Impact of Thrombophilia on Risk of Arterial Ischemic Stroke or Cerebral Sinovenous Thrombosis in Neonates and Children

A Systematic Review and Meta-Analysis of Observational Studies

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Background—The aim of this study was to estimate the impact of thrombophilia on risk of first childhood stroke through a meta-analysis of published observational studies.

Methods and Results—A systematic search of electronic databases (Medline via PubMed, EMBASE, OVID, Web of Science, The Cochrane Library) for studies published from 1970 to 2009 was conducted. Data on year of publication, study design, country of origin, number of patients/control subjects, ethnicity, stroke type (arterial ischemic stroke [AIS], cerebral venous sinus thrombosis [CSVT]) were abstracted. Publication bias indicator and heterogeneity across studies were evaluated, and summary odds ratios (ORs) and 95% confidence intervals (CIs) were calculated with fixed-effects or random-effects models. Twenty-two of 185 references met inclusion criteria. Thus, 1764 patients (arterial ischemic stroke [AIS], 1526; cerebral sinus venous thrombosis [CSVT], 238) and 2799 control subjects (neonate to 18 years of age) were enrolled. No significant heterogeneity was discerned across studies, and no publication bias was detected. A statistically significant association with first stroke was demonstrated for each thrombophilia trait evaluated, with no difference found between AIS and CSVT. Summary ORs (fixed-effects model) were as follows: antithrombin deficiency, 7.06 (95% CI, 2.44 to 22.42); protein C deficiency, 8.76 (95% CI, 4.53 to 16.96); protein S deficiency, 3.20 (95% CI, 1.22 to 8.40), factor V G1691A, 3.26 (95% CI, 2.59 to 4.10); factor II G20210A, 2.43 (95% CI, 1.67 to 3.51); *MTHFR* C677T (AIS), 1.58 (95% CI, 1.20 to 2.08); antiphospholipid antibodies (AIS), 6.95 (95% CI,

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3.67 to 13.14); elevated lipoprotein(a), 6.27 (95% CI, 4.52 to 8.69), and combined thrombophilias, 11.86 (95% CI, 5.93 to 23.73). In the 6 exclusively perinatal AIS studies, summary ORs were as follows: factor V, 3.56 (95% CI, 2.29 to 5.53); and factor II, 2.02 (95% CI, 1.02 to 3.99).

Conclusions—The present meta-analysis indicates that thrombophilias serve as risk factors for incident stroke. However, the impact of thrombophilias on outcome and recurrence risk needs to be further investigated. **(*Circulation*. 2010;121:1838–1847)**

Key Words: cerebrovascular disorders ■ meta-analysis ■ pediatrics ■ thrombophilia

The incidence of stroke in neonates and children (arterial ischemic stroke [AIS] or cerebral sinus venous thrombosis [CSVT]) is estimated to be between 2.6 and 6.4 per 100 000 per year, reflecting a trend toward a higher frequency in more current literature.[1–3] Underlying conditions in children with symptomatic cerebrovascular accidents include congenital heart malformations, hemolytic anemias, and collagen vascular diseases, as well as some rare inborn metabolic disorders.[4] In addition, risk factors include trauma and infectious diseases. Apart from acquired thrombophilic risk factors such as the presence of antiphospholipid antibodies,[5,6] inherited thrombophilia, particularly antithrombin, protein C, and protein S deficiency, variants of coagulation factor V (G1691A) and factor II (G20210A), and elevated lipoprotein(a), have been found in small case series and case-control studies to be associated with AIS or CSVT in infants and children.[7–52] Furthermore, an association of the thermolabile *MTHFR C677T* genotype with stroke is controversial in both adults and children.[5353] In fact, the increased likelihood of having a blood clot in the vasculature is related to elevated homocysteine levels, and mutations in the *MTHFR* gene only exploit their effect by contributing to the elevated homocysteine plasma level. Because adequate folate levels essentially cancel out the impaired regulation of homocysteine induced by *MTHFR* mutations, not all people will develop high homocysteine levels.[53–56]

Editorial see p 1795
Clinical Perspective on p 1847

Investigation of the influence of thrombophilia on first-episode stroke has recently begun to adopt the paradigm of pediatric cerebrovascular disease as a multifactorial disorder.[4] Over the past 3 years, research in pediatric stroke has emphasized not only single gene associations but also heritability of coagulation factors,[57] candidate gene polymorphisms, and haplotype associations.[58–60] The results of these individual studies on the risk of stroke onset associated with thrombophilia have been contradictory or inconclusive, mainly because of a lack of statistical power.[7–61]

Because in the pediatric age group it is unknown whether outcomes in children are affected by thrombophilia, it remains controversial whether stroke onset and outcomes in children with thromboembolism or offspring from thrombosis-prone parents benefit from screening for thrombophilia.[62–67] The aim of this systematic review and meta-analysis was to determine the impact of thrombophilia on first-episode stroke in children as a prerequisite to the evaluation of primary prevention efforts against stroke in children from families with thrombophilia.

Methods

This systematic review was performed in accordance with the Meta-Analysis of Observational Studies in Epidemiology and the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.[68,69]

Inclusion/Exclusion Criteria

Published studies of stroke in children <18 years of age from 1970 through June 2009 were evaluated for inclusion if the frequency of ≥1 thrombophilia traits was individually investigated in a given stroke cohort (descriptive analysis) and if the frequency of thrombophilia traits was compared between patients with AIS/CSVT and control subjects with no history of stroke in a given study (meta-analysis). Only pediatric stroke cases objectively confirmed by suitable imaging methods were included. In addition, for inclusion, publications must have reported the country of origin, study design, ethnicity, numbers of patients/control subjects, type of stroke, number of individuals tested for thrombophilia, screening tests performed, and laboratory methods (including criteria for normal/abnormal results). Case reports and case series/studies in which <90% of cases were systematically screened for thrombophilia and studies with unclear laboratory/analytic 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 June 2009 was conducted using the following key words in combination as both MeSH terms and text words: (“stroke” or “cerebral vein thrombosis” or “sinovenous thrombosis” or “sinus thrombosis” or “thromboembolism” or “anticoagulation” or “antithrombotic therapy”) and (“perinatal” or “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)” or “antiphospholipid antibodies” or “lupus anticoagulants” or “anticardiolipin”). In addition, reference lists of journal articles identified through the aforementioned search were then manually searched 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 C.H.v.O.).[70] Those meeting the inclusion criteria were retained. The decision to include or exclude studies was hierarchical, initially based on the study title, followed by the abstract and finally the complete body text. In the event of conflicting opinions, resolution was achieved though discussion.

Data Extraction

To avoid possible double counting of patients included in >1 report of 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 contacted to provide the missing data of interest. Data extractions were checked for accuracy by multiple authors (L.B., G.G., R.J., S.H., F.J.K., G.K., C.H.v.O., L.R., and U.N.-G.).

Missing Data

Studies in which symptomatic pediatric stroke patients were not screened for thrombophilia or studies in which the thrombophilia screening was <90% of cases or only in sporadic cases were not included in the present meta-analysis. For series in which the percentage of patients screened was not clear from the article, authors were asked for clarification.

Statistical Analyses

Data analyses were performed with STATA version 9 update (College Station, Tex), StatsDirect version 2.6.6 update (Altrincham, UK; www.statsdirect.com), and Comprehensive Meta-Analysis version 2.2.046 (Biostat Inc, Englewood, NJ). Continuous data are presented as median (minimum to maximum) values. For meta-analysis, summary odds ratios (ORs) and 95% confidence intervals (CIs) were calculated from the effect estimates of the individual studies weighted by standard error using a fixed-effects model (weighting each estimate by its standard error via the Mantel and Haenszel method) or a random-effects model (estimating between-study variance in effect measures according to DerSimonian and Laird)[71]; the latter approach was used to control for heterogeneity according to Higgins et al.[72] Data were pooled and ORs were calculated separately for AIS and CSVT because of their different physiologies (AIS, high flow and pulsatile with platelet-rich thrombi; CSVT, low flow and nonpulsatile with fibrin-rich thrombi) and for age groups (perinatal/neonatal versus older children). It was prespecified that we would proceed to calculate an overall pooled OR in case of statistically overlapping results for the previous separate analyses. For both the factor V and factor II variants, AA and GA alleles (ie, homozygosity and heterozygosity for A alleles) were analyzed together and compared with the absence of these genotypes as reference category. A value of $P<0.05$ was considered statistically significant. In addition, we assessed noncombinability of studies (Cochran Q test) and heterogeneity among studies using I^2 statistics: When $P<0.05$, noncombinability of studies was considered statistically significant, and when $I^2>50\%$, the magnitude of heterogeneity was considered substantial. Funnel (bias assessment) plots of effect size against standard error and a modified linear regression test were used to describe the presence of publication bias.[73] Furthermore, we assessed the robustness of our pooled estimates by performing a sensitivity analysis obtained by including/excluding studies with sample size above/below the median sample size and a meta-regression analysis of study effect size versus study sample size.

Of note, subject numbers for the analyses differ in the tables relative to the tables in the online-only Data Supplement because of the reliance on "zero" in the case/control population. The authors had full access to and take full responsibility for the integrity of the data. All authors gave their approval for submission of the final manuscript.

Results

Descriptive Analyses

From 185 potentially relevant citations ascertained from electronic databases and searches of reference lists, 22 cohort studies from 8 countries finally met the inclusion criteria for descriptive analysis (Figure 1 and Table Ia through Ic of the online-only Data Supplement).

Studies investigating thrombophilia at first episode of stroke are shown in Table Ia through Ic of the online-only Data Supplement. Ten of the 22 studies reported inherited deficiency states of protein C, protein S, or antithrombin. In these studies, 1031 patients with a first stroke onset and 1397 control children were investigated (Table Ia of the online-only Data Supplement).

Beginning in 1998, the factor V and factor II variants were systematically investigated in childhood stroke (22 studies; Table Ib of the online-only Data Supplement). In addition, studies reporting data on antiphospholipid antibodies/lupus anticoagulants (8 studies; 930 children versus 1096 control subjects) and combined thrombophilias (12 studies; 926 children versus 1416 control subjects) are summarized in Table Ic of the online-only Data Supplement; here, we have added data on elevated lipoprotein(a), a thrombogenic parameter that was investigated exclusively in a controlled design in German children with stroke.

Meta-Analyses

In 22 of 185 studies, eligible data on first-episode stroke children and population-based control subjects were reported. Tables 1 (AIS), 2 (CSVT), and 3 (AIS and CSVT) summarize the presence of antiphospholipid antibodies/lupus anticoagulants and 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 or random-effects model. In addition, results of testing for heterogeneity and noncombinability are shown. Publication bias also was calculated when >4 studies were pooled. No significant heterogeneity, noncombinability, or publication bias was discerned across studies. Borderline-significant heterogeneity was found for protein S (first AIS) and combination of genetic traits (first CSVT). Random-effects estimates were provided for those sets of studies. Age group (perinatal/neonatal versus older children) did not significantly affected the OR, so only the pooled analysis is reported.

A statistically significant association with stroke was demonstrated for each thrombophilia trait evaluated in the entire patient cohort (and for combined genetic traits), with summary ORs ranging from 1.58 (95% CI, 1.20 to 2.08) for the *MTHFR T677T* genotype (available for patients with AIS only) to 9.31 (95% CI, 4.81 to 18.02) for protein C deficiency. For perinatal AIS, 6 studies were available. Summary ORs were as follows: factor V G1691A, 3.56 (95% CI, 2.29 to 5.53); and factor II G20210A, 2.02 (95% CI, 1.02 to 3.99).

Forest plots under fixed-effects models show that pediatric carriers of the factor V G1691A mutation (Figure 2A), the factor II G20210A variant (Figure 2B), and acquired antiphospholipid antibodies (Figure 2C, AIS only) had an increased risk of developing a first symptomatic stroke. As shown exemplarily for factor V G1691A carriers, the cumulative meta-analysis did not show any significant change over time of the mean risk estimate (Figure 3). Forest plots (random-effects model) for perinatal/neonatal AIS/CVST[5,13,27,30,35,58] are shown for factor V G1691A and factor II G20210A in Figure Ia and Ib of the online-only Data Supplement. Funnel plots (bias assessment) of effect size against standard error were explored for each parameter investigated and were broadly symmetrical, which was consistent with the conclusion that there was no major publication bias (As an example, data of bias assessment plots are

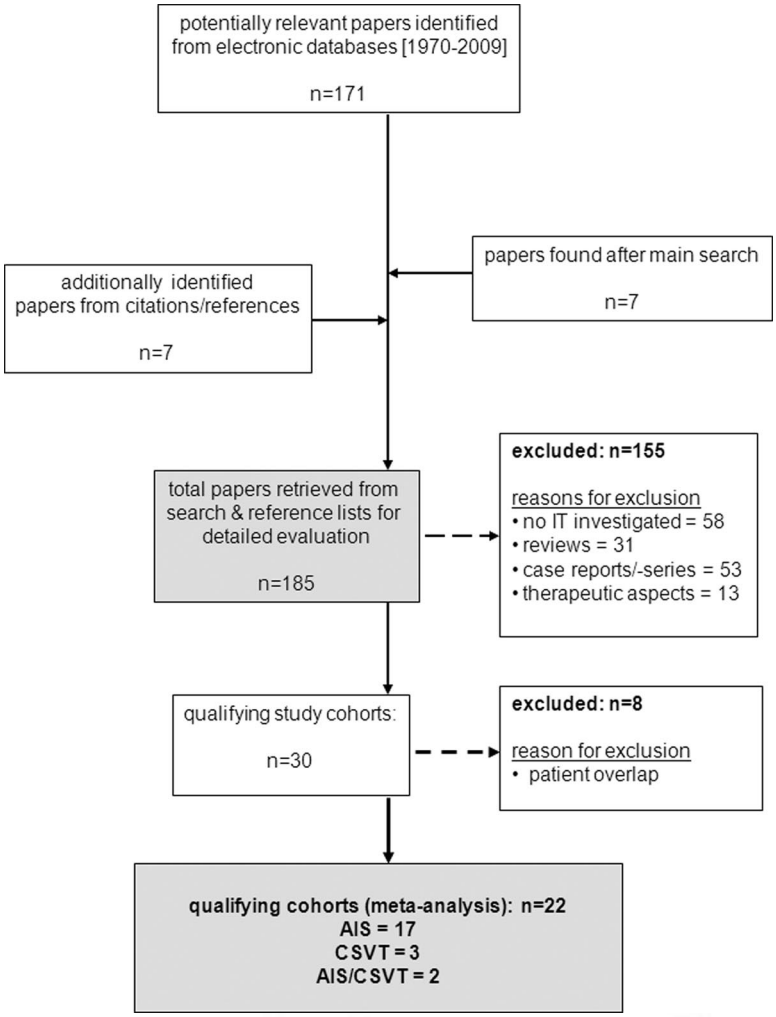

Figure 1. Flow chart showing the results of the search strategy and reasons for exclusion.

shown for protein C deficiency in Figure IIa of the online-only Data Supplement and the Factor V mutation in Figure IIb of the online-only Data Supplement). The absence of major publication bias was also underlined by the results of the linear regression method according to Harbord et al.[73]

Sensitivity Analyses

The median sample size for the set of included studies was 42. We thus assessed the variation in OR estimates obtained by including in the analysis only the studies with more or less than 42 cases. Because 42 might generally be considered a

Table 1. Summary ORs (95% CIs; Meta-Analysis) Including Testing for Heterogeneity (I^2), Noncombinability, and Publication Bias for Thrombophilic Risk Factors Associated With a First AIS Onset in Children

Thrombophilic Traits (No. of Studies)	Patients/Control Subjects, n	OR/95% CI (Fixed-Effects or Random-Effects Model)	I^2, %; P	Bias Indicator (Harbord et al[73]), P
Acquired risk factors				
APS/LA (8)	930/1194	6.95/3.67–13.14 (F)	0; 0.82	0.86
Genetic risk factors				
Antithrombin deficiency (4)	639/684	3.29/0.70–15.48 (F)	15; 0.31	NC
Protein C deficiency (8)	844/1207	11.0/5.13–23.59 (F)	0; 0.96	0.60
Protein S deficiency (4)	574/572	1.49/0.32–6.92 (R)	61; 0.05	NC
Lipoprotein(a) (4)	616/578	6.53/4.46–9.55 (F)	0; 0.85	NC
Factor V G1691A (17)	1014/2581	3.70/2.82–4.85 (F)	0; 0.67	0.22
Factor II G20210A (13)	1059/2278	2.60/1.66–4.08 (F)	0; 0.46	0.78
*MTHFR TT** (11)	777/1715	1.58/1.20–2.08 (F)	3.5; 0.40	0.42
≥2 Genetic traits (9)	701/1265	18.75/6.49–54.14 (F)	0; 0.59	0.61

*T677T. APS/LA indicates antiphospholipid antibodies/lupus anticoagulants; F, fixed-effects model; R, random-effects model; and NC, not calculated.

Table 2. Summary ORs (95% CIs; Meta-Analysis) Including Testing for Heterogeneity (I^2), Noncombinability, and Publication Bias for Thrombophilic Risk Factors Associated With a First CSVT Onset in Children

Genetic Traits (No. of Studies)	Patients/Control Subjects, n	OR/95% CI (Fixed-Effects or Random-Effects Model)	I^2, %; P	Bias Indicator (Harbord et al[73], P
Genetic risk factors				
Antithrombin deficiency (2)	187/469	18.41/3.25–104.29 (F)	19; 0.27	NC
Protein C deficiency (2)	1031/1468	6.30/1.56–25.40 (F)	0; 0.90	NC
Protein S deficiency (2)	187/369	5.27/1.53–18.21 (F)	0; 0.72	NC
Factor V G1691A (5)	1625/2842	2.74/1.73–4.34 (F)	0; 0.62	0.68
Factor II G20210A (5)	1409/2613	1.95/0.93–4.07 (F)	0; 0.82	0.79
≥2 Genetic traits (3)	926/1720	6.12/0.87–43.07 (R)	63.7; 0.25	NC

F indicates fixed-effects model; R, random-effects model; and NC, not calculated.

small sample size, we also assessed the effect of including only studies with more or less than 100 cases. The results showed that the OR estimates for AIS/CSVT are robust (the changes are not significant) for any thrombophilia, factor II mutation, factor V G1691A, protein C, and protein S deficiencies. The OR for antiphospholipid antibodies/lupus anticoagulants was found to be slightly higher for studies with sample size >100 cases (7.17; 95% CI, 2.24 to 23.00). The OR for antithrombin was found to be lower in larger studies (OR for AIS and CSVT, 4.39; 95% CI, 1.11 to 17.34; OR for AIS, 2.69; 95% CI, 0.45 to 16.22; OR for CSVT, 8.89; 95% CI, 1.02 to 76.82). No significant effect of study sample size (cases and controls) was found in a meta-regression analysis for any of the thrombophilia markers.

Discussion

Stroke events, including AIS and CSVT, are far less common in the pediatric population than in adults and are often associated with underlying medical conditions.[3,4] Bearing in mind that not all children with these underlying medical conditions will develop stroke, it appears that genetic risk factors contribute to the origin of first-episode childhood stroke. There have been recent systematic reviews on the role of thrombophilia in children with acute lymphoblastic leukemia and venous thrombosis.[74,75] However, to the best of our knowledge and apart from data reported by Haywood and coworkers[76] in 2005, this is one of the first comprehensive meta-analyses on observational studies investigating the association of genetic and acquired thrombophilia traits with stroke in children. In contrast to Haywood and coworkers, we have included in the statistical model only those studies that focused solely on childhood stroke (ie, exclusive of young adults[14]) and have referred to hospital- or population-based pediatric control subjects. In addition, cohorts reporting acquired deficiency states of antithrombin, protein C, or protein S were not ascertained.[33] Similar to data from a recent systematic review and meta-analyses in children with venous thrombosis,[75] each of the traits investigated shows a significant association with first onset of pediatric stroke. As shown exemplarily for factor V carriers, the results of cumulative meta-analysis showed that statistical significance was reached very early, indicating that a meta-analysis performed 5 to 10 years ago would have anticipated the results of all of the forthcoming studies for the association of factor V G1691A with AIS; similarly, cumulative analysis shows the robustness over time of the less precise estimates for CSVT. It is also noteworthy that the overall mean estimate of the risk associated with factor V G1691A increased for a while after the pioneer studies in the field and finally returned to a value very close to the initial value, as often happens when a set of confirmatory studies arise in a given field. This phenomenon is often cited to support the hypothesis that negative (or, in this case, less optimistic) studies need longer to get published. The highest ORs were found for combined genetic traits,

Table 3. Summary ORs (95% CIs; Meta-Analysis) Including Testing for Heterogeneity (I^2), Noncombinability, and Publication Bias for Thrombophilic Risk Factors Associated With a First AIS/CSVT Onset in Children

Genetic Traits (No. of Studies)	Patients/Control Subjects, n	OR/95% CI (Fixed-Effects or Random-Effects Model)	I^2, %; P	Bias Indicator (Harbord et al[73], P
Genetic risk factors				
Antithrombin deficiency (6)	826/1153	7.06/2.44–22.42 (F)	27; 0.23	0.53
Protein C deficiency (10)	1031/1468	9.31/4.81–18.02 (F)	0; 0.94	0.76
Protein S deficiency (6)	761/941	3.20/1.22–8.40 (F)	47; 0.09	0.57
Lipoprotein(a) (5)	722/727	6.27/4.52–8.69 (F)	0.0; 0.91	0.64
Factor V G1691A (21)	1625/2842	3.26/2.59–4.10 (F)	0; 0.67	0.42
Factor II G20210A (17)	1409/2613	2.43/1.67–3.51 (F)	0; 0.76	0.86
≥2 Genetic traits (12)	926/1720	11.86/5.93–23.73 (F)	19; 0.25	0.52

F indicates fixed-effects model.

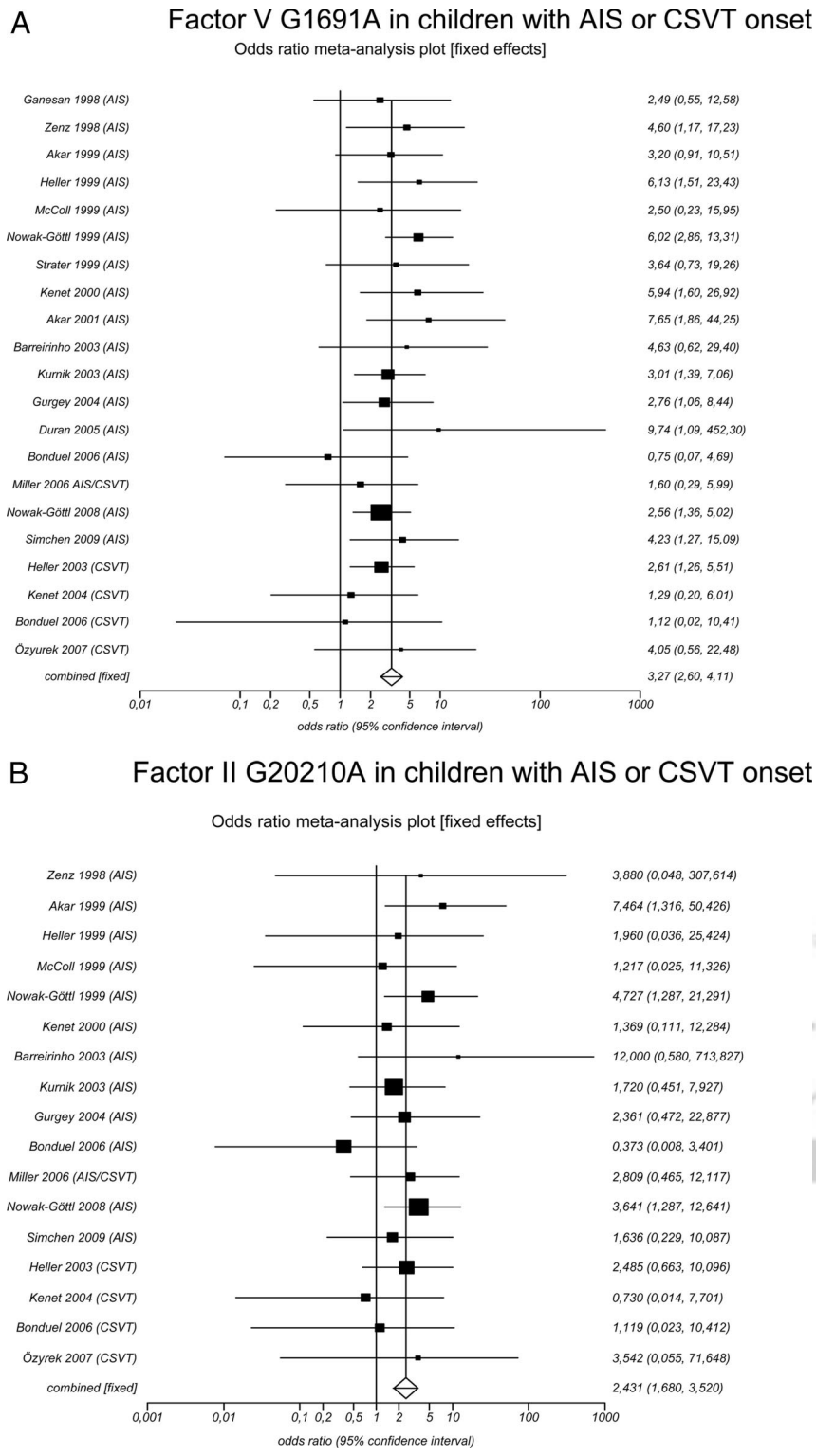

Figure 2. A, Forest plot shows ORs and 95% CIs for observational studies investigating the influence of the factor V G1691A mutation on the onset of symptomatic AIS/CSVT in children. The study author and year of publication are indicated on the *y* axis. The box for each study is proportional to the inverse of variance; horizontal lines show the 95% CIs of the ORs. The pooled estimate is based on a fixed-effects model shown by a vertical line and diamond (95% CI). Studies are in descending order by year of publication. Studies with patients/control subjects counted as "zero" are not depicted. B, Forest plot shows ORs and 95% CIs for observational studies investigating the influence of factor II G20210A variant on the onset of symptomatic AIS/CSVT 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 fixed-effects model shown by a vertical line and diamond (95% CI). Studies are in descending order by year of publication. Studies with patients/control subjects counted as "zero" are not depicted. C, Forest plot shows ORs and 95% CIs for observational studies investigating the influence of acquired antiphospholipid antibodies/lupus anticoagulants on the onset of symptomatic AIS 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 fixed-effects model shown by a vertical line and diamond (95% CI). Studies are in descending order by year of publication. Studies with patients/control subjects counted as "zero" are not depicted.

deficiency of protein C, and the presence of antiphospholipid antibodies. In addition, elevated lipoprotein(a), a low-density lipoprotein particle linked to apolipoprotein(a), showed an increased OR of 6.5, a finding that is in line with recent meta-analyses in adult patients with arterial cardiovascular events.[77,78] Furthermore, evidence is accumulating that elevated lipoprotein(a) resulting in inhibition of plasminogen activation is also a risk factor of venous thrombosis.[79,80]

Perinatal AIS, defined as infarction occurring between 28 weeks' gestation and 28 days of postnatal age,[81] is a unique entity occurring in ≈1 in 4000 to 5000 live births.[82,83] The pathophysiology of perinatal stroke is complex and in many cases is likely to be multifactorial. It is now recognized that

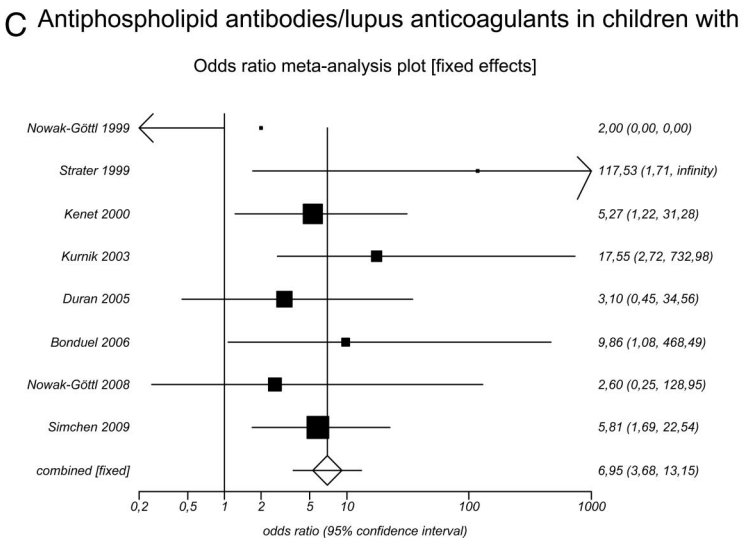

Figure 2 (Continued).

risk factors may relate to both maternal and placental problems and to fetal and neonatal disorders.[35,84–86] The role of genetic and acquired thrombophilia in the pathogenesis of perinatal AIS is controversial and not completely understood. Analysis of our results shows that for studies evaluating perinatal stroke only, thrombophilia was still a risk factor. There is a paucity of eligible studies with control subjects on neonatal perinatal AIS and CSVT, and the issue deserves further attention.

The present meta-analysis has several limitations. First, the included studies were conducted over different time periods; therefore, it is possible that diagnosis and treatment modalities and referral patterns may have changed over time. Second, most of the studies included in our meta-analysis were undertaken in white children; thus, it is unknown whether our findings can be extrapolated to other ethnic groups. It is well known that the allele frequencies for the factor V G1691A or factor II G20210A variants differ among various ethnic groups[87–91]; for example, the factor V G1691A and factor II G20210A polymorphisms are rarely observed in blacks and Asians. In children with first-episode stroke, the homozygous *MTHFR* C677T mutation has been shown to independently increase the risk of stroke.[53,55] However, because homocysteine was not always studied, the potential risks associated with elevated homocysteine could not be determined; this is another limitation of the present meta-

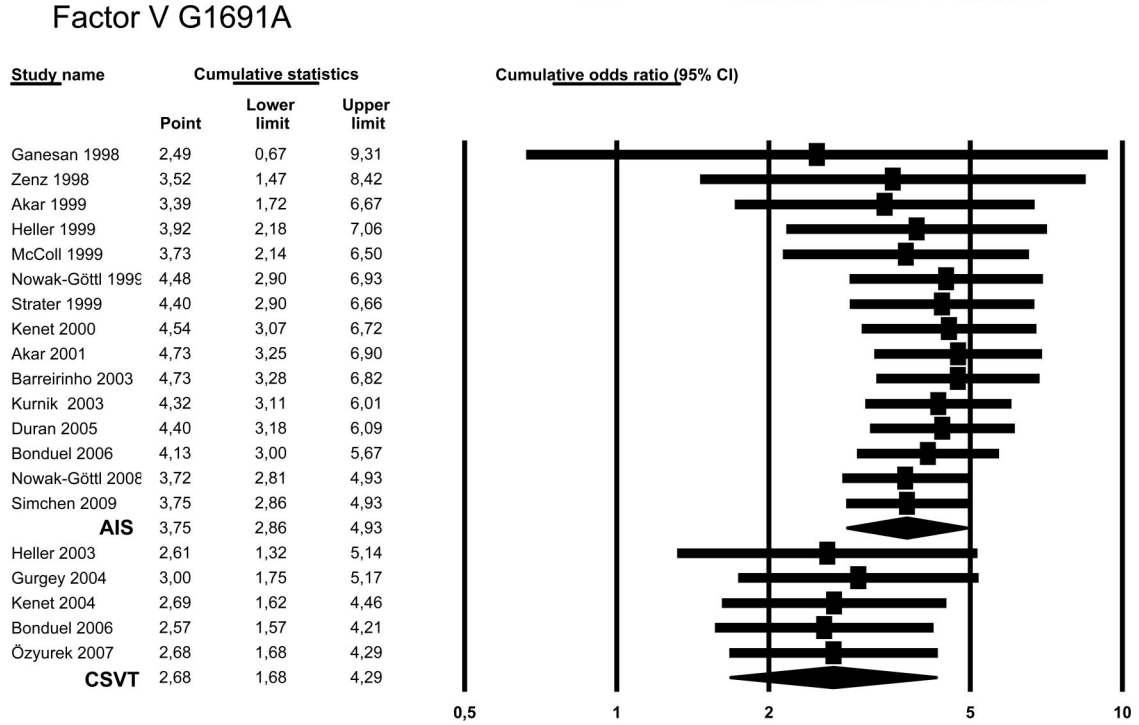

Figure 3. Forest plot shows cumulative ORs and 95% CIs for observational studies investigating the influence of the factor V G1691A mutation on the onset of symptomatic AIS and CSVT in children. The cumulative estimate is based on a fixed-effects model. Studies are in descending order by year of publication.

analysis. A clear warning has to be raised here to clinically test the patients for homocysteinemia but not for *MTHFR* mutation because it was clearly shown in adult patients that the former and not the latter identifies people at increased thrombotic risk.[56] A fourth 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 stroke. In the context of publication bias, we must mention here that data on lipoprotein(a) and AIS/CSVT are based on 4 different population-based studies, all of which share authorship with the senior author of this meta-analysis, so the data interpretation is restricted to the populations investigated. As noted above, newborns are particularly underrepresented in the present analysis. Thrombophilia screening and its interpretation are difficult in neonates and may therefore be postponed to later ages by the treating physicians with the increasing risk of patients being 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 after birth. A further limitation is the missing data between thrombophilia and recurrent stroke. So far, only 4 cohort studies are available on this topic.[19,27,50,92] In line with recurrence in children with venous thrombosis, Ganesan and coworkers[92] found in 2006 that a positive association between thrombophilia and recurrent AIS was detected solely in primarily "healthy" stroke children with a significantly increased hazard ratio for the prothrombin G20210A variant (hazard ratio/OR, 7.9; 95% CI, 1.8 to 34.9) during the patient follow-up.

These limitations notwithstanding, the findings of the present meta-analysis indicate that thrombophilias serve as risk factors for first stroke. However, the impact of thrombophilias on outcome and recurrence risk needs to be further investigated. The clinical value, economic effectiveness, and psychological implications of thrombophilia testing in this setting have to be further elucidated before proceeding to large-scale clinical application.

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Disclosures

None.

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CLINICAL PERSPECTIVE

Thrombotic events in children, including stroke, are increasingly recognized. Despite the fact that most children with stroke have other underlying risk factors, thrombophilias appear to play a role. Prior studies evaluating the association of thrombophilia in pediatric first-episode stroke are limited by relatively small patient numbers. In this meta-analysis, the impact of the most common thrombophilias on initial arterial ischemic stroke or cerebral sinovenous thrombosis in neonates and children <18 years of age was investigated. Twenty-two cohort studies were included in the final analysis, with a total of 1764 patients with stroke patients and 2867 control subjects. Each of the evaluated thrombophilias was associated with an increased risk of arterial ischemic stroke or cerebral sinovenous thrombosis, with odds ratios ranging from 1.58 (95% confidence interval, 1.20 to 2.08) for patients homozygous for the *MTHFR C677T* genotype to 9.31 (95% confidence interval, 4.81 to 18.02) for patients with protein C deficiency. Patients with combined defects had the highest risk with an odds ratio of 11.86 (95% confidence interval, 5.93 to 23.73). This meta-analysis greatly improves the current understanding of the contribution of thrombophilia to first-episode stroke in children. The analysis is most limited by the fact that the vast majority of patients were white, and some of the tests were performed in only select cohorts, so the results may not be generalizable to all populations. The clinical utility of performing thrombophilia testing in neonates and children with stroke will be determined only after the impact of these thrombophilias on outcome, therapeutic management, and stroke recurrence has been further evaluated in longitudinal studies.