

Impact of Inherited Thrombophilia on Venous Thromboembolism in Children

A Systematic Review and Meta-Analysis of Observational Studies

Guy Young, MD; Manuela Albisetti, MD; Mariana Bonduel, MD; Leonardo Brandao, MD; Anthony Chan, MD; Frauke Friedrichs, PhD; Neil A. Goldenberg, MD; Eric Grabowski, MD; Christine Heller, MD; Janna Journeycake, MD; Gili Kenet, MD; Anne Krümpel, MD; Karin Kurnik, MD; Aaron Lubetsky, MD; Christoph Male, MD; Marilyn Manco-Johnson, MD; Prasad Mathew, MD; Paul Monagle, MD; Heleen van Ommen, MD; Paolo Simioni, MD; Pavel Svirin, MD; Daniela Tormene, MD; Ulrike Nowak-Göttl, MD

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

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From the Division of Hematology/Oncology, Children's Hospital Los Angeles, Los Angeles, Calif (G.Y.); Division of Hematology, University Children's Hospital, Zurich, Switzerland (M.A.); Servicio de Hematología y Oncología, Hospital de Pediatría "Prof. Dr. J.P. Garrahan," Buenos Aires, Argentina (M.B.); Hospital for Sick Children, Toronto, Canada (L.B.); McMaster University, Hamilton, Canada (A.C.); Leibniz Institute for Arteriosclerosis Research, University of Münster, Münster, Germany (F.F.); Department of Pediatrics, Hematology/Oncology/BMT, University of Colorado and the Children's Hospital, Denver (N.A.G., M.M.-J.); Massachusetts General Hospital, Harvard Medical School, Boston, Mass (E.G.); Department of Pediatric Hematology/Oncology, University Hospital Frankfurt, Frankfurt, Germany (C.H.); Department of Pediatrics, Children's Medical Centre Dallas, University of Texas Southwestern Medical Center, Dallas (J.J.); Israel National Haemophilia Centre, Sheba Medical Centre, Tel-Hashomer, Israel (G.K., A.L.); Department of Pediatric Hematology/Oncology, University Hospital Münster, Münster, Germany (A.K., U.N.-G.); Department of Pediatrics, University Hospital Munich, Munich, Germany (K.K.); Department for Pediatrics, Medical University, Vienna, Austria (C.M.); Department of Pediatrics, University of New Mexico, Albuquerque (P. Mathew); The Royal Children's Hospital, Victoria, Australia (P. Monagle); Department of Pediatric Hematology, Emma Children's Hospital AMC, Amsterdam, the Netherlands (H.v.O.); Department of Medical and Surgical Sciences, University of Padua, Padua, Italy (P. Simioni, D.T.); and Russian National Center of Pediatric Hematology/Oncology, Moscow State Medical University, Moscow, Russian Federation (P. Svirin).

Apart from the first/senior author, authors are listed alphabetically and contributed equally.

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Correspondence to Professor Dr U. Nowak-Göttl, Pediatric Hematology and Oncology, University Hospital of Münster, Albert-Schweitzer-Str 33, D-48149 Münster, Germany. E-mail leagottl@uni-muenster.de

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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.² 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 reports^{12,13,17,62,63,67,69,78–81,93,100} and suggest a recurrence rate of $\approx 3\%$ 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 objectively confirmed by suitable imaging methods were included. In addition, to be included, publications must have reported the country of origin, study design, ethnicity, number of patients and controls, type of VTE, number of individuals tested for IT, screening tests performed, and laboratory methods (including criteria for normal/abnormal results). In addition, in children with recurrent events, data on the time to recurrence, VTE type and location of recurrence, associated clinical risk factors, and duration and type of anticoagulation¹¹⁰ were required. Case reports and case series/studies

in which $<50\%$ of cases were systematically screened for IT, publications reporting asymptomatic thrombosis, and studies with unclear laboratory/analytical methodology to differentiate between inherited and acquired deficiency states of protein C, protein S, or antithrombin were not included (except in instances when this distinction was subsequently clarified in personal communication with the responsible authors; only cases with inherited deficiency states were included in the analyses).

Search Strategy

A systematic search of publications listed in the electronic databases (Medline via PubMed, EMBASE, OVID, Web of Science, The Cochrane Library) from 1970 to August 2007 was conducted using the following key words in combination as both MeSH terms and text words: ["deep vein thrombosis" or "thromboembolism" or "venous thromboembolism" or "pulmonary embolism" or "renal venous thrombosis" or "cerebral venous thrombosis" or "anticoagulation" OR "antithrombotic therapy"] and ["neonate" or "infant" or "children" or "child" or "childhood" or "adolescents" or "pediatric" or "pediatric" not "adult"] and ["thrombophilia" or "prothrombotic" or "procoagulant" or "protein C" or "protein S" or "antithrombin" or "factor V" or "activated protein C resistance" or "prothrombin" or "factor II" or "lipoprotein (a)"]. The terms "catheter-related," "central-line-related," and "recurrence" or "recurrent" also were included in the search strategy. In addition, reference lists of journal articles identified through the aforementioned search were searched manually to locate additional studies. The search strategy had no language restrictions. Citations were screened and classified into cohort/case-control, case series, or registry data by 2 independent group members (L.B. and H.v.O.). Those meeting the inclusion criteria were retained. The decision to include or exclude studies was hierarchical, made initially on the basis of the study title, followed by the abstract, and finally the complete body text. In the event of conflicting opinions, resolution was achieved through discussion (L.B., F.F., N.G., J.J., G.K., A.K., M.M.-J., U.N.G., H.v.O., and P.S.).

Data Extraction

To avoid possible double counting of patients included in >1 report by the same authors/working groups, the patient recruitment periods and catchment areas were evaluated, and authors were contacted for clarification. If the required data could not be located in the published report, the corresponding author was asked to provide the missing data of interest. Data extractions were checked for accuracy by multiple reviewers (M.A., L.B., F.F., J.J., G.K., M.M.-J., H.v.O., P.S., and G.Y.).

Study Design Classification

In this meta-analysis, 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.

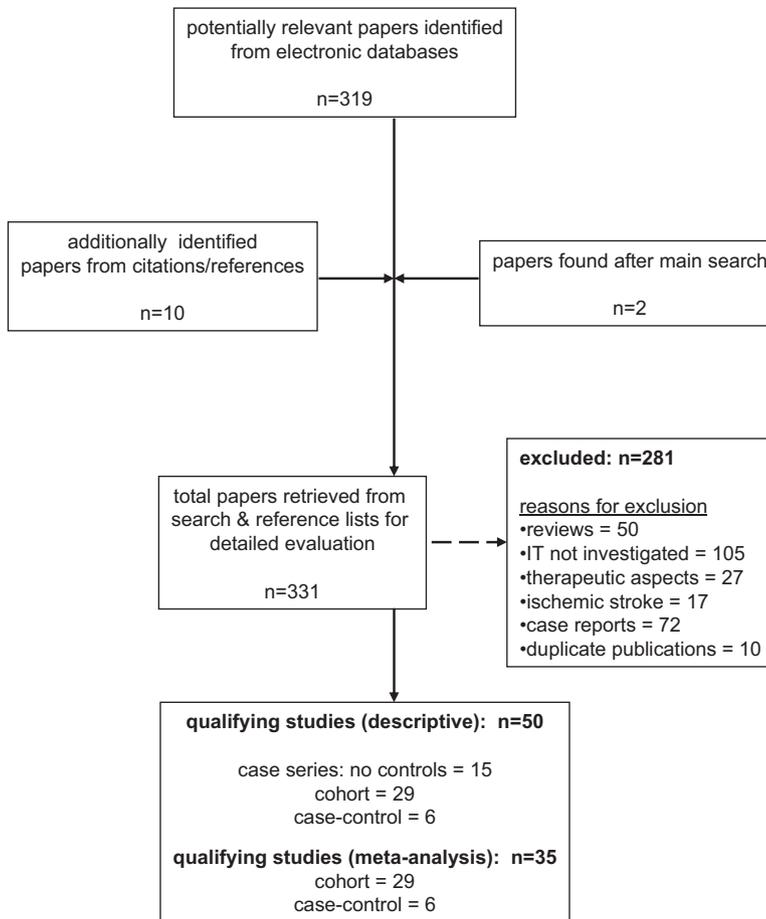


Figure 1. Flow chart showing results of the search strategy and reasons for exclusion.

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 κ 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 ($\kappa=0.90$; $Z=11.08$; $P < 0.001$), and in the analysis of VTE recurrence, the agreement beyond chance (24.8%) was 81.82% ($\kappa=0.76$; $Z=4.91$; $P < 0.001$).

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 anti-thrombin. 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

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

Genetic Traits (No. of Studies)	Patients/Controls, n	OR (95% CI), Fixed Model	OR (95% CI), Random Model	I ² , %	Bias Indicator ¹¹⁴
Protein C deficiency (16)	1079/1979	7.72 (4.440–13.42)	7.75 (4.48–13.38)	0	
<i>P</i>		<0.0001	<0.0001	0.75	0.13
Protein S deficiency (16)	1075/1979	5.77 (3.03–10.97)	5.77 (3.07–10.85)	0	
<i>P</i>		<0.0001	<0.0001	0.92	0.30
Antithrombin deficiency (16)	1072/1979	9.44 (3.34–26.66)	8.73 (3.12–24.42)	0.0	
<i>P</i>		<0.0001	<i>P</i> <0.0001	0.96	0.27
Factor V G1691A (23)	1430/2623	3.77 (2.98–4.77)	3.56 (2.57–4.93)	33.4	
<i>P</i>		<0.0001	<0.0001	0.08	0.78
Factor II G20210A (14)	916/1673	2.64 (1.60–4.41)	2.63 (1.61–4.29)	0	
<i>P</i>		<0.0001	0.0001	0.90	0.71
Lipoprotein(a) (8)	589/1441	4.49 (3.26–6.18)	4.50 (3.19–6.35)	8.3	
<i>P</i>		<0.0001	<0.001	0.36	0.14
≥2 Genetic traits (12)	965/1625	9.5 (4.92–18.39)	8.89 (3.43–23.06)	38.3	
<i>P</i>		<0.0001	<0.0001	0.11	0.57

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

Genetic Traits (No. of Studies)	Patients With Recurrence/Patients With No Recurrence, n	OR (95% CI), Fixed Model	OR (95% CI), Random Model	I ² , %	Bias Indicator ¹¹⁴
Protein C deficiency (13)	152/1296	2.39 (1.21–4.36)	2.53 (1.30–4.92)	0	
<i>P</i>		0.012	0.006	0.74	0.67
Protein S deficiency (11)	132/857	3.12 (1.50–6.45)	3.76 (1.76–8.04)	0	
<i>P</i>		0.001	0.0006	0.51	0.41
Antithrombin deficiency (12)	150/969	3.01 (1.43–6.33)	3.37 (1.57–7.20)	0	
<i>P</i>		0.003	0.001	0.74	0.59
Factor V G1691A (12)	115/1160	0.64 (0.35–1.18)	0.77 (0.40–1.45)	0	
<i>P</i>		0.18	0.42	0.68	0.48
Factor V G1691A including children with idiopathic/spontaneous VTE only (13)	179/1397	1.35 (0.91–1.98)	1.43 (0.91–2.24)	4.3	
<i>P</i>		0.107	0.114	0.40	0.004
Factor II G20210A (12)	171/1397	1.88 (1.01–3.49)	2.15 (1.12–410)	0	
<i>P</i>		0.049	0.020	0.66	0.52
Lipoprotein(a) (6)	135/1020	0.81 (0.49–1.36)	0.84 (0.50–1.40)	0	
<i>P</i>		0.51	0.50	0.90	0.78
≥2 Genetic traits (10)	144/1127	4.46 (2.89–6.89)	4.91 (3.12–7.74)	0.7	
<i>P</i>		0.0001	0.0001	0.43	0.82

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 ≥ 2 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 (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 children^{2,12–14} 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 $\approx 80\%$ 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 ≥ 2 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

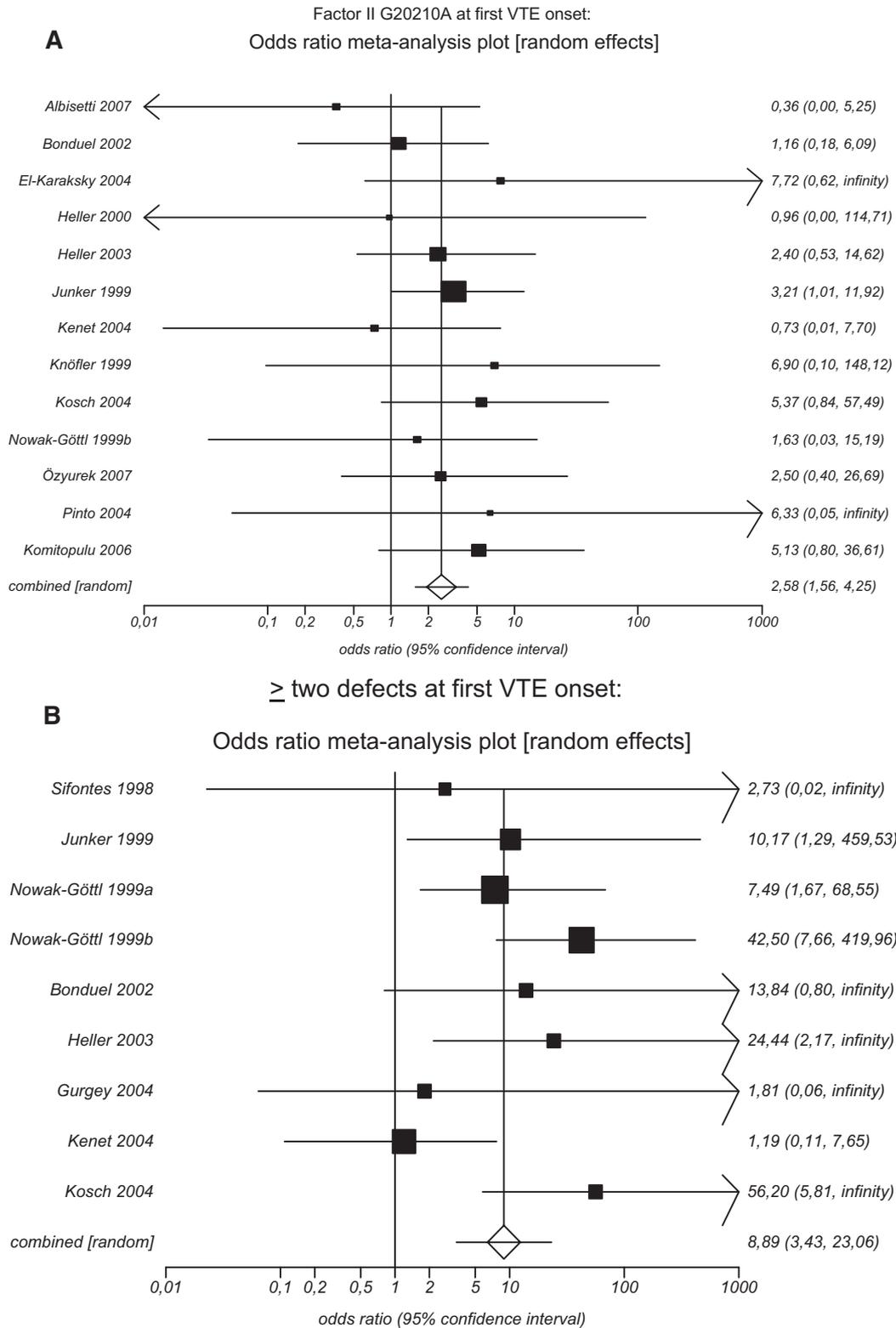


Figure 2. A, The Forest plot shows ORs and 95% CIs for observational studies investigating the influence of the factor II G20210A mutation on the onset of symptomatic venous thromboembolism in children. The study author and year of publication are indicated on the y axis. The box for each study is proportional 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 ≥ 2 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.^{110,125} 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.

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Disclosures

None.

References

1. Goldenberg N, Bernard TJ. Venous thromboembolism in children. *Pediatr Clin N Am*. 2008;55:305–322.
2. Andrew M. Developmental hemostasis: relevance to thromboembolic complications in pediatric patients. *Thromb Haemost*. 1995;74:415–425.
3. Athale UH, Chan AK. Thromboembolic complications in pediatric hematologic malignancies. *Semin Thromb Hemost*. 2007;33:416–426.
4. Journeycake JM, Buchanan GR. Thrombotic complications of central venous catheters in children. *Cur Opin Hematol*. 2003;10:369–374.
5. Newall F, Wallace T, Crock C, Campbell J, Savoia H, Barnes C, Monagle P. Venous thromboembolic disease: a single-centre case series study. *J Paediatr Child Health*. 2006;42:803–807.
6. Schmidt B, Andrew M. Neonatal thrombosis: report of a prospective Canadian and international registry. *Pediatrics*. 1995;96:939–943.
7. Nowak-Göttl U, von Kries R, Göbel U. Neonatal symptomatic thromboembolism in Germany: two year survey. *Arch Dis Child Fetal Neonatal Ed*. 1997;76:F163–F167.
8. Revel-Vilk S, Sharathkumar A, Massicotte P, Marzinotto V, Daneman A, Dix D, Chan A. Natural history of arterial and venous thrombosis in children treated with low molecular weight heparin: a longitudinal study by ultrasound. *J Thromb Haemost*. 2004;2:42–46.
9. Journeycake J, Eshelman D, Buchanan GR. Post-thrombotic syndrome is uncommon in childhood cancer survivors. *J Pediatr*. 2006;148:275–277.
10. Van Ommen CH, Ottenkamp J, Lam J, Hirasing RA, Heijmans HS, Peters M. The risk of postthrombotic syndrome in children with congenital heart disease. *J Pediatr*. 2002;141:582–586.
11. Kuhle S, Koloshuk B, Marzinotto V, Adams M, Bauman M, Massicotte P, Andrew M, Chan A, Abdolell M, Mitchell L. A cross-sectional study evaluating post-thrombotic syndrome in children. *Thromb Res*. 2003;111:227–233.
12. Monagle P, Adams M, Mahoney M, Ali K, Barnard D, Bernstein M, Brisson L, David M, Desai S, Scully MF, Halton J, Israels S, Jardine L, Leaker M, McCusker P, Silvia M, Wu J, Anderson R, Andrew M, Massicotte MP. Outcome of pediatric thromboembolic disease: a report from the Canadian Childhood Thrombophilia Registry. *Pediatr Res*. 2000;47:763–766.
13. van Ommen CH, Heijboer H, Büller HR, Hirasing RA, Heijmans HS, Peters M. Venous thromboembolism in childhood: a prospective two-year registry in the Netherlands. *J Pediatr*. 2001;139:676–681.
14. Kuhle S, Massicotte P, Chan A, Adams M, Abdolell M, de Veber G, Mitchell L. Systemic thromboembolism in children: data from the 1-800-NO-CLOTS Consultation Service. *Thromb Haemost*. 2004;92:722–728.
15. Male C, Mitchell L, Julian J, Vegh P, Joshua P, Adams M, David M, Andrew ME. Acquired activated protein C resistance is associated with lupus anticoagulants and thrombotic events in pediatric patients with systemic lupus erythematosus. *Blood*. 2001;97:844–849.
16. Levy DM, Massicotte MP, Harvey E, Hebert D, Silverman ED. Thromboembolism in paediatric lupus patients. *Lupus*. 2003;12:741–746.
17. Berkun Y, Padeh S, Barash J, Uziel Y, Harel L, Mukamel M, Revel-Vilk S, Kenet G. Antiphospholipid syndrome and recurrent thrombosis in children. *Arthritis Rheum*. 2006;55:850–855.
18. Günes AM, Baytan B, Günay U. The influence of risk factors in promoting thrombosis during childhood: the role of acquired factors. *Pediatr Hematol Oncol*. 2006;23:399–410.
19. Dahlbäck B, Carlsson M, Svensson PJ. Familial thrombophilia due to a previously unrecognized mechanism characterized by poor anticoagulant response to activated protein C: prediction of a cofactor to activated protein C. *Proc Natl Acad Sci U S A*. 1993;90:1004–1008.
20. Bertina RM, Koeleman BP, Koster T, Rosendaal FR, Dirven RJ, de Ronde H, van der Velden PA, Reitsma PH. Mutation in blood coagulation factor V associated with resistance to activated protein C. *Nature*. 1994;369:64–67.
21. Poort SR, Rosendaal FR, Reitsma PH, Bertina RM. A common genetic variation in the 3'-untranslated region of the prothrombin gene is associated with elevated plasma prothrombin levels and an increase in venous thrombosis. *Blood*. 1996;88:3698–3703.
22. Seligsohn U, Zivelin A. Thrombophilia as a multigenic disorder. *Thromb Haemost*. 1997;78:297–301.
23. Salomon O, Steinberg DM, Zivelin A, Gitel S, Dardik R, Rosenberg N, Berliner S, Inbal A, Many A, Lubetsky A, Varon D, Martinowitz U, Seligsohn U. Single and combined prothrombotic factors in patients with idiopathic venous thromboembolism: prevalence and risk assessment. *Arterioscler Thromb Vasc Biol*. 1999;19:511–518.
24. Ehrenforth S, von Depka Prondinski M, Aygören-Pürsün E, Nowak-Göttl U, Scharer I, Ganser A. Study of the prothrombin gene 20201 GA variant in FV:Q⁵⁰⁶ carriers in relationship to the presence or absence of juvenile venous thromboembolism. *Arterioscler Thromb Vasc Biol*. 1999;19:276–280.
25. Prandoni P, Lensing AW, Cogo A, Cuppini S, Villalta S, Carta M, Cattelan AM, Polistena P, Bernardi E, Prins MH. The long-term clinical course of acute deep venous thrombosis. *Ann Intern Med*. 1996;125:1–7.
26. van den Belt AG, Sanson BJ, Simioni P, Prandoni P, Büller HR, Girolami A, Prins MH. Recurrence of venous thromboembolism in patients with familial thrombophilia. *Arch Intern Med*. 1997;157:2227–2232.
27. Sanson BJ, Simioni P, Tormene D, Moia M, Friederich PW, Huisman MV, Prandoni P, Bura A, Rejto L, Wells P, Mannucci PM, Girolami A, Büller HR, Prins MH. The incidence of venous thromboembolism in asymptomatic carriers of a deficiency of antithrombin, protein C, or protein S: a prospective cohort study. *Blood*. 1999;94:3702–3706.
28. Simioni P, Sanson BJ, Prandoni P, Tormene D, Friederich PW, Girolami B, Gavasso S, Huisman MV, Büller HR, Wouter ten Cate J, Girolami A, Prins MH. Incidence of venous thromboembolism in families with inherited thrombophilia. *Thromb Haemost*. 1999;81:198–202.
29. Sofi F, Marcucci R, Abbate R, Gensini GF, Prisco D. Lipoprotein(a) and venous thromboembolism in adults: a meta-analysis. *Am J Med*. 2007;120:728–733.
30. Rees DC. The population genetics of factor V Leiden (Arg 506 Gln). *Br J Haematol*. 1996;95:579–586.

31. Rosendaal FR, Doggen CJ, Zivelin A, Arruda VR, Aiach M, Siscovick DS, Hillarp A, Watzke HH, Bernardi F, Cumming AM, Preston FE, Reitsma PH. Geographic distribution of the G2010A to A prothrombin variant. *Thromb Haemost*. 1998;79:706–708.
32. Pepe G, Rickards O, Vanegas OC, Brunelli T, Gori AM, Giusti B, Attanasio M, Prisco D, Gensini GF, Abbate R. Prevalence of factor V Leiden mutation in non-European populations. *Thromb Haemost*. 1997;77:329–331.
33. Nuss R, Hays T, Manco-Johnson M. Childhood thrombosis. *Pediatrics*. 1995;96:291–294.
34. Nowak-Göttl U, Koch HG, Aschka I, Kohlhasse B, Vielhaber H, Kurlmann G, Oleszczuk-Raschke K, Kehl HG, Jürgens H, Schneppenheim R. Resistance to activated protein C (APCR) in children with venous or arterial thromboembolism. *Br J Haematol*. 1996;92:992–998.
35. Ashka I, Aumann V, Bergmann F, Budde U, Eberl W, Eckhof-Donovan S, Krey S, Nowak-Göttl U, Schobess R, Sutor AH, Wendisch J, Schneppenheim R. Prevalence of factor V Leiden in children with thromboembolism. *Eur J Pediatr*. 1996;155:1009–1014.
36. Gürgey A, Mesci L, Renda Y, Olcay L, Kocak N, Erdem G. Factor V Q506 mutation in children with thrombosis. *Am J Hematol*. 1996;53:37–39.
37. Sifontes MT, Nuss R, Jacobson LJ, Griffin JH, Manco-Johnson MJ. Thrombosis in otherwise well children with the factor V Leiden mutation. *J Pediatr*. 1996;128:324–328.
38. Uttenreuther-Fischer MM, Vetter B, Hellmann C, Otting U, Ziemer S, Hausdorf G, Gaedicke G, Kulozik AE. Paediatric thromboembolism: the influence of non-genetic factors and the role of activated protein C resistance and protein C deficiency. *Eur J Pediatr*. 1997;156:277–281.
39. Sifontes MT, Nuss R, Hunger SP, Wilimas J, Jacobson LJ, Manco-Johnson MJ. The factor V Leiden mutation in children with cancer and thrombosis. *Br J Haematol*. 1997;96:484–489.
40. Toumi NH, Khaldi F, Ben Becheur S, Hammou A, Bouttière B, Sampol J, Boukef K. Thrombosis in congenital deficiencies of AT III, protein C or protein S: a study of 44 children. *Hematol Cell Ther*. 1997;39:295–299.
41. Nowak-Göttl U, Dübbers A, Kececioglu D, Koch HG, Kotthoff S, Runde J, Vielhaber H. Factor V Leiden, protein C, and lipoprotein(a) in catheter-related thrombosis in childhood: a prospective study. *J Pediatr*. 1997;131:608–612.
42. Seixas CA, Hessel G, Ribeiro CC, Arruda VR, Annichino-Bizzacchi JM. Factor V Leiden is not common in children with portal vein thrombosis. *Thromb Haemost*. 1997;77:1297–1298.
43. Fabri D, Belangero VM, Annichino-Bizzacchi JM, Arruda VR. Inherited risk factors for thrombophilia in children with nephrotic syndrome. *Eur J Pediatr*. 1998;157:939–942.
44. Sifontes MT, Nuss R, Hunger SP, Waters J, Jacobsen LJ, Manco-Johnson M. Activated protein C resistance and the factor V Leiden mutation in children with thrombosis. *Am J Hematol*. 1998;57:29–32.
45. deVeber G, Monagle P, Chan A, MacGregor D, Curtis R, Lee S, Vegh P, Adams M, Marzinotto V, Leaker M, Massicotte P, Lillcrap D, Andrew M. Prothrombotic disorders in infants and children with cerebral thromboembolism. *Arch Neurol*. 1998;55:1539–1543.
46. Hagstrom JN, Walter J, Bluebond-Langner R, Amatnick JC, Manno CS, High KA. Prevalence of the factor V Leiden mutation in children and neonates with thromboembolic disease. *J Pediatr*. 1998;133:777–781.
47. Vielhaber H, Ehrenforth S, Koch HG, Scharrer I, van der Werf N, Nowak-Göttl U. Cerebral venous thrombosis in infancy and childhood: role of genetic and acquired risk factors of thrombophilia. *Eur J Pediatr*. 1998;157:555–560.
48. Knöfler R, Siegert E, Lauterbach I, Taut-Sack H, Siegert G, Gehrlich S, Müller D, Rupperecht E, Kabus M. Clinical importance of prothrombotic risk factors in pediatric patients with malignancy: impact of central venous lines. *Eur J Pediatr*. 1999;158(suppl 3):S147–S150.
49. Ehrenforth S, Junker R, Koch HG, Kreuz W, Münchow N, Scharrer I, Nowak-Göttl U. Multicentre evaluation of combined prothrombotic defects associated with thrombophilia in childhood: Childhood Thrombophilia Study Group. *Eur J Pediatr*. 1999;158:S97–S104.
50. Schobess R, Junker R, Auberger K, Münchow N, Burdach S, Nowak-Göttl U. Factor V G1691A and prothrombin G20210A in childhood spontaneous venous thrombosis: evidence of an age-dependent thrombotic onset in carriers of the factor V G1691A and prothrombin G20210A mutation. *Eur J Pediatr*. 1999;158:S105–S108.
51. Münchow N, Kosch A, Schobess R, Junker R, Auberger K, Nowak-Göttl U. Role of genetic prothrombotic risk factors in childhood caval vein thrombosis. *Eur J Pediatr*. 1999;158(suppl 3):S109–S112.
52. Nowak-Göttl U, Junker R, Hartmeier M, Koch HG, Münchow N, Assmann G, von Eckardstein A. Increased lipoprotein(a) is an important risk factor for venous thromboembolism in childhood. *Circulation*. 1999;100:743–748.
53. Nowak-Göttl U, Wermes C, Junker R, Koch HG, Schobess R, Fleischhack G, Schwabe D, Ehrenforth S. Prospective evaluation of the thrombotic risk in children with acute lymphoblastic leukemia carrying the MTHFR TT677 genotype, the prothrombin G20210A variant, and further prothrombotic risk factors. *Blood*. 1999;93:1595–1599.
54. Bonduel M, Sciuccati G, Hepner M, Torres AF, Pieroni G, Frontroth JP. Prothrombotic disorders in children with arterial ischemic stroke and sinovenous thrombosis. *Arch Neurol*. 1999;56:967–971.
55. Heller C, Becker S, Scharrer I, Kreuz W. Prothrombotic risk factors in childhood stroke and venous thrombosis. *Eur J Pediatr*. 1999;158(suppl 3):S117–S121.
56. Lawson SE, Butler D, Enayat MS, Williams MD. Congenital thrombophilia and thrombosis: a study in a single centre. *Arch Dis Child*. 1999;81:176–178.
57. Salomvaara M, Riikonen P, Kekomäki R, Heinonen K. Clinically symptomatic central venous catheter-related deep venous thrombosis in newborns. *Acta Paediatr*. 1999;88:642–646.
58. Junker R, Koch HG, Auberger K, Münchow N, Ehrenforth S, Nowak-Göttl U. Prothrombin G20210A gene mutation and further prothrombotic risk factors in childhood thrombophilia. *Arterioscler Thromb Vasc Biol*. 1999;19:2568–2572.
59. Heller C, Schobess R, Kurnik K, Junker R, Günther G, Kreuz W, Nowak-Göttl U. Abdominal venous thrombosis in neonates and infants: role of prothrombotic risk factors: a multicentre case-control study: for the Childhood Thrombophilia Group. *Br J Haematol*. 2000;111:534–539.
60. Kosch A, Junker R, Kurnik K, Schobess R, Günther G, Koch HG, Nowak-Göttl U. Prothrombotic risk factors in children with spontaneous venous thrombosis and their asymptomatic parents: a family study. *Thromb Res*. 2000;99:531–537.
61. Kuhle S, Lane DA, Jochmanns K, Male C, Quehenberger P, Lechner K, Pabinger I. Homozygous antithrombin deficiency type II (99 Leu to Phe mutation) and childhood thromboembolism. *Thromb Haemost*. 2001;86:1007–1011.
62. Bonduel M, Hepner M, Sciuccati G, Torres AF, Pieroni G, Frontroth JP. Prothrombotic abnormalities in children with venous thromboembolism. *J Pediatr Hematol Oncol*. 2000;22:66–672.
63. Nowak-Göttl U, Junker R, Kreuz W, von Eckardstein A, Kosch A, Nohe N, Schobess R, Ehrenforth S, for the Childhood Thrombophilia Study Group. Risk of recurrent venous thrombosis in children with combined prothrombotic risk factors. *Blood*. 2001;97:858–862.
64. De Veber G, Andrew M, Adams C, Bjornson B, Booth F, Buckley DJ, Camfield CS, David M, Humphreys P, Langevin P, MacDonald AE, Gillett J, Meaney B, Shevell M, Sinclair DB, Yager J. Cerebral sinovenous thrombosis in children. *N Engl J Med*. 2001;345:417–423.
65. Bonduel M, Hepner M, Sciuccati G, Pieroni G, Feliú-Torres A, Mardaraz C, Frontroth JP. Factor V Leiden and prothrombin gene G20210A mutation in children with venous thromboembolism. *Thromb Haemost*. 2002;87:972–977.
66. Atalay S, Akar N, Tutar HE, Yilmaz E. Factor V 1691 G-A mutation in children with intracardiac thrombosis: a prospective study. *Acta Paediatr*. 2002;91:168–171.
67. Revel-Vilk S, Chan A, Bauman M, Massicotte P. Prothrombotic conditions in an unselected cohort of children with venous thromboembolic disease. *J Thromb Haemost*. 2003;1:915–921.
68. Bonduel M, Sciuccati G, Hepner M, Pieroni G, Torres AF, Mardaraz C, Frontroth JP. Factor V Leiden and prothrombin gene G20210A mutation in children with cerebral thromboembolism. *Am J Hematol*. 2003;73:81–86.
69. Van Ommen CH, Heijboer H, van den Dool EJ, Hutten BA, Peters M. Pediatric venous thromboembolic disease in one single center: congenital prothrombotic disorders and the clinical outcome. *J Thromb Haemost*. 2003;1:2516–2522.
70. Lee ACW, Li CH, Szeto SC, Ma ES. Symptomatic venous thromboembolism in Hong Kong Chinese children. *Hong Kong Med J*. 2003;9:259–262.
71. Young G, Manco-Johnson M, Gill JC, Dimichele DM, Tarantino MD, Abshire T, Nugent DJ. Clinical manifestations of the prothrombin G20210A mutation in children: a pediatric coagulation consortium study. *J Thromb Haemost*. 2003;1:958–962.

72. Atasay B, Arsan S, Günlemez A, Kemhali S, Akar N. Factor V Leiden and prothrombin gene 20210A variant in neonatal thromboembolism and in healthy neonates and adults: a study in a single center. *Pediatr Hematol Oncol*. 2003;20:627–634.
73. Heller C, Heinecke A, Junker R, Knöfler R, Kosch A, Kurnik K, Schobess R, von Eckardstein A, Sträter R, Zieger B, Nowak-Göttl U. Cerebral venous thrombosis in children: a multifactorial origin. *Circulation*. 2003;108:1362–1367.
74. El-Karaksy H, El-Koofy N, El-Hawary M, Mostafa A, Aziz M, El-Sonoon MA, A-Kadar H. Prevalence of factor V Leiden mutation and other hereditary thrombophilic factors in Egyptian children with portal vein thrombosis: results of a single-center case-control study. *Ann Hematol*. 2004;83:712–715.
75. Levy ML, Granville RC, Hart D, Meltzer H. Deep venous thrombosis in children and adolescents. *J Neurosurg*. 2004;101:32–37.
76. Gürgey A, Balta G, Gumruk F, Altay C. Analysis of some clinical and laboratory aspects of adolescent patients with thrombosis. *Blood Coagul Fibrinol*. 2004;15:657–662.
77. Pinto RB, Silveira TR, Bandinelli E, Röhsig L. Portal vein thrombosis in children and adolescents: the low prevalence of hereditary thrombophilic disorders. *J Pediatr Surg*. 2004;39:1356–1361.
78. Kenet G, Waldman D, Lubetsky A, Kornbrut N, Khalil A, Koren A, Wolach B, Fattal A, Kapelushnik J, Tamary H, Yacobovitch J, Raveh E, Revel-Vilk S, Toren A, Brenner B. Paediatric cerebral sinus vein thrombosis: a multi-center, case-controlled study. *Thromb Haemost*. 2004;92:713–718.
79. Goldenberg NA, Knapp-Clevenger R, Manco-Johnson MJ, for the Mountain States Regional Thrombophilia Group. Elevated plasma factor VIII and D-dimer levels as predictors of poor outcomes of thrombosis in children. *N Engl J Med*. 2004;351:1081–1088.
80. Kosch A, Kuwertz-Bröking E, Heller C, Kurnik K, Schobess R, Nowak-Göttl U. Renal venous thrombosis in neonates: prothrombotic risk factors and long-term follow-up. *Blood*. 2004;104:1356–1360.
81. Ören H, Devecioglu O, Ertem M, Vergin C, Kavakli K, Meral A, Canatan D, Toksoy H, Yildiz I, Küreci E, Özgen Ü, Önez H, Gürgey A. Analysis of pediatric thrombosis patients in Turkey. *Pediatr Hematol Oncol*. 2004;21:573–583.
82. Rask O, Berntorp E, Ljung R. Risk factors for venous thrombosis in Swedish children and adolescents. *Acta Paediatr*. 2005;94:717–722.
83. Gupta PK, Ahmed RP, Bhattacharyya M, Kannan M, Biswas A, Kalra V, Saxena R. Protein C system defects in Indian children with thrombosis. *Ann Hematol*. 2005;84:85–88.
84. Sébire G, Tabarki B, Saunders DE, Leroy I, Liesner R, Saint-Martin C, Husson B, Williams AN, Wade A, Kirkham FJ. Cerebral venous sinus thrombosis in children: risk factors, presentation, diagnosis and outcome. *Brain*. 2005;128:477–489.
85. Ünal S, Varan A, Yalcin B, Büyükpamukcu M, Gürgey A. Evaluation of thrombotic children with malignancy. *Ann Hematol*. 2005;84:395–399.
86. Marks SD, Massicotte P, Steele BT, Matsell DG, Filler G, Shah PS, Perlman M, Rosenblum ND, Shah VS. Neonatal renal venous thrombosis: clinical outcomes and prevalence of prothrombotic disorders. *J Pediatr*. 2005;146:811–816.
87. Gonzalez BE, Teruya J, Mahoney DH Jr, Hulten KG, Edwards R, Lamberth LB, Hammerman WA, Mason EO Jr, Kaplan SL. Venous thrombosis associated with staphylococcal osteomyelitis in children. *Pediatrics*. 2006;117:1673–1679.
88. Raffini LJ, Raybagkar D, Blumenstein MS, Rubenstein RC, Manno CS. Cystic fibrosis as a risk factor for recurrent venous thrombosis at a pediatric tertiary care hospital. *J Pediatr*. 2006;148:659–664.
89. Bonduel M, Sciuccati G, Hepner M, Pieroni G, Torres AF, Fronthof JP, Tenenbaum S. Arterial ischemic stroke and cerebral venous thrombosis in children: a 12-year Argentinean registry. *Acta Haematol*. 2006;115:180–185.
90. Morag I, Epelman M, Daneman A, Moineddin R, Parvez B, Shechter T, Hellmann J. Portal vein thrombosis in the neonate: risk factors, course, and outcome. *J Pediatr*. 2006;148:735–739.
91. Brandão LR, Williams S, Kahr WH, Ryan C, Temple M, Chan AK. Exercise-induced deep vein thrombosis of the upper extremity, 2: a case series in children. *Acta Haematol*. 2006;115:214–220.
92. Tavil B, Ozyurek E, Gumruk F, Cetin M, Gurgey A. Antiphospholipid antibodies in Turkish children with thrombosis. *Blood Coagul Fibrinol*. 2007;18:347–352.
93. Kreuz W, Stoll M, Junker R, Heinecke A, Schobess R, Kurnik K, Kelsch R, Nowak-Göttl U. Familial elevated factor VIII in children with symptomatic venous thrombosis and post-thrombotic syndrome: results of a multicenter study. *Arterioscler Thromb Vasc Biol*. 2006;26:1901–1906.
94. Sharma S, Kumar SI, Poddar U, Yaachha SK, Aggarwal R. Factor V Leiden and prothrombin gene G20210A mutations are uncommon in portal vein thrombosis in India. *Indian J Gastroenterol*. 2006;25:236–239.
95. Komitopoulou A, Platokouki H, Kapsimali Z, Moschovi M, Kattamis A. Mutation and polymorphisms in genes affecting haemostasis components in children with thromboembolic events. *Pathophysiol Haemost Thromb*. 2006;35:392–397.
96. Winyard PJD, Bharucha T, de Bruyn R, Dillon MJ, van't Hoff W, Trompeter RS, Liesner R, Wade A, Rees L. Perinatal renal venous thrombosis: presenting renal length predicts outcome. *Arch Dis Child Fetal Neonatal Ed*. 2006;91:F273–F278.
97. Tormene D, Gavasso S, Rossetto V, Simioni P. Thrombosis and thrombophilia in children: a systematic review. *Semin Thromb Hemost*. 2006;32:724–728.
98. Gentilomo C, Franzoi M, Laverda AM, Suppiej A, Battistella PA, Simioni P. Cerebral sinovenous thrombosis in children: thrombophilia and clinical outcome. *Thromb Res*. 2008;121:589–591.
99. Albisetti M, Moeller A, Waldvogel K, Bernet-Buettiker V, Cannizzaro V, Anagnostopoulos A, Balmer C, Schmutge M. Congenital prothrombotic disorders in children with peripheral venous and arterial thromboses. *Acta Haematol*. 2007;117:149–155.
100. Kenet G, Kirkham F, Niederstadt T, Heinecke A, Saunders D, Stoll M, Brenner B, Bidlingmaier C, Heller C, Knöfler R, Schobess R, Zieger B, Sébire G, Nowak-Göttl U. Risk factors for recurrent venous thromboembolism in the European collaborative paediatric database on cerebral venous thrombosis: a multicentre cohort study. *Lancet Neurol*. 2007;6:595–603.
101. Özyurek E, Balta G, Degerliyurt A, Parlak H, Aysun S, Gürgey A. Significance of factor V, prothrombin, MTHFR, and PAI-1 genotypes in childhood cerebral thrombosis. *Clin Appl Thromb Hemost*. 2007;13:154–160.
102. Tormene D, Simioni S, Prandoni P, Franz F, Zerbinati P, Tognin G, Girolami A. The incidence of venous thromboembolism in thrombophilic children: a prospective cohort study. *Blood*. 2002;100:2403–2405.
103. Sass AE, Neufeld EJ. Risk factors for thromboembolism teens: when should I test? *Curr Opin Pediatr*. 2002;14:370–378.
104. Williams MD, Chalmers E, Gibson BES. Guideline: the investigation and management of neonatal haemostasis and thrombosis. *Br J Haematol*. 2002;119:295–309.
105. Ruud E, Holmström H, Brosstad F, Wesenberg F. Diagnostic value of family histories of thrombosis to identify children with thrombophilia. *Pediatr Hematol Oncol*. 2005;22:453–462.
106. Johal SC, Garg BP, Heiny ME, LS, Saha C, Walsh LE, Golomb MR. Family history is a poor screen for prothrombotic genes in children with stroke. *J Pediatr*. 2006;148:68–71.
107. Dietrich JE, Hertweck SP, Perlman SE. Efficacy of familial history in determining thrombophilia risk. *J Pediatr Adolesc Gynecol*. 2007;20:221–224.
108. Gürgey A, Aslan D. Outcome of non-catheter-related thrombosis in children: influence of underlying or coexisting factors. *J Pediatr Hematol/Oncol*. 2001;23:159–164.
109. Vandenbroucke JP, von Elm E, Altman DG, Gotzsche PC, Mulrow CD, Pocock SJ, Poole C, Schlesselman JJ, Egger M. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. *Ann Intern Med*. 2007;147:W163–W194.
110. Monagle P, Chan A, Chalmers E, Michelson AD. Antithrombotic therapy in children: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest*. 2004;126:S645–S687.
111. Mayer D. *Essential Evidence-Based Medicine*. New York, NY: Cambridge University Press; 2004:347–360.
112. Kirkwood BR, Sterne JAC. *Medical Statistics*. 2nd ed. Boston, Mass: Blackwell Science; 2003:180–387.
113. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analysis. *BMJ*. 2003;327:557–560.
114. Harbord RM, Egger M, Sterne JAC. A modified test for small-study effects in meta-analyses of controlled trials with binary endpoints. *Stat Med*. 2006;25:3443–3457.
115. Gürgey A, Mesci L. The prevalence of factor V Leiden (1691 G-A) mutation in Turkey. *Turk J Pediatr*. 1997;39:313–315.
116. Gürgey A, Hicsönmez G, Parlak H, Günay B, Celiker A. The prothrombin gene 20210 G-A mutation in Turkish patients with thrombosis. *Am J Hematol*. 1998;59:179–180.

117. Caruso V, Iacoviello L, Di Castelnuovo A, Storti S, Mariani G, de Gaetano G, Donati MB. Thrombotic complications in childhood acute lymphoblastic leukemia: a meta-analysis of 17 prospective studies comprising 1752 pediatric patients. *Blood*. 2006;108:2216–2222.
118. Haywood S, Liesner R, Pindora S, Ganesan V. Thrombophilia and first ischaemic stroke: a systematic review. *Arch Dis Child*. 2005;90:402–405.
119. Vossen CY, Walker ID, Svensson P, Souto JC, Scharrer I, Preston FE, Palaretti G, Pabinger I, van der Meer FJ, Makris M, Fontcuberta J, Conard J, Rosendaal FR. Recurrence rate after first venous thrombosis in patients with familial thrombophilia. *Arterioscler Thromb Vasc Biol*. 2005;25:1992–1997.
120. De Stefano V, Rossi E, Paciaroni K, Leone G. Screening for inherited thrombophilia: indications and therapeutic implications. *Haematologica*. 2002;87:1095–1108.
121. Prandoni P, Noventa F, Ghirarduzzi A, Pengo V, Bernardi E, Pesavento R, Iotti M, Tormene D, Simioni P, Pagnan A. The risk of recurrent venous thromboembolism after discontinuing anticoagulation in patients with acute proximal deep vein thrombosis or pulmonary embolism: a prospective cohort study in 1,626 patients. *Haematologica*. 2007;92:199–205.
122. González-Porras JR, García-Sanz R, Alberca I, López ML, Balanzategui A, Gutierrez O, Lozano F, San Miguel J. Risk of recurrent venous thrombosis in patients with G20210A mutation in the prothrombin gene or factor V Leiden mutation. *Blood Coagul Fibrinol*. 2006;17:23–28.
123. De Stefano V, Simioni P, Rossi E, Tormene D, Za T, Pagnan A, Leone G. The risk of recurrent venous thromboembolism in patients with inherited deficiency of natural anticoagulants antithrombin, protein C, and protein S. *Haematologica*. 2006;91:695–698.
124. Ho WK, Hankey GJ, Quinlan DJ, Eikelboom JW. Risk of recurrent venous thromboembolism in patients with common thrombophilia: a systematic review. *Arch Intern Med*. 2006;166:729–736.
125. Büller H, Agnelli G, Hull RD, Hyres TM, Prins M, Raskob GE. Antithrombotic therapy for venous thromboembolic disease: the seventh ACCP conference on antithrombotic and thrombolytic therapy. *Chest*. 2004;126:S401–S428.

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.