Impact of Inherited Thrombophilia on Venous Thromboembolism in Children
A Systematic Review and Meta-Analysis of Observational Studies

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**Background**—The aim of the present study was to estimate the impact of inherited thrombophilia (IT) on the risk of venous thromboembolism (VTE) onset and recurrence in children by a meta-analysis of published observational studies.

**Methods and Results**—A systematic search of electronic databases (Medline, EMBASE, OVID, Web of Science, The Cochrane Library) for studies published from 1970 to 2007 was conducted using key words in combination as both MeSH terms and text words. Citations were independently screened by 2 authors, and those meeting the inclusion criteria defined a priori were retained. Data on year of publication, study design, country of origin, number of patients/controls, ethnicity, VTE type, and frequency of recurrence were abstracted. Heterogeneity across studies was evaluated, and summary odds ratios and 95% CIs were calculated with both fixed-effects and random-effects models. Thirty-five of 50 studies met inclusion criteria. No significant heterogeneity was discerned across studies. Although >70% of patients had at least 1 clinical risk factor for VTE, a statistically significant association with VTE onset was demonstrated for each IT trait evaluated (and for combined IT traits), with summary odds ratios ranging from 2.63 (95% CI, 1.61 to 4.29) for the factor II variant to 9.44 (95% CI, 3.34 to 26.66) for antithrombin deficiency. Furthermore, a significant association with recurrent VTE was found for all IT traits except the factor V variant and elevated lipoprotein(a).

**Conclusions**—The present meta-analysis indicates that detection of IT is clinically meaningful in children with, or at risk for, VTE and underscores the importance of pediatric thrombophilia screening programs. *(Circulation. 2008;118:1373-1382.)*

**Key Words:** meta-analysis ■ pediatrics ■ recurrence ■ thrombosis

Venous thromboembolism (VTE) in children is a rare disease that is being increasingly diagnosed and recognized, usually as a secondary complication of primary underlying medical diseases such as sepsis, cancer, and congenital heart disease, as well as therapeutic interventions such as the use of central venous lines.¹⁻⁶ Pediatric VTE is a severe condition for which long-term outcomes have included lack of thrombus resolution in 50% of cases and, excluding central line–associated thrombosis in children with malignancy, the development of postthrombotic syndrome in more than one
third of patients.7–11 Within the entire childhood population, neonates are at the greatest risk of thromboembolism (5.1/100,000 live births per year in white children), with a second peak in incidence during puberty and adolescence.3 In prospective pediatric registries in North America and Europe, the annual incidence of venous events was estimated to be 0.7 to 1.4 per 100,000 children or 5.3 per 10,000 hospital admissions of children and 24 per 10,000 admissions of neonates to neonatal intensive care units.6,12–14

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The results of single studies of the risk of VTE onset and recurrence associated with inherited thrombophilia (IT) have been contradictory or inconclusive, mainly because of a lack of statistical power. Apart from acquired thrombophilic risk factors such as the presence of antiphospholipid antibodies,15–18 IT—particularly antithrombin, protein C, and protein S deficiency, variants of coagulation factor V (G1691A) and factor II (G20210A), and elevated lipoprotein(a)—have been established as risk factors for venous thromboembolic events in adults.19–29 The allele frequencies for the factor V G1691A or factor II G20210A variants differ among various ethnic groups.30–32 In children with idiopathic VTE and in pediatric populations in which thromboses were associated with underlying medical diseases, IT has been described as an additional prothrombotic risk factor.33–101 Follow-up data for VTE recurrence in children are available from several reports12,13,17,62,63,67,69,78–81,93,100 and suggest a recurrence rate of ~3% in neonates and 8% in older children. Unfortunately, the duration of follow-up is variable across studies. However, in the pediatric age group, it is unknown whether thrombus recurrence and other thrombotic outcomes in children are affected by IT; thus, it remains controversial whether children with thrombosis or offspring in thrombosis-prone families benefit from screening for IT.102–108 The aim of this systematic review and meta-analysis was to determine the impact of IT on VTE onset and recurrence in children as a prerequisite to the evaluation of primary and secondary treatment options through randomized controlled trials.

Methods

The present systematic review and meta-analysis was performed in accordance with the recently published guidelines from Strengthening the Reporting of Observational Studies in Epidemiology (STROBE).109 with adaptations as further described below.

Inclusion/Exclusion Criteria

Published studies of VTE in children <20 years of age from 1970 through August 2007 were evaluated for inclusion if the frequency of ≥1 IT traits was individually investigated in a given VTE cohort (descriptive analysis) and if the frequency of IT traits was compared between VTE patients and control subjects without a history of VTE in a given study (meta-analysis). Pediatric VTEs of any location were classified as having a cohort/case-control, case series, or registry data when consisting of a multicenter population-based study design with no control group. Studies were classified as having a case-control design when individuals were followed up for development of the outcome of interest. Studies were classified as having a cohort design when subjects with and without a factor being investigated were followed up for development of the outcome of interest. Studies were classified as having a case-control design when individuals grouped by outcome (ie, cases having the outcome/disease of interest and controls without the outcome/disease) were compared for the presence of a risk factor of interest. A case report or case series was defined as 1 case or a group of cases of a particular outcome of interest with no control group. Studies were classified as having a registry design when consisting of a multicenter population-based (ascertainment of >90% of cases available) case series using predefined standardized data collection criteria.111

Missing Data

Studies in which symptomatic pediatric VTE patients were not screened for ITs and studies in which the thrombophilia screening was done in <50% of cases or was performed only sporadically were not included in the present meta-analysis. When the percentage of patients screened for IT was not clear from the article, authors were asked for clarification.
Statistical Analyses

Data analyses were performed with STATA version 9 update and StatsDirect version 2.6.6 update (Altrincham, Trafford, UK: WWW.STATSDIRECT.COM). Continuous data are presented as median (minimum and maximum) values. For meta-analysis, summary odds ratios (ORs) and 95% CIs were calculated from the effect estimates of the individual studies weighted by SE using both a fixed-effects model (weighting each estimate by its SE via the Mantel-Haenszel method) and a random-effects model (estimating between-study variance in effect measures according to DerSimonian and Laird).\(^{112}\) The latter approach was used to control for heterogeneity according to Higgins et al.\(^{113}\) For both the factor V and factor II variants, the AA and GA alleles (ie, homozygosity and heterozygosity for A alleles) were analyzed together and compared with the absence of these genotypes as the reference category. A value of \(P<0.05\) was considered statistically significant. In addition, we assessed heterogeneity among studies using \(I^2\) statistics. When \(P<0.05\), the presence of heterogeneity was considered statistically significant, and when \(I^2>50\%), the magnitude of heterogeneity was considered substantial. Funnel plots of effect size against SE and a modified linear regression test were used to describe the presence of publication bias.\(^{114}\) In study design classification, the degree of agreement beyond chance between first and second raters was measured by \(\kappa\) statistic.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

**Descriptive Analyses**

From 331 potentially relevant citations ascertained from electronic databases and search of reference lists, 50 cohort/case-control studies or case series registries from 16 countries finally met the inclusion criteria for descriptive analysis (Figure 1 and Tables Ia, Ib, and II of the online Data Supplement). Apart from Reference 63, which reported the follow-up of high-risk children with idiopathic VTE, in these studies, \(>70\%\) of patients with VTE had at least 1 clinical risk factor. In neonates and infants, these risk factors were predominantly medical diseases such as systemic sepsis, dehydration, congenital heart disease, or short-term central venous lines; in older children and adolescents, cancer and polychemotherapy, immobilization after surgery or plaster casts, obesity, rheumatic diseases, local infections, and the use of oral contraceptives pills (adolescent girls) were the leading exogenous triggers. Measurement of interrater reliability in study design classification showed a substantial agreement (92.68\%) beyond that expected by chance alone (22.78\%) in the analysis of VTE onset (\(k=0.90; Z=11.08; P<0.001\)), and in the analysis of VTE recurrence, the agreement beyond chance (24.8\%) was 81.82\% (\(k=0.76; Z=4.91; P<0.001\)).

Studies investigating IT at the onset of VTE are shown in the supplemental tables. Forty-one of the 50 studies reported inherited deficiency states of protein C, protein S, or antithrombin. In these studies, 2653 patients with a first VTE onset and 1979 control children were investigated (supplemental Table Ia). Beginning in 1996 and 1999, the factor V and factor II variants, respectively, were systematically investigated in childhood VTE (44 studies; supplemental Table...
For the rare event of VTE recurrence, patients derived from 6 to 13 studies met the inclusion criteria. The median follow-up time was 48 months (minimum, 12 months; maximum, 96 months). The median age at onset in studies reporting recurrent VTE was 7.2 years (minimum, 0.1 years; maximum, 14.0 years) with a median age at recurrence of 14 years (minimum, 3.6 years; maximum, 15.0 years). Data on anticoagulation at the time of recurrence were available for 127 children from 7 reports. In 25 of 127 patients (19.7%), recurrence presented during anticoagulation therapy, and in the majority of cases, ie, in 102 of the 127 patients (80.3%), the second VTE occurred after withdrawal of anticoagulation.

Study characteristics and the rates of recurrent VTE are shown in supplemental Table II. The proportion of children developing recurrent VTE over the median follow-up period was 11.4%. Of note, because of authors’ clarifications, individual numbers of patients and controls in the studies listed in supplemental Table I and Tables 1 and 2 may vary from the original study articles. In addition, subject numbers for the analyses differ in Table 2 and supplemental Table II relative to the prior tables because of the reliance on case-control studies in the estimation of risk of first VTE onset.

### Table 1. Summary ORs (95% CIs; Meta-Analysis) Including Testing for Heterogeneity (I²) and Publication Bias for Genetic Traits Associated With a First VTE Onset in Children

<table>
<thead>
<tr>
<th>Genetic Traits (No. of Studies)</th>
<th>Patients/Controls, n</th>
<th>OR (95% CI), Fixed Model</th>
<th>OR (95% CI), Random Model</th>
<th>I², %</th>
<th>Bias Indicator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein C deficiency (16)</td>
<td>1079/1979</td>
<td>7.72 (4.440–13.42)</td>
<td>7.75 (4.48–13.38)</td>
<td>0</td>
<td>0.13</td>
</tr>
<tr>
<td>Protein S deficiency (16)</td>
<td>1075/1979</td>
<td>5.77 (3.03–10.97)</td>
<td>5.77 (3.07–10.85)</td>
<td>0</td>
<td>0.30</td>
</tr>
<tr>
<td>Antithrombin deficiency (16)</td>
<td>1072/1979</td>
<td>9.44 (3.34–26.66)</td>
<td>8.73 (3.12–24.42)</td>
<td>0</td>
<td>0.27</td>
</tr>
<tr>
<td>Factor V G1691A (23)</td>
<td>1430/2623</td>
<td>3.77 (2.98–4.77)</td>
<td>3.56 (2.57–4.93)</td>
<td>33.4</td>
<td>0.78</td>
</tr>
<tr>
<td>Factor II G20210A (14)</td>
<td>916/1673</td>
<td>2.64 (1.60–4.41)</td>
<td>2.63 (1.61–4.29)</td>
<td>0</td>
<td>0.71</td>
</tr>
<tr>
<td>Lipoprotein(a) (8)</td>
<td>589/1441</td>
<td>4.49 (3.26–6.18)</td>
<td>4.50 (3.19–6.35)</td>
<td>8.3</td>
<td>0.14</td>
</tr>
<tr>
<td>≥2 Genetic traits (12)</td>
<td>965/1625</td>
<td>9.5 (4.92–18.39)</td>
<td>8.89 (3.43–23.06)</td>
<td>38.3</td>
<td>0.57</td>
</tr>
</tbody>
</table>

### Table 2. Summary ORs (95% CIs; Meta-Analysis) Including Testing for Heterogeneity (I²) and Publication Bias for Genetic Traits Associated With Recurrent VTE in Children

<table>
<thead>
<tr>
<th>Genetic Traits (No. of Studies)</th>
<th>Patients With Recurrence/Patients With No Recurrence, n</th>
<th>OR (95% CI), Fixed Model</th>
<th>OR (95% CI), Random Model</th>
<th>I², %</th>
<th>Bias Indicator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein C deficiency (13)</td>
<td>152/1296</td>
<td>2.39 (1.21–4.36)</td>
<td>2.53 (1.30–4.92)</td>
<td>0</td>
<td>0.67</td>
</tr>
<tr>
<td>Protein S deficiency (11)</td>
<td>132/857</td>
<td>3.12 (1.50–6.45)</td>
<td>3.76 (1.76–8.04)</td>
<td>0</td>
<td>0.41</td>
</tr>
<tr>
<td>Antithrombin deficiency (12)</td>
<td>150/969</td>
<td>3.01 (1.43–6.33)</td>
<td>3.37 (1.57–7.20)</td>
<td>0</td>
<td>0.59</td>
</tr>
<tr>
<td>Factor V G1691A (12)</td>
<td>115/1160</td>
<td>0.64 (0.35–1.18)</td>
<td>0.77 (0.40–1.45)</td>
<td>0</td>
<td>0.48</td>
</tr>
<tr>
<td>Factor V G1691A including children with idiopathic/spontaneous VTE only (13)</td>
<td>179/1397</td>
<td>1.35 (0.91–1.98)</td>
<td>1.43 (0.91–2.24)</td>
<td>4.3</td>
<td>0.48</td>
</tr>
<tr>
<td>Factor II G20210A (12)</td>
<td>171/1397</td>
<td>1.88 (1.01–3.49)</td>
<td>2.15 (1.12–410)</td>
<td>0</td>
<td>0.004</td>
</tr>
<tr>
<td>Lipoprotein(a) (6)</td>
<td>135/1020</td>
<td>0.81 (0.49–1.36)</td>
<td>0.84 (0.50–1.40)</td>
<td>0</td>
<td>0.78</td>
</tr>
<tr>
<td>≥2 Genetic traits (10)</td>
<td>144/1127</td>
<td>4.46 (2.89–6.89)</td>
<td>4.91 (3.12–7.74)</td>
<td>0.7</td>
<td>0.82</td>
</tr>
</tbody>
</table>
Meta-Analyses

In 35 of 50 studies, eligible data on VTE children and population-based controls were reported. For the event of VTE onset, patients derived from 8 to 23 studies were available. Table 2 summarizes the genetic traits investigated, the number of studies and patients included in the meta-analysis, and summary ORs and 95% CIs under a fixed-effects and random-effects model. In addition, results of testing for heterogeneity and publication bias are shown. No significant heterogeneity or publication bias was discerned across studies. ORs were first calculated separately by age groups (neonate, infant, child, adolescent). Because no statistically significant difference in ORs was detected with age (data not shown), summary ORs were then calculated for the overall pediatric age range. A statistically significant association with VTE onset was demonstrated for each IT trait evaluated (and for combined IT traits), with summary ORs ranging from 2.63 (95% CI, 1.61 to 4.29) for the factor II variant to 9.44 (95% CI, 3.34 to 26.66) for antithrombin deficiency. Forest plots under random-effects models show that pediatric carriers of the factor II variant (Figure 2A) and of $\approx2$ genetic traits (Figure 2b) had an increased risk of developing a first symptomatic VTE. Furthermore, a significant association with recurrent VTE was found for all IT traits except the factor V variant and elevated lipoprotein(a), with summary ORs ranging from 1.88 (95% CI, 1.01 to 3.49) for the factor II variant to 3.76 (95% CI, 1.76 to 8.04) for protein S deficiency. Substantial heterogeneity across studies was ruled out. When analyzing the role of factor V G1691A and recurrence, we achieved higher homogeneity and the absence of major publication bias after exclusion of Reference 63, which reported solely the follow-up of selected high-risk pediatric patients with idiopathic VTE. Substantial heterogeneity across studies was ruled out. When analyzing the role of factor V G1691A and recurrence, we achieved higher homogeneity and the absence of major publication bias after exclusion of Reference 63, which reported solely the follow-up of selected high-risk pediatric patients with idiopathic VTE (Table 2). Again, funnel plots of effect size against SE were explored for each parameter investigated and were broadly symmetrical, which was consistent with the conclusion that there was no major publication bias (data of bias assessment plots are exemplarily shown for the factor II mutation [supplemental Figure IIIa] and combined genetic traits at recurrent VTE [supplemental Figure IIIb]). The absence of major publication bias was also underlined by the results of the linear regression method according to Harbord et al.114

Discussion

VTE is far less common in children than in adults and often is associated with underlying medical conditions such as malignancy, autoimmune disease, and congenital heart disease or is caused by medical interventions such as central venous lines. Keeping in mind that not all children with these risk factors will develop VTE, it is apparent that genetic risk factors play an important role in which children will develop thrombosis.33–101,115,116 Apart from a recent systematic review of the role of thrombophilia in children with acute lymphoblastic leukemia and ischemic stroke,117,118 to the best of our knowledge, this is the first meta-analysis of observational studies investigating the association of genetic traits and VTE in children. Each of the traits investigated shows a significant association with first onset of pediatric VTE, with the highest ORs found for combined genetic traits and deficiencies of antithrombin, protein C, and protein S. Our findings are concordant with adult studies demonstrating that inherited deficiencies of the natural anticoagulants protein C, protein S, and antithrombin are present in $<10\%$ of patients with VTE but that patients with these deficiency states are considered at higher risk for a first VTE onset.119 In the white adult population, the factor V mutation increases the risk of a first episode of VTE by 3- to 7-fold, whereas the factor II variant increases the risk by 2- to 3-fold.120,121 In addition, it has been demonstrated in a recent meta-analysis that elevated lipoprotein(a) increases the risk of a first symptomatic VTE in adults nearly 2-fold.29

A history of thrombosis is a predictor for VTE recurrence in adults in 3% to 13% of consecutive patients after 1 year and in 12% to 28% after 5 years.119 In pediatric cohorts, the proportion of children developing recurrent VTE ranged from 3% in neonates to 8% in older children2,12–14 and as high as 21% in children reported with a first idiopathic VTE.63 The results of this meta-analysis show that 11.4% of children with nonidiopathic thrombosis overall (ie, regardless of IT status) developed a second VTE, which is consistent with the rate reported in large pediatric cohort studies not systematically investigating genetic traits.2,12,14,79 Second events, however, were observed mainly in adolescents and occurred in $\approx80\%$ of affected children after withdrawal of anticoagulant therapy. In the present meta-analysis, a significant association with recurrent VTE in children was found for protein C, protein S, and antithrombin deficiency; the factor II variant; and $\approx2$ genetic traits. Pediatric carriers of the factor V mutation or elevated lipoprotein(a) did not show an increased risk for recurrent VTE in the present analysis. The summary ORs determined in this meta-analysis for recurrent VTE in children are consistent with results obtained from adult cohort studies of patients not receiving long-term anticoagulation.119,122–124

The present meta-analysis has several limitations. First, the included studies were conducted over different time periods; therefore, it has to be taken into consideration that diagnosis and treatment modalities, including referral patterns, might have changed over time. Second, most of the studies included in our meta-analysis were undertaken in white children with VTE; thus, it is unknown whether our findings can be extrapolated to other ethnic groups. A third limitation is the possible presence of publication bias. Although formal testing did not show a publication bias, it cannot be completely ruled out, considering the rarity of the disease and the small number of studies available in the field of pediatric VTE. It should also be mentioned here that the pediatric age groups most affected, ie, newborns and adolescents, are underrepresented in the present analysis. The former may be due to the fact that apart from genetic testing, thrombophilia screening and its interpretation are difficult in small children and may therefore be postponed by the treating physicians, with the increasing risk of patients lost to follow-up. As a consequence, data obtained from this meta-analysis have to be interpreted with caution, especially for infants within the first year of life. A fourth limitation of the study, specifically with regard to the VTE recurrence analysis, is that data were not available for the duration of follow-up on a per-patient level, so recurrence...
Figure 2. A, The Forest plot shows ORs and 95% CIs for observational studies investigating the influence of the factor II G20210A mutation on the onset of symptomatic venous thromboembolism in children. The study author and year of publication are indicated on the y axis. The box for each study is proportional to the inverse of variance; horizontal lines show the 95% CIs of the ORs. The pooled estimate is based on a random-effects model shown by a vertical line and diamond (95% CI). Studies are in descending order by year of publication. Studies with patients/controls counted as “zero” are not depicted (Reference 94). B, The Forest plot shows ORs and 95% CIs for observational studies investigating the influence of two genetic traits on the onset of symptomatic venous thromboembolism in children. The study author and year of publication are indicated on the y axis. The box for each study is proportional to the inverse of variance; horizontal lines show the 95% CIs of the ORs. The pooled estimate is based on a random-effects model shown by a vertical line and diamond (95% CI). Studies are in descending order by year of publication. Studies with patients/controls counted as “zero” are not depicted (References 48 and 59).
risk may be biased by differences in duration of follow-up across studies.

These limitations notwithstanding, the finding of the present meta-analysis that IT is associated with VTE onset and its recurrence in children has important implications for future advances in the field. Decisions on extending anticoagulation therapy are individually based on the perceived risks of VTE recurrence and anticoagulation-related bleeding, and whether long-term continuation of anticoagulation treatment should be considered after a first VTE in carriers of a thrombophilic trait is still a matter of debate. Randomized controlled trials are lacking in children with a first VTE, and treatment guidelines are mainly adapted from adults. More than in the typical elderly adult with VTE, the prolonged use of anticoagulation treatment in a physically active pediatric group must be weighed against the risk of bleeding. The results of this meta-analysis suggest that future investigation of secondary prevention in pediatric VTE should include trials of prolonged anticoagulation treatment duration targeting high-risk IT groups, particularly children with VTE who have combined IT but do not presently meet the criteria (eg, severe anticoagulant deficiency) for indefinite anticoagulation.

Acknowledgments

We thank Klaus Berger of help in epidemiological discussions and Sandra Bergs and Doris Kunkel for technical support.

Sources of Funding

The study was supported by grants from the Karl Bröcker Stiftung and the local university research project Innovative Medizinische Forschung in Münster. These study supporters had no role in the study design, data collection, data analysis, or data interpretation or in the writing of this report.

Disclosures

None.

References


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**CLINICAL PERSPECTIVE**

The role of inherited thrombophilia in the onset and recurrence of pediatric venous thromboembolism (VTE) is unclear. Previous publications reporting the occurrence of inherited thrombophilia in pediatric patients with VTE consist largely of case reports and case series. Although there are a number of prospective and retrospective controlled studies, they generally suffer from methodological problems (often sample sizes that are too small) that preclude any from being definitive. As a result, physicians caring for children with VTE cannot appropriately decide on the utility of thrombophilia testing, leading some physicians to evaluate all such patients and others to perform no testing. Thus, we performed a meta-analysis to provide more definitive answers that can provide some guidance on this controversial issue. The results of this meta-analysis demonstrate that all thrombophilia traits included in the study are associated with the onset of VTE and most are associated with recurrence [except factor V Leiden and lipoprotein(a)]. These results suggest that thrombophilia testing based on the individual genetic background of the patient may be important in the management of children with VTE.
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_Circulation._ 2008;118:1373-1382; originally published online September 8, 2008; doi: 10.1161/CIRCULATIONAHA.108.789008

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/118/13/1373

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