatric stroke is not a recent disease. Its estimated incidence is approximately 2.6 per 100 000 per year,<sup>1,2</sup> and half of the events reported presented as ischemic strokes. Risk factors of cerebrovascular accidents in children include congenital heart malformations, vascular abnormalities, endothelial damage, infectious diseases, and collagen tissue diseases as well as some rare inborn metabolic disorders.<sup>1-5</sup> In addition, as recently demonstrated, hypercoagulable states associated with prothrombotic risk factors also represent a risk factor for stroke in childhood.<sup>6-16</sup>

Until very recently, ischemic strokes in children have been reported to have a good prognosis, with a low recurrence rate and a good recovery of motor function and school performance.<sup>4</sup> Therefore, the assumption that management would not alter this outcome has resulted in failure to extensively investigate pediatric stroke patients. New data show, however, that only one third of children suffering a stroke in the neonatal period have a normal long-term development.<sup>17</sup> In

addition, the rate of recurrent stroke reported in children ranges from 8% in children with no identified underlying disorder to 42% in pediatric patients with multiple risk factors.<sup>18</sup> Thus, there is the need to develop evidence-based strategies for antithrombotic therapy aimed at recurrence prevention in children and adolescents, but no controlled data are available thus far on short- and long-term recurrent stroke prevention in pediatric patients. It has been recently suggested by Kirkham<sup>4</sup> that a low-dose regimen of aspirin is probably justified in pediatric stroke patients. In addition, very recently Dix et al<sup>19</sup> reported in a prospective follow-up study that low-molecular-weight heparin (LMWH) appears to be efficacious and safe not only in children with venous thrombosis but also in pediatric stroke patients.

The following study of white pediatric stroke patients was based on the fact that stroke types differ between children and adults<sup>20</sup> and that genetic prothrombotic risk factors in children with ischemic stroke are similar to those in pediatric

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patients with venous thrombosis.<sup>6,21</sup> To evaluate the rate of stroke recurrence and possible drug-related side effects, antithrombotic treatment, ie, aspirin or low-dose LMWH, was administered in a nonrandomized fashion to infants and children suffering from a first ischemic stroke event.<sup>4,22</sup>

## Subjects and Methods

### Ethics

The present prospective multicenter follow-up study was performed in accordance with the ethical standards established in the updated version of the 1964 Declaration of Helsinki and was approved by the medical ethics committee of the University of Münster (Germany).

### Inclusion Criteria

White infants and children aged  $\geq 6$  months to  $\leq 18$  years with first onset of ischemic stroke confirmed by results of CT and MRI according to previously published criteria were included.<sup>12,13</sup> After a first stroke, the patients had to have received prophylactic antithrombotic treatment in the form of antiplatelet therapy (aspirin) or anticoagulant therapy (LMWH).

### Exclusion Criteria

Neonates and infants  $< 6$  months of age, pediatric patients not receiving prophylactic antithrombotic therapy, and patients who had received clopidogrel ( $n=2$ )<sup>23</sup> or coumarin ( $n=4$ ) were not enrolled for statistical analysis in the present study. In addition, children with a 2-phase initial stroke onset were not included as recurrent stroke patients.

### Study End Point

Recurrent ischemic stroke was confirmed by appropriate MRI methods (MR angiography in all cases). In addition, Doppler ultrasound and conventional angiography were used in selected cases (suspected vasculopathy, stroke associated with infection) acutely and during the follow-up period. The suspected clinical diagnosis of a recurrent ischemic stroke was confirmed by an independent neuroradiologist.<sup>12</sup>

### Definition of Drug-Related Side Effects

Hemorrhage, heparin-induced thrombocytopenia, Reye syndrome, allergic reactions, and gastrointestinal disorders were defined as drug-related side effects.

### Study Population

From October 1995 to October 2000, 135 consecutive white patients (median age at first stroke onset, 7 years; range, 7 months to  $\leq 18$  years; 61% male) with a first ischemic stroke and antithrombotic treatment were recruited from different geographic areas of Germany, as recently described.<sup>12</sup> According to the individual physicians' preference and decision, the patients received either aspirin or LMWH for a minimum of 6 months after their first stroke event.

In addition to the aforementioned 135 patients, 2 adolescent patients initially treated with heparin ( $n=1$ ) and aspirin ( $n=1$ ) received clopidogrel because of early recurrent transient ischemic attack within the first 14 days after stroke onset.<sup>23</sup> Clopidogrel was administered in these 2 cases because it was thought that the benefit of this agent might be better in recurrent transient ischemic attacks compared with ischemic stroke.<sup>23</sup> In 4 patients the study centers administered coumarin. However, since the groups of 2 and 4 patients are too small, these 6 patients were not included in the statistical analysis presented here.

### Classification of Stroke Subtypes

Classification of initial stroke subtypes was performed with reference to Mathews,<sup>24</sup> to Kirkham et al,<sup>25</sup> and to results obtained from MRI methods. In all 135 patients enrolled, the following information was obtained: on the basis of associated underlying diseases and

anamnestic data, results of MRI methods including MR angiography (conventional angiography and Doppler ultrasound in selected cases), transthoracic and transesophageal echocardiography with saline contrast, and ECG, the stroke population presented here was classified into 4 subgroups: (1) cardiac stroke (tetralogy of Fallot, single ventricle, double-outlet right ventricle, transposition of great arteries, tricuspid atresia, interrupted aortic arch, truncus arteriosus, Ebstein malformation, ventricular septal defect, atrioventricular septal defect, atrial septal defect, patent foramen ovale, mitral valve anomalies, cardiomyopathy, inflammatory heart disease, rhythm disturbances); (2) vascular stroke (fibromuscular dysplasia, dissection, moyamoya, vasculitis, artery hypoplasia, longstanding artery stenosis); (3) stroke directly associated with infectious diseases (varicella zoster, febrile episodes associated with sinusitis, meningitis, tonsillitis, pharyngitis, and additional infections of the upper respiratory system); and (4) idiopathic stroke (ischemic stroke not associated with other defined causes).

### Brain Lesions at Stroke Onset

The corresponding brain lesions at first stroke onset were found predominantly in territory of the left middle cerebral artery ( $n=69$ ), right middle cerebral artery ( $n=33$ ), or vertebrobasilar system ( $n=16$ ). In addition, bilateral cerebral infarction was diagnosed ( $n=17$ ).

### Clinical Data With Respect to Antithrombotic Therapy Performed

At the participating study centers, pediatric patients received either aspirin (4 mg/kg body wt per day; range, 2 to 5;  $n=49$ ) or low-dose LMWH (enoxaparin [1 to 1.5 mg/kg body wt per day] or dalteparin [75 to 125 anti-Xa U/kg body wt per day]; 4-hour anti-Xa activity, 0.2 to 0.4 IU;  $n=86$ ) over a period of 9 months (range, 6 to 14 months). Table 1 summarizes age, brain lesions, and prothrombotic risk factors in the aspirin and LMWH groups. No statistical difference was found between these 2 largest treatment arms. In addition, the clinical presentation at acute stroke onset<sup>12,13</sup> was no different between aspirin- or LMWH-treated children.

### Prothrombotic Risk Factors

As previously described, and with informed parental consent, the factor V G1691A mutation, the prothrombin G20210A variant, lipoprotein(a), protein C, protein S, and antithrombin were investigated with standard laboratory techniques.<sup>6,21,26–30</sup>

### Statistical Analysis

Because of their nongaussian frequency distribution, continuous data are presented as medians and ranges and evaluated by nonparametric statistics with the Wilcoxon-Mann-Whitney *U* test. Ischemic brain lesions and the prevalence of prothrombotic risk factors in the treatment groups were compared by  $\chi^2$  analysis or, if necessary, Fisher's exact test. In addition, odds ratios (ORs) and 95% CIs were calculated to compare brain lesions, prothrombotic risk factors, and risk of recurrence between the aspirin and LMWH groups. The significance level was set at 0.05. All statistical analyses were performed with the StatView 5 software package (SAS Institute Inc).

## Results

To evaluate the risk of recurrent ischemic stroke in white pediatric patients with prophylactic antithrombotic therapy, 135 consecutively recruited children aged  $\geq 6$  months to  $\leq 18$  years with a first episode of ischemic stroke (idiopathic,  $n=79$ ; cardiac,  $n=15$ ; vascular,  $n=30$ ; infectious,  $n=11$ ) were prospectively followed up for a median (range) of 36 (8 to 48) months.

**TABLE 1. Brain Lesions and Prothrombotic Risk Factors With Respect to Antithrombotic Treatment Performed**

	Aspirin (n=49)*	LMWH (n=86)†	OR (95% CI)
Brain lesions			
Left middle cerebral artery	21/49 (42.8%)	48/86 (55.8%)	0.6 (0.3–1.2)
Right middle cerebral artery	17/49 (34.7%)	16/86 (18.6%)	2.3 (0.9–5.2)
Bilateral cerebral infarction	4/49 (8.2%)	13/86 (15.1%)	0.5 (0.2–1.6)
Vertebrobasilar system	7/49 (14.3%)	9/86 (10.5%)	1.4 (0.5–4.1)
Prothrombotic risk factors			
	46.9%	56.9%	0.7 (0.3–1.4)
Factor V G1691A‡	4/49 (8.2%)	13/86 (15.1%)	0.5 (0.1–1.6)
Prothrombin G20210A‡	4/49 (8.2%)	1/86 (1.2%)	7.6 (0.8–69.9)
Lipoprotein(a) >30 mg/dL§	9/49 (18.4%)	24/86 (27.9%)	0.6 (0.2–1.4)
Protein C deficiency‡	1/49 (2.0%)	9/86 (10.5%)	0.2 (0.0–1.5)
Protein S deficiency‡	3/49 (6.1%)	1/86 (1.2%)	5.5 (0.6–54.8)
Antithrombin deficiency‡	2/49 (4.1%)	1/86 (1.2%)	3.6 (0.3–41.0)

\*Median age, 8 years (range, 9 months to ≤18 years).

†Median age, 7.5 years (range, 7 months to 17 years).

‡Heterozygote mutation or deficiency state.

§Median (range) lipoprotein(a) concentrations in patients with lipoprotein(a) values >30 mg/dL: 55 (32–120) mg/dL.

### Time of Recurrent Ischemic Stroke

Recurrent ischemic stroke was diagnosed at a median (range) of 5 (2 to 13) months after first ischemic stroke in 13 of the 135 children (9.6%) with antithrombotic medication still being administered.

Three additional patients (not included as recurrent stroke patients) developed 2-phase stroke within 12 to 36 hours after the first clinical stroke onset. Two patients (dissection, n=1; idiopathic, n=1) did not receive antithrombotic therapy at the time of the second phase, and in 1 other infant (cardiac disease) heparin treatment was initiated 10 hours before the second thromboembolic phase.

### Brain Lesions at Recurrent Ischemic Stroke

In the majority of cases (11 of 13), the same vascular territory was involved as in the first ischemic stroke. The brain lesions at recurrent stroke onset were found in the left middle cerebral artery (n=5), right middle cerebral artery (n=3), bilateral infarction (n=2), or vertebrobasilar system (n=1). The remaining 2 children presented with recurrent ischemic stroke at the contralateral middle cerebral artery (n=1) and bilateral infarction (n=1), respectively.

### Death Due to Recurrent Stroke

Death occurred in 3 of the 13 subjects (23%) with recurrent stroke as a result of stroke-associated complications (n=2)

and underlying cardiac disorder (n=1). Two of these 3 children had been treated in the LMWH group, and the third had received 3 mg/kg body wt aspirin per day.

### Distribution of Stroke Types With Respect to Antithrombotic Treatment and Recurrent Stroke

Table 2 summarizes the antithrombotic treatment administered with respect to stroke subtypes. Four of 49 children with aspirin and 9 of 86 patients with LMWH (enoxaparin, n=7; dalteparin, n=2) suffered recurrent stroke. No significant difference was found with respect to the antithrombotic medication used (OR, 1.3; 95% CI, 0.4 to 4.5; *P*=0.76, Fisher's exact test). No difference was found in this subgroup analysis with respect to recurrent stroke in patients with idiopathic first event versus children suffering from underlying cardiac diseases, vasculopathies, or associated infections (*P*=0.38).

### Adverse Effects of Antithrombotic Treatment

During the observation period, no patient in the aspirin group showed drug-associated side effects, ie, hemorrhage, allergic reactions, Reye syndrome, or gastrointestinal symptoms such as diarrhea or vomiting. No local or systemic hemorrhage or heparin-induced thrombocytopenia was observed in the LMWH treatment arm.

**TABLE 2. Stroke Types and Recurrent Stroke Rate With Respect to Antithrombotic Treatment Performed in 135 Pediatric Patients**

Prophylaxis	Spontaneous Stroke	Cardiac Stroke	Vascular Stroke	Infection	Total
Aspirin	0/21	0/5	3/18 (16.7%)	1/5 (20%)	4/49 (8.2%)†
LMWH*	6/58 (10.3%)	1/10 (10.0%)	2/12 (16.7%)	0/6	9/86 (10.5%)†
Total	6/79 (7.6%)	1/15 (6.7%)	5/30 (16.7%)	1/11 (9.1%)	13/135 (9.6%)

\*Recurrent stroke in LMWH-treated children occurred during enoxaparin treatment.

†*P*=0.76, Fisher's exact test (aspirin vs LMWH).

## Discussion

According to the current state of knowledge, no controlled or prospective data on antithrombotic therapy in pediatric patients with ischemic stroke are available.<sup>3-5</sup> This is due mainly to stroke being a rare vascular disorder in this age period and to the existence of various underlying diseases that differ from those of adult stroke populations and that have not yet been adequately defined. In addition, as recently stated, children with stroke have not been extensively investigated on the assumption that management would not change the outcome of generally agreed good prognosis, low recurrence risk, and good recovery of motor function and school performance.<sup>4</sup>

The subgroup analysis presented here covered white pediatric patients with ischemic stroke receiving antithrombotic treatment with either aspirin or LMWH. Even with these efforts at secondary prevention, recurrent stroke was diagnosed in 9.6% of treated patients within a median period of 5 months after the first stroke onset. The highest proportion of recurrent stroke (16.7%) was found in children with underlying vascular diseases, eg, fibromuscular dysplasia, stenosis, dissection, or moyamoya, followed by 9.1% in subjects suffering additionally from infections, 7.6% in patients with idiopathic stroke, and 6.7% in children with stroke of cardiac origin. The rate reported by us, ie, 13 of 135 white patients (9.6%) enrolled, is lower than the 20% reported by Lanthier and coworkers<sup>18</sup> in a cohort of 51 pediatric stroke patients from different ethnic backgrounds; this is due mainly to different patient populations, the different number of children enrolled, and varying underlying diseases. In addition, it is not clear from the data presented on that group whether the patients received antithrombotic therapy. Thus, the reduced recurrent stroke rate in our cohort treated with anticoagulation or antiplatelet agents might be the outcome of antithrombotic medication. However, a limitation of the present study is that the difference in recurrence risk shows no statistical significance, possibly because of the small number of subjects enrolled in the respective subgroups. Thus, results obtained from this white pediatric population must be interpreted with caution until larger numbers of patients have been prospectively studied in adequately sized randomized trials. Such further studies will also automatically increase the numbers of patients in the different subgroups, and it is hoped that multivariate analysis will provide more detailed information.

Ischemic stroke types in adults are classified as atherosclerotic cerebrovascular diseases (29%), penetrating artery diseases (25%), cardiac embolism (20%), cryptogenic stroke (30%), and stroke of other unusual causes, ie, prothrombotic states, dissections, arteritis, vasospasm, or drug abuse (5%).<sup>23</sup> On the basis of this classification, recommendations for stroke prevention after a first stroke onset of atherothrombotic origin, published by the Fifth American College of Chest Physicians Antithrombotic Consensus Conference in 1998, include antiplatelet agents, ie, aspirin and clopidogrel, whereas long-term oral anticoagulation is recommended for patients with a first cardioembolic cerebral event.<sup>23,31</sup> In contrast, stroke types in children differ essentially from those in adults.<sup>4,5,20</sup> Because of ethnic differences in the pediatric populations studied and the imaging methods used, the incidence of cerebral vasculopathies ranged from 15% to 80%.<sup>1,4,18,24,25</sup> In the past, invasive angiography was needed to demonstrate underlying vascular abnormalities,<sup>32</sup> but the in-

creasing sensitivity of MR angiography and Doppler ultrasound means that large-vessel disease can be diagnosed with the use of these techniques.<sup>1,4,18,24,25</sup> In adults, prothrombotic risk factors have little importance as risk factors for arterial thrombosis, ie, myocardial infarction or stroke.<sup>33-36</sup> In contrast, data recently reported in pediatric stroke patients indicate that these prothrombotic variants (the FV G1691A mutation, the PT G20210A genotype, protein C deficiency, protein S deficiency, or anti-thrombin deficiency), mainly known as risk factors in venous thrombosis, also play a role as risk factors for first ischemic stroke in children and young adults and, in addition, may also play a role as risk factors in patients with recurrent disease.<sup>9-16,18</sup> Thus, although aspirin is more cost-effective and its administration is more convenient than LMWH, LMWH is more appropriate in venous vascular accidents associated with prothrombotic risk factors. In contrast to trials in adult stroke populations,<sup>37</sup> hemorrhage as a potentially fatal side effect of LMWH was not observed by Dix et al<sup>19</sup> and in our small-scale study; this may be due to underlying diseases and arterial wall structures differing between pediatric stroke patients and the elderly, thereby raising the question of whether LMWH has a preferable therapeutic rank in childhood ischemic stroke despite the more invasive treatment condition. In addition, recently published experimental animal data provide evidence that standard nonhemorrhagic doses of an LMWH, eg, enoxaparin, have neuroprotective properties and reduce ischemic damage in previously healthy arteries.<sup>38</sup> Therefore, in the present and in future studies it seems of importance to investigate aspirin versus low-dose LMWH with respect to neurological outcome and recurrent ischemic stroke in children. In this study the median dose of aspirin administered in the patients was 4 mg/kg body wt (range, 2 to 5 mg/kg body wt). This is a low- to medium-dose regimen, which has also been used in adult treatment protocols.<sup>23</sup> Thus, when a multicenter randomized study in pediatric stroke patients is conducted, not only the drugs themselves but also the dose range, duration of treatment, and time from stroke onset to initiation of the treatment to be randomized must be considered.

We did not randomize the treatment modalities performed. Although the 2 treatment arms (Table 1) showed no statistical difference with respect to age, vascular territory involved, or the presence of inherited thrombophilia, and no significant difference was observed between aspirin and low-dose LMWH with respect to stroke recurrence (aspirin 8.2% versus LMWH 10.5%), the data presented here are based on a nonrandomized intervention or individual decision or choice of the treatment modalities and therefore have the potential for considerable bias. In view of the aforementioned statistical margins and wide ranges (ORs and CIs), adequately sized randomized trials are required to obtain reliable information on safety and efficacy with respect to the antithrombotic medications used. However, although we are aware that the nonrandomization of the 2 treatment arms represents a limitation of this study, with the current state of knowledge these data provide preliminary information on the treatment of white children with stroke.

In conclusion, this multicenter follow-up study provides evidence that drug-related side effects were rare in both treatment arms and that low-dose LMWH is not superior to medium-dose aspirin or vice versa as recurrent stroke prophylaxis in white pediatric patients. However, since stroke types, basic

diseases, and underlying prothrombotic risk factors differ essentially from those of adults, further international randomized prospective trials need to be conducted to clarify the question of treatment of pediatric ischemic vascular accidents not only in whites but in other ethnic subgroups as well.

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