Inherited Thrombophilia and the Risk of Arterial Ischemic Stroke: A Systematic Review and Meta-Analysis

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***Background*—**Inherited thrombophilias are well-established predisposing factors for venous thromboembolism, but their role in arterial thrombosis, such as arterial ischemic stroke, remains uncertain. We aimed to evaluate the association between inherited thrombophilia (factor V Leiden, prothrombin G20210A mutation, protein C deficiency, protein S deficiency, and antithrombin deficiency) and risk of arterial ischemic stroke in adults.

***Methods and Results*—**We searched PubMed, EMBASE, and Cochrane Library Databases from inception to December 31, 2018. We included case-control or cohort studies of adults reporting the prevalence of inherited thrombophilias in those with arterial ischemic stroke and subjects without arterial ischemic stroke. Two reviewers (T.C., E.D.) independently searched the literature and extracted data. Pooled odds ratios (ORs) and 95% CIs were calculated using random-effects model. We identified 68 eligible studies, which collectively enrolled 11 916 stroke patients and 96 057 controls. The number of studies reporting factor V Leiden, prothrombin G20210A mutation, protein C deficiency, protein S deficiency, and antithrombin deficiency were 56, 45, 15, 17, and 12, respectively. Compared with controls, patients with arterial ischemic stroke were significantly more likely to have the following inherited thrombophilias: factor V Leiden (OR, 1.25; 95% CI, 1.08–1.44; I^2=0%), prothrombin G20210A mutation (OR, 1.48; 95% CI, 1.22–1.80; I^2=0%), protein C deficiency (OR, 2.13; 95% CI, 1.16–3.90; I^2=0%), and protein S deficiency (OR, 2.26; 95% CI, 1.34–3.80; I^2=8.8%). Statistical significance was not reached for antithrombin deficiency (OR, 1.25; 95% CI, 0.58–2.67; I^2=8.8%).

***Conclusions*—**Inherited thrombophilias (factor V Leiden, prothrombin G20210A mutation, protein C deficiency, and protein S deficiency) are associated with an increased risk of arterial ischemic stroke in adults. The implications of these findings with respect to clinical management of patients with ischemic stroke require further investigation. **(*J Am Heart Assoc*. 2019;8: e012877. DOI: 10.1161/JAHA.119.012877.)**

Key Words: hypercoagulopathy • stroke • stroke, ischemic • thrombosis

The inherited thrombophilias, factor V Leiden (FVL), the prothrombin G20210A mutation (PTM), protein C deficiency (PCD), protein S deficiency (PSD), and antithrombin deficiency (ATD), are well-established predisposing factors for venous thromboembolism,[1,2] but their role in arterial thrombosis, such as arterial ischemic stroke, remains uncertain.

In patients with arterial ischemic stroke, inherited thrombophilia testing is often ordered to identify the cause of stroke. However, the benefit of screening for inherited thrombophilia is unknown and such practice is controversial.[3,4] Indeed, the 2018 American Heart Association/American Stroke Association clinical practice guideline recommends against thrombophilia testing in patients with ischemic stroke,[5] although such testing remains common in clinical practice.[6]

Current evidence about the association of inherited thrombophilia and the risk of ischemic stroke is conflicting.[7] Individual studies carry the limitations of small sample size

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Accompanying Data S1, Tables S1 through S9, and Figures S1 through S15 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.012877

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Clinical Perspective

What Is New?

- Inherited thrombophilias (factor V Leiden, prothrombin G20210A mutation, protein C deficiency, and protein S deficiency) are associated with an increased risk of arterial ischemic stroke in adults, particularly in younger adults.

What Are the Clinical Implications?

- The role of inherited thrombophilia testing in patients with ischemic stroke as well as its influence on clinical management warrant further study.

and reduced statistical power. Therefore, we conducted a systematic review and meta-analysis to evaluate the association of inherited thrombophilia (FVL, PTM, PCD, PSD, and ATD) and the risk of arterial ischemic stroke in adults.

Methods

The study protocol is registered on PROSPERO (CRD42018090020). We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses[8] and the Meta-Analysis of Observational Studies in Epidemiology guidelines.[9] The data that support the findings of this study are available from the corresponding author on request.

Data Sources and Search Strategies

We searched PubMed, EMBASE, and the Cochrane Library Databases from inception to December 31, 2018. The following search terms were used: "stroke" OR "cerebrovascular accident" AND "factor V" OR "prothrombin" OR "antithrombin" OR "protein C" OR "protein S" OR "thrombophilia." No language restriction was applied. The detailed search queries are presented in Data S1. Additional searches were performed by manual review of abstracts from the American Society of Hematology annual meeting, the Congress of the International Society on Thrombosis and Hemostasis, the American Academy of Neurology annual meeting, and the International Stroke Conference (from 2015 to 2018). Reference lists of relevant studies and review articles were screened for potentially eligible studies.

Study Selection

Two authors (T.C., E.D.) independently searched the literature, screened titles and abstracts, and reviewed full texts to identify potentially eligible studies. Disagreements were resolved by consensus or a third reviewer (A.C.) when necessary.

The primary outcome of interest was arterial ischemic stroke. Eligible studies included case-control or cohort studies of adults, aged ≥15 years, that reported the prevalence of at least one of the inherited thrombophilias of interest (FVL, PTM, PCD, PSD, or ATD) in both subjects with a history of arterial ischemic stroke and subjects without arterial ischemic stroke. Both prospective and retrospective studies were included. Studies were required to have ≥10 subjects in each group. Studies that enrolled patients with transient ischemic attack, hemorrhagic stroke, cerebral venous sinus thrombosis, and other arterial thromboses were excluded unless data for arterial ischemic stroke could be disaggregated. Studies that included neonates or children were also excluded.

If multiple studies used the same or overlapping samples, we included only the one with the largest sample size in the quantitative analysis. Cohen's κ coefficient was calculated to evaluate interobserver agreement for study selection.

We did not attempt to control for method used to diagnose thrombophilia, nor did we limit how the control population was constituted, assuming it appeared to be a valid comparator group.

Data Extraction

Two authors (T.C., E.D.) independently extracted data from included studies in duplicate using a standardized evidence table. Discrepancies were resolved by consensus or a third reviewer (A.C.) when necessary. The following data were collected: study period, country of study, number of cases and controls, case and control identification method, method of stroke diagnosis, matched variables for cases and controls, baseline characteristics of cases and controls (eg, age, sex, ethnicity, and cardiovascular risk factors), type(s) of thrombophilia reported, methods and timing of thrombophilia testing, and number of cases and controls testing positive and negative for each type of thrombophilia.

Quality Assessment

Methodological quality assessment was performed independently by 2 authors (T.C., E.D.) using either the National Institutes of Health–National Heart, Lung, and Blood Institute Quality Assessment of Case-Control Studies assessment tool[10] or the National Institutes of Health–National Heart, Lung, and Blood Institute Quality Assessment for Observational Cohort and Cross-Sectional Studies assessment tool,[11] as appropriate. Studies were categorized by their risk of bias as good, fair, or poor quality. Any differences in quality rating were resolved by consensus or adjudication by a third reviewer (A.C.).

Statistical Analysis

Data analysis was performed using R, Version 3.4.4 (R Foundation for Statistical Computing, Vienna, Austria). Pooled odds ratios (ORs) and 95% CIs were calculated using the bayesian method with random-effects model. Interstudy heterogeneity was evaluated using the Cochran Q test and I^2 statistic. A Cochran Q test $P<0.05$ is considered significant for heterogeneity. An I^2 value of 0% to 25% represents insignificant heterogeneity, 26% to 50% represents low heterogeneity, 51% to 75% represents moderate heterogeneity, and >75% represents high heterogeneity. For FVL and PTM, separate analyses for homozygosity and heterozygosity were performed if studies provided stratified data by zygosity status. Prespecified subgroup analyses were performed in young patients (aged <65 years), patients with a patent foramen ovale (PFO), and patients with cryptogenic stroke, where reported. Sensitivity analyses were performed between age-matched versus non–age-matched studies and studies among different continents. Funnel plots of OR versus SE and Egger's test for asymmetry were used to assess for the presence of publication bias. $P<0.05$ was considered statistically significant. When publication bias was detected, Copas selection model was used and adjusted pooled ORs were reported to estimate the effect of publication bias on the results.[12]

Results

Study Identification

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram is shown in Figure 1. A total of 1875 records were retrieved from the literature search. After screening by title and abstract, 1661 records were excluded. The remaining 214 references underwent full-text review, 68 of which met eligibility criteria and were included in the analysis. These 68 studies collectively enrolled 11 916 stroke patients and 96 057 controls. All 68 studies were case-control studies. We did not identify any cohort studies that met eligibility criteria. The complete list of included studies is provided in Supplemental References. The number of studies that reported on FVL, PTM, PCD, PSD, and ATD were 56, 45, 15, 17, and 12, respectively. There was excellent agreement between the 2 independent reviewers with respect to study selection (κ=0.96).

Study Characteristics

Characteristics of included studies are listed in Tables S1 and S2. The results from individual studies are listed in Tables S3 through S7. We included 64 case-control and 4 nested case-control studies. One study was published as a conference abstract.

The publication year of included studies ranged from 1993 to 2017. Twenty-eight studies enrolled only young and middle-aged adults, with an upper age limit ranging from 40 to 65 years. All included studies enrolled ≥20 cases and controls, with most (87% of studies) enrolling >40 subjects in each group. A few studies focused on specific subgroups with certain comorbidities, such as atrial fibrillation,[13] HIV infection,[14,15] and systemic lupus erythematosus.[16] Most studies recruited healthy subjects in the same geographic area as controls. In 4 studies, historical controls were used, whereas the remaining 64 studies recruited contemporaneous controls. Although most studies matched cases and controls by age and sex, only 4 studies matched by ethnicity and only 1 study matched controls for the presence of cardiovascular risk factors.[17] A comparison of demographic data and clinical risk factors between cases and controls in each study is listed in Table S2. Most studies did not provide detailed information about clinical risk factors in the control group. When reported, clinical stroke risk factors, such as hypertension, diabetes mellitus, and smoking, were more frequent in cases than controls in most studies.

Ischemic stroke was diagnosed by neuroimaging in most studies. In 9 studies, the method of diagnosis was not described. One epidemiologic study used self-reported history of stroke to define cases.[18] Studies varied in terms of stroke subtypes included. Some exclusively enrolled cases with cryptogenic stroke,[19–25] whereas in other studies, the proportion of cryptogenic stroke among cases ranged from 6% to 55% when reported. In 24 studies, only cases with first-ever ischemic stroke were included. Forty-one studies did not specify whether recurrent stroke was included, whereas 3 studies included cases of both first-ever and recurrent stroke (16%–42% of cases), but did not provide disaggregated data for the recurrent stroke group.[26–28] Almost all of the included studies reported use of standard and widely accepted test methods for the diagnosis of thrombophilia (Table S3 through S7).

Quality Appraisal

Using the National Institutes of Health–National Heart, Lung, and Blood Institute Quality Assessment of Case-Control Studies tool, the included studies were rated as good (N=22), fair (N=43), and poor (N=3) quality. The studies with good, fair, and poor rating contributed 31%, 56%, and 13% of cases and 9%, 90%, and 1% of controls, respectively. Details of study quality assessment items for each study are reported in Table S8.

Studies with a good quality rating carry the least risk of bias. Studies were rated as fair quality when they were susceptible to some degree of bias. These included studies

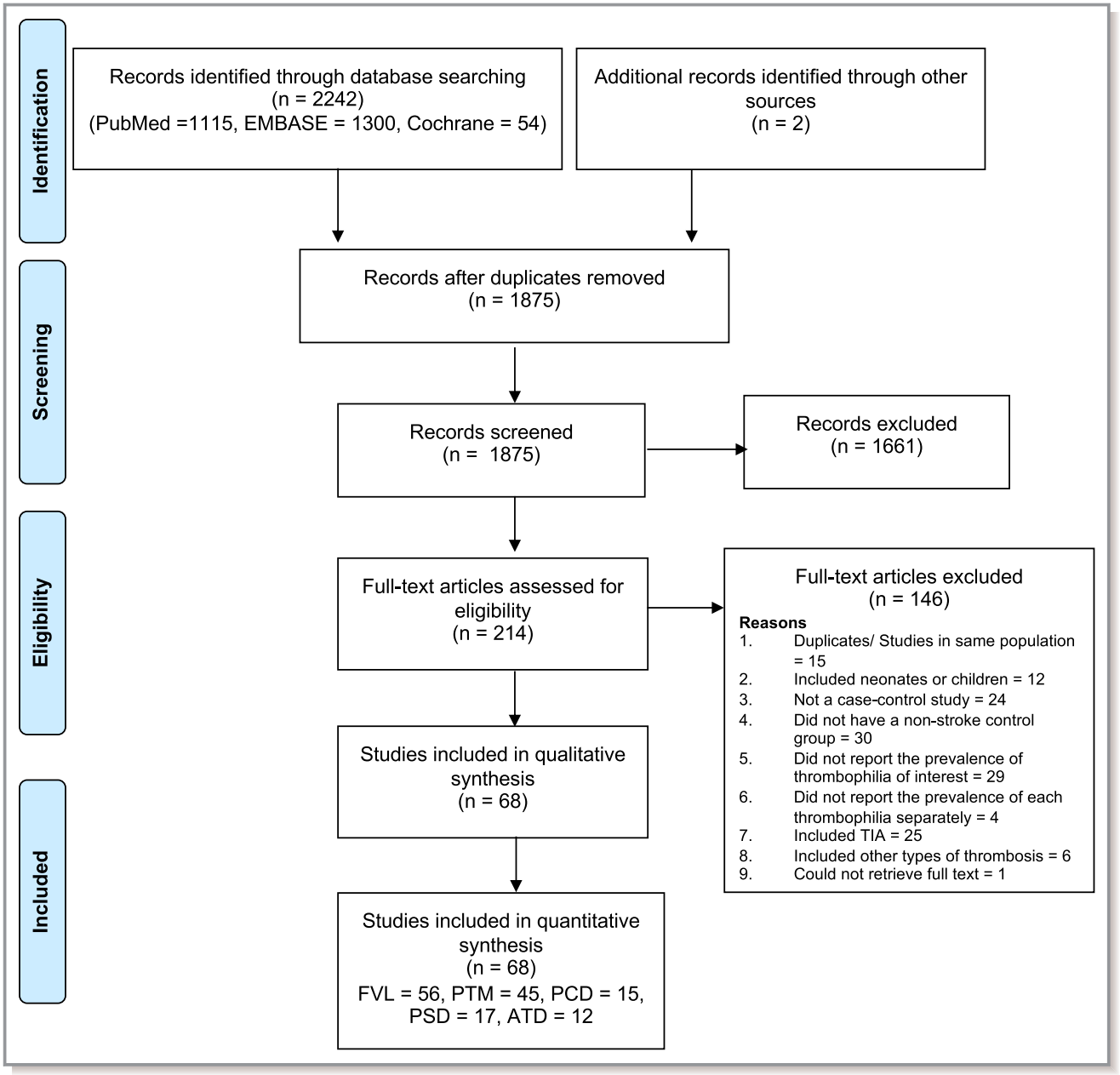

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram. ATD indicates antithrombin deficiency; FVL, factor V Leiden; PCD, protein C deficiency; PSD, protein S deficiency; PTM, prothrombin G20210A mutation; TIA, transient ischemic attack.

that did not recruit cases and controls from the same population, studies that did not match controls or did not adjust for confounders, and studies that did not specify valid and reliable methods of stroke diagnosis or thrombophilia testing. Studies were rated as poor quality when the definition of cases and controls was not explicitly described.

Genetic testing was used to identify FVL and PTM, whereas functional tests were used in most studies to identify PCD, PSD, and ATD. Protein C, protein S, and antithrombin levels may be reduced in the setting of anticoagulant therapy and acute thromboembolism. Eight of the studies excluded patients receiving anticoagulants, whereas 9 studies did not specifically mention anticoagulant use. All but 2 studies required testing at a distant time from the stroke event (with time frames ranging from 2 days to 6 months) or a second confirmatory test if the first one was abnormal. Although several studies reported blinding of exposure assessor to case/control status,[17,20,25,27,29–36] most did not specify whether the assessor was blinded.

Thrombophilia and Arterial Ischemic Stroke

The pooled ORs of arterial ischemic stroke for each thrombophilia are summarized in Figure 2.

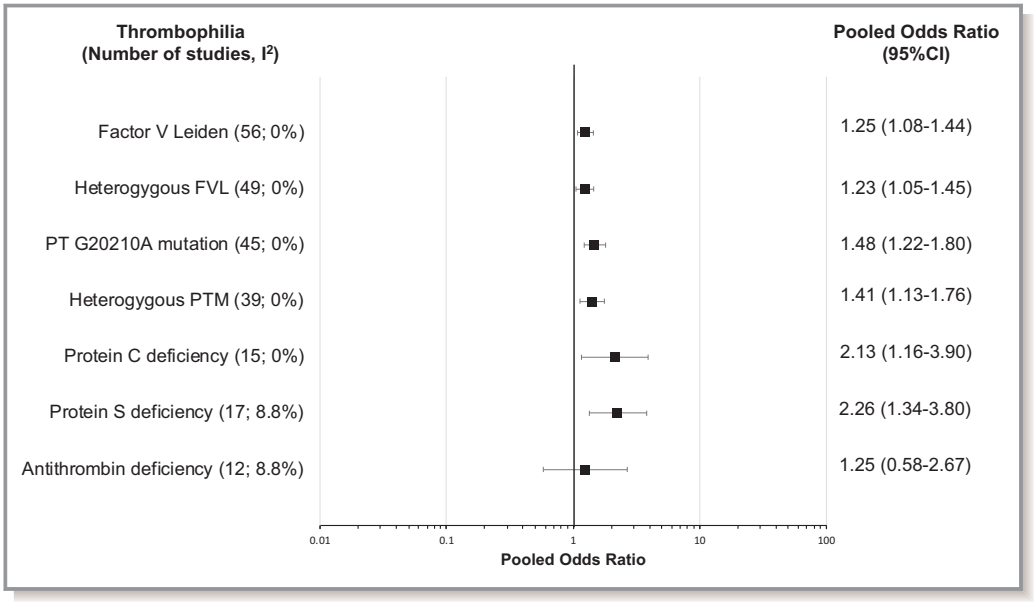

Figure 2. Forest plot showing association between inherited thrombophilia and risk of arterial ischemic stroke. The forest plot shows the results from the meta-analysis for each type of thrombophilia and its association with arterial ischemic stroke. The pooled odds ratio (OR) is represented by the square box. The whiskers represent 95% CIs. The I^2 statistic was used to evaluate study heterogeneity. FVL indicates factor V Leiden; PTM, prothrombin G20210A mutation.

Factor V Leiden

FVL was assessed in 56 studies (10 229 cases and 31 816 controls), 49 of which reported homozygosity and heterozygosity status. FVL, irrespective of zygosity status, was found in significantly more arterial ischemic stroke cases than controls, with a pooled OR of 1.25 (95% CI, 1.08–1.44). Heterogeneity among studies was insignificant (P=0.93; I^2=0%). The forest plot is shown in Figure S1.

For homozygous FVL, the pooled OR was 0.72 (95% CI, 0.39–1.34; I^2=0%) (Figure S2). Of 49 studies that tested for FVL, 33 (67%) did not identify homozygous FVL in any of the cases or controls. When such studies with zero events were excluded from the analysis, the pooled OR for homozygous FVL was 2.24 (95% CI, 1.26–4.71). For heterozygous FVL, the pooled OR was 1.23 (95% CI, 1.05–1.45; I^2=0%) (Figure S3).

A funnel plot was symmetrical (Figure S4A) and Egger's test was nonsignificant (P=0.46), suggesting absence of publication bias.

Prothrombin G20210A mutation

PTM was assessed in 45 studies (7921 cases and 83 574 controls), 39 of which reported homozygosity and heterozygosity status. PTM, irrespective of zygosity status, was found in significantly more arterial ischemic stroke cases than controls, with a pooled OR of 1.48 (95% CI, 1.22–1.80). Heterogeneity among studies was insignificant (P=0.93; I^2=0%). The forest plot is shown in Figure S5.

For homozygous PTM, the pooled OR was 0.31 (95% CI, 0.11–0.83; I^2=35%) (Figure S6). Of 39 studies that tested for PTM, 31 (79%) did not identify homozygous PTM in any of the cases or controls. When such studies with zero events were excluded from the analysis, the pooled OR for homozygous PTM was 7.19 (95% CI, 2.47–20.94). For heterozygous PTM, the pooled OR was 1.41 (95% CI, 1.13–1.76; I^2=0%) (Figure S7).

A funnel plot was symmetrical (Figure S4B) and Egger's test was nonsignificant (P=0.05), suggesting absence of publication bias.

Protein C deficiency

Protein C was measured in 15 studies (1676 cases and 11 895 controls). Of these studies, 7 excluded patients receiving anticoagulants, whereas 8 did not specifically mention anticoagulant use. PCD was found in significantly more arterial ischemic stroke cases than controls, with a pooled OR of 2.13 (95% CI, 1.16–3.90) (Figure S8). Heterogeneity among studies was insignificant (P=0.52; I^2=0%). A funnel plot was symmetrical (Figure S4C) and Egger's test was nonsignificant (P=0.05), suggesting absence of publication bias.

Protein S deficiency

Protein S was measured in 16 studies (1803 cases and 6133 controls). Of these studies, 8 excluded patients receiving anticoagulants, whereas 8 did not specifically

mention anticoagulant use. PSD was found in significantly more arterial ischemic stroke cases than controls, with a pooled OR of 2.26 (95% CI, 1.34–3.80) (Figure S9). Heterogeneity among studies was insignificant (P=0.31; I^2=8.8%). A funnel plot was symmetrical (Figure S4D) and Egger's test was nonsignificant (P=0.45), suggesting absence of publication bias.

Antithrombin deficiency

Antithrombin was measured in 12 studies (1407 cases and 11 796 controls). Of these studies, 5 excluded patients receiving anticoagulants, whereas 7 did not specifically mention anticoagulant use. ATD was numerically more common in arterial ischemic stroke cases than controls, but statistical significance was not reached (pooled OR, 1.25; 95% CI, 0.58–2.67) (Figure S10). Heterogeneity among studies was insignificant (P=0.22; I^2=8.8%). A funnel plot was asymmetrical (Figure S4E) and Egger's test was significant (P=0.01), suggesting possible publication bias. The pooled OR adjusted for publication bias using the Copas selection model was 1.39 (95% CI, 0.34–5.73).

Subgroup Analyses

We conducted prespecified subgroup analyses in young patients (aged ≤65 years), patients with a PFO, and patients with cryptogenic stroke. Results of these subgroup analyses for each thrombophilia are summarized in Figure 3.

Young patients

Twenty-eight studies exclusively enrolled young patients (aged ≤65 years). In the subgroup of young patients, the association of FVL, PTM, PCD, and PSD and arterial ischemic stroke remained significant. In general, the pooled ORs for young patients were greater than the overall pooled ORs across all thrombophilias (Figure 3 and Figures S11 through S15).

Patients with PFO

Two studies[25,37] exclusively enrolled patients with PFO, whereas two[21,38] reported disaggregated data for cases with and without PFO. A significant association between thrombophilia and arterial ischemic stroke was not detected in the subgroups of patients with PFO, except for PTM (OR, 2.62; 95% CI, 1.11–6.16) (Figure 3 and Figures S11 through S15).

Patients with cryptogenic stroke

Seven studies[19–25] exclusively enrolled patients with cryptogenic stroke. A significant association between thrombophilia and arterial ischemic stroke was not detected in the subgroups of patients with cryptogenic stroke (Figure 3 and Figures S11 through S15).

Sensitivity Analyses

We prespecified sensitivity analyses according to geographic region and whether studies used age-matched versus non–age-matched controls.

Age-matched versus unmatched controls

The number of studies with and without age-matched controls and their corresponding pooled ORs for each thrombophilia are shown in Table 1. In general, pooled ORs were similar irrespective of whether studies used age-matched or non–age-matched controls. However, significant associations were found in studies with age-matched controls only.

Geographic region

Most studies were conducted in Europe (50%), Asia (19%), and North America (17%), with a smaller number from Africa (6%), Australia (3%), and South America (3%). Results were fairly consistent across geographic regions, except for the notably higher ORs for PCD and PSD in studies conducted in Asia (Table 2).

First-ever ischemic stroke

After the analysis was restricted to the 24 studies that exclusively enrolled cases with first-ever ischemic stroke, the association with arterial ischemic stroke remained significant for PTM (OR, 1.46; 95% CI, 1.10–2.00) and PSD (OR, 3.58; 95% CI 1.12–11.42), but not for FVL (OR, 1.16; 95% CI, 0.92–1.47) or PCD (OR, 1.62; 95% CI, 0.51–5.40).

Additional sensitivity analyses

Sensitivity analyses were performed by excluding each of the following: studies with enriched case population (those who were referred for thrombophilia testing because of a clinical indication or recruited from a thrombophilia center),[19,31,39] studies that used self-reported history of stroke rather than imaging to define cases,[18] studies that were rated as poor quality,[40–42] and studies that reported inclusion of cases of recurrent ischemic stroke (but including studies that failed to report whether recurrent ischemic stroke was included or not).[26–28] After each of these exclusions, the association of FVL, PTM, PCD, and PSD with arterial ischemic stroke remained significant, with similar pooled OR to the original analysis (Table S9).

Discussion

The results from our systematic review and meta-analysis suggest that inherited thrombophilias, including FVL, PTM, PCD, and PSD, are associated with a significant but small increase in the risk of arterial ischemic stroke in adults (Figure 2), particularly in young patients (Figure 3). When

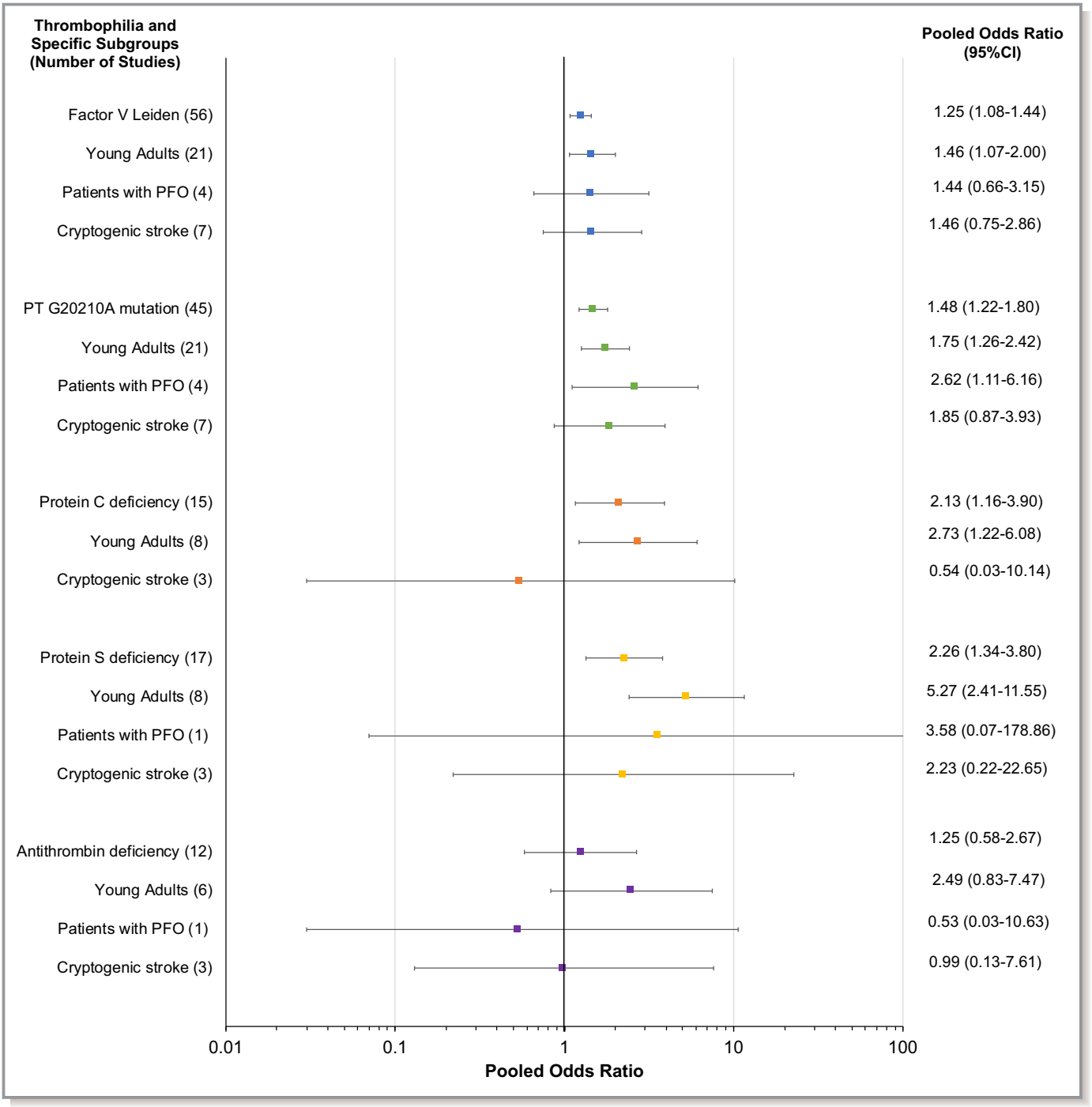

Figure 3. Forest plot showing pooled odds ratio (OR) for each thrombophilia in specific subgroups of patients. The forest plot shows the results from the prespecified subgroup analyses for each type of thrombophilia. The pooled ORs are represented by the square boxes. The horizontal lines represent the 95% CIs. PFO indicates patent foramen ovale.

studies with zero events in both groups were excluded from analysis, the association of FVL and PTM was stronger in the homozygous than in the heterozygous state, suggesting a potential dose-response relationship and a causal role for inherited thrombophilia in arterial ischemic stroke.

Arterial ischemic stroke is a multicausal disease that involves complex interactions of genetic and environmental risk factors. Several lines of evidence implicate the coagulation pathway in the pathophysiological characteristics of arterial ischemic stroke. Increased levels of clotting proteins, such as factor VIII and factor XI, have been posited as independent risk factors for ischemic stroke.[43,44] Conversely, congenital deficiency of factors VIII, IX, and XI is protective against stroke and cardiovascular disease.[45,46] Anticoagulants

Table 1. Sensitivity Analysis of Studies That Used Age-Matched versus Non–Age-Matched Controls

	Age-Matched Studies		Non–Age-Matched Studies	
Thrombophilia	No. of Studies	Pooled OR (95% CI)	No. of Studies	Pooled OR (95% CI)
FVL	24	1.58 (1.16–2.15)*	32	1.09 (0.92–1.28)
Homozygous FVL	19	1.18 (0.51–2.71)	30	0.42 (0.17–1.08)
Heterozygous FVL	19	1.69 (1.19–2.40)*	30	1.07 (0.89–1.28)
PT G20210A mutation	22	1.86 (1.38–2.49)*	23	1.21 (0.90–1.61)
Homozygous PTM	18	0.27 (0.06–1.11)	21	0.33 (0.08–1.42)
Heterozygous PTM	18	1.91 (1.35–2.70)*	21	1.10 (0.79–1.53)
Protein C deficiency	9	2.54 (1.21–5.37)*	6	1.39 (0.44–4.33)
Protein S deficiency	11	2.28 (1.21–4.33)*	6	2.30 (0.95–5.59)
Antithrombin deficiency	7	1.73 (0.70–4.28)	5	0.47 (0.09–2.38)

FVL indicates factor V Leiden; OR, odds ratio; PTM, prothrombin G20210A mutation.
*Significant association.

reduce the risk of ischemic stroke. Compared with aspirin (the "standard of practice" in many studies for prevention of first or recurrent stroke), warfarin is noninferior for the secondary prevention of noncardioembolic ischemic stroke.[47] Although rivaroxaban was not superior to aspirin in preventing recurrence after embolic stroke of undetermined source,[48] the addition of rivaroxaban to aspirin reduced cardiovascular events, including stroke, in patients with stable atherosclerosis.[49] Extended-duration treatment with betrixaban for prevention of venous thrombosis among hospitalized medically ill patients reduced the risk of subsequent stroke.[50]

Although inherited thrombophilias have not been traditionally recognized as risk factors for arterial thrombosis,[7] there are several potential mechanisms by which they could contribute to arterial ischemic stroke. First, ischemic stroke may arise in the setting of deep vein thrombosis and subsequent paradoxical embolism via a PFO. In a prespecified subgroup analysis of subjects with PFO in our study, ischemic stroke was significantly associated with PTM, but not with other thrombophilias (Figure 3), possibly because of the limited number of studies in which PFO status was assessed. A previous meta-analysis focusing on patients with PFO yielded similar results.[51] Second, the unbalanced thrombin activation in individuals with inherited thrombophilia may contribute to formation and progression of atherosclerotic lesions through various mechanisms, including platelet activation, endothelial and vascular smooth muscle cell dysregulation, and recruitment of monocytes and macrophages.[52,53]

For FVL and PTM, our results are consistent with previous meta-analyses. One report included 15 studies in FVL (pooled OR, 1.27; 95% CI, 0.86–1.87) and 10 studies in PTM (pooled OR, 1.30; 95% CI, 0.91–1.87).[54] The association was more robust in young patients (aged <55 years). In another meta-analysis,[55] only studies that enrolled young adults (aged <50 years) were included. Among the 18 eligible studies, FVL was significantly associated with ischemic stroke (pooled OR, 1.89; 95% CI, 1.31–2.72). Although a meta-analysis of PCD, PSD, and ATD has not previously been performed in adults, a meta-analysis in children with arterial ischemic stroke identified a significant association with PCD (OR, 11.0; 95% CI, 5.13–23.59), but not with PSD (OR, 1.49; 95% CI, 0.32–6.92) or ATD (OR, 3.29; 95% CI, 0.70–15.48).[56]

Genome-wide association studies have identified genetic loci associated with stroke,[57,58] many of which share associations with other cardiovascular diseases, such as hypertension, atrial fibrillation, coronary artery disease, and venous thromboembolism. In the MEGASTROKE study, the weighted genetic risk score for venous thromboembolism was significantly associated with large-artery atherosclerotic stroke and cardioembolic stroke, but not small-vessel stroke.[57] However, none of the inherited thrombophilias we investigated in the present study was significantly associated with stroke in genome-wide association studies. This could be, in part, because of the inadequate statistical power to detect an association with rare variants in genome-wide association studies, allelic heterogeneity inherent in certain thrombophilias (PCD, PSD, and ATD), and/or heterogeneity in stroke subtypes and ethnicity of the study populations. Interestingly, data extracted from multiple genome-wide association studies have shown that genetic variants indicative of high protein C level were associated with lower risk of coronary artery disease/myocardial infarction,[59] suggesting a potential role for natural anticoagulants in the pathogenesis of arterial thrombosis. A similar analysis for arterial ischemic stroke would be an insightful topic for future studies.

Among the studies included in our analysis, interstudy heterogeneity was low, with I^2 values ranging from 0% to 35%, suggesting that the results could appropriately be combined.

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Table 2. Sensitivity Analysis by Study Region

Thrombophilia	Africa		Asia		Australia		Europe		North America		South America	
	No. of Studies	Pooled OR (95% CI)	No. of Studies	Pooled OR (95% CI)	No. of Studies	Pooled OR (95% CI)	No. of Studies	Pooled OR (95% CI)	No. of Studies	Pooled OR (95% CI)	No. of Studies	Pooled OR (95% CI)
FVL	1	0.00 (0.00–259.67)	11	1.68 (1.08–2.61)*	2	1.45 (0.37–5.70)	33	1.31 (1.08–1.58)*	7	0.78 (0.52–1.18)	2	1.31 (0.39–4.33)
Homozygous FVL	1	0.00 (0.00–197.19)	11	1.15 (0.37–3.61)	1	0.00 (0.00–201.44)	29	0.72 (0.35–1.50)	5	0.00 (0.00–23.31)	2	0.00 (0.00–116.06)
Heterozygous FVL	1	0.00 (0.00–678.42)	11	1.51 (0.99–2.29)	1	0.30 (0.01–6.66)	29	1.32 (1.05–1.67)*	5	0.68 (0.37–1.27)	2	1.32 (0.40–4.36)
PTM	1	2.32 (0.54–9.68)	7	0.90 (0.45–1.78)	2	2.33 (0.54–10.07)	28	1.57 (1.21–2.05)*	6	1.35 (0.77–2.37)	1	2.00 (0.39–10.23)
Homozygous PTM	1	0.00 (0.00–243.44)	7	0.18 (0.01–2.59)	1	0.00 (0.00–160.03)	24	0.34 (0.10–1.13)	5	0.36 (0.02–6.16)	1	0.00 (0.00–160.03)
Heterozygous PTM	1	2.29 (0.54–9.76)	7	0.81 (0.39–1.67)	1	8.37 (0.23–308.69)	24	1.52 (1.12–2.08)*	5	1.23 (0.64–2.37)	1	2.04 (0.40–10.36)
Protein C deficiency	2	3.91 (0.75–20.44)	4	4.94 (1.52–16.06)*	1	0.61 (0.09–4.19)	7	1.28 (0.46–3.55)	…	…	…	…
Protein S deficiency	3	1.83 (0.69–4.83)	4	7.46 (2.43–22.93)*	1	0.73 (0.07–7.59)	7	1.96 (0.86–4.43)	1	1.05 (0.28–4.02)	…	…
Antithrombin deficiency	1	5.22 (0.91–30.00)	3	0.60 (0.06–6.21)	1	1.26 (0.29–5.44)	7	0.75 (0.22–2.51)	…	…	…	…

FVL indicates factor V Leiden; OR, odds ratio; PTM, prothrombin G20210A mutation.
*Significant association.

Sources of heterogeneity among studies included the following: study population (number of participants, age groups, geographic region and ethnicity, baseline clinical risk of stroke, and presence of comorbidities); outcome measurement (methods of stroke diagnosis and types of stroke included); and exposure measurement (thrombophilia test methods, timing of testing after stroke in cases, and exclusion of patients taking anticoagulants).

From our sensitivity analysis by study region, the ORs for PCD and PSD were notably higher in studies conducted in Asia than other regions (Table 2). These disparities could be, in part, because of differences in the prevalence of inherited thrombophilias in different regions. For example, PCD, PSD, and ATD have been reported to be more common in the Asian population than in whites.[60–62] In one included study from Taiwan,[63] the prevalence of these natural anticoagulant deficiencies was distinctly high, affecting 27% of the cases.

Our study has several limitations. First, because this is a meta-analysis of case-control studies, the results may be affected by biases inherent to case-control studies, including selection bias and misclassification bias. In a small number of studies, controls were not drawn from the same population as cases. For instance, cases were recruited from patients referred for clinical thrombophilia testing, whereas controls were recruited from a population without a history of thrombosis in 3 studies.[19,31,39] In such studies, the presence of inherited thrombophilia in the cases may be overrepresented because of selection bias. In most studies in which clinical stroke risk factors were reported in both cases and controls, the risk factors were more prevalent in cases than controls. These imbalances could have confounded the results of these studies. Moreover, cases with recurrent stroke were included in a few studies,[26–28] possibly resulting in overrepresentation of thrombophilia in the cases for such studies. However, a sensitivity analysis excluding these 3 studies reassuringly yielded similar results to the original analysis. Misclassification of exposure status could have arisen if the exposure assessors were not blinded or if there were confounders that influenced the results of thrombophilia testing. This is especially true in the case of natural anticoagulant deficiencies (PCD, PSD, and ATD), where thrombophilia status was defined by phenotypic assays as opposed to genetic testing. Acute thrombosis, including stroke, may cause acquired natural anticoagulant deficiencies and lead to the appearance of higher frequencies of such conditions in stroke cases. However, most studies avoided this issue by requiring repeated testing after the short-term phase to define deficiencies. The use of anticoagulants and the presence of certain medical conditions (eg, liver disease) can also cause acquired deficiencies of natural anticoagulants. Attempts to account for these factors varied between studies. Second, we were not able to perform subgroup analyses by ethnicity or stroke subtype because of a lack of disaggregated data for these variables. Finally, although we found a significant association between inherited thrombophilia and ischemic stroke, this cannot be taken as evidence of a causal relationship nor can it be considered supportive of thrombophilia testing in clinical practice. Further studies are needed to determine whether thrombophilia testing in patients with otherwise unexplained arterial ischemic stroke is beneficial and whether and how the results should influence management.

Despite its limitations, our study has several strengths. First, our meta-analysis included the largest number of studies and participants to date. Second, to minimize publication bias, our literature search included "gray literature," such as conference abstracts and letters to editors. Third, the included studies originated from a wide range of geographic regions and the results may, therefore, be applicable to clinicians and patients around the world.

Conclusions

Our systematic review and meta-analysis demonstrates an association between multiple inherited thrombophilias and the risk of arterial ischemic stroke in adults. Further studies are needed to determine whether inherited thrombophilias have an impact on clinical outcomes, such as recurrent stroke, and whether the finding of inherited thrombophilia should influence clinical management of patients with arterial ischemic stroke.

Disclosures

None.

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Supplemental Material

Data S1.

Supplemental Methods: Search Strategies

Database: MEDLINE (PubMed) (From 1946 to December 31st, 2018)
Search Strategy:

1. Stroke[MeSH] OR "brain ischemia"[MesH] OR stroke[tiab] OR "cerebrovascular accident"[tiab] (298198)
2. Thrombophilia[MeSH] OR thrombophili* [tiab] OR "inherited thrombophilia"[tiab] (28458)
3. Factor V"[MeSH] OR "Factor V Leiden"[tiab] OR "activated protein C resistance"[MeSH](8387)
4. Prothrombin[MeSH] OR prothrombin mutation [tiab] (10665)
5. Protein C deficiency[MesH] OR protein C deficiency[tiab] (1966)
6. Protein S deficiency[MeSH] OR protein S deficiency[tiab] (1704)
7. Antithrombin III Deficiency[MeSH] OR antithrombin deficiency[tiab] (1565)
8. 2 OR 3 OR 4 OR 5 OR 6 OR 7 (56664)
9. 1 AND 8 (2073)
10. Filters: Publication date to 2018/12/31; Humans; English; Adolescent: 13-18 years; Adult: 19+ year (1115)

MEDLINE (PubMed) Query:

((((((("thrombophilia"[MeSH Terms] OR (thrombophilia[tiab] OR thrombophilia'[tiab] OR thrombophilia's[tiab] OR thrombophiliac[tiab] OR thrombophiliacs[tiab] OR thrombophilias[tiab] OR thrombophilias'[tiab] OR thrombophilic[tiab] OR thrombophilic'[tiab] OR thrombophilicity[tiab] OR thrombophilics[tiab] OR thrombophilie[tiab] OR thrombophilies[tiab] OR thrombophilis[tiab]) OR "inherited thrombophilia"[tiab] OR "genetic polymorphisms"[tiab]) OR ("Factor V"[MeSH] OR "Factor V Leiden"[tiab] OR "activated protein C resistance"[MeSH])) OR ("prothrombin"[MeSH Terms] OR prothrombin mutation[tiab])) OR ("protein c deficiency"[MeSH Terms] OR "Protein C deficiency"[tiab])) OR ("protein s deficiency"[MeSH Terms] OR protein S deficiency[tiab])) OR ("antithrombin iii deficiency"[MeSH Terms] OR antithrombin deficiency[tiab])) AND ("stroke"[MeSH Terms] OR "brain ischemia"[MesH] OR stroke[tiab] OR "cerebrovascular accident"[tiab]) AND (("0001/01/01"[PDAT] : "2018/12/31"[PDAT]) AND "humans"[MeSH Terms] AND English[lang] AND ("adolescent"[MeSH Terms] OR "adult"[MeSH Terms]))

Database: EMBASE (From inception to December 31st, 2018)
Search Strategy:

1. 'cerebrovascular accident'/exp OR 'cerebrovascular accident':ti,ab OR 'brain ischemia'/exp OR 'brain ischemia':ti,ab OR 'stroke':ti,ab (513281)
2. 'thrombophilia'/exp OR 'thrombophili*':ti,ab OR 'inherited thrombophilia'/exp OR 'inherited thrombophilia':ti,ab OR 'genetic polymorphis*':ti,ab (45868)
3. 'blood clotting factor 5'/exp OR 'blood clotting factor 5 leiden'/exp OR 'factor v leiden':ti,ab OR 'activated protein c resistance'/exp OR 'activated protein c resistance':ti,ab (15829)
4. 'prothrombin'/exp OR (prothrombin NEAR/2 mutation):ti,ab (21764)
5. 'protein c deficiency'/exp OR 'protein c deficiency':ti,ab (3310)
6. 'protein s deficiency'/exp OR 'protein s deficiency':ti,ab (3066)
7. 'antithrombin deficiency'/exp OR 'antithrombin deficiency':ti,ab (2951)
8. 2 OR 3 OR 4 OR 5 OR 6 OR 7 (75736)
9. 1 AND 8 (4356)
10. #9 AND ([adolescent]/lim OR [adult]/lim OR[aged]/lim OR [middle aged]/lim OR [very elderly]/lim OR [young adult]/lim) AND [<1966-2018]/py AND [english]/lim NOT 'case report'/de (1300)

EMBASE Query:

('cerebrovascular accident'/exp OR 'cerebrovascular accident':ti,ab OR 'brain ischemia'/exp OR 'stroke':ti,ab) AND ('thrombophilia'/exp OR 'thrombophili*':ti,ab OR 'inherited thrombophilia'/exp OR 'inherited thrombophilia':ti,ab OR 'genetic polymorphis*':ti,ab OR 'blood clotting factor 5'/exp OR 'blood clotting factor 5 leiden'/exp OR 'factor v leiden':ti,ab OR 'activated protein c resistance'/exp OR 'activated protein c resistance':ti,ab OR 'prothrombin'/exp OR ((prothrombin NEAR/2 mutation):ti,ab) OR 'antithrombin deficiency'/exp OR 'antithrombin deficiency':ti,ab OR 'protein c deficiency'/exp OR 'protein c deficiency':ti,ab OR 'protein s deficiency'/exp OR 'protein s deficiency':ti,ab) AND ([adolescent]/lim OR [adult]/lim OR [aged]/lim OR [middle aged]/lim OR [very elderly]/lim OR [young adult]/lim) AND [<1966-2018]/py AND [english]/lim NOT 'case report'/de

Database: Cochrane Library (From 1946 to December 31st, 2018)
Search Strategy:

1. Stroke[MeSH] OR "brain ischemia"[MesH] OR stroke:ti,ab,kw OR "cerebrovascular accident":ti,ab,kw (52117)
2. Thrombophilia[MeSH] OR thrombophili*:ti,ab,kw OR "inherited thrombophilia*":ti,ab,kw (700)
3. Factor V"[MeSH] OR "Factor V Leiden":ti,ab,kw OR "activated protein C resistance"[MeSH](178)
4. Prothrombin[MeSH] OR “prothrombin mutation”:ti,ab,kw (461)
5. Protein C deficiency[MesH] OR “protein C deficiency”:ti,ab,kw (44)
6. Protein S deficiency[MeSH] OR “protein S deficiency”:ti,ab,kw (30)
7. Antithrombin III Deficiency[MeSH] OR “antithrombin deficiency”:ti,ab,kw (48)
8. 2 OR 3 OR 4 OR 5 OR 6 OR 7 (1189)
9. 1 AND 8 (70)
10. 9 limit to December 2018 (54)

Table S1. Characteristics of Included Studies: Types of Thrombophilias, Numbers of Participants, and Study Population.

Reference	Country	Study period	Types of thrombophilia tested					Number of cases/controls	Study population	Control Identification	Stroke diagnosis	Case-control matching for
			FVL	PTM	PCD	PSD	ATD					
Anadure 2017(1)	India	2010-2014	+					120/120	Hospitalized stroke ward patients, National Institute of Mental Health and Neuro Sciences, Bangalore Age 15-45 Partial or complete occlusion of common carotid, internal carotid and vertebral arteries/ anterior circulation strokes/ posterior circulation stroke/ occlusive disease of the large vessels of the brain on MRA or DSA Exclude: Hemorrhagic stroke; stroke due to trauma, infection, or tumors; vessel dissection; CNS vasculitis; malignancy or blood dyscrasia; aortoarteritis; nephrotic syndrome; cardioembolic stroke; vascular malformations and aneurysms; immunocompromised patients	Unrelated healthy subjects	CT/MRI/MRA	Age, sex
Aznar 2004(2)	Spain	NR	+	+				49/294	Age 18-50 Unit of thrombophilia Cryptogenic stroke without signs of atherosclerosis, heart disease, foramen ovale or vessel occlusive disease	Healthy subjects from the same geographic area and ethnic background	CT/MRI	Age, geographic area, ethnicity
Belvis 2006(3)	Spain	2001-2004	+	+				89/150	Stroke Unit, Hospital de la Santa Creu I Sant Pau, Barcelona First-ever cryptogenic stroke by TOAST criteria Exclude: Pregnancy and puerperal stage; TIA; strokes in other TOAST criteria	Previously published study in Barcelona population	CT/MRI	-
Bentolila 1997(4)	France	1993-1995		+				125/134	Age < 45 Non-transient arterial cerebral ischemia	Young healthy white men and women without history of thrombosis	CT	-
Biswas 2009(5)	India	NR	+	+	+	+		120/120	Outpatient Departments and Wards of the Departments of Neurosciences and Hematology, All India Institute of Medical Sciences, New Delhi Age <40 with acute ischemic stroke Stroke of non-cardioembolic origin Present within 4 weeks of onset Of Northern Indian origin Exclude: Cardioembolic stroke; past history of cardiovascular disease; on oral anticoagulants during the first sample collection; DM, hyperlipoproteinemia, cancer, sickle cell anemia, and liver disease	Apparently healthy hospital staffs and their relatives or from unrelated attendants of the patients Exclude: Taking medication; history of surgery or trauma in the past 30 days; History of bleeding, thrombotic, or cardiac disorders; pregnancy	CT/MRI	Age, sex

Reference	Country	Study period	Types of thrombophilia tested					Number of cases/controls	Study population	Control Identification	Stroke diagnosis	Case-control matching for
			FVL	PTM	PCD	PSD	ATD					
Bolaman 2009(6)	Turkey	2003-2004	+	+				24/53	Department of Neurology, Adnan Menderes University, Aydin Stroke from cerebral infarct Exclude: cerebral venous thrombosis; previous thromboembolic events; cerebrovascular thromboembolic and hemorrhagic event; TIA, drug use to influence the coagulation pathways; age <45	Healthy subjects	CT/MRI	-
Buyru 2005(7)	Turkey	NR	+					29/20	Neurology Clinic, Haydarpasa Numune Hospital, Istanbul Ischemic stroke patients	Healthy subjects	CT/MRI	-
Catto 1995(8)	United Kingdom	NR	+					386/247	Four acute-care hospitals in Leeds Acute ischemic stroke by WHO definition	Leeds blood transfusion service and general practitioners	WHO definition	-
Celiker 2009(9)	Turkey	2000-2003	+	+				162/285	Neurology Department of Baskent University Hospital Acute ischemic stroke	Previously published study	MRI	-
Chatterjee 2013(10)	India	NR		+	+	+	+	52/52	Stroke Clinic, Department of Neurology, All India Institute of Medical Sciences, New Delhi Age <45 with non-embolic arterial ischemic stroke Exclude: Cardioembolic, hemorrhagic stroke; systemic diseases (cancer, sickle cell anemia, vasculitis)	Healthy individuals	CT/MRI	Age, sex
Chen 2003(11)	Taiwan	NR			+	+	+	104/35	Non-cardiac cerebral ischemia Exclude: SLE; APS; collagen diseases; taking anticoagulants and hormonal drugs; TIA	Hospital employees, family of patients, or individuals asking for neurologic examination free of medical disorders	CT/MRI	-
Cushman 1998(12)	USA	1989-1990	+					149/482	Cardiovascular Health Study (Random sample of Medicare eligibility list) Age ≥65 Development of stroke in participants free of baseline history of stroke	Cardiovascular Health Study	Review by committee	-
D'Amico 1998(13)	Italy	1996-1997	+		+	+		31/124	C. Besta Neurological Institute, Milan and Ospedale L. Mandic Age <45 with ischemic stroke	Healthy volunteer from staff Age <45	CT/MRI	-
De Lucia 1999(14)	Italy	1994-1995	+		+	+	+	50/100	Ischemic stroke	Healthy subjects	WHO definition	Age, sex
Djordjevic 2012(15)	Serbia	NR	+	+				73/120	Young adults having cerebral infarcts	Healthy blood donors	MRI	-
Egan 2000(16)	USA	1997-1998		+				42/635	Oregon Health Sciences University Hospital Age ≤55 with an arterial stroke	Normal healthy individuals from Portland	CT/MRI	-
Erten 2015(17)	Turkey	2007-2009	+	+				212/238	Research and Training Hospital Neurology Clinic, Süleyman Demirel University Ischemic stroke patients	Individuals without history of stroke	NR	Age, Sex

Reference	Country	Study period	Types of thrombophilia tested					Number of cases/controls	Study population	Control Identification	Stroke diagnosis	Case-control matching for
			FVL	PTM	PCD	PSD	ATD					
Eterovic 2007(18)	Croatia	1999-2003	+	+				120/120	Department of Neurology, Clinical Hospital Split First-time acute ischemic stroke Exclude: Age >65, secondary hypercoagulability status, DM type 1, significant obstruction of carotid arteries	Persons attending regular checkups, blood donors, volunteer staffs without cerebrovascular disease	CT/MRI	Age, Sex, cardiovascular risk factors
Fan 2010(19)	USA	1991-1994	+	+				156/5817	Second phase of The Third National Health and Nutrition Examination Survey (NHANES III) Age ≥17 with self-reported stroke	Same population without self-reported stroke	Interview	-
Favaretto 2012(20)	Italy	2008-2011	+	+	+	+	+	340/272	Angiology Unit, S. Orsola-Malpighi University Hospital Stroke of unknown cause by TOAST criteria Exclude: Large vessel, small vessel, cardioembolic stroke; stroke from multiple etiologies; neoplasia, dementia	Out-patients referred for varicose veins and/or early venous insufficiency in the legs without clinical indication of stroke Exclude: ABI≤0.9; previous coronary event; neoplasia; DVT	CT/MRI	-
Go 2003(21)	USA	1996-1997	+					137/214	Cohort from Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) study Ambulatory adults with nonvalvular AF Patients Ischemic stroke	Same cohort with no prior hospitalization for ischemic stroke	ICD-9 with record review	Follow-up time
Haeusler 2012(22)	Germany	NR	+	+				44/282	Stroke outpatient clinic Cryptogenic stroke by TOAST criteria Exclude: Age ≥55	Healthy blood donors without vascular diseases	CT/MRI	-
Halbmayer 1998(23)	Austria	NR	+	+				20/20	Unexplained juvenile stroke	Healthy subjects	NR	Age, sex
Hamedani 2013(24)	USA	1992-1996 2001-2003 2003-2007	+					830/907	Genetics of Early Onset Stroke (GEOS) study First ischemic stroke Age 15-49 Exclude: trauma; procedure; hemorrhage; CVST; infection; vasculitis	Baltimore-Washington area Participants without history of stroke	Record review	Age, region of residence
Hankey 2001(25)	Australia	1996-1998	+	+	+	+	+	219/205	A university teaching hospital in Western Australia First-ever ischemic stroke	Randomly selected from the Western Australian electoral roll	CT/MRI	Age, sex, postal code
Jerrard-Dunne 2003(26)	England	NR			+	+	+	130/130	Stroke services in South London Age ≤65 Acute ischemic stroke	Sampling of primary care lists in the same geographic area Stroke-free individuals	CT/MRI	Age, sex, ethnicity
Jiang 2014(27)	USA	1992-1996 2001-2003 2003-2007		+				397/426	Genetics of Early Onset Stroke (GEOS) study First ischemic stroke Age 15-49 Exclude: trauma; procedure; hemorrhage; CVST; infection; vasculitis	Baltimore-Washington area Participants without history of stroke	Record review	Age, region of residence

Reference	Country	Study period	Types of thrombophilia tested					Number of cases/controls	Study population	Control Identification	Stroke diagnosis	Case-control matching for
			FVL	PTM	PCD	PSD	ATD					
Juul 2002(28)	Denmark	1991-1997	+					641/7907	The Copenhagen City Heart Study and Copenhagen University Hospital Age 20-95 Ischemic stroke	Control subjects from the Copenhagen City Heart Study free of MI, IS, and non-MI IHD	CT	-
Kamberi 2016(29)	Macedonia	2008-2010	+	+				39/102	Neurology Department, Clinical Hospital, Tetovo Age 18-90 First-ever ischemic stroke Exclude: Renal failure; MI; recent inflammatory or immunologic disease.	Healthy subjects from local residents	CT/MRI	-
Karakus 2005(30)	Turkey	NR	+	+	+	+	+	21/81	Age< 50 Cerebral infarction	Volunteer physicians and laboratory staff	CT/MRI	-
Karttunen 2003(31)	Finland	1991-1998	+	+	+	+	+	58/104	Age 15-60 Ischemic brain infarction of undetermined cause and PFO	Spouse, friend , or randomly selected controls from the population register of the hospital catchment area	CT	Age, sex
Kholodkova 2015(32)	Ukraine	NR	+	+				122/40	Neurology Unit, Kyiv City Hospital Acute ischemic stroke	Healthy donors without previous history of stroke	CT/MRI	-
Krajcoviechova 2015(33)	Czech Republic	2009-2012	+	+				423/614	Thomayer Hospital or Charles University Hospital Age 18-81 First-ever acute ischemic stroke	Participants of the Czech post-MONICA study residing in Prague East and Pilsen districts Age 50-75 Free of vascular diseases	CT/MRI	-
Kumar 2017(34)	India	NR	+					250/250	All India Institute of Medical Sciences, New Delhi Age 18-85, North Indian Ischemic stroke within three years before recruitment	Spouses, relatives or patients attending neurology department for treatment other than stroke Age 18-85, North Indian No prior stroke	CT	Age, sex
Linnemann 2008(35)	Germany	2000-2006	+	+	+	+	+	41/993	Patients with history of VTE registered in the MAISTHRO Database Age 17-90 with ischemic stroke	Same cohort without stroke	CT/MRI	-
Longstreth 1998(36)	USA	1991-1995	+	+				41/382	King, Pierce, Snohomish counties, Washington Women age 18-44 Diagnosed of first stroke	Random-digit dialing Same area Healthy women age 18-44	CT/MRI	Age
Lopaciuk 2001(37)	Poland	1996-1999	+	+				100/238	Age ≤45 History of ischemic stroke without a cardiac embolic source	Healthy blood donor and hospital staff	CT/MRI	-
Martinelli 2006(38)	Italy	1994-2005	+	+				105/293	Referred for thrombophilia screening at Thrombosis Center, University of Milan and IRCCS Maggiore Hospital Caucasian women of fertile age	Partners and friends of patients	CT/MRI	-

Reference	Country	Study period	Types of thrombophilia tested					Number of cases/controls	Study population	Control Identification	Stroke diagnosis	Case-control matching for
			FVL	PTM	PCD	PSD	ATD					
									First ischemic stroke	Caucasian women of fertile age without previous thrombosis		
Mayer 1993(39)	USA	1990-1991				+		94/94	Columbia-Presbyterian Medical Center North Manhattan Stroke Study Age >39 Residing in fie Zip code if northern Manhattan	Patients admitted to the medicine and neurology services Age >39 in same area Exclude: Thrombosis; bleeding; renal/liver failure; malignancy; infection	NR	-
Mochan 2005(40)	South Africa	NR				+		33/33	Chris Hani Baragwanath Hospital in Soweto HIV-infected Stroke with cerebral infarction	Inpatients of same hospital HIV-infected No cerebral infarction	CT	Age, sex, CD4 count
Moskau 2010(41)	Germany	1999-2000	+	+				167/500	Of German descent Ischemic stroke	Blood donors of German descent	CT/MRI	-
Nagayama 1996(42)	Japan	NR	+					106/37	Chronic ischemic stroke	Patients with neurological diseases without vascular involvement	NR	-
Pahus 2016(43)	Denmark	2004-2012	+	+	+	+	+	377/64631	Center of Hemophilia and Thrombosis, Aarhus University Hospital Age 18 - 50 referred to thrombophilia investigation Ischemic stroke	Previously published data of general western population	WHO and record review	-
Pestana 2009(44)	Venezuela	2005-2007	+					54/134	Banco Municupal de Sangre, Caracas Stroke	Randomly selected, unrelated, and apparently healthy subjects without personal and family history of vascular, arterial, or thromboembolic diseases	CT	-
Petrovic 2003(45)	Slovenia	NR	+					96/115	Acute cerebral infarction	General population in the same region Exclude: History of CVD, CHD, PAD; carotid bruit	CT/MRI	-
Pezzini 2005(46)	Italy	1997-2002	+	+				163/158	Department of Neurology, University of Brescia, Brescia Age <45 Admitted patients with first-ever ischemic stroke	Staff of same hospital No vascular diseases	CT/MRI	Age, sex
Pezzini 2007(47)	Italy	NR	+	+				108/216	Department of Neurology, University of Brescia, Brescia Age <45 Unselected, unrelated women admitted first-ever acute ischemic stroke	Women from the staff of same hospital	CT/MRI	Age, sex

Reference	Country	Study period	Types of thrombophilia tested					Number of cases/controls	Study population	Control Identification	Stroke diagnosis	Case-control matching for
			FVL	PTM	PCD	PSD	ATD					
Press 1996(48)	USA	NR	+					161/367	Wards and clinics at Portland Veterans Affairs Medical Center and Oregon Health Sciences University Acute ischemic stroke within 7 days of enrollment	Healthy elderly (N=54) Stroke risk group (N=116) Blood donors (N=197)	NR	-
Pullmann 2004(49)	Slovakia	NR	+	+				23/71	White SLE patients with thromboembolic stroke Exclude: Hemorrhage; vasculitis	SLE patients without CVA/CHD	CT/MRI	-
Ranellou 2015(50)	Greece	NR	+	+				51/70	Evangelismos General Hospital Age 18-50 Ischemic stroke within 24 hour of onset Native Greek Exclude: Major systemic diseases; coagulopathy; anticoagulants; trauma	Healthy blood donors from the same area without history of stroke/thrombosis	CT/MRI	Age
Ridker 1995(51)	USA	NR	+					209/704	Physicians' Health Study Apparently healthy US male physicians Age 40-84 Developed stroke during 10-year follow-up	Randomly selected participants from the same study No cardiovascular disease at the time of event in cases	CT and record review	Age, smoking status, time since randomization in study
Ridker 1999(52)	USA	NR		+				259/1774	Physicians' Health Study Apparently healthy US male physicians Age 40-84 Developed stroke during 10-year follow-up	Randomly selected participants from the same study No cardiovascular disease during follow up	CT and record review	Age, smoking status
Ripoll 1997(53)	French	NR	+					321/428	Age >65 Ischemic cerebrovascular events	Age >65 No personal or familial history of CVA/CHD	NR	-
Romdhane 2011(54)	Tunisia	NR			+	+	+	20/54	Age <50 First non-cardioembolic ischemic stroke	NR	NR	Age
Rubattu 2005(55)	Italy	1998-2003	+	+				294/286	Neurological Department, University of Sassari, Sardinia Ischemic stroke	Randomly selected patients admitted to the same hospital with vascular risk factors or history of cardiovascular disease Exclude: Current or previous CVA	CT/MRI	-
Rubattu 2005(56)	Italy	NR	+	+				115/180	Neurological Institute, University La Sapienza, Rome Age 15-45 First-ever ischemic stroke within the 8 weeks preceding the admission into the hospital	Healthy blood donors from the same center No drug/OCP use No family history of stroke	CT/MRI	Age
Sastry 2006(57)	United Kingdom	1993-1998	+	+	+	+	+	101/101	Hospitals in the North West and Mersey Regions, Manchester Age 16-39 at the time of stroke First ischemic stroke identified by ICD-9	Age 16-39 Resides in Manchester Exclude: History of cardiovascular	WHO and record review	Age, sex

Reference	Country	Study period	Types of thrombophilia tested					Number of cases/controls	Study population	Control Identification	Stroke diagnosis	Case-control matching for
			FVL	PTM	PCD	PSD	ATD					
									Exclude: Surgery/injury within 10 weeks; malignancy	disease; stroke; arterial thrombosis		
Shi 2008(58)	China	2006-2007	+					97/99	Neurological department, Beijing Tiantan Hospital Age 18-45 Acute ischemic stroke Exclude: AF; hemorrhage	Other departments of the Tiantan Hospital Age 18-45 No cardiovascular or cerebrovascular diseases	CT/MRI	Age, sex
Slooter 2005(59)	Netherlands	1990-2001	+	+				193/767	Nine participating Dutch hospitals University Medical Center Utrecht Women age 18–49 Hospitalized for a first ischemic stroke Exclude: TIA; hemorrhagic stroke; CSVT; dissection; history of CHD/CVD; terminal illness; aphasia or cognitive impairment	Random-digit dialing Women age 18–49 No history of CHD/CVD/PAD	CT/MRI	Age, residence, year of stroke
Smiles 2002(60)	USA	NR		+				182/453	Cardiovascular Health Study (Random sample of Medicare eligibility list) Age ≥65 (free of clinical CVD at baseline) Had stroke during 6-year follow up	Cardiovascular Health Study Free of subclinical CVD group African-American group Population-based controls	CT	-
Supanc 2014(61)	Croatia	2009-2012	+	+				155/150	Department of Neurology, Sestre milosrdnice University Hospital Center, Zagreb Ischemic stroke Age <55	Subjects treated at Pain Clinic of same center No history of vascular or thromboembolic disease	CT/MRI	Age, sex
Szolnoki 2003(62)	Hungary	1998-2002	+	+				867/743	Department of Neurology and Neurophysiology, Pandy Kalman County Hospital Consecutive Hungarian patients First acute ischemic stroke	Randomly selected from local GP registers Healthy Caucasian Hungarian No evidence of stroke on CT/MRI	MRI	Age, sex
Tatarskyy 2010(63)	Ukraine	2008-2009	+	+				183/188	Randomly selected from different regions in Ukraine Survivor of ischemic stroke referred for rehabilitation	I: General population of Ukraine II: Healthy individuals age >65 without history of ischemic stroke	NR	-
They-They 2012(64)	Morocco	2008-2009	+	+				91/182	University Hospital Center, Casablanca Admitted for ischemic stroke	Presumably healthy blood donors	CT/MRI	Age, sex, ethnicity
Tupitsyna 2013(65)	Russia	NR	+	+				1450/817	Stroke patients from Russian and Ukranian population	Russian and Ukranian population	NR	-
Voetsch 2000(66)	Brazil	1996-1998	+	+				153/225	University Hospitals of the State University of Campinas and the University of Sao Paulo First cerebral ischemic event occurring at age 15-45 Absence of systemic disease or cancer	Randomly selected hospital staffs	CT/MRI	Age, sex

Reference	Country	Study period	Types of thrombophilia tested					Number of cases/controls	Study population	Control Identification	Stroke diagnosis	Case-control matching for
			FVL	PTM	PCD	PSD	ATD					
									Exclude: PCD, PSD, ATD; Antiphospholipid antibodies			
Wypasek 2009(67)	Poland	NR	+	+				100/107	PFO patients Age <65 History of first-ever cryptogenic ischaemic stroke after a median of 8 (3–19) months before enrollment Exclude: Inflammatory states; cancer; AF; DM; valvular heart disease; CAD; carotid artery stenosis	Apparently healthy white individuals	CT/MRI	Age, sex
Zimba 2017(68)	Zambia	2014-2015			+	+		52/52	In-patients and Out-patients at University Teaching Hospital, Lusaka Age ≥18 HIV positive Ischemic stroke	Same center HIV positive patients without ischemic stroke	CT/MRI	Age, sex, ethnicity

NR, not reported; FVL, Factor V Leiden; PTM, Prothrombin G20210A Mutation; PCD, Protein C Deficiency; PSD, Protein S Deficiency; ATD, Antithrombin Deficiency; CT, computed tomography; MRI, Magnetic Resonance Imaging; MRA Magnetic Resonance Angiogram; TIA, transient ischemic attack; DM, Diabetes Mellitus; WHO, World Health Organization; SLE, systemic lupus erythematosus; APS, antiphospholipid syndrome; PFO, patent foramen ovale; VTE, venous thromboembolism; CVD, cerebrovascular disease; CHD, coronary heart disease; CVA, cerebrovascular accidents; AF, atrial fibrillation; OCP, oral contraceptive pills; PAD; peripheral arterial disease; CSVT, cerebral venous sinus thrombosis; HIV, human immunodeficiency virus.

Table S2. Characteristics of Included Studies: Demographic Data of Cases and Controls.

References	Mean Age, year Cases/Controls	Male, % Cases/Controls	Cryptogenic stroke in cases, %	Ethnicity, % Cases/Controls	Diabetes, % Cases/Controls	Hypertension, % Cases/Controls	Dyslipidemia, % Cases/Controls	Hormonal Drug Use, % Cases/Controls	Smoking, % Cases/Controls
Anadure 2017(1)	33/35	93/93	NR	NR/NR	NR/NR	13/NR	33/NR	NR/NR	63/43*
Aznar 2004(2)	18-50 (Range)/NR	NR/NR	100	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR
Belvis 2006(3)	57/48	60/45	100	NR/NR	17/2.7	36/13	38/14	6/NR	51/37
Bentolila 1997(4)	41/34	58/50	44	White 100/100	NR/NR	NR/NR	NR/NR	25/NR	NR/NR
Biswas 2009(5)	NR/NR	NR/NR	NR	Indian 100/100	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR
Bolaman 2009(6)	64/59	67/58	NR	NR/NR	33/32	63/60	38/36	NR/NR	21/19
Buyru 2005(7)	67/61 (Median)	NR/NR	NR	NR/NR	21/NR	59/NR	NR/NR	NR/NR	10/NR
Catto 1995(8)	74/76 (Median)	NR/NR	NR	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR
Celiker 2009(9)	70/NR	54/NR	30	NR/NR	27/NR	65/NR	39/NR	NR/NR	NR/NR
Chatterjee 2013(10)	23/NR	63/63	NR	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR
Chen 2003(11)	62/61	68/69	NR	NR/NR	28/0	70/0	NR/NR	NR/NR	NR/NR
Cushman 1998(12)	76/72	48/37	NR	NR/NR	39/16	60/34	NR/NR	NR/NR	45/50
D'Amico 1998(13)	34/33	65/32	NR	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR
De Lucia 1999(14)	35/NR	76/NR	NR	NR/NR	NR/NR	30/NR	54/NR	0/NR	NR/NR
Djordjevic 2012(15)	40/39	56/70	NR	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR
Egan 2000(16)	43/41	52/49	NR	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR
Erten 2015(17)	66/62*	52/45	51	NR/NR	30/24	61/43*	28/23	NR/NR	38/37
Eterovic 2007(18)	61/61 (Median)	64/64	NR	White 100/ 100	30/30	56/56	32/32	NR/NR	38/38
Fan 2010(19)	68/44*	44/48	NR	White 82/82 Black 15/12 Hispanic 3/6	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR
Favaretto 2012(20)	51/52.2	PFO 49 Non- PFO 46 /74	100	White 100/100	PFO 5 Non- PFO 3 /4	PFO 14 Non- PFO 13 /20	PFO 19 Non- PFO 23 /21.7	PFO 12 Non- PFO 12 /0	PFO 21 Non- PFO 24 /17
Go 2003(21)	74/69*	51/62*	NR	White 80/84 Black 6/2 Hispanic 4/2 Native American 1/0 Others 4/9	20/14	66/44*	NR/NR	NR/NR	NR/NR
Haeusler 2012(22)	36/39 (Median)	41/36	100	NR/NR	5/NR	223/NR	36/NR	NR/NR	40.9/NR
Halbmayer 1998(23)	39/39	50/50	100	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR
Hamedani 2013(24)	41/40*	57/55	50.4	White 56/60 Black 44/40	17/5*	43/19*	NR/NR	16/8*	41/28*
Hankey 2001(25)	66/67	64/64	20	NR/NR	25/11*	54/33*	24/22	NR/NR	33/18*
Jerrard-Dunne 2003(26)	White 53/54 Black Caribbean 57/56 Black African 53/55	62/50	NR	White 39/39 Black Caribbean 39/39 Black African 23/23	26/10	59/39	49/42	NR/NR	40/23
Jiang 2014(27)	41/39*	63/55*	NR	White 100/100	11/2*	32/16*	NR/NR	23/11*	43/24*
Juul 2002(28)	63/56*	61/43*	NR	White >99/>99	14/3*	46/17*	NR/NR	NR/NR	80/73*
Kamberi 2016(29)	63/49*	NR/NR	NR	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR
Karakus 2005(30)	40/42	38/52	100	NR/NR	10/5	33/1*	43/43	NR/NR	38/22
Karttunen 2003(31)	44/45	55/57	100	NR/NR	2/4	16/13	NR/NR	27/27	29/24
Kholodkova 2015(32)	73/NR	NR/NR	0	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR
Krajcoviechova 2015(33)	66/61*	61/49*	36	NR/NR	30/10*	87/58*	93/86*	NR/NR	60/53*

References	Mean Age, year Cases/Controls	Male, % Cases/Controls	Cryptogenic stroke in cases, %	Ethnicity, % Cases/Controls	Diabetes, % Cases/Controls	Hypertension, % Cases/Controls	Dyslipidemia, % Cases/Controls	Hormonal Drug Use, % Cases/Controls	Smoking, % Cases/Controls
Kumar 2017(34)	51/53	81/81	NR	North Indian 100/100	32/10*	58/17*	23/6*	NR/NR	39/27*
Linnemann 2008(35)	66/48 (Median)*	56/38*	NR	NR/NR	15/6*	56/25*	46/19*	NR/NR	15/21
Longstreth 1998(36)	37/38	0/0	NR	White 83/90 Black 6/2 Others 11/8	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR
Lopaciuk 2001(37)	38/33	51/66	55	NR/NR	20/NR	42/NR	35/NR	NR/NR	61/NR
Martinelli 2006(38)	35/35	0/0	52	White 100/100	NR/NR	12/3*	10/0*	NR/NR	27/21
Mayer 1993(39)	68/68	48/40	17.1	White 14/21 Black 38/37 Hispanic 46/39 Others 2/2	30/18	75/46*	NR/NR	NR/NR	48/36
Mochan 2005(40)	NR/NR	NR/NR	NR	Black 100/NR	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR
Moskau 2010(41)	55/33*	38/29*	17	White 100/100	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR
Nagayama 1996(42)	40/55	63/18	NR	Japanese 100/100	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR
Pahus 2016(43)	43/NR	51/NR	NR	NR/NR	8/NR	32/NR	37/NR	22/NR	50/NR
Pestana 2009(44)	39/39	39/39	NR	NR/NR	2/2	13/16	NR/NR	13/10	14/21
Petrovic 2003(45)	62/63	63/57	NR	White 100/100	31/4*	66/33*	NR/NR	NR/NR	44/25*
Pezzini 2005(46)	35/35	52/54	31	White 100/100	3/3	17/6*	28/20*	NR/NR	47/25*
Pezzini 2007(47)	34/35	0/0	38	White 100/100	0/2	12/4*	25/11*	40/14	41/13*
Press 1996(48)	64/68	91/80	NR	NR/NR	36/21	72/64	26/30	NR/NR	41/10
Pullmann 2004(49)	37/46	4/1	NR	White 100/100	18/16	41/35	51/37	NR/NR	24/25
Ranellou 2015(50)	37/38	49/54	NR	NR/NR	2/0	16/0*	10/3	NR/NR	35/36
Ridker 1995(51)	63/60	100/100	NR	Predominantly white/Predominantly white	13/4	36/17	12/9	NR/NR	60/58
Ridker 1999(52)	60/59	100/100	NR	Predominantly white/Predominantly white	7/3*	28/16*	12/9*	NR/NR	56/57
Ripoll 1997(53)	66/NR	NR/NR	NR	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR
Romdhane 2011(54)	37/NR	55/NR	NR	NR/NR	NR/NR	<1/NR	NR/NR	<1/NR	<1/NR
Rubattu 2005(55)	75/73 (Median)*	60/57	NR	NR/NR	24/29	65/49*	22/13*	NR/NR	41/38
Rubattu 2005(56)	36/35	44/54	12	NR/NR	2/0	22/4*	18/18	44/Excluded	57/49
Sastry 2006(57)	33/33	43/43	NR	NR/NR	3/1	21/8*	NR/NR	16/16	47/41
Shi 2008(58)	39/39	81/81	NR	Asian 100/100	20/5*	50/13*	NR/NR	NR/NR	72/42*
Slooter 2005(59)	39/40	0/0	0	NR/NR	4/1*	32/6*	8/3*	52/36*	35/32
Smiles 2002(60)	76/72	41/39	NR	White 95/94 Black 5/5 Other 0/5	24/14	53/34	NR/NR	NR/NR	45/55
Supanc 2014(61)	NR/NR	NR/NR	36	White 100/100	4/3	37/19*	63/53	NR/NR	45/24*
Szolnoki 2003(62)	61/60	53/53	NR	White 100/100	32/6*	51/18*	NR/NR	NR/NR	33/11*
Tatarskyy 2010(63)	65/30*	52/45	NR	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR
They-They 2012(64)	49/46	51/52	6.6	NR/NR	18/9*	51/10*	NR/NR	NR/NR	22/7*
Tupitsyna 2013(65)	NR/NR	NR/NR	NR	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR
Voetsch 2000(66)	33/34	41/44	NR	White 75/53 Black 25/47	5/NR	39/NR	31/NR	NR/NR	52/NR
Wypasek 2009(67)	43/44	30/32	NR	White 100/100	NR/NR	NR/NR	NR/NR	NR/NR	19/34

References	Mean Age, year Cases/Controls	Male, % Cases/Controls	Cryptogenic stroke in cases, %	Ethnicity, % Cases/Controls	Diabetes, % Cases/Controls	Hypertension, % Cases/Controls	Dyslipidemia, % Cases/Controls	Hormonal Drug Use, % Cases/Controls	Smoking, % Cases/Controls
Zimba 2017(68)	52/46*	44/44	13	NR/NR	15/6	50/17*	8/8	Excluded/Excluded	4/4

* denotes significant difference; NR, not reported

Table S3. Results of Included Studies: Factor V Leiden.

References	Test Method	Odds Ratio (95%CI)	Number of All FVL (%)		Number of Homozygous FVL (%)		Number of Heterozygous FVL (%)	
			Cases	Controls	Cases	Controls	Cases	Controls
Anadure 2017(1)	PCR/RFLP	3.10 (0.61-15.7; *P* = .15)	6/120 (5)	2/120 (1.7)	0/120 (0)	0/120 (0)	6/120 (5)	2/120 (1.7)
Aznar 2004(2)	PCR/RFLP	2.62 (0.43-13.95)	2/49 (4.1)	5/294 (1.7)				
Belvis 2006(3)	PCR	NR	2/89 (2.2)	6/150 (4)	0/89 (0)	0/150 (0)	2/89 (2.2)	6/150 (4)
Biswas 2009(5)	PCR/RFLP	10.8 (1.3-229.5; *P* = .005)	10/120 (8.3)	1/120 (0.8)	4/120 (3.3)	0/120 (0)	6/120 (5)	1/120 (0.8)
Bolaman 2009(6)	PCR	0.431 (0.074-2.504; *P* > .05)	2/24 (8.3)	2/53 (3.8)	0/24 (0)	0/53 (0)	2/24 (8.3)	2/53 (3.8)
Buyru 2005(7)	PCR/RFLP	NR	1/29 (3.4)	0/20 (0)	1/29 (3.4)	0/20 (0)	0/29 (0)	0/20 (0)
Catto 1995(8)	PCR/RFLP	NR	16/386 (4.1)	14/247 (5.7)	0/386 (0)	0/247 (0)	16/386 (4.1)	14/247 (5.7)
Celiker 2009(9)	PCR/RFLP	NR	21/162 (13)	28/285 (9.8)	1/162 (0.6)	0/285 (0)	20/162 (12.3)	28/285 (9.8)
Cushman 1998(12)	PCR	0.76 (0.32-1.81)	8/149 (5.4)	34/482 (7.1)	0/149 (0)	0/482 (0)	8/149 (5.4)	34/482 (7.1)
D'Amico 1998(13)	PCR	NR	5/31 (16.1)	4/124 (3.2)	0/31 (0)	0/124 (0)	5/31 (16.1)	4/124 (3.2)
De Lucia 1999(14)	PCR	NR	11/50 (22)	2/100 (2)	2/50 (4)	0/100 (0)	9/50 (18)	2/100 (2)
Djordjevic 2012(15)	PCR/RFLP	1.45 (0.47-4.48)	6/73 (8.2)	7/120 (5.8)				
Erten 2015(17)	PCR/in situ hybridization	NR	32/212 (15.1)	21/238 (8.8)	3/212 (1.4)	0/238 (0)	29/212 (13.7)	21/238 (8.8)
Eterovic 2007(18)	PCR/RFLP	NR (*P* = .023)	10/120 (8.3)	3/120 (2.5)	0/120 (0)	0/120 (0)	10/120 (8.3)	3/120 (2.5)
Fan 2010(19)	PCR	0.82 (0.29-2.34)	6/156 (3.8)	262/5817 (4.5)				
Favaretto 2012(20)	PCR	NR	16/340 (4.7) PFO: 3/136 (2.2) Non-PFO: 13/204 (6.4)	14/272 (5.1)	0/340 (0) PFO: 0/136 (2.2) Non-PFO: 0/204 (6.4)	0/272 (0)	16/340 (4.7) PFO: 3/136 (2.2) Non-PFO: 13/204 (6.4)	14/272 (5.1)
Go 2003(21)	PCR/RFLP	Crude OR 1.59 (0.58-4.36) Adjusted OR for age and prior ischemic stroke: 1.81 (0.65-5.05)	8/137 (5.8)	8/214 (3.7)	0/137 (0)	0/214 (0)	8/137 (5.8)	8/214 (3.7)
Haeusler 2012(22)	PCR	NR (*P* = .073)	7/41 (17.1)	22/282 (7.8)	0/41 (0)	0/282 (0)	7/41 (17.1)	22/282 (7.8)
Halbmayer 1998(23)	PCR	NR (*P* = 1.00)	1/20 (5)	2/20 (10)	0/20 (0)	0/20 (0)	1/20 (5)	2/20 (10)
Hamedani 2013(24)	SNP array	1.00 (0.60-1.66; *P* = 1.00)	30/830 (3.6)	34/907 (3.7)				
Hankey 2001(25)	PCR/RFLP	2.1 (0.6-6.8)	10/219 (4.6)	4/205 (2)				
Juul 2002(28)	PCR/RFLP	Age-adjusted OR 0.92 (0.56-1.53)	17/231 (7.4)	629/7907 (8)	1/231 (0.4)	17/7907 (0.2)	16/231 (6.9.)	612/7907 (7.7)
Kamberi 2016(29)	PCR/ hybridization	1.15 (0.33-4.02; *P* = .83)	3/39 (7.7)	9/102 (8.8)	0/39 (0)	0/102 (0)	3/39 (7.7)	9/102 (8.8)
Karakus 2005(30)	PCR	NR	3/21 (14.3)	4/81 (4.9)	0/21 (0)	1/81 (1.2)	3/21 (14.3)	3/81 (3.7)
Karttunen 2003(31)	PCR	7.8 (0.8-71.3)	4/57 (7)	1/104 (1)	0/57 (0)	0/104 (0)	4/57 (7)	1/104 (1)
Kholodkova 2015(32)	PCR	NR	3/114 (2.6)	0/40 (0)	0/114 (0)	0/40 (0)	3/114 (2.6)	0/40 (0)
Krajcoviechova 2015(33)	PCR	Multivariate adjusted OR 1.22 (0.74-2.00; *P* =.43)	44/423 (10.4)	53/614 (8.6)	2/423 (0.5)	2/614 (0.3)	42/423 (9.9)	51/614 (8.3)
Kumar 2017(34)	PCR	1.80 (0.60-5.37; *P* =.29)	9/250 (3.6)	5/250 (2)	0/250 (0)	0/250 (0)	9/250 (3.6)	5/250 (2)
Linnemann 2008(35)	PCR	0.87 (0.42-1.79; *P* =.86)	10/41 (24.4)	278/1020 (27.3)	0/41 (0)	22/1020 (2.2)	10/41 (24.4)	256/1020 (25.1)
Longstreth 1998(36)	PCR/RFLP	0 (0-2.5)	0/40 (0)	16/388 (4.1)	0/40 (0)	0/388 (0)	0/40 (0)	16/388 (4.1)
Lopaciuk 2001(37)	PCR/RFLP	0.7 (0.2-2.6)	3/100 (3)	10/238 (4.2)	0/100 (0)	0/238 (0)	3/100 (3)	10/238 (4.2)
Martinelli 2006(38)	NR ("DNA analysis")	Crude OR 2.5 (0.8-7.5) Adjusted OR for age 2.6 (0.8-8.0)	6/105 (5.7)	7/293 (2.4)	0/105 (0)	0/293 (0)	6/105 (5.7)	7/293 (2.4)
Moskau 2010(41)	PCR	NR (*P* = .35)	11/167 (6.6)	30/500 (6)	1/167 (0.6)	1/500 (0.2)	10/167 (6)	29/500 (5.8)
Nagayama 1996(42)	PCR/RFLP	NR	0/106 (0)	0/37 (0)	0/106 (0)	0/37 (0)	0/106 (0)	0/37 (0)

References	Test Method	Odds Ratio (95%CI)	Number of All FVL (%)		Number of Homozygous FVL (%)		Number of Heterozygous FVL (%)	
			Cases	Controls	Cases	Controls	Cases	Controls
Pahus 2016(43)	PCR	Homozygous 4.06 (0.86-36.51) Heterozygous 1.02 (0.54-1.79)	15/207 (7.2)	282/4188 (6.7)	1/207 (0.5)	5/4188 (0.1)	14/207 (6.8)	277/4188 (6.6)
Pestana 2009(44)	PCR	2.60 (0.52-12.98)	4/54 (7.4)	4/134 (3)	0/54 (0)	0/134 (0)	4/54 (7.4)	4/134 (3)
Petrovic 2003(45)	PCR	1 (0.26-3.76; *P* = .97)	4/96 (4.2)	5/115 (4.3)	1/96 (1)	0/115 (0)	3/96 (3.1)	5/115 (4.3)
Pezzini 2005(46)	PCR	1.17 (0.35-3.92)	6/163 (3.7)	5/158 (3.2)	0/163 (0)	0/158 (0)	6/163 (3.7)	5/158 (3.2)
Pezzini 2007(47)	PCR	1.10 (0.51-5.70)	5/108 (4.6)	6/216 (2.8)	0/108 (0)	0/216 (0)	5/108 (4.6)	6/216 (2.8)
Press 1996(48)	PCR	NR	4/161 (2.5)	19/367 (5.2)	0/161 (0)	0/367 (0)	4/161 (2.5)	19/367 (5.2)
Pullmann 2004(49)	PCR	NR	2/23 (8.7)	3/71 (4.2)	0/23 (0)	0/71 (0)	2/23 (8.7)	3/71 (4.2)
Ranellou 2015(50)	PCR/ hybridization	NR (*P* = .20)	7/51 (13.7)	4/70 (5.7)	0/51 (0)	0/70 (0)	7/51 (13.7)	4/70 (5.7)
Ridker 1995(51)	PCR	Crude RR 0.7 (0.3-1.4; *P* =.3) Multivariate adjusted RR 1.0 (0.4-2.2; *P* =.9)	9/209 (4.3)	42/704 (6)	0/209 (0)	0/704 (0)	9/209 (4.3)	42/704 (6)
Ripoll 1997(53)	PCR	1.7 (0.8-3.4)	17/321 (5.3)	14/428 (3.3)	0/321 (0)	0/428 (0)	17/321 (5.3)	14/428 (3.3)
Rubattu 2005(55)	PCR/RFLP	NR (*P* = .27)	5/294 (1.7)	2/286 (0.7)	0/294 (0)	0/286 (0)	5/294 (1.7)	2/286 (0.7)
Rubattu 2005(56)	PCR/RFLP	NR	4/115 (3.5)	10/180 (5.6)	1/115 (0.9)	0/180 (0)	3/115 (2.6)	10/180 (5.6)
Sastry 2006(57)	NR	0.50 (0.15-1.66; *P* =.26)	4/101 (4)	8/101 (7.9)				
Shi 2008(58)	PCR/RFLP	NR	0/97 (0)	0/99 (0)	0/97 (0)	0/99 (0)	0/97 (0)	0/99 (0)
Slooter 2005(59)	PCR	Adjusted OR for age, index year, and residence: 1.8 (0.9-3.6)	14/179 (7.8)	42/763 (5.5)				
Supanc 2014(61)	PCR/RFLP	2.88 (1.01-8.20; *P* =.40)	14/155 (9)	5/150 (3.3)	2/155 (1.3)	0/150 (0)	12/155 (7.7)	5/150 (3.3)
Szolnoki 2003(62)	PCR	NR	72/867 (8.3)	49/743 (6.6)	3/867 (0.3)	2/743 (0.3)	69/867 (8)	47/743 (6.3)
Tatarskyy 2010(63)	PCR/RFLP	NR	6/183 (3.3)	5/188 (2.7)	0/183 (0)	1/188 (0.5)	6/183 (3.3)	4/188 (2.1)
They-They 2012(64)	PCR/RFLP	NR	0/91 (0)	0/182 (0)	0/91 (0)	0/182 (0)	0/91 (0)	0/182 (0)
Tupitsyna 2013(65)	PCR	Russian: 0.9 (0.50-1.76) Ukranian: 1.9 (0.40-8.97)	42/1450 (2.9)	16/577 (2.8)	0/1450 (0)	0/577 (0)	42/1450 (2.9)	16/577 (2.8)
Voetsch 2000(66)	PCR/RFLP	NR	5/153 (3.3)	8/225 (3.6)	0/153 (0)	0/225 (0)	5/153 (3.3)	8/225 (3.6)
Wypasek 2009(67)	SNP analysis	NR (*P* = .22)	9/100 (9)	5/107 (4.7)	0/100 (0)	0/107 (0)	9/100 (9)	5/107 (4.7)

NR, not reported; FVL, Factor V Leiden; PCR, polymerase chain reaction; RFLP, restriction fragment length polymorphism; OR, Odds ratio; RR, risk ratio; CI, confidence interval; SNP, Single nucleotide polymorphisms.

Table S4. Results of Included Studies: Prothrombin G20210A Mutation.

References	Test Method	Odds Ratio (95%CI)	Number of All PTM (%)		Number of Homozygous PTM (%)		Number of Heterozygous PTM (%)	
			Cases	Controls	Cases	Controls	Cases	Controls
Aznar 2004(2)	PCR/RFLP	3.75 (1.05-13.34)	4/49 (8.2)	7/294 (2.4)				
Belvis 2006(3)	PCR	NR	3/89 (3.4)	13/201 (6.5)	0/89 (0)	0/201 (0)	3/89(3.4)	13/201 (6.5)
Bentolila 1997(4)	NR	NR	8/125 (6.4)	5/134 (3.7)	0/125(0)	0/134 (0)	8/125 (6.4)	5/134 (3.7)
Biswas 2009(5)	PCR/RFLP	NR	0/120 (0)	0/120 (0)	0/120 (0)	0/120 (0)	0/120 (0)	0/120 (0)
Bolaman 2009(6)	PCR	NR	0/24 (0)	0/53 (0)	0/24 (0)	0/53 (0)	0/24 (0)	0/53 (0)
Celiker 2009(9)	PCR/RFLP	NR	3/162 (1.9)	5/182 (2.7)	0/162 (0)	0/182 (0)	3/162 (1.9)	5/182 (2.7)
Chatterjee 2013(10)	PCR/RFLP	1.00 (0.02-51.35; *P* = 1)	0/52 (0)	0/52 (0)	0/52(0)	0/52 (0)	0/52 (0)	0/52 (0)
Djordjevic 2012(15)	PCR/RFLP	1.33 (0.35-5.13)	4/73 (5.5)	5/120 (4.2)				
Egan 2000(16)	NR	NR	0/42 (0)	13/635 (2)	0/42(0)	0/635 (0)	0/42 (0)	13/635 (2)
Erten 2015(17)	PCR/in situ hybridization	NR	13/212 (6.1)	10/238 (4.2)	0/212 (0)	0/238 (0)	13/212 (6.1)	10/238 (4.2)
Eterovic 2007(18)	PCR/RFLP	NR (*P* = .047)	9/120 (7.5)	3/120 (2.5)	0/120 (0)	0/120 (0)	9/120 (7.5)	3/120 (2.5)
Fan 2010(19)	PCR	1.69 (0.26-10.82)	6/156 (3.8)	122/5817 (2.1)				
Favaretto 2012(20)	PCR	2.97 (1.32-6.69)	29/340 (8.5) PFO: 12/136 (8.8) Non-PFO: 17/204 (8.3)	9/272 (3.3)	0/340 (0) PFO: 0/136 (0) Non-PFO: 0/204 (0)	0/272 (0)	29/340 (8.5) PFO: 12/136 (8.8) Non-PFO: 17/204 (8.3)	9/272 (3.3)
Haeusler 2012(22)	PCR	NR (*P* = >.995)	1/38 (2.6)	10/282 (3.5)	0/38 (0)	0/282 (0)	1/38 (2.6)	10/282 (3.5)
Halbmayer 1998(23)	PCR	NR (*P* = .46)	2/20 (10)	0/20 (0)	0/20 (0)	0/20 (0)	2/20 (10)	0/20 (0)
Hankey 2001(25)	PCR	1.9 (0.5-6.2)	8/219 (3.7)	4/205 (2)				
Jiang 2014(27)	PCR	2.5 (0.9-6.5, *P* = .07)	14/397 (3.5)	6/426 (1.4)	1/397(0.3)	0/426 (0)	13/397 (3.3)	6/426 (1.4)
Kamberi 2016(29)	PCR	2.80 (0.33-23.53 *P* = .32)	1/39 (2.6)	7/102 (6.9)	0/39 (0)	0/102 (0)	1/39 (2.6)	7/102 (6.9)
Karakus 2005(30)	PCR	NR	1/21 (4.8)	1/81 (1.2)	1/21 (4.8)	0/81 (0)	0/21 (0)	1/81 (1.2)
Karttunen 2003(31)	PCR	1.0 (1.0-1.1)	2/57 (3.5)	0/104 (0)	0/57 (0)	0/104 (0)	2/57 (3.5)	0/104 (0)
Kholodkova 2015(32)	PCR	NR	6/114 (5.3)	0/40 (0)	0/114 (0)	0/40 (0)	6/114 (5.3)	0/40 (0)
Krajcoviechova 2015(33)	PCR	Multivariate adjusted OR 2.29 (1.04-5.02, *P* =.04)	22/423 (5.2)	15/614 (2.4)	1/423 (0.2)	0/614 (0)	21/423 (5)	15/614 (2.4)
Linnemann 2008(35)	PCR	0.63 (0.15-2.7, *P* =.76)	2/41 (4.9)	76/930 (8.2)	1/41 (2.4)	2/930 (0.2)	1/41 (2.4)	74/930 (8)
Longstreth 1998(36)	PCR/RFLP	1.6 (0.03-13.4)	1/41 (2.4)	6/382 (1.6)	0/41 (0)	0/382 (0)	1/41 (2.4)	6/382 (1.6)
Lopaciuk 2001(37)	PCR	0.9 (0.2-5.0)	2/100 (2)	5/238 (2.1)	0/100 (0)	0/238 (0)	2/100 (2)	5/238 (2.1)
Martinelli 2006(38)	NR ("DNA analysis")	Crude OR 0.9 (0.3-2.6) Adjusted OR for age 0.9 (0.1-11.2)	5/105 (4.8)	15/293 (5.1)	0/105 (0)	0/293 (0)	5/105 (4.8)	15/293 (5.1)
Moskau 2010(41)	PCR	NR (*P* = .88)	7/167 (4.2)	10/500 (2)	0/167 (0)	0/500 (0)	7/167 (4.2)	10/500 (2)
Pahus 2016(43)	PCR	Heterozygous 1.59 (0.32-4.81)	3/92 (3.3)	1377/64631 (2.1)	0/92 (0)	8/64631 (0)	3/92 (3.3)	1369/64631 (2.1)
Pezzini 2005(46)	PCR	2.68 (0.70-10.3)	9/163 (5.5)	3/158 (1.9)	1/163 (0.6)	0/158 (0)	8/163 (4.9)	3/158 (1.9)
Pezzini 2007(47)	PCR	6.52 (1.73-24.6)	10/108 (9.3)	3/216 (1.4)	1/108 (0.9)	0/216 (0)	9/108 (8.3)	3/216 (1.4)
Pullmann 2004(49)	PCR	NR	0/23 (0)	3/71 (4.2)	0/23 (0)	0/71 (0)	0/23 (0)	3/71 (4.2)
Ranellou 2015(50)	PCR	NR (*P* = .70)	7/51 (13.7)	4/70 (5.7)	0/51 (0)	0/70 (0)	7/51 (13.7)	4/70 (5.7)
Ridker 1999(52)	PCR	Crude RR 1.1 (0.6-2.1; *P* =.8)	11/259 (4.2)	69/1774 (3.9)	0/259(0)	1/1774 (0.1)	11/259 (4.2)	68/1774 (3.8)

		Multivariate adjusted RR 1.1 (0.5-2.4; *P* =.7)						
Rubattu 2005(55)	PCR/RFLP	NR (*P* = .95)	12/294 (4.1)	12/286 (4.2)	0/294 (0)	0/286 (0)	12/294 (4.1)	12/286 (4.2)
Rubattu 2005(56)	PCR	NR	8/115 (7)	10/180 (5.6)	0/115 (0)	0/180 (0)	8/115 (7)	10/180 (5.6)
Sastry 2006(57)	NR	NR	2/101 (2)	0/101 (0)				
Slooter 2005(59)	PCR	Adjusted OR for age, index year, and residence: 1.0 (0.3-3.0)	5/188 (2.7)	18/763 (2.4)				
Smiles 2002(60)	PCR	Crude OR 1.25 (0.46-3.39) Adjusted OR for sex, race, and clinic site: 1.40 (0.51-3.86)	6/182 (3.3)	12/453 (2.6)	0/182(0)	0/453 (0)	6/182 (3.3)	12/453 (2.6)
Supanc 2014(61)	PCR	3.50 (0.72-17.24; *P* =.17)	7/155 (4.5)	2/150 (1.3)	0/155 (0)	0/150 (0)	7/155 (4.5)	2/150 (1.3)
Szolnoki 2003(62)	PCR	NR	5/867 (0.6)	4/743 (0.5)	0/867 (0)	0/743 (0)	5/867 (0.6)	4/743 (0.5)
Tatarskyy 2010(63)	PCR/RFLP	NR	8/183 (4.4)	3/188 (1.6)	0/183 (0)	0/188 (0)	8/183 (4.4)	3/188 (1.6)
They-They 2012(64)	PCR/RFLP	2.3 (0.97-5.8; *P* =.60)	11/91 (12.1)	10/182 (5.5)	0/91 (0)	0/182 (0)	11/91 (12.1)	10/182 (5.5)
Tupitsyna 2013(65)	PCR	Russian: 0.7 (0.35-1.30)	29/1450 (2)	20/817 (2.4)	0/1450 (0)	0/817 (0)	29/1450 (2)	20/817 (2.4)
Voetsch 2000(66)	PCR/RFLP	NR	7/153 (4.6)	5/229 (2.2)	0/153 (0)	0/229 (0)	7/153 (4.6)	5/229 (2.2)
Wypasek 2009(67)	SNP analysis	NR (*P* = .15)	1/100 (1)	1/107 (0.9)	0/100 (0)	0/107 (0)	1/100 (1)	1/107 (0.9)

NR, not reported; PTM, Prothrombin G20210A Mutation; PCR, polymerase chain reaction; RFLP, restriction fragment length polymorphism; OR, Odds ratio; RR, risk ratio; CI, confidence interval; SNP, Single nucleotide polymorphisms.

Table S5. Results of Included Studies: Protein C Deficiency.

References	Test Method	Definition of deficiency	Timing of test after stroke	Exclusion of anticoagulants	Odds Ratio (95%CI)	Number of PCD (%)	
						Cases	Controls
Biswas 2009(5)	ELISA	<65%	3-6 months after stroke	Yes	NR	4/120 (3.3)	0/120 (0)
Chatterjee 2013(10)	Clot-based assay	<70%	≥4 months after stroke	NR	0.15 (0.01-1.30; *P* = .12)	6/52 (11.5)	1/52 (1.9)
Chen 2003(11)	Chromogenic assay	<70%	NR (If a first test was abnormal, a second test was done 6 weeks later; a deficiency was defined by <70% in two tests)	Yes	5.29 (NR)	14/104 (13.5)	1/35 (2.9)
D'Amico 1998(13)	NR	NR	2-15 days after stroke	NR	NR	0/31 (0)	0/124 (0)
De Lucia 1999(14)	NR	<76.9% (<2.5th percentile)	At 3 months after stroke	Yes	NR	2/50 (4)	1/100 (1)
Favaretto 2012(20)	Chromogenic assay	<68%	1 month after discharge	NR	NR	0/340 (0)	0/272 (0)
Hankey 2001(25)	Chromogenic assay	<70%	Within 7 days and at 3-6 months (any low level is considered deficiency)	NR	0.7 (0.2-3.1; *P* = .6)	3/219 (1.4)	4/205 (2)
Jerrard-Dunne 2003(26)	Chromogenic assay	<-2SD of ethnic-specific controls	First test at presentation If abnormal, repeated test at ≥3 months after stroke Results of the repeated test were used	Yes	3.05 (0.60-15.39; *P* = .16)	6/130 (4.6)	2/130 (1.5)
Karakus 2005(30)	Chromogenic assay	NR	NR	NR	NR	1/21 (4.8)	1/81 (1.2)
Karttunen 2003(31)	Chromogenic assay	NR	>2 months after stroke	NR	NR	0/57 (0)	0/104 (0)
Linnemann 2008(35)	Chromogenic assay	<74%	NR (a deficiency was defined by repeatedly low activity)	Yes	0.98 (0.97-0.99; *P* =1.00)	0/31 (0)	20/817 (2.4)
Pahus 2016(43)	Chromogenic and clot-based assay	<0.65 U/L (both assays)	Average 2 months after stroke (Repeated in cases of deficiency)	NR	1.90 (0.04-12.55)	1/363 (0.3)	14/9648 (0.1)
Romdhane 2011(54)	Chromogenic assay	NR	NR	NR	2 (NR; *P* =.6)	2/20 (10)	3/54 (5.6)
Sastry 2006(57)	Functional assay	NR	NR	Yes	NR	1/86 (1.2)	0/101 (0)
Zimba 2017(68)	Chromogenic assay	<70%	More than 48 hour, up to 1 month	Yes	NR (*P* = .06)	5/52 (9.6)	0/52 (0)

NR, not reported; PCD, protein C Deficiency; ELISA, enzyme-linked immunosorbent assay; CI, confidence interval.

Table S6. Results of Included Studies: Protein S Deficiency.

References	Test Method	Definition of deficiency	Timing of test after stroke	Exclusion of anticoagulants	Odds Ratio (95%CI)	Number of PSD (%)	
						Cases	Controls
Biswas 2009(5)	ELISA	<50%	3-6 months after stroke	Yes	NR	6/120 (5)	0/120 (0)
Chatterjee 2013(10)	Clot-based assay	<65%	≥4 months after stroke	NR	0.05 (0.01-0.38; *P* <.001)	15/52 (28.8)	1/52 (1.9)
Chen 2003(11)	Chromogenic assay	<60%	NR (If a first test was abnormal, a second test was done 6 weeks later; a deficiency was defined by <60% in two tests)	Yes	2.86 (NR)	22/104 (21.2)	3/35 (8.6)
D'Amico 1998(13)	NR	NR	2-15 days after stroke (Repeated at >6 months after stroke; a deficiency was defined by abnormalities in both tests)	NR	NR	2/31 (6.5)	0/124 (0)
De Lucia 1999(14)	NR	<74.6% (<2.5th percentile)	At 3 months after stroke	Yes	NR	3/50 (6)	1/100 (1)
Favaretto 2012(20)	Chromogenic assay	<62%	1 month after discharge	NR	NR	0/340 (0)	0/272 (0)
Hankey 2001(25)	Immunoelectrophoresis	<55%	Within 7 days and at 3-6 months (any low level is considered deficiency)	NR	0.9 (0.1-6.7; *P* = .5)	2/219 (0.9)	2/205 (1)
Jerrard-Dunne 2003(26)	Immunoassay	<-2SD of ethnic-specific controls	First test at presentation If abnormal, repeated test at ≥3 months after stroke Results of the repeated test were used	Yes	2.00 (0.36-11.1; *P* = .42)	4/130 (3.1)	2/130 (1.5)
Karakus 2005(30)	Immunoassay	NR	NR	NR	NR	1/21 (4.8)	0/81 (0)
Karttunen 2003(31)	Clot-based assay	NR	>2 months after stroke	NR	1.0 (1.0-1.1)	1/57 (1.8)	0/104 (0)
Linnemann 2008(35)	Clot-based assay	Male <70%, Female <60%	NR (a deficiency was defined by repeatedly low activity)	Yes	0.97 (0.13-7.39; *P* =1.00)	1/30 (3.3)	28/788 (3.6)
Mayer 1993(39)	Free protein S: Immunoelectrophoresis	Free PS <20% of normal total PS	Cases: Average 2.4 days after onset of stroke Controls: Average 5.2 days after admission	Yes	1.1 (0.5-2.2)	20/94 (21.3)	19/94 (20.2)
Mochan 2005(40)	Clot-based assay	NR	Cases: Repeated at 3 months after stroke Controls: NR	NR	NR	11/33 (33.3)	12/33 (36.4)
Pahus 2016(43)	Clot-based assay, ELISA	Clot-based assay: <0.65 U/L AND Free PS ELISA: <0.13 U/L (until 2005) and <0.55 U/L (from 2006)	Average 2 months after stroke (Repeated in cases of deficiency)	NR	2.32 (0.24-11.27)	2/364 (0.5)	9/3788 (0.2)
Romdhane 2011(54)	Clot-based assay	NR	NR	NR	11.3 (NR; *P* =.003)	6/20 (30)	2/54 (3.7)
Sastry 2006(57)	Functional assay	NR	NR	Yes	NR	1/86 (1.2)	1/101 (1)
Zimba 2017(68)	Immunoassay	<60%	More than 48 hour, up to 1 month	Yes	NR (*P* = .42)	22/52 (42.3)	18/52 (34.6)

NR, not reported; PSD, protein S Deficiency; ELISA, enzyme-linked immunosorbent assay; CI, confidence interval.

Table S7. Results of Included Studies: Antithrombin Deficiency.

References	Test Method	Definition of deficiency	Timing of test after stroke	Exclusion of anticoagulants	Odds Ratio (95%CI)	Number of ATD (%)	
						Cases	Controls
Chatterjee 2013(10)	Chromogenic assay	<75%	≥4 months	NR	1.00 (0.02-51.35; *P* = 1)	0/52 (0)	0/52 (0)
Chen 2003(11)	Chromogenic assay	<70%	NR (If a first test was abnormal, a second test was done 6 weeks later; a deficiency was defined by <70% in two tests)	Yes	0.33 (NR)	1/104 (1)	1/35 (2.9)
De Lucia 1999(14)	NR	NR	3 months	Yes	NR	0/50 (0)	0/100 (0)
Favaretto 2012(20)	Chromogenic assay	<80%	1 month after discharge	NR	NR	0/340 (0)	0/272 (0)
Hankey 2001(25)	Chromogenic assay	82	Within 7 days and at 3-6 months (any low level is considered deficiency)	NR	1.3 (0.5-3.3; *P* = .6)	11/219 (5.2)	8/205 (3.7)
Jerrard-Dunne 2003(26)	Chromogenic assay	<-2SD of ethnic-specific controls	First test at presentation If abnormal, repeated test at ≥3 months after stroke Results of the repeated test were used	Yes	NR	0/130 (0)	0/130 (0)
Karakus 2005(30)	Chromogenic assay	NR	NR	NR	NR	1/21 (4.8)	0/81 (0)
Karttunen 2003(31)	Chromogenic assay	NR	>2 months after stroke	NR	0.9 (0.1-10.5)	1/57 (1.8)	2/104 (1.9)
Linnemann 2008(35)	Chromogenic assay	<86%	NR (a deficiency was defined by repeatedly low activity)	Yes	0.88 (0.12-6.60, *P* = 1.00)	1/40 (2.5)	29/993 (2.9)
Pahus 2016(43)	Functional assay	<0.60 x 10^3 U/L	Average 2 months (Repeated in cases of deficiency)	NR	NR	0/288 (0)	16/9669 (0.2)
Romdhane 2011(54)	Chromogenic assay	NR	NR	NR	5.6 (NR; *P* =.01)	7/20 (35)	5/54 (9.3)
Sastry 2006(57)	Functional assay	NR	NR	Yes	NR	3/86 (3.5)	0/101 (0)

NR, not reported; ATD, Antithrombin Deficiency; CI, confidence interval.

Table S8. Components of Quality Assessment.

References	Research question	Study population	Target population and case representation	Sample size justification	Groups recruited from the same population	Inclusion and exclusion criteria prespecified and applied uniformly	Case and control definitions	Random selection of study participants	Concurrent controls	Exposure assessed prior to outcome measurement	Exposure measures and assessment	Blinding of exposure assessors	Statistical analysis	Study Quality
Anadure 2017(1)	Y	Y	NR	Y	CD	CD	Y	N	N	N	Y	NR	Y	Good
Aznar 2004(2)	Y	N	NR	N	Y	Y	Y	N	N	N	N	NR	N	Fair
Belvis 2006(3)	Y	Y	NR	N	N	N	Y	N	N	N	Y	Y	N	Fair
Bentolila 1997(4)	Y	Y	NR	N	CD	Y	Y	N	N	N	N	NR	N	Fair
Biswas 2009(5)	Y	N	NR	N	Y	Y	Y	N	N	N	N	NR	N	Fair
Bolaman 2009(6)	Y	N	NR	N	CD	Y	Y	N	N	N	Y	NR	N	Fair
Buryu 2005(7)	Y	N	NR	N	CD	CD	Y	N	N	N	Y	NR	N	Fair
Catto 1995(8)	Y	N	NR	N	Y	CD	Y	N	N	N	Y	NR	N	Fair
Celiker 2009(9)	Y	Y	NR	N	Y	N	Y	NA	N	N	Y	NR	N	Fair
Chatterjee 2013(10)	Y	N	NR	N	CD	Y	Y	N	N	N	N	NR	N	Fair
Chen 2003(11)	Y	N	NR	N	Y	CD	Y	N	N	N	Y	N	Y	Fair
Cushman 1998(12)	Y	Y	NR	N	Y	Y	Y	Y	N	Y	Y	NR	Y	Good
D'Amico 1998(13)	Y	Y	NR	N	Y	Y	Y	N	N	N	N	NR	N	Fair
De Lucia 1999(14)	Y	Y	NR	N	CD	Y	Y	N	N	N	N	Y	N	Fair
Djordjevic 2012(15)	Y	N	NR	N	Y	Y	Y	N	N	N	Y	NR	N	Fair
Egan 2000(16)	Y	Y	NR	N	Y	CD	Y	N	N	N	N	NR	N	Fair
Erten 2015(17)	Y	Y	NR	N	CD	Y	N	N	N	N	Y	NR	Y	Fair
Eterovic 2007(18)	Y	Y	NR	N	Y	Y	Y	N	N	N	Y	Y	Y	Good
Fan 2010(19)	Y	N	NR	N	Y	Y	N	NA	N	CD	Y	NR	Y	Fair
Favaretto 2012(20)	Y	Y	NR	N	Y	N	Y	N	N	N	Y	NR	Y	Fair
Go 2003(21)	Y	Y	NR	N	Y	Y	Y	NA	N	N	Y	NR	Y	Good
Haeusler 2012(22)	Y	N	NR	N	N	N	Y	N	N	N	Y	N	N	Fair
Halbmayer 1998(23)	Y	N	NR	N	CD	CD	N	N	N	N	Y	NR	N	Poor
Hamedani 2013(24)	Y	Y	NR	N	Y	Y	Y	Y	N	N	Y	NR	Y	Fair
Hankey 2001(25)	Y	Y	NR	N	Y	Y	Y	Y	N	N	Y	NR	Y	Good
Jerrard-Dunne 2003(26)	Y	N	NR	N	Y	CD	Y	Y	N	N	Y	NR	Y	Good
Jiang 2014(27)	Y	Y	NR	N	Y	Y	Y	Y	N	N	Y	NR	Y	Fair
Juul 2002(28)	Y	Y	NR	N	Y	Y	Y	NA	N	Y	Y	NR	Y	Fair
Kamberi 2016(29)	Y	Y	NR	N	Y	Y	Y	N	N	N	Y	NR	N	Fair
Karakus 2005(30)	Y	N	NR	N	Y	Y	N	Y	N	N	N	NR	N	Fair
Karttunen 2003(31)	Y	Y	NR	N	Y	Y	Y	Y	N	N	Y	Y	Y	Good
Kholodkova 2015(32)	Y	N	NR	N	Y	Y	Y	N	N	N	Y	NR	N	Fair
Krajcoviechova 2015(33)	Y	Y	NR	Y	Y	N	Y	N	N	N	Y	NR	Y	Fair
Kumar 2017(34)	Y	N	NR	Y	Y	Y	Y	NA	N	N	Y	Y	Y	Good
Linneman 2008(35)	Y	Y	NR	N	Y	Y	Y	NA	N	N	Y	NR	Y	Good

References	Research question	Study population	Target population and case representation	Sample size justification	Groups recruited from the same population	Inclusion and exclusion criteria prespecified and applied uniformly	Case and control definitions	Random selection of study participants	Concurrent controls	Exposure assessed prior to outcome measurement	Exposure measures and assessment	Blinding of exposure assessors	Statistical analysis	Study Quality
Longstreth 1998(36)	Y	Y	NR	N	Y	Y	Y	Y	N	N	Y	Y	N	Good
Lopaciuk 2001(37)	Y	Y	NR	N	Y	Y	Y	N	N	N	Y	NR	N	Good
Martinelli 2006(38)	Y	Y	NR	N	Y	Y	Y	N	N	N	N	NR	Y	Fair
Mayer 1993(39)	Y	Y	NR	N	Y	Y	CD	N	N	N	Y	NR	N	Fair
Mochan 2005(40)	Y	Y	NR	N	N	N	Y	NA	N	N	N	NR	N	Fair
Moskau 2010(41)	Y	N	NR	N	N	CD	Y	N	N	N	Y	NR	N	Fair
Nagayama 1996(42)	Y	N	NR	N	Y	CD	Y	N	N	N	Y	NR	N	Fair
Pahus 2016(43)	Y	Y	NR	N	N	N	Y	NA	N	N	N	Y	N	Fair
Pestana 2009(44)	Y	N	NR	N	Y	Y	Y	Y	N	N	Y	NR	Y	Fair
Petrovic 2003(45)	Y	N	NR	N	Y	Y	Y	N	N	N	Y	Y	Y	Fair
Pezzini 2005(46)	Y	Y	NR	N	Y	Y	Y	N	N	N	Y	NR	Y	Good
Pezzini 2007(47)	Y	Y	NR	Y	Y	Y	Y	N	N	N	Y	NR	Y	Good
Press 1996(48)	Y	N	NR	N	Y	N	N	N	N	N	Y	NR	N	Fair
Pullmann 2004(49)	Y	N	NR	N	Y	Y	Y	NA	N	N	Y	NR	Y	Fair
Ranellou 2015(50)	Y	N	NR	N	Y	Y	Y	N	N	N	Y	NR	N	Fair
Ridker 1995(51)	Y	Y	NR	N	Y	Y	Y	Y	N	Y	Y	NR	Y	Good
Ridker 1999(52)	Y	Y	NR	N	Y	Y	Y	Y	N	Y	Y	NR	Y	Good
Ripoll 1997(53)	Y	N	NR	N	CD	CD	N	N	N	N	Y	NR	N	Fair
Romdhane 2011(54)	Y	N	NR	N	CD	CD	CD	N	N	N	N	NR	N	Poor
Rubattu 2005(55)	Y	Y	NR	N	Y	Y	Y	Y	N	N	Y	Y	Y	Fair
Rubattu 2005(56)	Y	N	NR	N	Y	N	Y	N	N	N	Y	NR	Y	Fair
Sastry 2006(57)	Y	Y	NR	Y	Y	Y	Y	N	N	N	N	NR	Y	Fair
Shi 2008(58)	Y	Y	NR	N	Y	Y	Y	N	N	N	Y	NR	Y	Good
Slooter 2005(59)	Y	Y	NR	N	Y	Y	Y	Y	N	N	Y	Y	Y	Good
Smiles 2002(60)	Y	Y	NR	N	Y	Y	Y	NA	N	Y	Y	Y	Y	Good
Supanc 2014(61)	Y	Y	NR	N	Y	Y	Y	N	N	N	Y	NR	Y	Good
Szolnoki 2003(62)	Y	N	NR	N	Y	Y	Y	Y	N	N	Y	Y	Y	Good
Tatarsky 2010(63)	Y	N	NR	N	Y	CD	N	N	N	N	Y	NR	N	Fair
They-They 2012(64)	Y	Y	NR	N	Y	Y	Y	N	N	N	Y	N	Y	Good
Tupitsyna 2013(65)	Y	N	NR	N	Y	CD	N	N	N	N	Y	NR	N	Poor
Voetsch 2000(66)	Y	Y	NR	N	Y	N	Y	Y	N	N	Y	NR	N	Fair
Wypasek 2009(67)	Y	N	NR	N	NR	Y	Y	N	N	N	Y	NR	N	Fair
Zimba 2017(68)	Y	Y	NR	Y	Y	Y	Y	N	N	N	N	NR	Y	Good

Y, Yes; N, No; NR, not reported; CD, cannot determined; NA, not applicable

Table S9. Additional sensitivity analyses.

Types of studies that were excluded from the analysis	Excluded studies	Thrombophilias	Pooled OR (95%CI)	I^2,%
Studies with enriched case population (those who were referred for thrombophilia testing because of a clinical indication or recruited from a thrombophilia center)	Aznar 2004, Martinelli 2006, Pahus 2016	FVL	1.24 (1.07, 1.44)	0
		PTM	1.47 (1.21, 1.77)	0
		PCD	2.17 (1.15, 4.11)	0
		PSD	2.30 (1.36, 4.07)	13.2
		ATD	1.37 (0.59, 2.94)	6.8
Studies that used self-reported history of stroke rather than imaging to define cases	Fan 2010	FVL	1.26 (1.09, 1.47)	0
		PTM	1.47 (1.20, 1.80)	0
Studies that were rated as poor quality	Halbmayer 1998, Romdhane 2011, Tupitsyna 2013	FVL	1.26 (1.09, 1.48)	0
		PTM	1.53 (1.26, 1.86)	0
		PCD	2.16 (1.14, 4.09)	0
		PSD	2.01 (1.22, 3.48)	0
		ATD	0.91 (0.38, 1.97)	0
Studies that included cases of recurrent ischemic stroke	Chatterjee 2013, Kumar 2017, They-They 2012	FVL	1.24 (1.08, 1.45)	0
		PTM	1.46 (1.20, 1.78)	0
		PCD	1.93 (1.01, 3.60)	0
		PSD	1.88 (1.19, 3.20)	0
		ATD	1.33 (0.59, 2.76)	8.0

FVL, Factor V Leiden; PTM, Prothrombin G20210A Mutation; PCD, Protein C Deficiency; PSD, Protein S Deficiency; ATD, Antithrombin Deficiency; CI, confidence interval

Figure S1. Forest plot showing pooled odds ratio for Factor V Leiden.

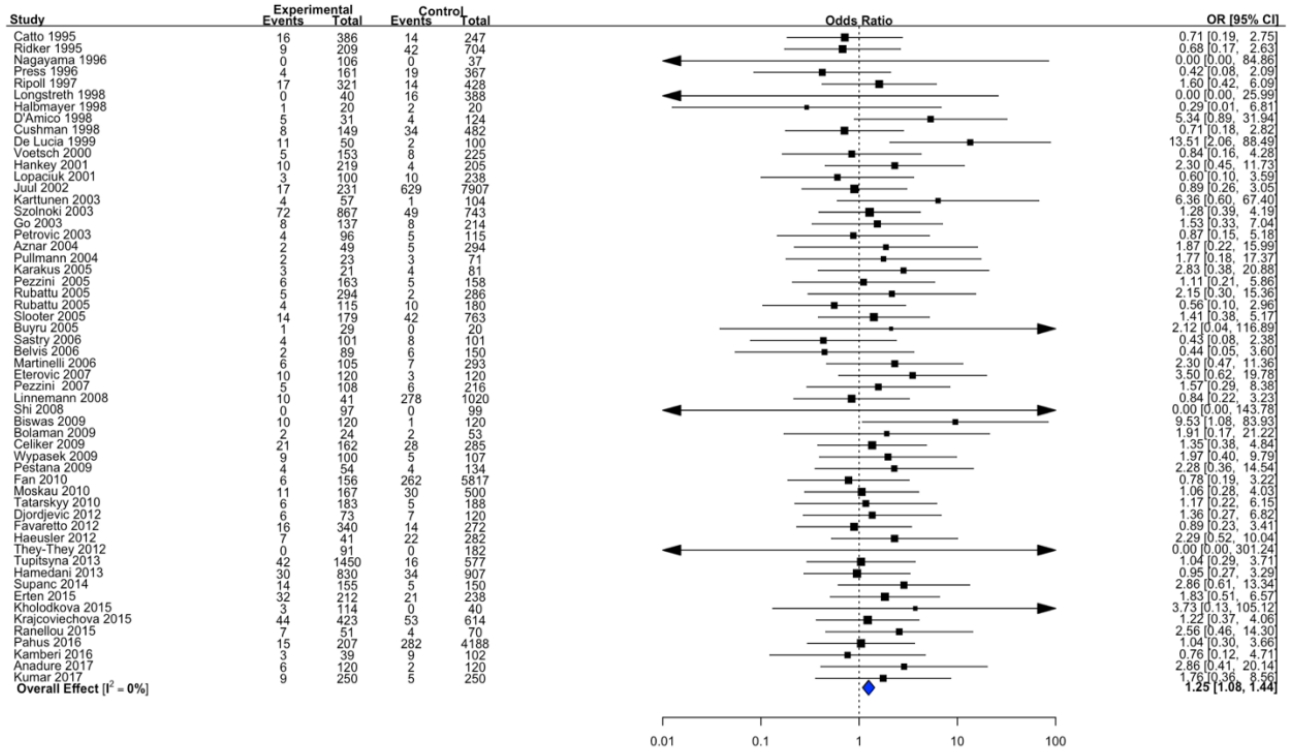


Figure S2. Forest plot showing pooled odds ratio for Factor V Leiden (Homozygous).

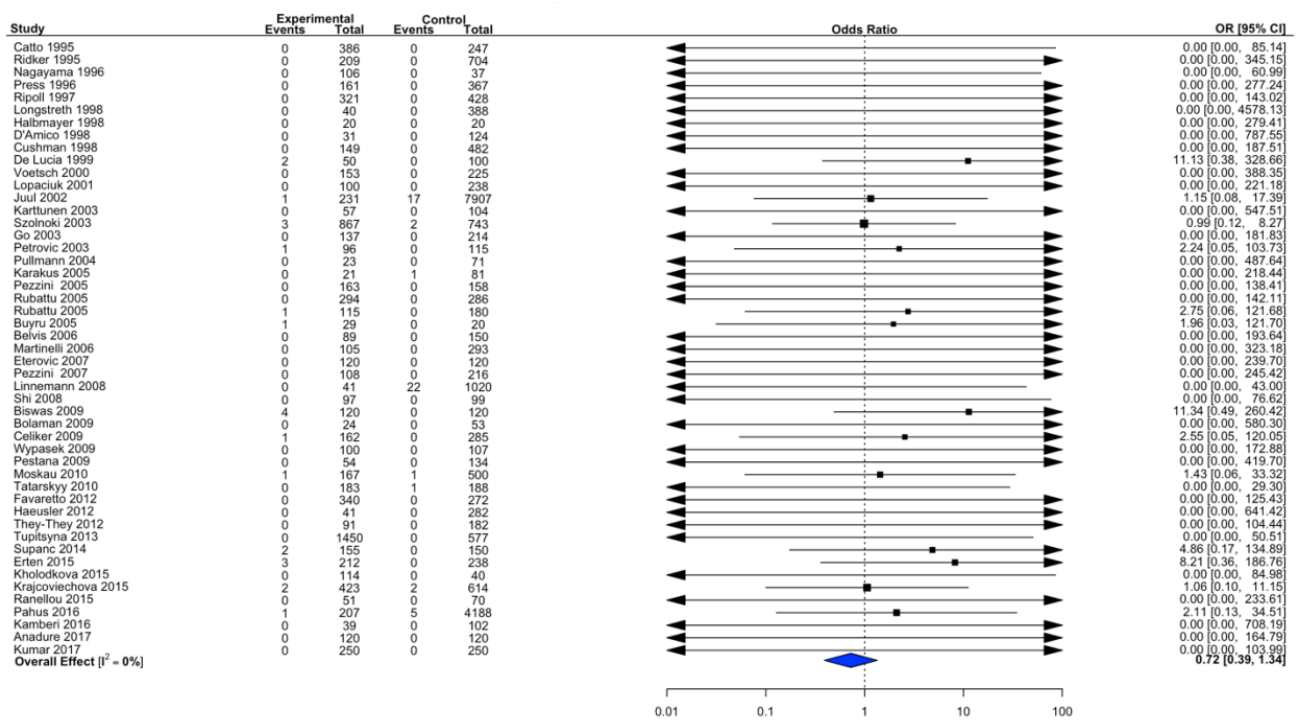


Figure S3. Forest plot showing pooled odds ratio for Factor V Leiden (Heterozygous).

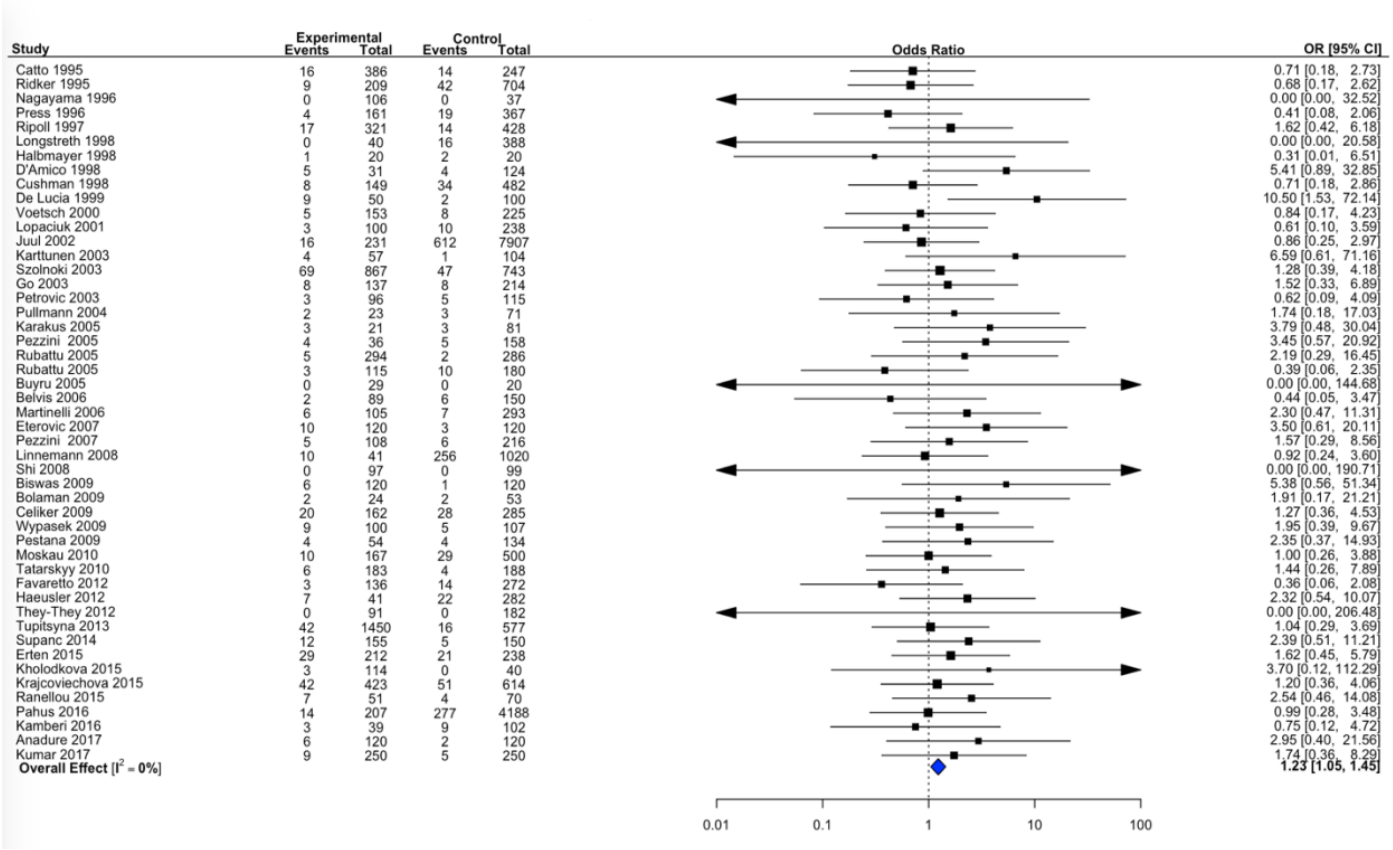
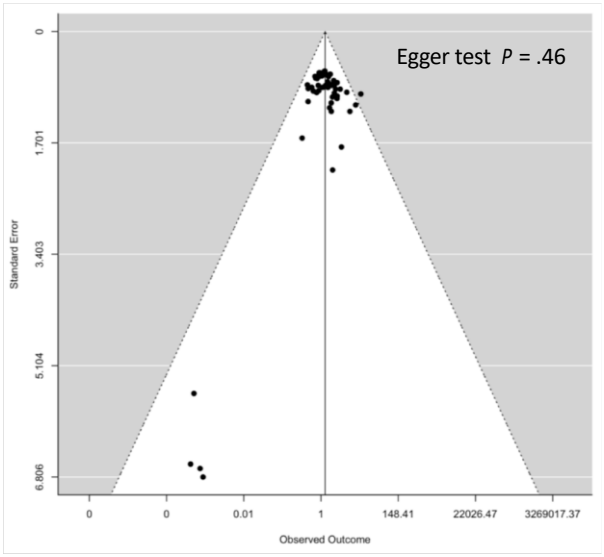
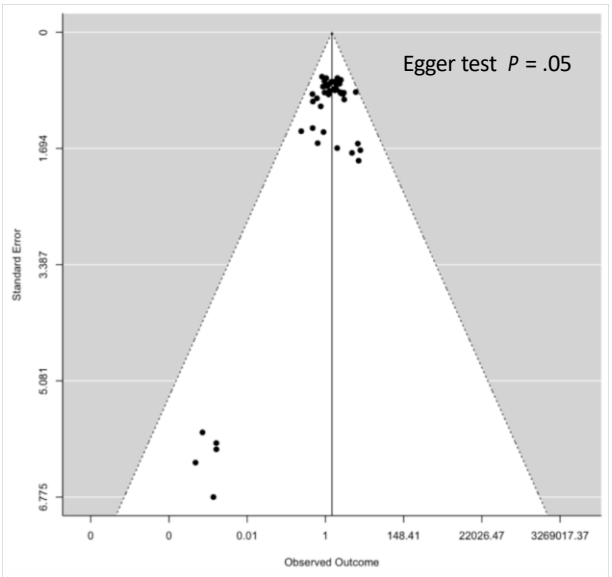


Figure S4. Funnel plot of included studies.

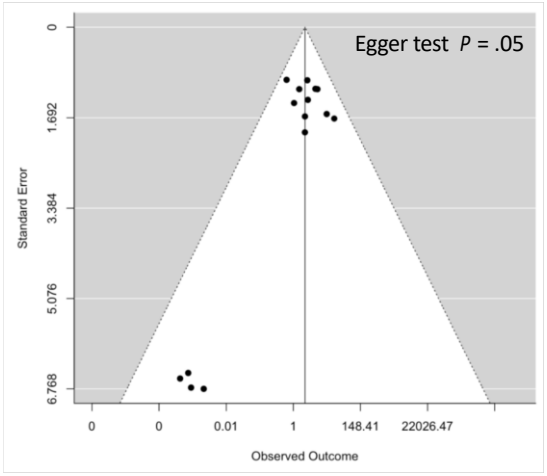
A. Factor V Leiden



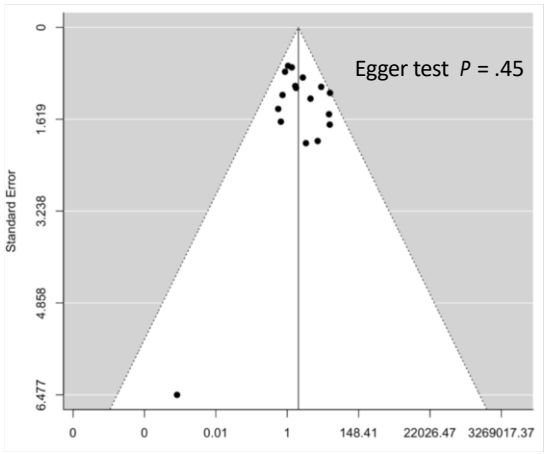
B. Prothrombin G20210A Mutation



C. Protein C Deficiency



D. Protein S Deficiency



E. Antithrombin Deficiency

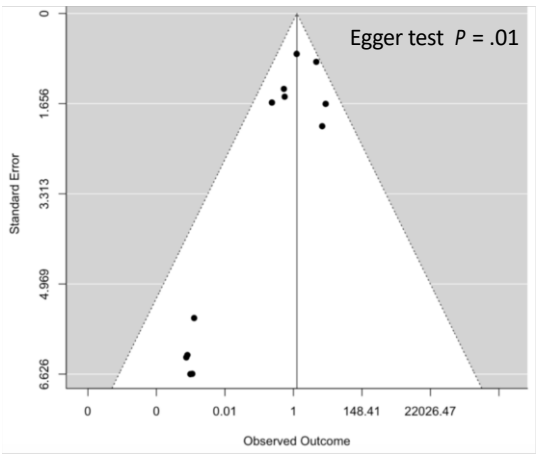


Figure S5. Forest plot showing pooled odds ratio for Prothrombin G20210A Mutation.

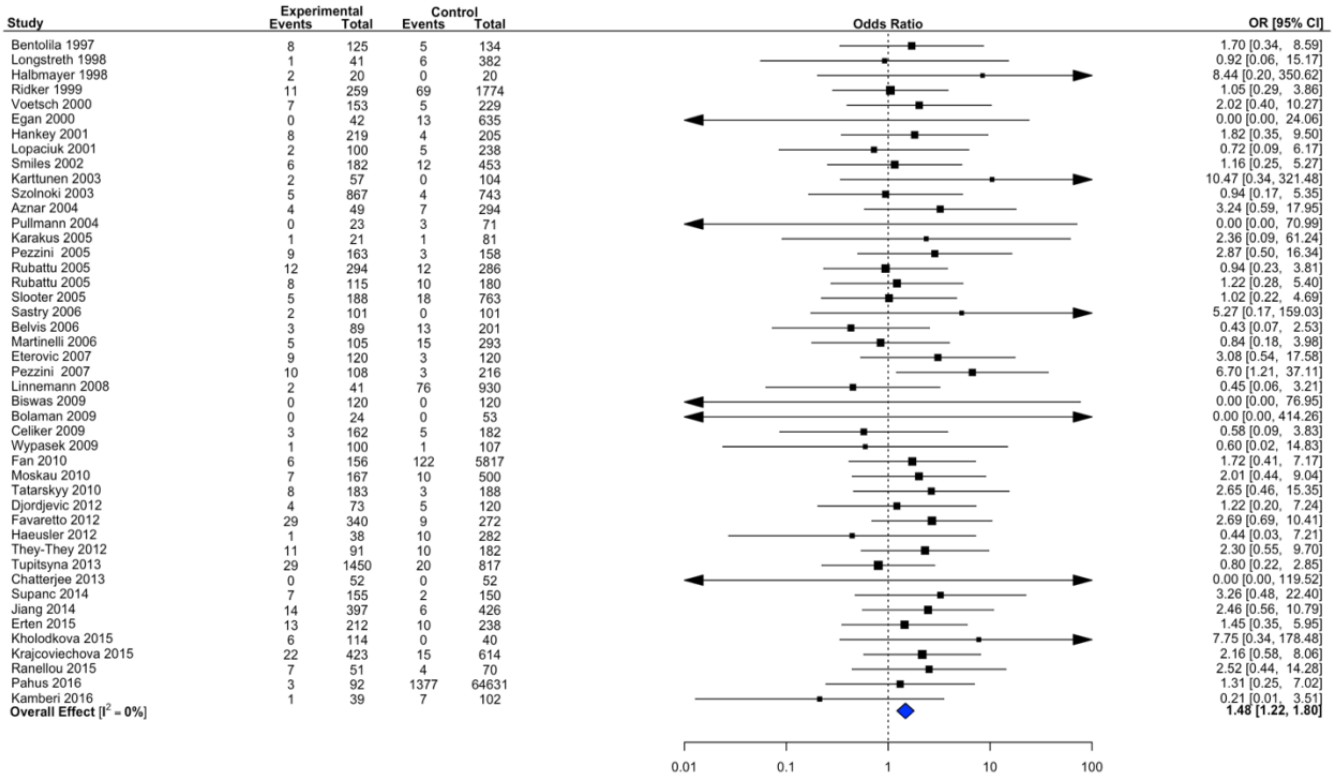


Figure S6. Forest plot showing pooled odds ratio for Prothrombin G20210A Mutation (Homozygous).

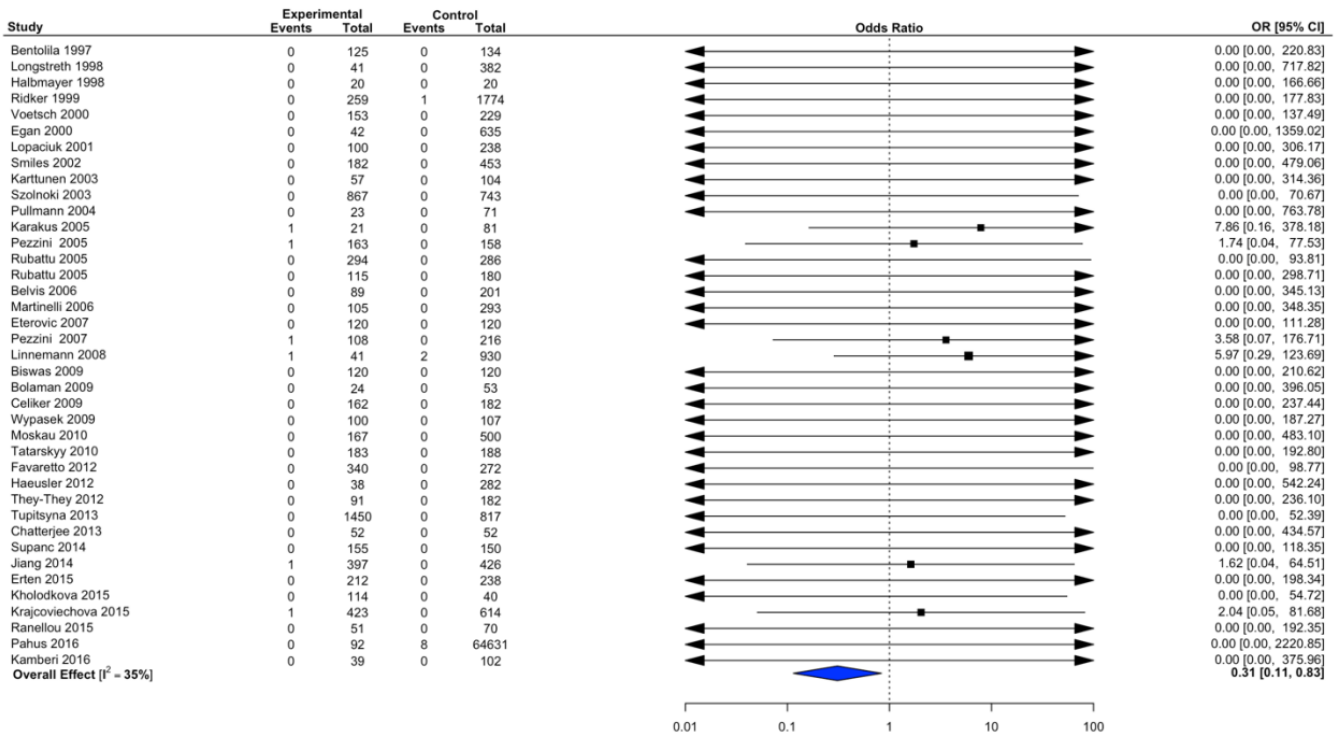


Figure S7. Forest plot showing pooled odds ratio for Factor V Leiden (Heterozygous).

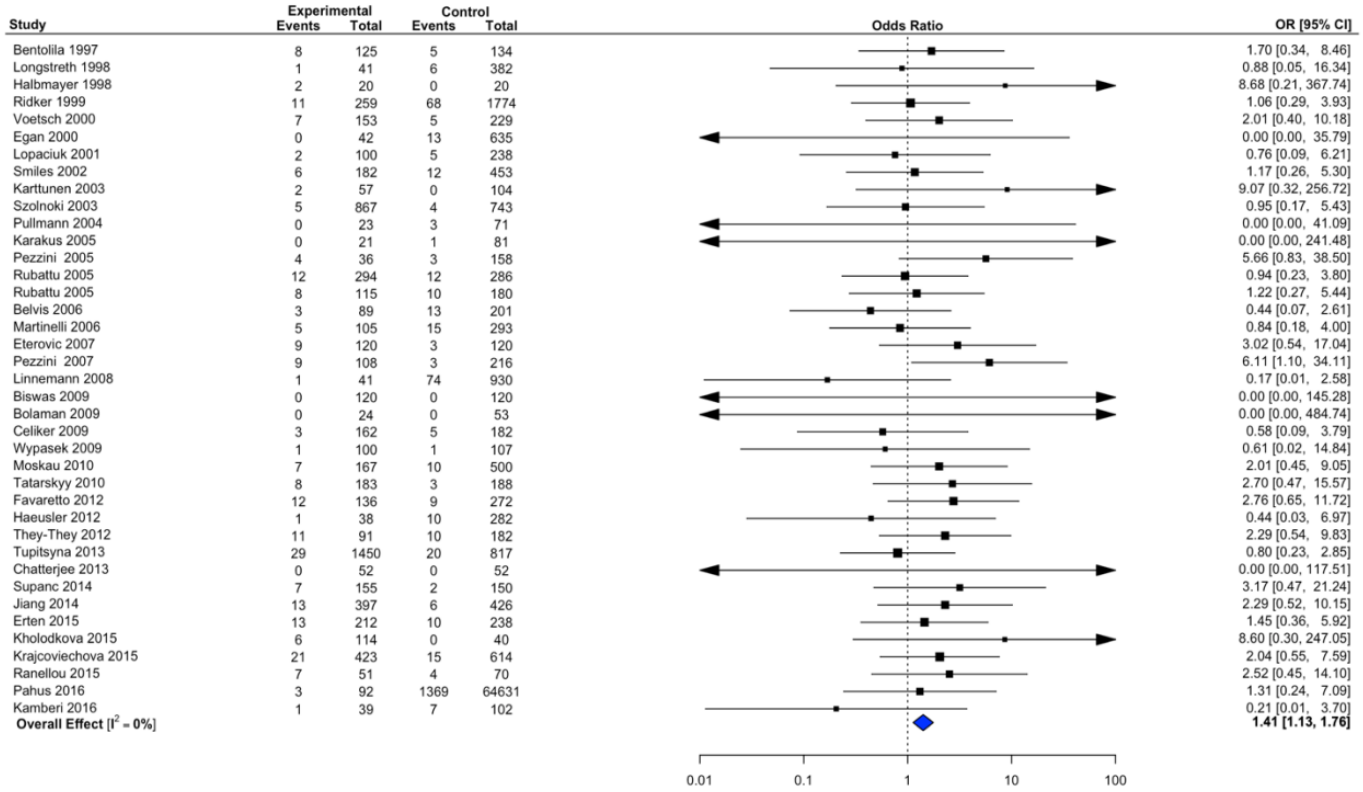


Figure S8. Forest plot showing pooled odds ratio for protein C deficiency.

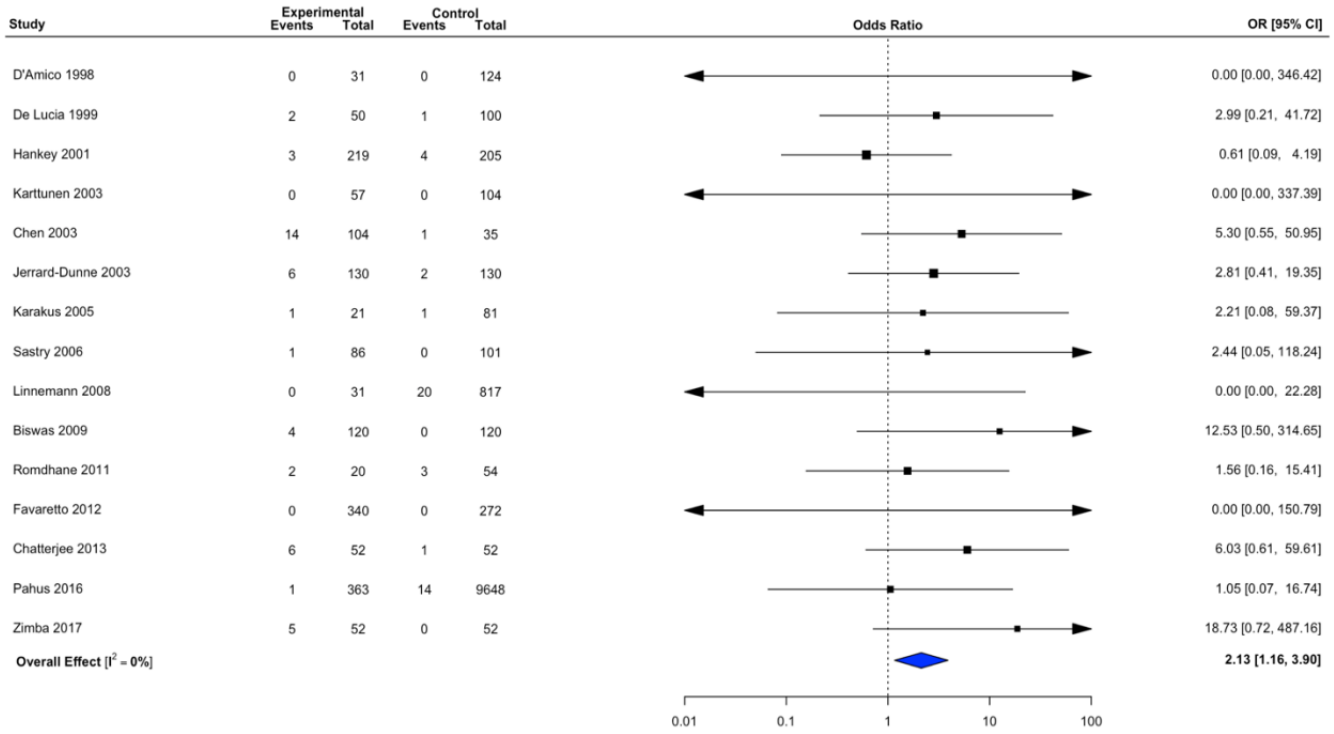


Figure S9. Forest plot showing pooled odds ratio for protein S deficiency.

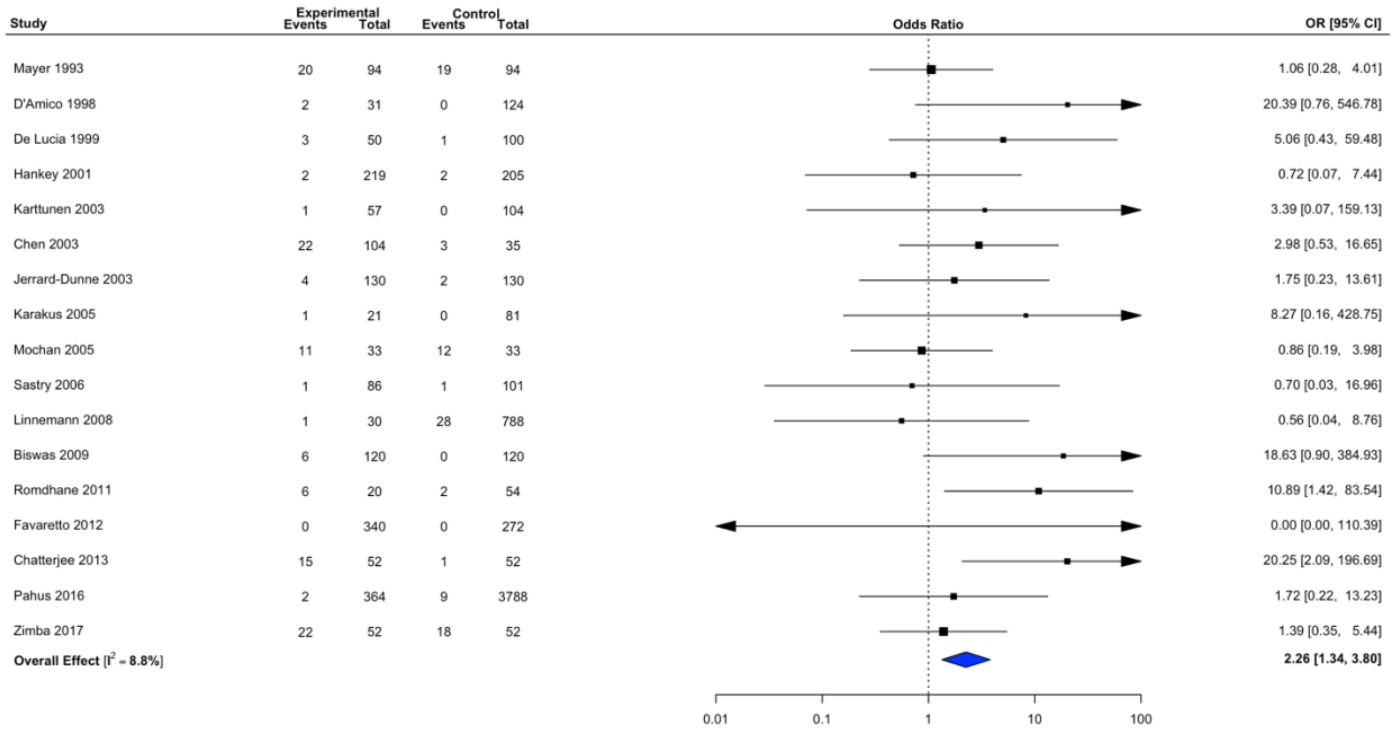


Figure S10. Forest plot showing pooled odds ratio for antithrombin deficiency.

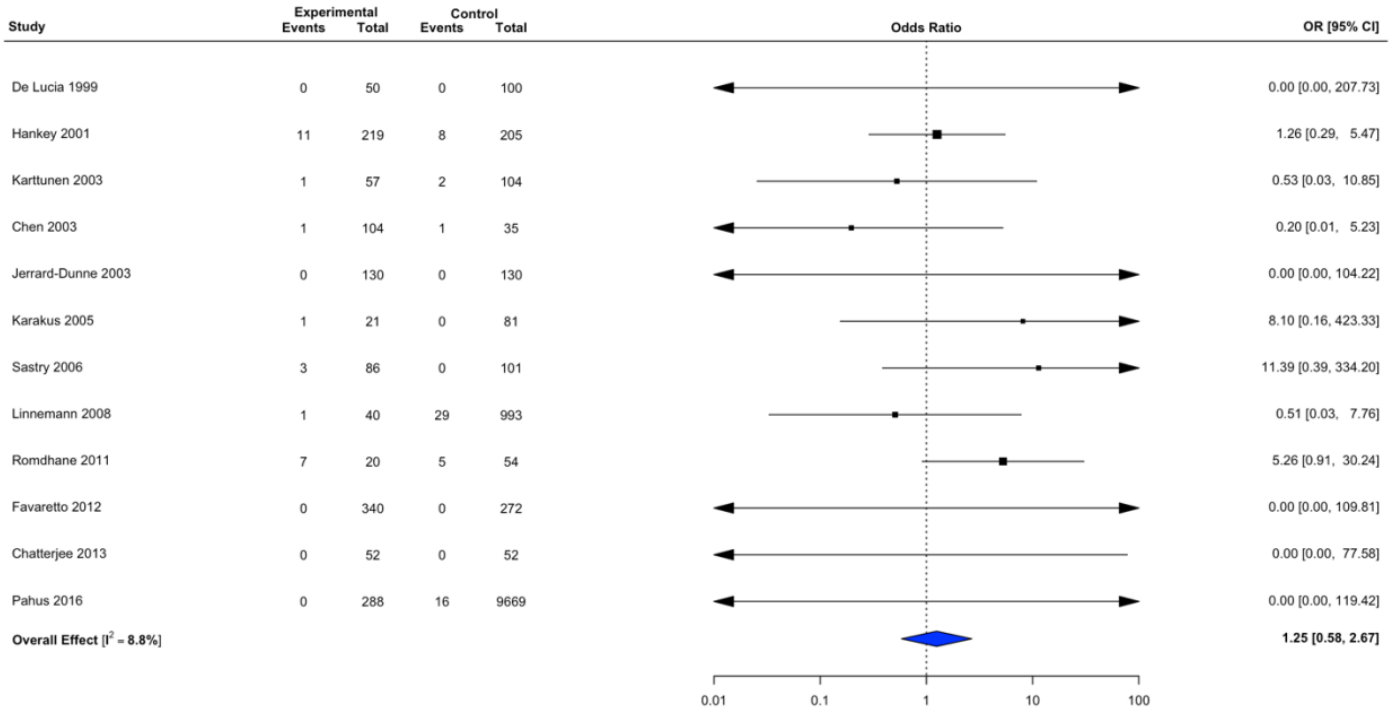


Figure S11. Subgroup Analyses: Factor V Leiden.

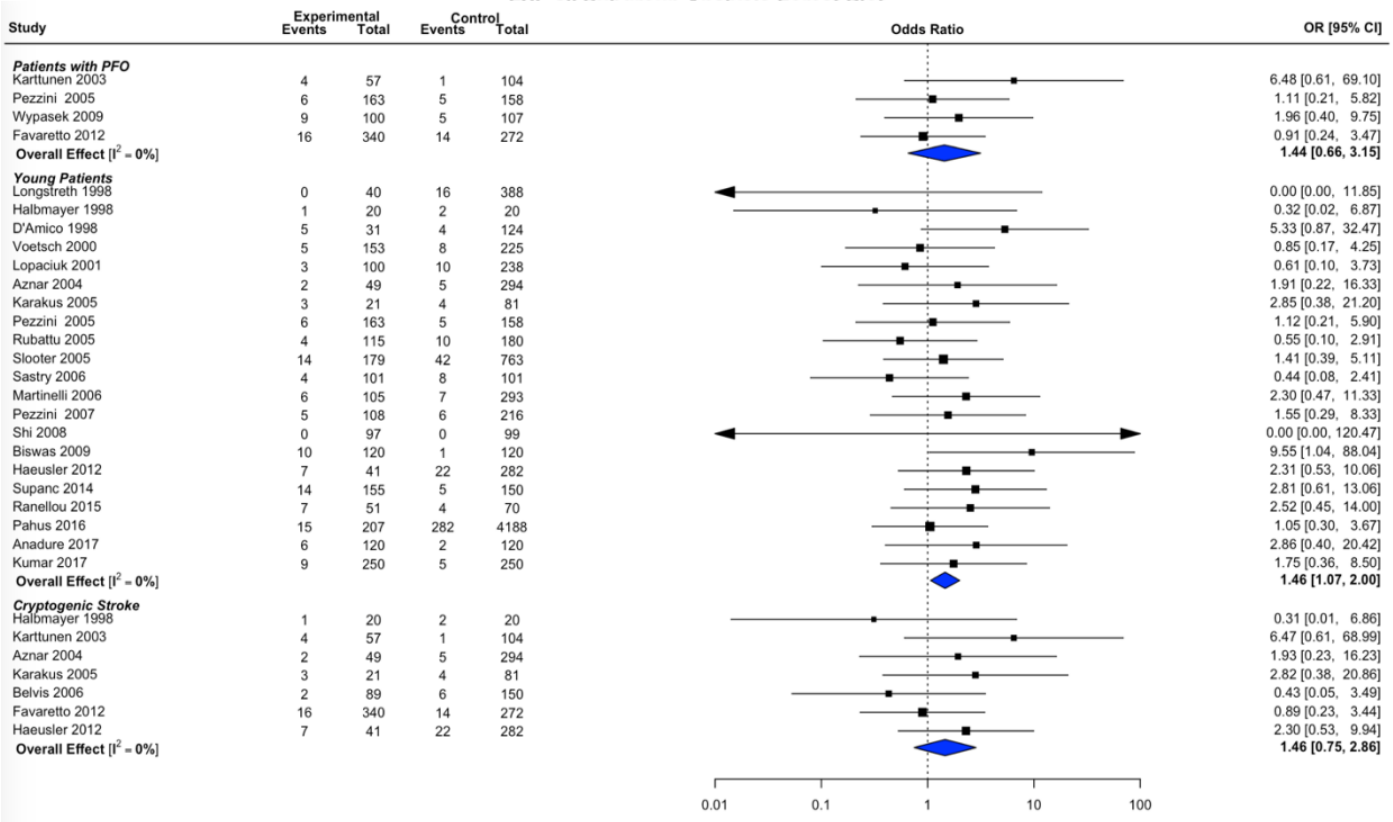


Figure S12. Subgroup Analyses: Prothrombin G20210A Mutation.

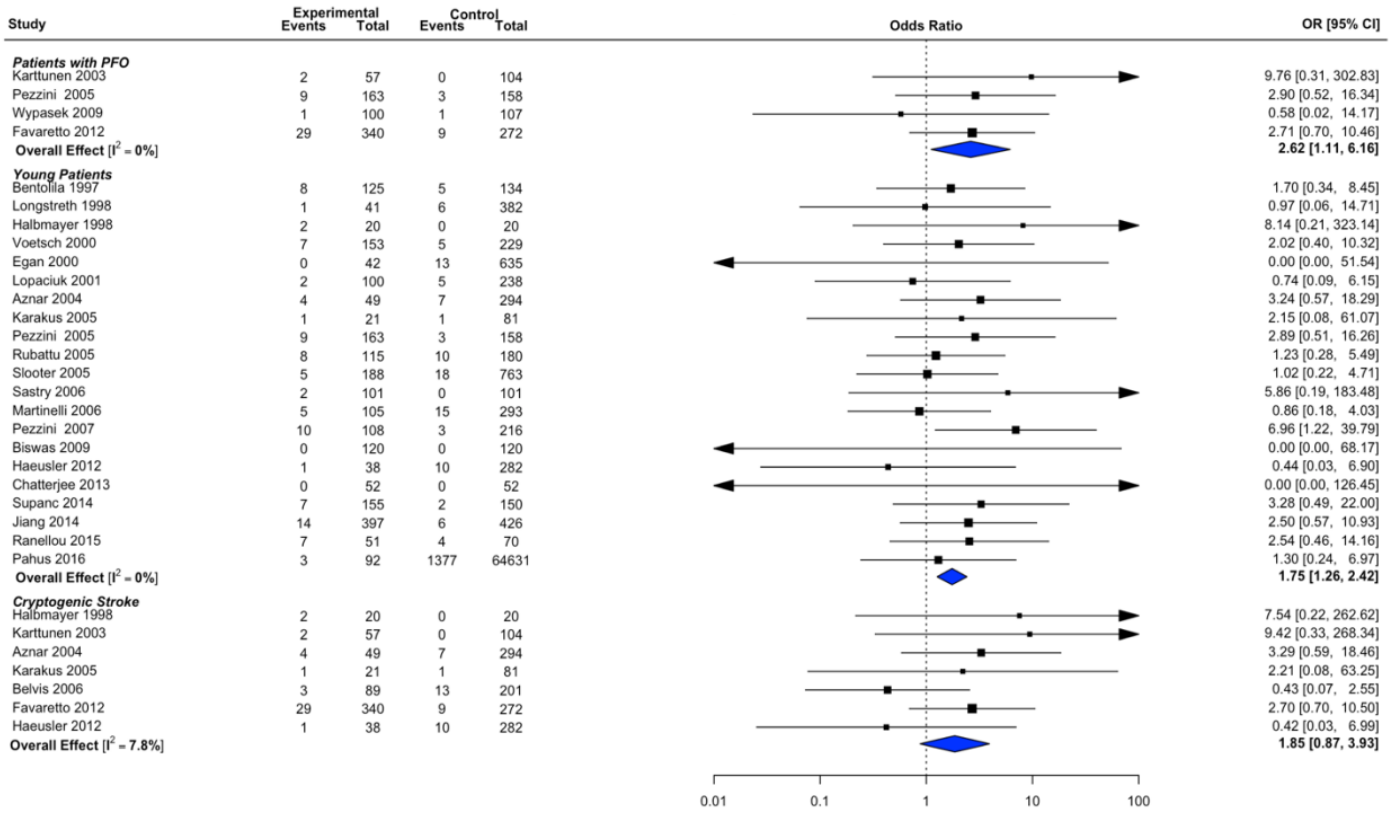


Figure S13. Subgroup Analyses: Protein C Deficiency.

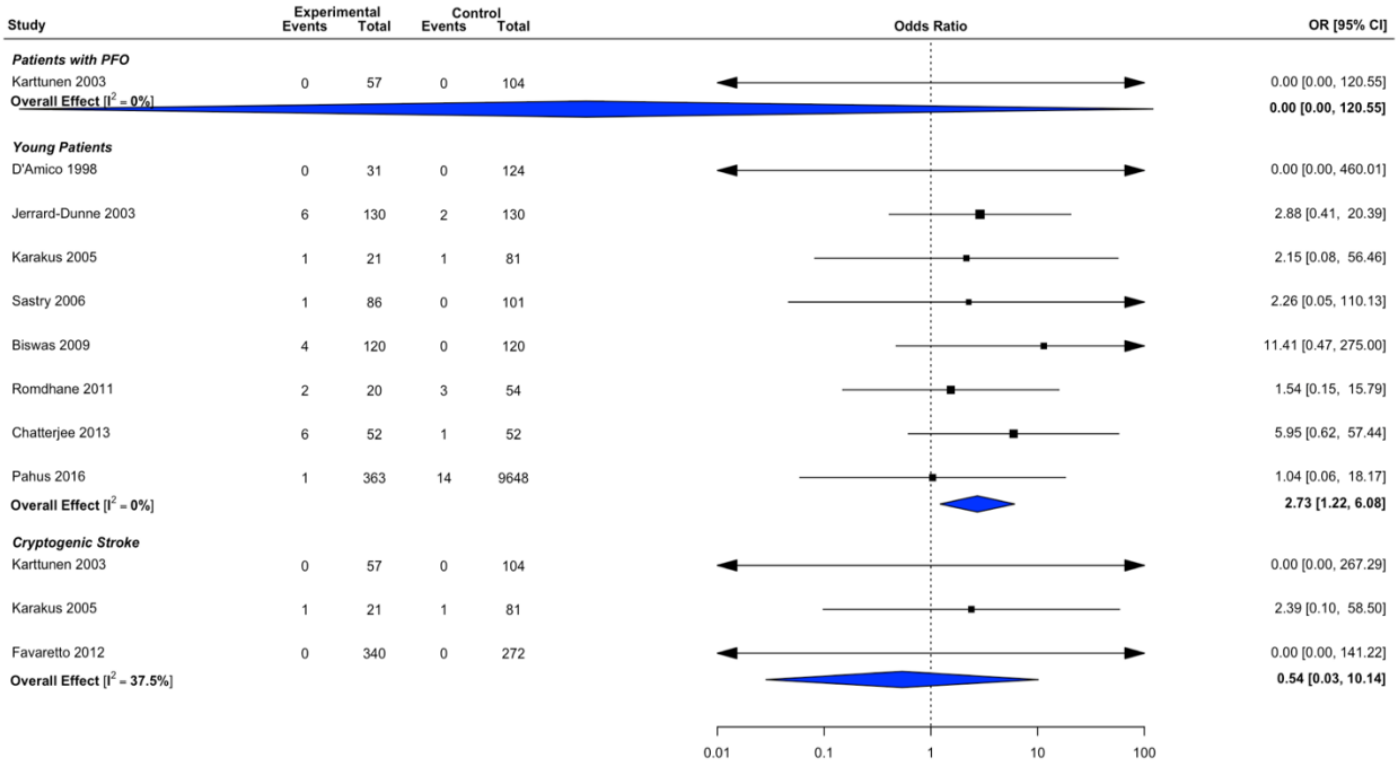


Figure S14. Subgroup Analyses: Protein S Deficiency.

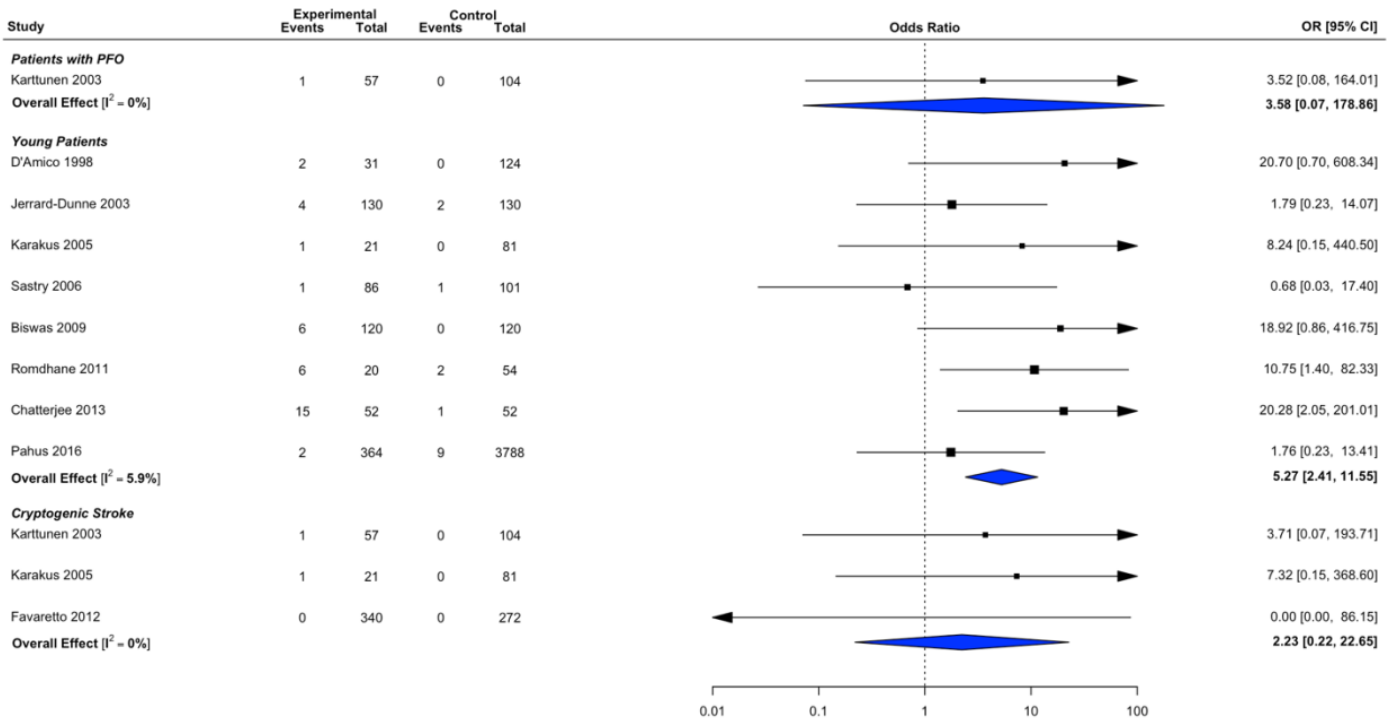
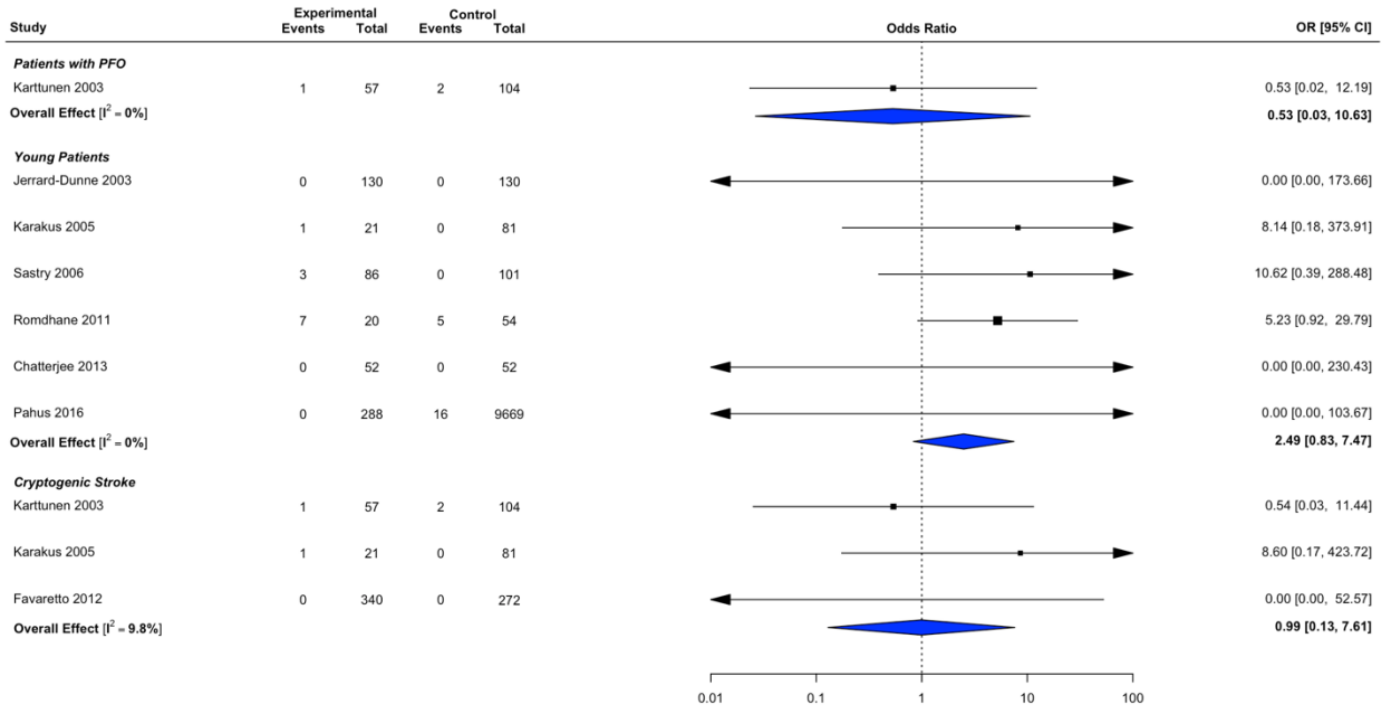


Figure S15. Subgroup Analyses: Antithrombin Deficiency.



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