

ORIGINAL ARTICLE

# Elevated Plasma Factor VIII and D-Dimer Levels as Predictors of Poor Outcomes of Thrombosis in Children

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## ABSTRACT

### BACKGROUND

Elevated levels of plasma factor VIII and D-dimer predict recurrent venous thromboembolism in adults. We sought to determine whether an elevation of factor VIII, D-dimer, or both at diagnosis and persistence of the laboratory abnormality after three to six months of anticoagulant therapy correlate with poor outcomes of thrombosis in children.

### METHODS

We evaluated levels of factor VIII and D-dimer and additional components of an extensive laboratory thrombophilia (i.e., hypercoagulability) panel at the time of diagnosis in 144 children with a radiologically confirmed acute thrombotic event. All patients were treated initially with heparin and then with either warfarin or low-molecular-weight heparin for at least three to six months, according to the current standard of care. Patients were examined at follow-up visits 3, 6, and 12 months after diagnosis and then annually, at which times testing was repeated in children with previously abnormal factor VIII and D-dimer test results and a uniform evaluation for the post-thrombotic syndrome was performed.

### RESULTS

Among 82 children for whom complete data were available regarding laboratory test results at diagnosis and thrombotic outcomes during follow-up, 67 percent had factor VIII levels above the cutoff value of 150 IU per deciliter, D-dimer levels above 500 ng per milliliter, or both at diagnosis, and at least one of the two laboratory values was persistently elevated in 43 percent of the 75 patients in whom testing was performed after three to six months of anticoagulant therapy. Fifty-one percent of the 82 patients had a poor outcome (i.e., a lack of thrombus resolution, recurrent thrombosis, or the post-thrombotic syndrome) during a median follow-up of 12 months (range, 3 months to 5 years). Elevated levels of factor VIII, D-dimer, or both at diagnosis were highly predictive of a poor outcome (odds ratio, 6.1;  $P=0.008$ ), as was the persistence of at least one laboratory abnormality at three to six months (odds ratio, 4.7;  $P=0.002$ ). The combination of a factor VIII level above 150 IU per deciliter and a D-dimer level above 500 ng per milliliter at diagnosis was 91 percent specific for a poor outcome, and after three to six months of standard anticoagulation, the combination was 88 percent specific.

### CONCLUSIONS

Elevated levels of plasma factor VIII, D-dimer, or both at diagnosis and a persistent elevation of at least one of these factors after standard-duration anticoagulant therapy predict a poor outcome in children with thrombosis.

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**T**HROMBOSIS IS AN INCREASING CONCERN in pediatrics, but few prospective studies have evaluated the outcome in children. Congenital deficiencies of protein C, protein S, and antithrombin are known risk factors for recurrent thromboembolism in children, and it is often assumed that idiopathic thrombosis carries the same risk of recurrence in adults and children. Little is known, however, about factors that underlie the risk of recurrent thromboembolism and adverse long-term sequelae of thrombosis in children.<sup>1</sup> Recurrent venous thromboembolism and the post-thrombotic syndrome develop in approximately 25 percent and 28 percent, respectively, of unselected adults by five years of follow-up<sup>2</sup>; in children these rates have been reported as 8 to 11 percent and 12 to 70 percent, respectively, by two to three years of follow-up.<sup>3-5</sup>

In the past several years, elevated factor VIII and D-dimer levels have emerged as risk factors for recurrent venous thromboembolism in adults. Among adults with first thromboembolic episodes, factor VIII levels above the 90th percentile three months after completion of anticoagulant therapy have been found to increase the risk of recurrence by a factor of nearly seven,<sup>6</sup> and D-dimer levels greater than 500 ng per milliliter at three months have been found to more than double the risk.<sup>7</sup> We sought to determine whether elevated factor VIII and D-dimer levels at the time of diagnosis of acute thrombotic episodes and after three to six months of standard anticoagulant therapy also predict poor outcomes of thrombosis in children.

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## METHODS

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### PATIENTS AND STUDY DESIGN

The establishment of a pediatric thrombophilia registry and the evaluation of thrombotic outcomes in children were approved by the Colorado Multiple Institution Review Board. Children, defined for purposes of this study as those from birth to 21 years old, with radiologically diagnosed acute thrombotic events at the Children's Hospital and at the Mountain States Regional Hemophilia and Thrombosis Center between March 1998 and August 2003 were eligible for inclusion in this analysis. Investigators obtained written informed consent for the patients to participate in the study, as required. All patients with pulmonary embolism or non-catheter-related deep venous thrombosis received anticoagulant

therapy for at least three months.<sup>8</sup> Therapy was targeted to achieve the following levels: for unfractionated heparin, 0.2 to 0.7 anti-Xa activity units per milliliter; for low-molecular-weight heparin, 0.5 to 1.0 anti-Xa activity units per milliliter; and for warfarin, an international normalized ratio (INR) of 2.0 to 3.0 (2.5 to 3.5 for children who were positive for the lupus anticoagulant). Thrombolytic therapy was also used at diagnosis in five children. Exclusion criteria were a congenital deficiency of protein C, protein S, or antithrombin III; long-term anticoagulant therapy or prophylaxis at the time of the diagnosis of thrombosis; and the absence of measurement of factor VIII or D-dimer at the time of diagnosis. A control group for laboratory testing included 32 unrelated healthy children (median age, 12 years; range, 2 months to 17 years) who did not have a first-degree relative with thrombosis or bleeding.

Atraumatic venipuncture was performed at diagnosis for comprehensive thrombophilia (i.e., hypercoagulability) testing in accordance with the recommendations of the Subcommittee for Perinatal and Pediatric Thrombosis of the International Society on Thrombosis and Haemostasis.<sup>9</sup> If laboratory results were abnormal, testing was repeated at follow-up at 3 months, 6 months, and 12 months and yearly thereafter, at which times investigators took an interim history, performed a physical examination and an assessment for the post-thrombotic syndrome, and repeated the diagnostic radiologic imaging study if thrombus was present on the previous study or new signs or symptoms had developed. A poor thrombotic outcome was defined as the presence of residual thrombosis at three to six months, recurrent thromboembolism within two years, or the development of the post-thrombotic syndrome during the follow-up period.

### ASSESSMENT OF OUTCOMES

During repeated imaging, venous thromboembolic events were characterized as persistent when residual thrombus was evident. For ischemic stroke, "persistent" was used to denote residual ischemia; in the case of initial infarction, no follow-up characterization was made. In all circumstances, the adjudicating radiologist was unaware of the laboratory results. Recurrent thromboembolism was defined as the occurrence, within two years, of a thrombus in a previously unaffected venous system (or, in the case of ischemic arterial stroke, of ischemia in a previously uninvolved arterial distribution).

Development of the post-thrombotic syndrome was assessed with the use of the validated pediatric scale of Manco-Johnson et al.,<sup>10</sup> which integrates a physical-examination scale adapted from Rutherford et al.<sup>11</sup> with a pain-assessment scale incorporating the Wong-Baker faces method.<sup>12</sup> The post-thrombotic syndrome was defined as the presence of pain with aerobic exercise, with activities of daily living, or at rest or by at least one of the following: visible or measurable edema, collateral circulation, venous stasis dermatitis, or ulceration.

#### LABORATORY ANALYSIS

Factor VIII and D-dimer assays were performed on fresh plasma isolated by double centrifugation of citrated venous blood specimens at 4°C for 10 minutes at 3000 rpm. Factor VIII levels were determined on fresh platelet-poor plasma (or platelet-poor plasma stored for less than one week at 70°C) with the use of a one-stage clotting assay (HemosIL, Instrumentation Laboratory). Levels of D-dimer were analyzed in fresh platelet-poor plasma by means of a latex-agglutination assay (IL Test D-dimer, Instrumentation Laboratory). When nonquantitative D-dimer testing was used, negative results were designated as 499 ng per milliliter, corresponding to the upper limit of the normal quantitative D-dimer values, on the basis of laboratory standardization of qualitative testing.

#### STATISTICAL ANALYSIS

Either the chi-square test or Fisher's exact test, as appropriate, was used to detect differences in descriptor variables and in the frequencies of outcomes between laboratory groups (i.e., children with elevated levels of factor VIII, D-dimer, or both and children with normal values) at diagnosis and at follow-up. Median age and laboratory values were compared between these laboratory groups and between outcome groups (i.e., children with a good outcome and those with a poor outcome) by the Mann-Whitney test. Logistic-regression analyses were performed to determine whether laboratory values above a threshold level, both at diagnosis and after three to six months, predicted a poor outcome. The results of univariate and multivariate logistic-regression analyses are reported as odds ratios with 95 percent confidence intervals, along with P values, for which the level of statistical significance was set at less than 0.05. All analyses were performed with the use of SAS statistical software (SAS Institute).

In many cases, D-dimer testing was semiquantitative (in which elevated results are quantified numerically and normal results are simply designated as values that are below the upper limit of normal), so for our analyses the D-dimer comparisons were of dichotomized results (i.e., elevated vs. normal), rather than of continuous data with respect to marker levels. The D-dimer data are reported as the frequency of abnormal values in each group.

The sensitivity of an elevation in the levels of both factor VIII and D-dimer for detecting a poor outcome was calculated from the proportion of all patients with a poor outcome in whom both test results were abnormal. Specificity was defined as the proportion of all patients with a good outcome in whom both test results were normal. Positive likelihood ratios were calculated as sensitivity ÷ (1 – specificity) and negative likelihood ratios as (1 – sensitivity) ÷ specificity, with corresponding likelihood ratios determined as previously described.<sup>13</sup>

## RESULTS

From 1998 to 2003, levels of factor VIII and D-dimer were measured at presentation with a radiologically confirmed acute thrombotic event in 144 consecutive children, who were followed for up to five years (Table 1). After the exclusion of three patients with congenital anticoagulant deficiencies, complete data regarding laboratory results for factor VIII and D-dimer levels at diagnosis and outcome at follow-up were available for 82 children, who served as the cohort for the present analysis. The distribution of 84 thromboses at initial diagnosis in these children (2 children presented with a second, non-embolic site of thrombosis) was deep venous thrombosis with or without concomitant pulmonary embolism in 52 children (63 percent), isolated pulmonary embolism in 4 children (5 percent), cerebral sinovenous thrombosis in 15 children (18 percent), renal-vein thrombosis in 5 children (6 percent), and ischemic arterial stroke in 8 children (10 percent). Deep venous thrombosis was more common among patients in whom laboratory values were elevated at diagnosis, and ischemic arterial stroke was more frequent among patients with laboratory values that were not initially elevated, but these differences were not statistically significant. Likewise, neither sex nor median age differed significantly between groups.

Among the 82 children in the cohort, levels of factor VIII or D-dimer or both at diagnosis were

**Table 1. Levels of Factor VIII and D-Dimer in 82 Patients with Thrombosis.\***

Variable	Initial Elevation		Persistent Elevation		All Patients (N=82)
	Yes (N=55)	No (N=27)	Yes (N=32)	No (N=43)	
Age at diagnosis (yr)					
Median	13	7.5	14	8	12
Range	0–19	0–20	0–19	0–20	0–20
Duration of anticoagulation (mo)†					
Median	3	3	3	3	3
Range	0–42	0–29	0–42	0–29	0–42
Factor VIII (IU/dl)					
Median	182	96	214	114	—
Range	64–432	56–242	97–310	74–138	—
D-Dimer (ng/ml)					
Median	1335	499	800	499	—
Range	311–10,746	307–499	499–3362	229–499	—
Sex (%)					
Male	45	50	53	44	46
Female	55	50	47	56	54
Clinical diagnosis (%)					
Idiopathic thrombosis	7	0	3	2	5
Catheter-related thrombosis	31	11	22	25	24
Acute infection at diagnosis	15	11	—	—	13
Lupus anticoagulant–positive	43	35	—	—	40
Chronic inflammatory state‡	13	4	13	9	10
Thrombotic events§					
Deep venous thrombosis (with or without pulmonary embolism)	70	48	67	61	63
Isolated pulmonary embolism	4	7	3	5	5
Cerebral sinovenous thrombosis	15	24	18	18	18
Renal-vein thrombosis	6	3	6	6	6
Ischemic arterial stroke	6	17	6	9	10
Outcome (%)					
Resolution	51	89	50	80	63
Persistence or progression	49	11	50	20	37
Recurrence	6	7	9	5	6
Post-thrombotic syndrome¶	41	10	56	14	33

\* Percentages may not sum to 100 because of rounding to the nearest whole number. Elevated laboratory values at diagnosis were defined by cutoff values of 150 IU per deciliter for factor VIII and 500 ng per milliliter for D-dimer. An evaluation for persistence of laboratory abnormalities was performed at three to six months. For 7 children in whom both laboratory values were elevated at diagnosis, only one abnormality was retested at follow-up; hence, 75 of the initial 82 patients are included in the follow-up group. Outcomes are reported as cumulative incidence rates during the follow-up period; however, adverse outcomes were evident by one year of follow-up in all patients.

† The duration of anticoagulation applies only to children with venous thromboembolism.

‡ Chronic inflammatory states were systemic lupus erythematosus (in three patients), inflammatory bowel disease (in one), cancer (in two), and chronic infection, including infection in children with cystic fibrosis (in two). There were no children with juvenile rheumatoid arthritis.

§ Eighty-four thromboses were evident among the 82 children (in 2 children, a second, nonembolic site of thrombosis was identified at diagnosis).

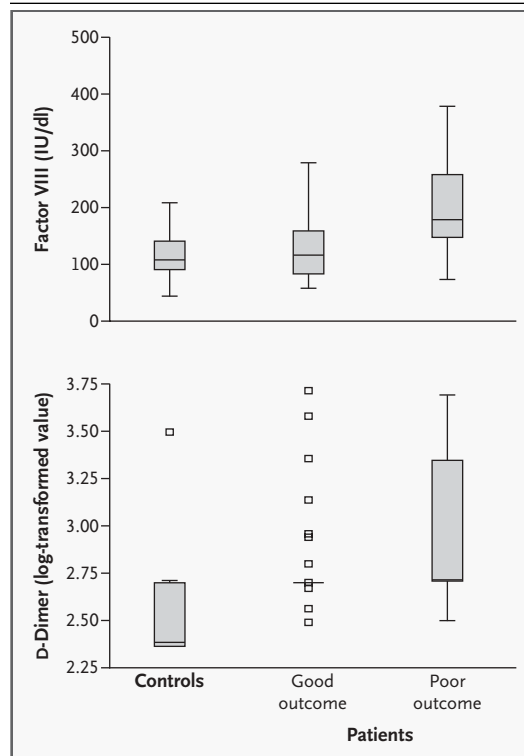
¶ The post-thrombotic syndrome was evaluated only in patients with deep venous thrombosis in an extremity; the numbers of affected patients were as follows: at diagnosis, 32 with elevation and 10 without; at follow-up, 18 with persistent elevation and 22 without; overall, 42 patients were included in this analysis.

above cutoff values of 150 IU per deciliter and 500 ng per milliliter, respectively, in 55 children (67 percent), and at least one of the two laboratory values was persistently elevated in 42 (51 percent) after three to six months of anticoagulant therapy.

With a median follow-up of 12 months (range, 3 months to 5 years), the cumulative incidence of a poor outcome was 51 percent. The cumulative incidence of persistent thrombosis was 37 percent and that of recurrent thromboembolism was 6 percent, and the prevalence of the post-thrombotic syndrome (among patients with deep venous thrombosis in an arm or a leg) was 33 percent. The cumulative incidences of these adverse outcomes among the 62 patients who had been excluded from the analysis because of incomplete data regarding levels of factor VIII and D-dimer were 20 percent, 3 percent, and 38 percent, respectively. In all patients studied, the aforementioned complications were evident by one year, with no new occurrences observed during the second year of follow-up.

Figures 1 and 2 show median levels of factor VIII and log-transformed D-dimer levels for healthy controls and for the patients according to outcome. At diagnosis and after three to six months of standard anticoagulant therapy, median levels of factor VIII were higher among patients with poor outcomes than they were among patients with good outcomes or controls. Furthermore, the proportion of patients with elevated D-dimer levels at diagnosis was significantly greater in the poor-outcome group (67 percent) than in the good-outcome group (38 percent,  $P=0.01$ ) or in the control group (6 percent,  $P<0.001$ ). This was also the case after three to six months of standard anticoagulation; 56 percent of patients in the poor-outcome group had elevated D-dimer levels, as compared with 24 percent in the good-outcome group ( $P=0.03$ ) and 6 percent in the control group ( $P<0.001$ ). There was no significant difference between the good-outcome group and the poor-outcome group in terms of sex, median age, or the presence of either acute infection or the lupus anticoagulant at diagnosis.

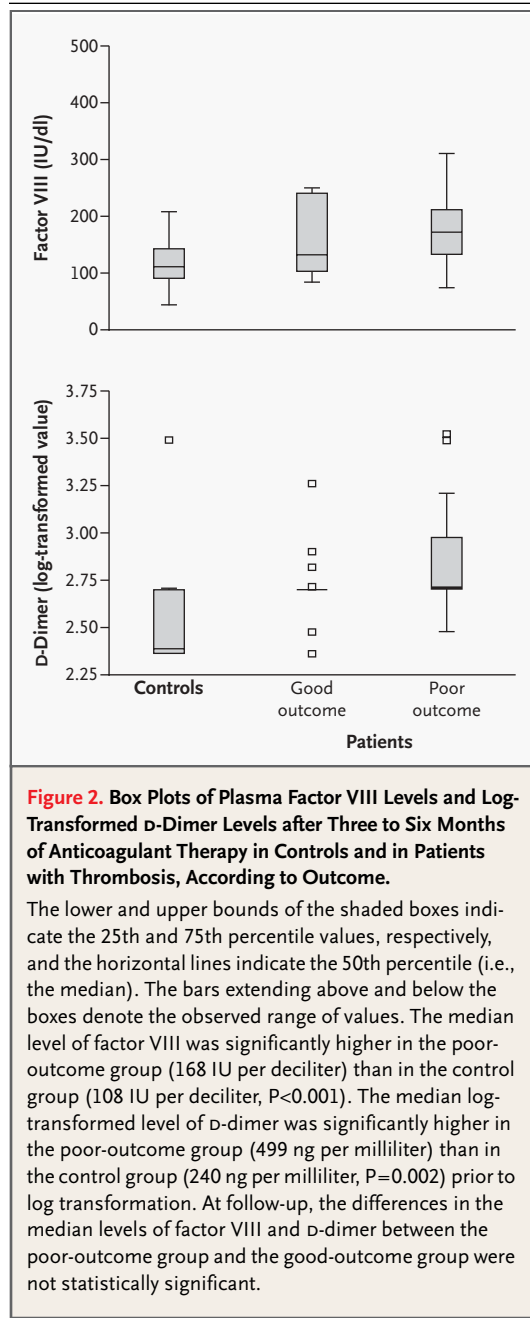
The frequency of persistent thrombosis was higher among children with thrombosis whose initial levels of factor VIII, D-dimer, or both were elevated than among children with thrombosis whose initial factor VIII and D-dimer levels were not elevated (49 percent vs. 11 percent,  $P<0.001$ ); the frequency of the post-thrombotic syndrome did not differ significantly between the two groups ( $P=0.07$ ). After three to six months of anticoagulant



**Figure 1. Box Plots of Plasma Factor VIII Levels and Log-Transformed D-Dimer Levels at Diagnosis in Controls and in Patients with Thrombosis, According to Outcome.**

The lower and upper bounds of the shaded boxes indicate the 25th and 75th percentile values, respectively, and the horizontal lines indicate the 50th percentile (i.e., the median). The bars above and below the boxes denote the observed range of values. The median level of factor VIII for the poor-outcome group (180 IU per deciliter) was significantly higher than that of both the good-outcome group (117 IU per deciliter,  $P<0.001$ ) and the control group (108 IU per deciliter,  $P<0.001$ ). Similarly, the median log-transformed D-dimer level was greater in the poor-outcome group (517 ng per milliliter,  $P=0.03$ ) and in both the good-outcome group (499 ng per milliliter,  $P=0.03$ ) and the control group (240 ng per milliliter,  $P<0.001$ ) before log transformation. When nonquantitative D-dimer testing was used, negative results were designated as 499 ng per milliliter, corresponding to the upper limit of the normal quantitative D-dimer values, on the basis of laboratory standardization of qualitative testing. Individual data points are shown where insufficient data were available for a box plot.

therapy, children with at least one persistently elevated laboratory value had a significantly higher rate of persistent thrombosis and the post-thrombotic syndrome than did children who had either no initial laboratory abnormality or an abnormal value that had returned to normal (persistent thrombosis, 50



percent vs. 20 percent,  $P=0.007$ ; post-thrombotic syndrome, 56 percent vs. 14 percent,  $P=0.005$ ).

In a univariate logistic-regression analysis, levels of factor VIII above 150 IU per deciliter, D-dimer levels above 500 ng per milliliter, or both at the time of diagnosis of the thrombotic event were found to be highly predictive of a poor outcome. Children were six times as likely to have a poor outcome when at least one of these laboratory values

exceeded the cutoff at diagnosis as when both values were normal (odds ratio, 6.1; 95 percent confidence interval, 2.1 to 17.7;  $P=0.008$ ). The persistence of elevated levels of factor VIII, D-dimer, or both at follow-up after three to six months also predicted a poor outcome. Patients who had persistently elevated laboratory values were five times as likely to have a poor outcome as patients who did not have elevated values (odds ratio, 4.7; 95 percent confidence interval, 1.8 to 12.6;  $P=0.002$ ).

The evidence suggests that persistence of a thrombus influences the development of the post-thrombotic syndrome,<sup>14</sup> and it was postulated that the effect of factor VIII and D-dimer levels on outcome may be modulated by age, the duration of anticoagulation, the presence or absence of the lupus anticoagulant, or the presence or absence of an underlying chronic inflammatory condition (e.g., systemic lupus erythematosus, inflammatory bowel disease, cancer, juvenile rheumatoid arthritis, or chronic infection). On this basis, we performed a multiple logistic-regression analysis with adjustment for intergroup differences in all these factors. The elevation of levels of factor VIII, D-dimer, or both at diagnosis remained significantly and independently predictive of a poor outcome (odds ratio, 8.9; 95 percent confidence interval, 2.2 to 36.3;  $P=0.002$ ), as did the persistence of at least one elevated value after three to six months of anticoagulant therapy (odds ratio, 4.1; 95 percent confidence interval, 1.4 to 11.6;  $P=0.008$ ).

Using the aforementioned laboratory cutoff values, we found that the elevation of levels of both factor VIII and D-dimer at diagnosis was 91 percent specific and had a positive likelihood ratio of 6.1 (95 percent confidence interval, 3.8 to 9.8) for a poor outcome; after three to six months of standard anticoagulant therapy, an elevation in both levels was 88 percent specific and had a positive likelihood ratio of 5.2 (95 percent confidence interval, 0.8 to 33.4) (Table 2).

## DISCUSSION

Although often perceived as an acute disorder, thrombosis entails a long-term risk of persistent or progressive thrombosis, recurrent thromboembolism, and the post-thrombotic syndrome. Previous studies of the outcome of thrombotic events in children were based on analyses of data from registries in Canada, the Netherlands, and Germany.<sup>3,15,16</sup> Unfortunately, whether we can generalize from such

outcome data is difficult to assess, owing to variations in treatment and follow-up investigations. In our study, as in the investigation of the group of German children with thrombophilia,<sup>16</sup> treatment was uniformly administered according to the current standard of care, and diagnostic and follow-up investigations were standardized.

Risk factors for poor outcomes after a thrombotic event have been well defined in adults, in whom ipsilateral recurrent thrombosis has been associated with subsequent development of the post-thrombotic syndrome,<sup>2</sup> and multiple clinical and laboratory abnormalities, including elevated levels of factor VIII<sup>6</sup> and D-dimer,<sup>7,17</sup> increase the risk of recurrent thromboembolism.

In contrast to the breadth of studies in adults, very few published studies have evaluated risk factors for recurrent thrombosis in children. Among 301 consecutive German children who had a first episode of venous thromboembolism without obvious clinical risk factors, recurrent thromboembolism occurred in 21 percent of the children a median of 3.5 years after the cessation of anticoagulant therapy, and thrombosis-free survival was significantly shortened among patients with two or more thrombophilic traits.<sup>16</sup> The duration of anticoagulant therapy in that study was uniform at six months, and serial follow-up imaging of the thrombus was performed as part of the outcome assessment. However, the results of the German study may have limited general applicability, given that thrombophilia registries of unselected cases of pediatric thrombosis indicate that the vast majority of events are not spontaneous but, rather, occur in association with an underlying clinical risk factor.<sup>3,15</sup>

Other studies in children have noted an increased risk of recurrent thromboembolism among children with lupus anticoagulant antibodies; however, because of the small number of patients, statistical significance could not be assessed.<sup>18,19</sup> In addition, the question of whether underlying thrombophilia other than congenital anticoagulant deficiency predisposes children to recurrent thromboembolism and other poor outcomes is controversial. Although a positive relationship with recurrence<sup>15</sup> and the post-thrombotic syndrome<sup>16</sup> was found in two pediatric registries, other preliminary work suggests no such relationship in children,<sup>20</sup> and there may even be a negative relationship with the post-thrombotic syndrome in adults.<sup>21</sup> Larger prospective studies in children are needed to investigate this issue.

Our results in children agree with findings in

**Table 2. Predictive Value of the Combination of Elevated Factor VIII and D-Dimer Levels at Diagnosis and Follow-up for a Poor Outcome of Thrombosis in Children.\***

	At Diagnosis	At Follow-up
Sensitivity (%)	55	65
Specificity (%)	91	88
Positive likelihood ratio†	6.1 (3.8–9.8)	5.2 (0.8–33.4)
Negative likelihood ratio‡	0.49 (0.33–0.74)	0.40 (0.2–0.8)

\* Elevations were defined as factor VIII levels above 150 IU per deciliter and D-dimer levels above 500 ng per milliliter. Follow-up values were determined after three to six months of standard anticoagulant therapy. Values in parentheses are 95 percent confidence intervals.

† The positive likelihood ratio was calculated as sensitivity ÷ (1 – specificity).

‡ The negative likelihood ratio was calculated as (1 – sensitivity) ÷ specificity.

adults that support the value of measuring factor VIII and D-dimer levels to predict outcomes after a thrombotic event<sup>6,7,17</sup> and suggest that these markers may be more powerful predictors in children than in adults. Furthermore, our demonstration that the value of levels of factor VIII in predicting the outcome of thrombosis in children is independent of systemic inflammatory states is concordant with findings in adults.<sup>6</sup>

Elevated levels of fibrinogen<sup>22</sup> and coagulation factors VII,<sup>22</sup> VIII,<sup>23</sup> IX,<sup>24</sup> and XI<sup>25</sup> have each been associated with an increased risk of venous thrombosis; among these, only factor VIII has been implicated in recurrent thromboembolism as well. The mechanisms by which elevated factor VIII levels promote primary and recurrent venous thromboembolism are unclear. Our findings, and those of Kyrle et al.,<sup>6</sup> indicate that the mechanism is not based on an acute-phase reaction. Rather, it may be that elevated factor VIII levels are familial or result from endothelial hyperreactivity in response to a vascular insult, such as an event that triggers thrombus formation or the thrombus itself. Efforts are ongoing to discern whether the elevations of factor VIII levels that were found in our analysis are predominantly inherited.

Our findings have implications for the management of thrombosis in children. Given the poor outcomes associated with elevated levels of factor VIII, D-dimer, or both (i.e., greater than 150 IU per deciliter and 500 ng per milliliter, respectively) at the time of diagnosis of a thrombosis, consideration should be given to more aggressive antithrombotic therapy in such cases. This could include targeting therapy to achieve and maintain an intensity of anti-

coagulation at the upper end of the therapeutic range or adding thrombolytic therapy during the initial period of anticoagulation, in cases in which such therapy is clinically appropriate. Furthermore, our finding that a poor outcome of thrombosis appears to be heralded by persistently abnormal levels of factor VIII, D-dimer, or both points to another area for further investigation: evaluating the use of extended anticoagulation in children with such abnormalities.

Thus far, only one published pediatric study has undertaken preliminary evaluation of the effect of the aggressiveness of initial antithrombotic therapy on thrombotic outcomes.<sup>26</sup> Given the risk of impairment in critical growth and development that may be associated with thromboembolism and the post-thrombotic syndrome in children and the po-

tential for compromised physical function during a lifetime, it is imperative that large cooperative pediatric trials be conducted to evaluate optimal antithrombotic strategies in order to enhance preventive efforts and improve future thrombotic outcomes in children.

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**CORRECTION**

**Elevated Plasma Factor VIII and D-Dimer Levels as Predictors of Poor Outcomes of Thrombosis in Children**

Elevated Plasma Factor VIII and D-Dimer Levels as Predictors of Poor Outcomes of Thrombosis in Children . On page 1084, in Table 1, the range for factor VIII among patients who had no initial elevation in levels of factor VIII and D-dimer should have been 56 to 142 IU per deciliter, rather than 56 to 242, as printed.