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; I²=0%), prothrombin G20210A mutation (OR, 1.48; 95% CI, 1.22–1.80; I²=0%), protein C deficiency (OR, 2.13; 95% CI, 1.16–3.90; I²=0%), and protein S deficiency (OR, 2.26; 95% CI, 1.34–3.80; I²=8.8%). Statistical significance was not reached for antithrombin deficiency (OR, 1.25; 95% CI, 0.58–2.67; I²=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 (CRD42018 090020). We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses3 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 tool10 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.).
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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 ($\kappa=0.96$).

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
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.
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. PS was found in significantly more arterial ischemic stroke cases than controls, with a pooled OR of 1.25 (95% CI, 0.58–2.67) (Figure S9). Heterogeneity among studies was insignificant ($P$=0.93; $I^2$=0%). A funnel plot was symmetrical (Figure S4D) and Egger’s test was nonsignificant ($P$=0.05), suggesting absence of publication bias.
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; I²=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; I²=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 exclusively enrolled patients with PFO, whereas two 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 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), studies that used self-reported history of stroke rather than imaging to define cases, studies that were rated as poor quality, 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). 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).
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. Conversely, congenital deficiency of factors VIII, IX, and XI is protective against stroke and cardiovascular disease. Anticoagulants

### Table: Thrombophilia and Specific Subgroups

| Thrombophilia and Specific Subgroups (Number of Studies) | Pooled Odds Ratio (95%CI) |
|----------------------------------------------------------|--------------------------|
| Factor V Leiden (56)                                      | 1.25 (1.08-1.44)         |
| Young Adults (21)                                         | 1.46 (1.07-2.00)         |
| Patients with PFO (4)                                     | 1.44 (0.66-3.15)         |
| Cryptogenic stroke (7)                                   | 1.46 (0.75-2.86)         |
| PT G20210A mutation (45)                                 | 1.48 (1.22-1.80)         |
| Young Adults (21)                                         | 1.75 (1.26-2.42)         |
| Patients with PFO (4)                                     | 2.62 (1.11-6.16)         |
| Cryptogenic stroke (7)                                   | 1.85 (0.87-3.93)         |
| Protein C deficiency (15)                                | 2.13 (1.16-3.90)         |
| Young Adults (8)                                          | 2.73 (1.22-6.08)         |
| Cryptogenic stroke (3)                                   | 0.54 (0.03-10.14)        |
| Protein S deficiency (17)                                | 2.26 (1.34-3.80)         |
| Young Adults (8)                                          | 5.27 (2.41-11.55)        |
| Patients with PFO (1)                                    | 3.58 (0.07-178.86)       |
| Cryptogenic stroke (3)                                   | 2.23 (0.22-22.65)        |
| Antithrombin deficiency (12)                             | 1.25 (0.58-2.67)         |
| Young Adults (6)                                          | 2.49 (0.83-7.47)         |
| Patients with PFO (1)                                    | 0.53 (0.03-10.63)        |
| Cryptogenic stroke (3)                                   | 0.99 (0.13-7.61)         |

**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.
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 recurrence 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 (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.

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

| Thrombophilia | Age-Matched Studies | Non–Age-Matched Studies |
|---------------|---------------------|-------------------------|
|               | 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.
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) |
| 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. In one included study from Taiwan, 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. 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, 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
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 thrombophil*[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's[tiab] OR thrombophilias[tiab] OR thrombophiliac[tiab] OR thrombophilic'[tiab] OR thrombophilicity[tiab] OR thrombophilia's[tiab] OR thrombophilia[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 'thrombophilia'*:ti,ab OR 'inherited thrombophilia'/exp OR 'inherited thrombophilia':ti,ab OR 'genetic polymorphisms'*: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 NEAR2 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 'prothrombin mutation':ti,ab OR 'Factor V Leiden':ti,ab OR 'activated protein C resistance'[MeSH](178)
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 |
|-------------|---------|--------------|-------------------------------|--------------------------|----------------------------------------------------------------------------------|------------------------|---------------------|-------------------------|
| Anadure 2017(1) | India | 2010-2014 | +                             | 120/120                  | Hospitalized stroke ward patients, National Institute of Mental Health and Neuro Sciences, Bangalore | Unrelated healthy subjects | CT/MRI/MRA        | Age, sex                |
|             |         |              |                               |                          | 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 |
| 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 | 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 | 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 |
|-----------------|-----------|--------------|-------------------------------|--------------------------|-------------------------------------------------------------------------------------------------------|------------------------------|----------------------------------|------------------------------|
| Bolaman 2009(6) | Turkey    | 2003-2004    | +                             | 24/53                    | Department of Neurology, Adnan Menderes University, Aydin Stroke from cerebral infarct                  | Healthy subjects             | CT/MRI                          | -                            |
| Buyru 2005(7)   | Turkey    | NR           | +                             | 29/20                    | Neurology Clinic, Haydarpaşa 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 | MRI                            | -                            |
| Celiker 2009(9) | Turkey    | 2000-2003    | +                             | 162/285                  | Neurology Department of Baskent University Hospital Acute ischemic stroke                             | Previously published study   | MRI                            | Age, sex                      |
| 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 | Healthy individuals          | CT/MRI                          | Age, sex                      |
| Chen 2003(11)   | Taiwan    | NR           | +                             | 104/35                   | Non-cardiac cerebral ischemia Exclude: Cardioembolic, hemorrhagic stroke; systemic diseases (cancer, sickle cell anemia, vasculitis) | Hospital employees, family of patients, or individuals asking for neurologic examination free of medical disorders | MRI                            | -                            |
| Cushman 1998(12) | USA       | 1989-1990    | +                             | 149/482                  | Cardiovascular Health Study (Random sample of Medicare eligibility list) 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 <65                                 | Healthy volunteer from staff | CT/MRI                          | Age, sex                      |
| De Lucia 1999(14) | Italy     | 1994-1995    | +                             | 50/100                   | Ischemic stroke Age <45 with ischemic stroke                                                           | Healthy subjects             | CT/MRI                          | 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                  | 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                                      |
|----------------|-------------|-----------------------|-------------------------------|--------------------------|----------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|------------------|---------------------------------------------------------------|
| 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 Age ≥65, secondary hypercoagulability status, DM type 1, significant obstruction of carotid arteries 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 | Same population without self-reported stroke | Interview        | -                                                             |
| Favaretto 2012(20) | Italy       | 2008-2011             | + + + + + +                   | 340/272                  | Angiography 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 | Same cohort with no prior hospitalization for ischemic stroke | 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 Sampling of primary care lists in the same geographic area Stroke-free individuals | CT/MRI          | Age, sex, postal code                                       |
| Jerrard-Dunne 2003(26) | England    | NR                    | + + + +                      | 130/130                  | Stroke services in South London Age ≥65 Acute ischemic stroke | Randomly selected from the Western Australian electoral roll 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 |
|----------------|-------------|--------------|-------------------------------|--------------------------|-----------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|------------------|---------------------------|
| 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               | -                         |
| Kamberl 2016(29) | Macedonia | 2008-2010    | + +                           | 39/102                   | Neurology Department, Clinical Hospital, Tetro Age 18-90 First-ever ischemic stroke | Healthy subjects from local residents                                                 | CT/MRI           | -                         |
| Karakus 2005(30) | Turkey    | NR           | + + + + + +                   | 21/81                    | Age< 50 Cerebral infarction Age 15-60 Ischemic brain infarction of undetermined cause and PFO | Volunteer physicians and laboratory staff Spouse, friend , or randomly selected controls from the population register of the hospital catchment area | CT/MRI           | -                         |
| Kuttunen 2003(31) | Finland  | 1991-1998    | + + + + + +                   | 58/104                   | Age 15-60 Ischemic stroke                                                      |                                                                                          | 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           | -                         |
| Krajcowiechova 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 Same cohort without stroke | CT               | Age, sex                  |
| Linnemann 2008(35) | Germany | 2000-2006    | + + + + + +                   | 41/993                   | Patients with history of VTE registered in the MAISTHRD Database Age 17-90 with ischemic stroke King, Pierce, Snohomish counties, Washington Women age 18-44 Diagnosed of first stroke | Patients with history of VTE registered in the MAISTHRD Database Age 17-90 with ischemic stroke King, Pierce, Snohomish counties, Washington Women age 18-44 Diagnosed of first 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 Healthy blood donor and hospital staff | CT/MRI           | Age                       |
| Lopaciucl 2001(37) | Poland    | 1996-1999    | + +                           | 100/238                  | Age 545 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 |
|--------------------|-------------|--------------|-------------------------------|--------------------------|-----------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|------------------|---------------------------|
| Mayer 1993(39)     | USA         | 1990-1991    | +                             | 94/94                    | First ischemic stroke                                                              | Caucasian women of fertile age without previous thrombosis                              | NR               | -                         |
|                    |             |              |                               |                          | Columbia-Presbyterian Medical Center                                               | Patients admitted to the medicine and neurology services                                 |                  |                           |
|                    |             |              |                               |                          | North Manhattan Stroke Study                                                        | Age >39 Postmenopausal women residing in the Zip code of northern Manhattan             |                  |                           |
| Mochan 2005(40)    | South Africa| NR           | +                             | 33/33                    | Chris Hani Baragwanath Hospital in Soweto                                           | Inpatients of same hospital                                                              | CT               | Age, sex, CD4 count       |
|                    |             |              |                               |                          | HIV-infected Stroke with cerebral infarction                                       | HIV-infected No cerebral infarction                                                     |                  |                           |
| 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    | +                             | 377/6431                   | Center of Hemophilia and Thrombosis, Aarhus University Hospital                    | Previously published data of general western population                                  | WHO and record review                      |                           |
|                    |             |              |                               |                          | Ischemic stroke Banco Municipal de Sangre, Caracas Stroke                           | WHO and record review                      |                  |                           |
| Pestana 2009(44)   | Venezuela   | 2005-2007    | +                             | 54/134                    | Ischemic stroke Banco Municipal de Sangre, Caracas Stroke                           | Randomly selected, unselected, 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                                                    | CT/MRI           | -                         |
|                    |             |              |                               |                          | Exclude: History of CVD, CHD, PAD; carotid bruit                                    |                                               |                  |                           |
| Pezzini 2005(46)   | Italy        | 1997-2002    | +                             | 163/158                   | Department of Neurology, University of Brescia, Brescia Age <45                    | Staff of same hospital                                                                   | CT/MRI           | Age, sex                  |
|                    |             |              |                               |                          | Admitted patients with first-ever ischemic stroke                                   | No vascular diseases                                                                     |                  |                           |
| Pezzini 2007(47)   | Italy        | NR           | +                             | 108/216                   | Department of Neurology, University of Brescia, Brescia Age <45                    | Women from the staff of the 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 |
|----------------|------------|--------------|-------------------------------|--------------------------|----------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|-----------------|----------------------------|
| 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        |
| 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                  | Ischemic cerebrovascular events Age >65                                          | Age >65 No personal or familial history of CVA/CHD                                    | NR             | -                          |
| Romdhane 2011(54) | Tunisia    | NR           | +                             | 20/54                    | First non-cardioembolic ischemic stroke Neurological Department, University of Sassari, Sardinia Ischemic stroke |                                              | NR             | Age                        |
| Rubattu 2005(55) | Italy      | 1998-2003    | +                             | 294/286                  | Neurological Institute, University La Sapienza, Rome Age 15-45 First-ever ischemic stroke within the 8 weeks preceding the admission into the hospital Hospitals in the North West and Mersey Regions, Manchester Age 16-39 at the time of stroke First ischemic stroke identified by ICD-9 | Healthy blood donors from the same center No drug/OCP use No family history of stroke | CT/MRI          | Age                        |
| 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 Hospitals in the North West and Mersey Regions, Manchester Age 16-39 at the time of stroke First ischemic stroke identified by ICD-9 | 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                  | Neurological Institute, University La Sapienza, Rome Age 15-45 First-ever ischemic stroke within the 8 weeks preceding the admission into the hospital Hospitals in the North West and Mersey Regions, Manchester Age 16-39 at the time of stroke First ischemic stroke identified by ICD-9 | Healthy blood donors from the same center No drug/OCP use No family history of stroke | CT/MRI          | Age                        |
| Reference | Country | Study period | Types of thrombophilia tested | Number of cases/controls | Study population | Control Identification | Stroke diagnosis | Case-control matching for |
|-----------|---------|--------------|-------------------------------|--------------------------|-----------------|------------------------|-----------------|-----------------------------|
| Shi 2008(58) | China | 2006-2007 | + | 97/99 | Exclude: Surgery/injury within 10 weeks; malignancy Neurological department, Beijing Tiantan Hospital Age 18-45 Acute ischemic stroke | 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: AF; hemorrhage | 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 | | 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 |
| Tatarsky 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 Ukrainian population | Russian and Ukrainian 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, Year | Country | Study period | Types of thrombophilia tested | Number of cases/controls | Study population | Control Identification | Stroke diagnosis | Case-control matching for |
|-----------------|---------|--------------|-------------------------------|-------------------------|-----------------|------------------------|----------------|--------------------------|
| Wypasek 2009(67) | Poland | NR           | FVL + PTM + PCD + PSD + ATD | 100/107                 | PFO patients    | 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 | 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.
| 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/RR                     | 13/RR                       | NR/RR                       | 33/RR                            | NR/RR                        |
| Aznar 2004(2)                   | 18-50 (Range)/NR                | NR/RR                    | 100                             | NR/RR                       | NR/RR                     | NR/RR                       | NR/RR                       | NR/RR                            | NR/RR                        |
| Belvis 2006(3)                  | 57/48                           | 60/45                    | 100                             | NR/RR                       | 17/2.7                    | 36/13                      | 38/14                      | NR/RR                            | NR/RR                        |
| Bentollia 1997(4)               | 41/34                           | 58/50                    | 44                              | White 100/100               | NR/RR                     | NR/RR                       | NR/RR                       | NR/RR                            | NR/RR                        |
| Biswas 2009(5)                  | NR/NR                           | NR/RR                    | Indian 100/100                  | NR/RR                       | NR/RR                     | NR/RR                       | NR/RR                       | NR/RR                            | NR/RR                        |
| Bolaman 2009(6)                 | 64/59                           | 67/58                    | NR                              | NR/RR                       | 33/32                     | 63/60                      | 38/36                      | NR/RR                            | 21/19                        |
| Buyu 2005(7)                   | 67/61 (Median)                  | NR/RR                    | 21/11                           | NR/RR                       | NR/RR                     | NR/RR                       | NR/RR                       | NR/RR                            | 10/RR                        |
| Catto 1995(8)                   | 74/76                           | NR/RR                    | NR/RR                           | NR/RR                       | NR/RR                     | NR/RR                       | NR/RR                       | NR/RR                            | NR/RR                        |
| Celiker 2009(9)                 | 70/NR                           | 54/NR                    | 30                              | NR/RR                       | NR/RR                     | NR/RR                       | NR/RR                       | NR/RR                            | NR/RR                        |
| Chatterjee 2013(10)             | 23/NR                           | 63/63                    | NR                              | NR/RR                       | NR/RR                     | NR/RR                       | NR/RR                       | NR/RR                            | NR/RR                        |
| Chen 2003(11)                   | 62/61                           | 68/69                    | NR                              | NR/RR                       | 28/0                      | 70/0                       | NR/RR                       | NR/RR                            | NR/RR                        |
| Cushman 1998(12)               | 76/72                           | 48/37                    | NR                              | NR/RR                       | 39/16                     | 60/34                      | NR/RR                       | NR/RR                            | 45/50                        |
| D'Amico 1998(13)               | 34/33                           | 65/32                    | NR                              | NR/RR                       | NR/RR                     | NR/RR                       | NR/RR                       | NR/RR                            | NR/RR                        |
| De Lucia 1999(14)               | 35/45                           | 76/45                    | NR                              | NR/RR                       | NR/RR                     | NR/RR                       | NR/RR                       | NR/RR                            | NR/RR                        |
| Djordjevic 2012(15)            | 40/39                           | 56/70                    | NR                              | NR/RR                       | NR/RR                     | NR/RR                       | NR/RR                       | NR/RR                            | NR/RR                        |
| Egan 2000(16)                  | 43/41                           | 52/49                    | NR                              | NR/RR                       | NR/RR                     | NR/RR                       | NR/RR                       | NR/RR                            | NR/RR                        |
| Erten 2015(17)                 | 56/62                           | 52/45                    | 51                              | NR/RR                       | 30/24                     | 61/43*                     | 28/23                      | NR/RR                            | 38/37                        |
| Eterovic 2007(18)              | 61/61 (Median)                  | NR/RR                    | White 100/100                   | NR/RR                       | NR/RR                     | NR/RR                       | NR/RR                       | NR/RR                            | NR/RR                        |
| Fan 2010(19)                   | 68/44                           | 44/48                    | NR                              | White 82/82                 | 30/30                     | 56/56                      | NR/RR                       | NR/RR                            | NR/RR                        |
| Favaretto 2012(20)             | 51/52.2                         | PFO 49/ Non- PFO 46 /74  | 100                             | White 100/100               | NR/RR                     | NR/RR                       | NR/RR                       | NR/RR                            | NR/RR                        |
| Go 2003(21)                    | 74/69*                          | 51/62*                   | NR                              | White 80/84                 | 20/14                     | 66/44*                     | NR/RR                       | NR/RR                            | NR/RR                        |
| Haeusler 2012(22)              | 36/39 (Median)                  | 41/36                    | 100                             | NR/RR                       | 5/5                       | 223/39                     | 36/39                      | NR/RR                            | 40.9/RR                     |
| Halbmayer 1998(23)              | 39/39                           | 50/50                    | 100                             | NR/RR                       | NR/RR                     | NR/RR                       | NR/RR                       | NR/RR                            | NR/RR                        |
| Hamedani 2013(24)              | 41/40*                          | 57/55                    | 50.4                            | White 56/60                 | 17/5*                     | 43/19*                     | NR/RR                       | 16/8*                            | 41/28*                       |
| Hankey 2001(25)                | 66/67                           | 64/64                    | 20                              | NR/RR                       | 25/11*                    | 54/33*                     | 24/22                      | NR/RR                            | 33/18*                       |
| Jerrard-Dunne 2003(26)         | White 53/54                     | 62/50                    | NR                              | White 39/39                 | 26/10                     | 59/39                      | 49/42                      | NR/RR                            | 40/23                       |
| Jerrard-Dunne 2003(26)         | Black Caribbean 57/56           | NR/RR                    | Black Caribbean 59/39           | NR/RR                       | NR/RR                     | NR/RR                       | NR/RR                       | NR/RR                            | NR/RR                        |
| Jerrard-Dunne 2003(26)         | Black African 53/55             | NR/RR                    | Black African 23/23             | NR/RR                       | NR/RR                     | NR/RR                       | NR/RR                       | NR/RR                            | NR/RR                        |
| Jiang 2014(27)                 | 41/39*                          | 63/55*                   | NR                              | White 100/100               | 11/2*                     | 32/16*                     | NR/RR                       | 23/11*                           | 43/24*                       |
| Juul 2002(28)                  | 63/56*                          | 61/43*                   | NR                              | White >9/>9                  | 14/3*                     | 46/17*                     | NR/RR                       | NR/RR                            | 80/73*                       |
| Kamberti 2016(29)              | 63/49*                          | NR/RR                    | NR/RR                           | NR/RR                       | NR/RR                     | NR/RR                       | NR/RR                       | NR/RR                            | NR/RR                        |
| Karakus 2005(30)               | 40/42                           | 38/52                    | 100                             | NR/RR                       | NR/RR                     | NR/RR                       | NR/RR                       | NR/RR                            | NR/RR                        |
| Kartunen 2003(31)              | 44/45                           | 55/57                    | 100                             | NR/RR                       | NR/RR                     | 2/4                        | 16/13                      | NR/RR                            | 27/27                        |
| Khodskova 2015(32)             | 73/NR                           | NR/RR                    | 0                               | NR/RR                       | NR/RR                     | NR/RR                       | NR/RR                       | NR/RR                            | NR/RR                        |
| Krafkovicheva 2015(33)         | 66/61*                          | 61/49*                   | 36                              | NR/RR                       | 30/10*                    | 87/58*                     | 93/86*                     | NR/RR                            | 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/0                        | 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                     |
| Lupaciuk 2001(37)         | 38/33                         | 51/66                  | 55                             | NR/0                        | 20/0                       | NR/NR                         | 42/0NR                        | NR/NR                            | 61/27                     |
| Martinelli 2006(38)       | 35/35                         | 0/0                    | 52                             | White 100/100               | 0/0                        | 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 100/100               | 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                      | NR/NR                         | 32/ NR                        | NR/NR                            | 50/ NR                     |
| Pestana 2009(44)          | 39/39                         | 39/39                  | NR                             | NR/ NR                      | 2/2                        | 13/16                         | NR/NR                         | 13/16                            | 14/21                     |
| Petrovic 2003(45)         | 62/63                         | 63/57                  | NR                             | White 100/100               | 31/4*                      | 66/33*                        | 28/20*                        | NR/NR                            | 44/25*                    |
| Pezzini 2005(46)          | 35/35                         | 52/54                  | 31                             | White 100/100               | 3/3                        | 17/6*                         | 25/11*                        | NR/NR                            | 47/25*                    |
| Pezzini 2007(47)          | 34/35                         | 0/0                    | 38                             | White 100/100               | 0/0                        | 12/4*                         | 25/11*                        | NR/NR                            | 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                      | 41/5                         | 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 1999(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                      | 57/40                     |
| 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*                    |
| Sloot 2005(59)            | 34/40                         | 0/0                    | 0                              | NR/ NR                      | 4/1*                       | 32/6*                         | 8/3*                          | NR/NR                            | 52/36*                    |
| 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*                    |
| Tatarsky 2010(63)         | 65/30*                        | 52/45                  | NR                             | NR/ NR                      | 19/8*                      | 51/10*                        | NR/NR                         | NR/NR                            | 22/7*                     |
| They-They 2012(64)        | 49/46                         | 51/52                  | 6.6                            | NR/ NR                      | 18/9*                      | NR/NR                         | NR/NR                         | NR/NR                            | NR/NR                     |
| Tupitsyna 2013(65)        | NR/NR                         | NR/NR                  | NR                             | NR/ NR                      | NR/NR                      | NR/NR                         | NR/NR                         | NR/NR                            | NR/NR                     |
| Voss1sch 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 Heterozyzous 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) |
| Aznan 2004(2) | PCR/RFLP   | 2.62 (0.43-13.95) | 2/49 (4.1) | 5/294 (1.7) | 0/100 (0) | 0/120 (0) | 2/67 (3.0) | 6/150 (4.0) |
| Biswas 2006(3) | PCR/RFLP   | 10.8 (1.3-229.5; P = .005) | 0/120 (0) | 4/120 (3.3) | 0/120 (0) | 0/120 (0) | 0/120 (0) | |
| 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   | 1/29 (3.4) | 0/20 (0) | 1/29 (3.4) | 0/20 (0) | 0/20 (0) | 0/20 (0) | |
| Catto 1995(8) | PCR/RFLP   | 16/39 (4.1) | 14/247 (5.7) | 0/386 (0) | 0/247 (0) | 16/386 (4.1) | 14/247 (5.7) |
| 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 1999(13) | PCR  | 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  | 11/50 (22) | 2/100 (2) | 2/50 (4) | 0/100 (0) | 9/50 (18) | 2/100 (2) |
| Djordjevic 2012(15) | PCR  | 1.45 (0.47-4.48) | 6/73 (8.2) | 7/120 (5.8) | 0/100 (0) | 0/100 (0) | 0/100 (0) | 0/100 (0) |
| Enren 2015(17) | PCR/RFLP   | 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  | 0.82 (0.29-2.34) | 0/156 (0) | 262/5817 (4.5) | 0/137 (0) | 8/137 (5.8) | 8/137 (5.8) |
| Fan 2010(19) | PCR  | 16/340 (4.7) | 14/272 (5.1) | 0/340 (0) | 0/137 (0) | 8/137 (5.8) | 8/137 (5.8) |
| Favarottto 2012(20) | PCR  | 7/41 (17.1) | 22/282 (7.8) | 0/41 (0) | 0/282 (0) | 7/41 (17.1) | 22/282 (7.8) |
| Haesler 2012(22) | PCR  | 1/20 (5) | 2/20 (10) | 0/20 (0) | 0/20 (0) | 1/20 (5) | 2/20 (10) |
| Halbmayer 1998(23) | PCR  | 30/830 (3.6) | 34/907 (3.7) | 0/120 (0) | 0/120 (0) | 0/120 (0) | 0/120 (0) |
| Hammedi 2013(24) | SNP array | 2.1 (0.6-6.8) | 10/219 (4.6) | 4/205 (2) | 0/120 (0) | 0/120 (0) | 0/120 (0) |
| Juul 2002(28) | PCR/RFLP   | 17/231 (7.4) | 629/7907 (8) | 1/231 (0.4) | 17/7907 (0.2) | 16/231 (6.9) | 9/102 (8.8) |
| Kamperi 2016(29) | PCR/ hybridization | 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 | 7/8 (0.8-71.3) | 4/57 (7) | 1/104 (1) | 0/57 (0) | 0/104 (0) | 4/57 (7) |
| Kartunnen 2003(31) | PCR  | 3.114 (2.6) | 0/40 (0) | 0/114 (0) | 0/40 (0) | 3.114 (2.6) | 0/40 (0) |
| Kolodkova 2015(32) | PCR  | 44/423 (10.4) | 53/614 (8.6) | 2/423 (0.5) | 2/614 (0.3) | 42/423 (9.9) | 51/614 (8.3) |
| Krajcovicheva 2015(33) | 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) |
| Kumar 2017(34) | PCR  | 0.87 (0.42-1.79; P = .88) | 10/41 (24.4) | 278/1020 (27.3) | 0/41 (0) | 0/1020 (0) | 10/41 (24.4) | 256/1020 (25.1) |
| Linnemann 2008(35) | PCR/RFLP | 0.0 (0-2.5) | 16/388 (4.1) | 0/40 (0) | 0/288 (0) | 16/388 (4.1) | 0/288 (0) |
| Longstreth 1998(36) | 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) |
| Lopaciuk 2001(37) | PCR | 6/105 (5.7) | 7/293 (2.4) | 0/105 (0) | 0/293 (0) | 6/105 (5.7) | 7/293 (2.4) |
| Martellini 2006(38) | NR ("DNA analysis") | 11/167 (6.6) | 30/500 (6) | 1/167 (0.6) | 1/500 (0.2) | 10/167 (6) | 29/500 (5.8) |
| Moskau 2010(41) | PCR  | 0/106 (0) | 0/37 (0) | 0/106 (0) | 0/37 (0) | 0/106 (0) | 0/37 (0) |
| Nagayama 1996(42) | PCR  | 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) | 15/207 (7.2) | 282/1488 (6.6) | 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)  | 10/58 (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)  |
| Rider 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) | 42/760 (6)  | 0/209 (0)   | 0/760 (0)   | 9/209 (4.3) | 42/760 (6)  |
| Ripoll 1997(53) | PCR/RFLP    | 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)  | 2/296 (0.7) | 0/294 (0)  | 0/296 (0)   | 5/294 (1.7) | 2/296 (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) | PCR/RFLP    | NR                 | 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) |         |           |         |           |         |           |
| Supanc 2014(61) | PCR/RFLP    | 2.88 (1.0-8.20; 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) |
| Tatarksky 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)    |
| Tuptysna 2013(65)| PCR         | Russian: 0.9 (0.50-1.76) Ukrainian: 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.
| 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  | 7/294    | 0/89  | 0/201    | 0/89  | 3/201    |
| Belotilla 1997(4)   | PCR        | NR                 | 3/89  | 13/201   | 0/89  | 0/201    | 0/89  | 13/201   |
| Biswas 2005(5)      | PCR/RFLP   | NR                 | 8/125 | 5/134    | 0/125 | 0/134    | 0/125 | 5/134    |
| Bolaman 2009(6)     | PCR        | NR                 | 0/24  | 0/53     | 0/24  | 0/53     | 0/24  | 0/53     |
| Celiker 2009(9)     | PCR/RFLP   | NR                 | 3/162 | 5/182    | 0/162 | 0/182    | 3/162 | 5/182    |
| Chatterjee 2013(10) | PCR/RFLP   | 1.00 (0.02-51.35;  | 0/52  | 0/52     | 0/52  | 0/52     | 0/52  | 0/52     |
| Djordjevic 2012(15)| PCR/RFLP   | 1.33 (0.35-5.13)   | 4/73  | 5/120    | 4/73  | 5/120    |       |          |
| Egan 2000(16)       | PCR        | NR                 | 0/42  | 13/635   | 0/42  | 6/635    | 0/42  | 13/635   |
| Ertens 2015(17)     | PCR        | NR                 | 13/212| 10/238   | 0/212 | 0/238    | 13/212| 10/238   |
| Eterovic 2007(18)   | PCR/RFLP   | NR (P = .047)      | 3/120 | 0/120    |       |          | 3/120 |          |
| Fan 2010(19)        | PCR        | 1.69 (0.26-10.82)  | 6/156 | 122/581  | 6/156 | 122/581  |       |          |
| Favaretto 2012(20)  | PCR        | 2.97 (1.32-6.69)   | 29/340| 9/272    | 0/340 | 0/272    | 29/340| 9/272    |
| Haeusler 2012(22)   | PCR        | NR (P = >.995)     | 1/38  | 10/282   | 0/38  | 0/282    | 1/38  | 10/282   |
| Habmayr 1998(23)    | PCR        | NR (P = .46)       | 2/20  | 0/20     | 2/20  | 0/20     | 2/20  | 0/20     |
| Hankey 2001(25)     | PCR        | 1.9 (0.5-6.2)      | 8/219 | 4/205    |       |          |       |          |
| Jiang 2014(27)      | PCR        | 2.5 (0.9-6.5; P = .07) | 14/397 | 6/426 | 1/397 | 6/426 | 13/397 | 6/426 |
| Kamberi 2016(29)    | PCR        | 2.80 (0.33-23.53 P = .32) | 1/39 | 7/102 | 0/39 | 1/102 | 7/102 | 1/102 |
| Karakus 2003(30)    | PCR        | NR                 | 1/21  | 1/81     | 1/21  | 1/81     | 1/21  | 1/81     |
| Karttunen 2003(31)  | PCR        | 1.0 (1.0-1.1)      | 2/57  | 0/104    | 2/57  | 0/104    | 2/57  | 0/104    |
| Khodolkov 2015(32)  | PCR        | NR                 | 6/114 | 0/40     | 6/114 | 0/40     | 6/114 | 0/40     |
| Krajcovicca 2015(33)| PCR        | Multivariate adjusted OR 2.29 (1.04-5.02; P = .04) | 22/423 | 15/614 | 22/423 | 15/614 | 22/423 | 15/614 |
| Linnemann 2008(35)  | PCR        | 0.63 (0.15-2.7; P = .76) | 2/41 | 76/930 | 1/41 | 2/930 | 1/41 | 76/930 |
| Longstreth 1998(36) | PCR/RFLP   | 1.6 (0.03-13.4)    | 1/41  | 6/382    | 0/41  | 0/382    | 1/41  | 6/382    |
| Lopaciuk 2001(37)   | PCR        | 0.9 (0.2-5.0)      | 2/100 | 5/238    | 0/100 | 0/238    | 2/100 | 5/238    |
| Martinelli 2006(38) | PCR        | NR ("DNA analysis") | 5/105 | 15/293 | 5/105 | 15/293 | 5/105 | 15/293 |
| Moskau 2010(41)     | PCR        | NR (P = .88)       | 7/167 | 0/167    | 7/167 | 0/167    | 7/167 | 0/167    |
| Pahus 2016(42)      | PCR        | Heterozygous 1.59 (0.32-4.81) | 3/92 | 1377/6463 | 0/92 | 0/6463 | 3/92 | 1369/6463 |
| Pazzini 2005(46)    | PCR        | 2.68 (0.70-10.3)   | 9/163 | 1/163    | 0/158 | 1/163    | 0/158 | 1/163    |
| Pazzini 2007(47)    | PCR        | 6.52 (1.73-24.6)   | 10/108| 3/216    | 1/108 | 0/216    | 9/108 | 3/216    |
| Pullmann 2004(48)   | PCR        | NR                 | 0/23  | 3/71     | 0/23  | 0/71     | 0/23  | 0/71     |
| Ranelli 2015(50)    | PCR        | NR (P = .70)       | 7/51  | 4/70     | 0/51  | 0/70     | 7/51  | 4/70     |
| Ridker 1999(52)     | PCR        | Crude RR 1.1 (0.6-2.1; P = .8) | 11/259 | 69/1774 | 0/259 | 1/1774 | 11/259 | 68/1774 |

Table S4. Results of Included Studies: Prothrombin G20210A Mutation.
| Study                        | Methodology | PCR/RFLP | PTM | Multivariate adjusted RR | RR (95% CI) |
|------------------------------|-------------|----------|-----|--------------------------|-------------|
| Rubattu 2005(55)             | PCR/RFLP   | NR (P = .95) | 1.1 (0.5-2.4; P = .7) | 12/294 (4.1) | 0/294 (0) | 0/294 (0) | 12/294 (4.2) | 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) |
| Saeter 2006(57)              | PCR        | NR       | 2/101 (2) | 0/101 (0)   |             |             |             |             |
| Slooter 2006(59)             | PCR        | NR       | 5/188 (2.7) | 18/763 (2.4) |             |             |             |             |
| Smiles 2002(60)              | PCR        | NR       | 6/182 (3.3) | 0/453 (0)  | 6/182 (3.3) | 12/453 (2.6) |             |             |
| Supanc 2014(61)              | PCR        | NR       | 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-Thy 2012(64)            | PCR/RFLP   | NR (P = .60) | 2.3 (0.97-5.8; P = .5) | 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) | 5/229 (2.2) | 0/153 (0)  | 0/229 (0) | 7/153 (4.6) | 5/229 (2.2) |             |
| 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.
| References     | Test Method          | Definition of deficiency | Timing of test after stroke | Exclusion of anticoagulants | Odds Ratio (95% CI) | Number of PCD Cases (%) |
|---------------|----------------------|--------------------------|-----------------------------|-----------------------------|---------------------|--------------------------|
| Biswas 2009(5)| ELISA                | <65%                     | 3-6 months after stroke     | Yes                         | NR                  | 4/120 (3.3)              |
| Chatterjee    | Clot-based assay     | <70%                     | ≥4 months after stroke      | NR                          | 0.15 (0.01-1.30; P = .12) | 6/52 (11.5)             |
| 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)            |
| D'Amico 1998(13) | NR                  | NR                       | 2-15 days after stroke      | NR                          | NR                  | 0/31 (0)                 |
| De Lucia 1999(14) | NR                  | <76.9% (<2.5th percentile) | At 3 months after stroke   | Yes                         | NR                  | 2/50 (4)                 |
| Favaretto 2012(20) | Chromogenic assay | <68%                     | 1 month after discharge     | NR                          | NR                  | 0/340 (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)              |
| 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)              |
| Karakus 2005(30) | Chromogenic assay    | NR                       | NR                          | NR                          | NR                  | 1/21 (4.8)               |
| Karttunen 2003(31) | Chromogenic assay    | NR                       | >2 months after stroke      | NR                          | NR                  | 0/57 (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)                 |
| 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)              |
| Romdhane 2011(54) | Chromogenic assay    | NR                       | NR                          | 2 (NR; P =.6)               | 2/20 (10)            |
| Sastry 2006(57) | Functional assay     | NR                       | NR                          | Yes                         | NR                  | 1/86 (1.2)               |
| Zimba 2017(68)  | Chromogenic assay    | <70%                     | More than 48 hour, up to 1 month | Yes                         | NR (P =.06)         | 5/52 (9.6)               |

NR, not reported; PCD, protein C Deficiency; ELISA, enzyme-linked immunosorbent assay; CI, confidence interval.
| References     | Test Method        | Definition of deficiency | Timing of test after stroke | Exclusion of anticoagulants | Odds Ratio (95% CI) | Number of PSD (%) |
|---------------|--------------------|--------------------------|-----------------------------|------------------------------|---------------------|-------------------|
| 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 <0.001) | 15/52 (28.8) | 1/52 (1.9) |
| Chen 2003(11)  | Chromogenic assay | <60% (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)                   | 22/10 (21.2) | 3/35 (8.6) |
| D’Amico 1998(13) | 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 | 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 | 1/21 (4.8) | 0/81 (0) |
| Karttunen 2003(31) | Clot-based assay | >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) | 29/788 (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 | 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 | 11.3 (NR; P =0.003) | 6/20 (30) | 2/54 (3.7) |
| Sastry 2006(57) | Functional assay | NR | NR | Yes | NR (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 anticoagulant s | Odds Ratio (95% CI) | Number of ATD (%) |
|------------------|-------------|--------------------------|-----------------------------|-----------------------------|---------------------|--------------------|
| Chatterjee 2013(10) | Chromogenic assay | <75%                      | 24 months                   | NR                          | 1.00 (0.02-51.35; P = 1) | 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)           |
|                  |              |                          | 3 months                    | Yes                        | NR                  | 0/50 (0)            |
| De Lucia 1999(14) | NR          | NR                       | NR                          | NR                          | 0.9 (0.1-10.5)       | 1/57 (1.8)          |
| Favaretto 2012(20) | Chromogenic assay | <80%                      | 1 month after discharge     | NR                          | 0.88 (0.12-6.60; P = .8) | 0/340 (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)  | 11/21 (5.2)         |
| 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                      | NR                  | 0/130 (0)           |
| Karakus 2005(30)  | NR          | NR                       | NR                          | NR                          | NR                  | 1/21 (4.8)          |
| Karttunen 2003(31) | Chromogenic assay | NR                        | >2 months after stroke      | NR                          | 0.9 (0.1-10.5)       | 1/57 (1.8)          |
| 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)         |
| Linnemann 2010(54) | Functional assay | <0.60 x 10^3 U/L         | Average 2 months (Repeated in cases of deficiency) | NR                        | NR                  | 0/1288 (0)          |
| Linnemann 2011(54) | Chromogenic assay | NR                       | NR                          | NR                          | 5.6 (NR; P = 0.01)    | 7/20 (3.5)          |
| Sastry 2006(57)   | Functional assay | NR                       | NR                          | Yes                        | NR                  | 3/86 (3.5)          |

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 prescribed 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 | Quality |
|-----------------------|-------------------|-------------------|--------------------------------------------|---------------------------|--------------------------------------|-------------------------------------------------|-------------------------------|------------------------------------------|---------------------|-----------------------------------------------|-------------------------------|-------------------------------|------------------------|---------|
| Anadure 2017(1)       | Y                 | Y                 | NR                                         | Y                         | CD                                  | CD                                              | Y                            | N                                        | N                   | NR                            | Y                             | NR                   | Good                  |         |
| Aznar 2004(2)         | Y                 | N                 | NR                                         | N                         | Y                                   | Y                                               | Y                            | N                                        | N                   | N                              | N                             | NR                   | Fair                  |         |
| Belvis 2006(3)        | Y                 | Y                 | NR                                         | N                         | Y                                   | N                                               | N                            | N                                        | N                   | Y                              | N                             | Y                    | Fair                  |         |
| Bentolila 1997(4)     | Y                 | N                 | NR                                         | Y                         | Y                                   | Y                                               | Y                            | N                                        | N                   | N                              | Y                             | N                    | Fair                  |         |
| Biswas 2009(5)        | Y                 | N                 | NR                                         | N                         | Y                                   | Y                                               | Y                            | N                                        | N                   | N                              | NR                            | N                    | Fair                  |         |
| Bolaman 2009(6)       | Y                 | Y                 | NR                                         | N                         | Y                                   | Y                                               | Y                            | N                                        | N                   | N                              | NR                            | Y                    | Fair                  |         |
| Buryu 2005(7)         | Y                 | N                 | NR                                         | Y                         | Y                                   | Y                                               | Y                            | N                                        | N                   | Y                              | Y                             | N                    | Fair                  |         |
| Catto 1995(8)         | Y                 | N                 | Y                                           | CD                        | Y                                   | Y                                               | N                            | N                                        | N                   | Y                              | NR                            | N                    | Fair                  |         |
| Celiker 2009(9)       | Y                 | Y                 | NR                                         | N                         | Y                                   | N                                               | N                            | N                                        | N                   | N                              | Y                             | NR                   | Fair                  |         |
| Chatterjee 2013(10)   | Y                 | N                 | NR                                         | N                         | Y                                   | Y                                               | N                            | N                                        | N                   | N                              | NR                            | N                    | Fair                  |         |
| Chen 2003(11)         | Y                 | N                 | NR                                         | N                         | CD                                  | Y                                               | Y                            | N                                        | N                   | Y                              | Y                             | Y                    | Fair                  |         |
| Cushman 1998(12)      | Y                 | Y                 | NR                                         | N                         | Y                                   | Y                                               | Y                            | N                                        | Y                   | Y                              | NR                            | Y                    | Good                  |         |
| D’Amico 1998(13)      | Y                 | Y                 | NR                                         | N                         | Y                                   | Y                                               | Y                            | N                                        | N                   | N                              | NR                            | Y                    | Fair                  |         |
| De Lucía 1999(14)     | Y                 | Y                 | NR                                         | N                         | CD                                  | Y                                               | Y                            | N                                        | N                   | N                              | Y                             | N                    | Fair                  |         |
| Djordjevic 2012(15)   | Y                 | N                 | NR                                         | Y                         | Y                                   | Y                                               | Y                            | N                                        | N                   | Y                              | NR                            | N                    | Fair                  |         |
| Egan 2000(16)         | Y                 | N                 | NR                                         | Y                         | Y                                   | CD                                              | Y                            | N                                        | N                   | N                              | NR                            | Y                    | Fair                  |         |
| Erten 2015(17)        | Y                 | Y                 | NR                                         | N                         | Y                                   | CD                                              | Y                            | N                                        | N                   | N                              | N                             | Y                    | Fair                  |         |
| Eterovic 2007(18)     | Y                 | Y                 | NR                                         | N                         | Y                                   | Y                                               | N                            | N                                        | Y                   | Y                              | Y                             | Y                    | Good                  |         |
| Fan 2010(19)          | Y                 | N                 | NR                                         | Y                         | Y                                   | N                                               | NA                           | N                                        | CD                  | Y                              | NR                            | Y                    | Fair                  |         |
| Favaretto 2012(20)    | Y                 | Y                 | NR                                         | N                         | Y                                   | N                                               | Y                            | N                                        | N                   | Y                              | NR                            | Y                    | Fair                  |         |
| Go 2003(21)           | Y                 | Y                 | NR                                         | N                         | Y                                   | Y                                               | N                            | N                                        | N                   | N                              | Y                             | Y                    | Good                  |         |
| Haesler 2012(22)      | Y                 | N                 | NR                                         | N                         | N                                   | N                                               | Y                            | N                                        | N                   | N                              | Y                             | N                    | Fair                  |         |
| Halmayer 1998(23)     | Y                 | N                 | NR                                         | N                         | CD                                  | CD                                              | N                            | N                                        | N                   | N                              | Y                             | NR                   | Poor                  |         |
| Hamedani 2013(24)     | Y                 | Y                 | NR                                         | N                         | Y                                   | Y                                               | Y                            | Y                                        | N                   | N                              | Y                             | NR                   | Fair                  |         |
| Hankey 2001(25)       | Y                 | N                 | NR                                         | N                         | Y                                   | Y                                               | Y                            | Y                                        | N                   | N                              | Y                             | NR                   | Good                  |         |
| Jerrard-Dunne 2003(26)| Y                 | N                 | NR                                         | Y                         | Y                                   | CD                                              | Y                            | Y                                        | N                   | N                              | NR                            | Y                    | Good                  |         |
| Jiang 2014(27)        | Y                 | Y                 | NR                                         | N                         | Y                                   | Y                                               | Y                            | Y                                        | N                   | Y                              | NR                            | N                    | Fair                  |         |
| Juul 2002(28)         | Y                 | Y                 | NR                                         | N                         | Y                                   | Y                                               | NA                           | N                                        | Y                   | Y                              | NR                            | N                    | Fair                  |         |
| Kamberi 2016(29)      | Y                 | Y                 | NR                                         | N                         | Y                                   | Y                                               | Y                            | N                                        | N                   | Y                              | NR                            | N                    | Fair                  |         |
| Karakus 2005(30)      | Y                 | N                 | NR                                         | Y                         | Y                                   | Y                                               | N                            | Y                                        | N                   | N                              | NR                            | N                    | Fair                  |         |
| Karttunen 2003(31)    | Y                 | Y                 | NR                                         | N                         | Y                                   | Y                                               | Y                            | N                                        | N                   | N                              | Y                             | Y                    | Good                  |         |
| Khloptorkova 2015(32) | Y                 | N                 | NR                                         | N                         | Y                                   | Y                                               | Y                            | N                                        | N                   | N                              | Y                             | NR                   | Fair                  |         |
| Krajcovicheva 2015(33)| Y                 | Y                 | NR                                         | Y                         | N                                   | Y                                               | N                            | N                                        | N                   | Y                              | NR                            | Y                    | Fair                  |         |
| Kumar 2017(34)        | Y                 | N                 | NR                                         | Y                         | Y                                   | Y                                               | Y                            | N                                        | N                   | N                              | Y                             | Y                    | Good                  |         |
| Linneman 2008(35)     | Y                 | Y                 | NR                                         | N                         | Y                                   | Y                                               | Y                            | N                                        | N                   | Y                              | NR                            | Y                    | Good                  |         |
| References                  | Study Quality |
|-----------------------------|---------------|
| Longstreth 1998(36)         | Good          |
| Lopaciuk 2001(37)           | Good          |
| Martinelli 2006(38)         | Fair          |
| Mayer 1993(39)              | Fair          |
| Mochan 2005(40)             | Fair          |
| Moskau 2010(41)             | Fair          |
| Nagayama 1996(42)           | Fair          |
| Pahus 2016(43)              | Fair          |
| Pestana 2009(44)            | Good          |
| Petrovic 2003(45)           | Good          |
| Pezzini 2005(46)            | Good          |
| Pezzini 2007(47)            | Good          |
| Press 1996(48)              | Fair          |
| Pullmann 2004(49)           | Fair          |
| Ranellou 2015(50)           | Good          |
| Ridker 1995(51)             | Fair          |
| Ridker 1999(52)             | Good          |
| Ripoll 1997(53)             | Good          |
| Romdhane 2011(54)           | Poor          |
| Rubattu 2005(55)            | Fair          |
| Rubattu 2005(56)            | Fair          |
| Sastry 2006(57)             | Fair          |
| Shi 2008(58)                | Good          |
| Sloot 2005(59)              | Good          |
| Smiles 2002(60)             | Good          |
| Supanc 2014(61)             | Good          |
| Szolnoki 2003(62)           | Good          |
| Tatarksky 2010(63)          | Fair          |
| They-They 2012(64)          | Good          |
| Tupitsyna 2013(65)          | Poor          |
| Voetsch 2000(66)            | Fair          |
| Wypasek 2009(67)            | Fair          |
| Zimba 2017(68)              | 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) | I², % |
|------------------------------------------------------|-----------------|----------------|-------------------|------|
| 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).
A. Factor V Leiden

B. Prothrombin G20210A Mutation

C. Protein C Deficiency

D. Protein S Deficiency

E. Antithrombin Deficiency

Figure S4. Funnel plot of included studies.
**Figure S5.** Forest plot showing pooled odds ratio for Prothrombin G20210A Mutation.

**Figure S6.** Forest plot showing pooled odds ratio for Prothrombin G20210A Mutation (Homzygous).
Figure S7. Forest plot showing pooled odds ratio for Factor V Leiden (Heterozygous).

| Study                  | Experimental Events | Control Events | Odds Ratio OR (95% CI) |
|------------------------|---------------------|----------------|-----------------------|
| Bonnati 1997           | 8                   | 125            | 1.79 [0.34, 8.46]     |
| Longstreth 1996        | 1                   | 41             | 0.88 [0.05, 16.34]    |
| Halbmayer 1996         | 2                   | 20             | 8.68 [0.21, 367.74]   |
| Ricci 1999             | 11                  | 259            | 1.09 [0.28, 3.93]     |
| Voetsh 2000            | 7                   | 153            | 2.01 [0.49, 10.18]    |
| Egan 2000              | 0                   | 42             | 0.00 [0.00, 35.79]    |
| Lopucki 2001           | 2                   | 100            | 0.70 [0.09, 6.21]     |
| Smiles 2002            | 6                   | 152            | 1.17 [0.26, 5.30]     |
| Karumun 2003           | 2                   | 57             | 9.07 [0.32, 256.72]   |
| Szolnoki 2003          | 5                   | 867            | 0.95 [0.17, 5.43]     |
| Pullmann 2004          | 0                   | 23             | 0.00 [0.00, 41.09]    |
| Karaka 2005            | 0                   | 21             | 0.00 [0.00, 241.48]   |
| Pezzini 2005           | 4                   | 36             | 5.66 [0.83, 38.50]    |
| Rubatto 2005           | 12                  | 294            | 0.94 [0.23, 3.80]     |
| Rubatto 2005           | 8                   | 115            | 1.22 [0.27, 5.44]     |
| Rubatto 2005           | 3                   | 89             | 0.44 [0.07, 2.61]     |
| Martel 2006            | 5                   | 105            | 0.84 [0.18, 4.00]     |
| Emenec 2007            | 9                   | 120            | 3.02 [0.54, 17.04]    |
| Pezzini 2007           | 9                   | 108            | 6.11 [1.10, 34.11]    |
| Limomann 2008          | 1                   | 41             | 0.17 [0.01, 2.58]     |
| Biesay 2009            | 0                   | 120            | 0.00 [0.00, 145.28]   |
| Biesay 2009            | 0                   | 24             | 0.00 [0.00, 484.74]   |
| Coliar 2009            | 3                   | 162            | 0.58 [0.09, 3.79]     |
| Wypaek 2009            | 1                   | 100            | 0.61 [0.02, 14.84]    |
| Moslau 2010            | 7                   | 167            | 2.01 [0.45, 9.05]     |
| Tatamsky 2010          | 8                   | 183            | 2.70 [0.47, 15.57]    |
| Faverento 2012         | 12                  | 136            | 2.76 [0.65, 11.72]    |
| Hansler 2012           | 1                   | 38             | 0.46 [0.03, 6.97]     |
| Thwy-Thwy 2012         | 11                  | 91             | 2.29 [0.54, 9.83]     |
| Tuzdkyana 2013         | 29                  | 1430           | 0.80 [0.23, 2.85]     |
| Chatterjee 2013        | 0                   | 52             | 0.00 [0.00, 117.51]   |
| Supanc 2014            | 7                   | 155            | 3.17 [0.47, 21.34]    |
| Jiang 2014             | 13                  | 397            | 2.29 [0.52, 10.15]    |
| Ertem 2015             | 13                  | 212            | 1.45 [0.56, 4.02]     |
| Khotovlova 2015        | 6                   | 114            | 6.80 [0.30, 247.05]   |
| Kraycochovka 2015      | 21                  | 423            | 2.04 [0.55, 7.59]     |
| Ramelu 2015            | 7                   | 51             | 2.52 [0.58, 11.10]    |
| Pahus 2016             | 3                   | 92             | 1.31 [0.24, 7.09]     |
| Kemar 2016             | 1                   | 39             | 0.21 [0.07, 0.70]     |

Overall Effect [I² = 0%]

0.01 0.1 1 10 100
Figure S8. Forest plot showing pooled odds ratio for protein C deficiency.

| Study                | Experimental Events | Control Events | Odds Ratio | OR [95% CI] |
|----------------------|---------------------|----------------|------------|-------------|
| D’Amico 1998         | 0                   | 31             | 0          | 124         | 0.00 [0.00, 346.42] |
| De Lucia 1999        | 2                   | 50             | 1          | 100         | 2.99 [0.21, 41.72]  |
| Hankey 2001          | 3                   | 219            | 4          | 205         | 0.61 [0.06, 6.19]   |
| Karttunen 2003       | 0                   | 57             | 0          | 104         | 0.00 [0.00, 337.39] |
| Chen 2003            | 14                  | 104            | 1          | 35          | 5.30 [0.55, 50.96]  |
| Jernard-Dunne 2003   | 6                   | 130            | 2          | 130         | 2.81 [0.41, 14.35]  |
| Kanakus 2005         | 1                   | 21             | 1          | 81          | 2.21 [0.08, 59.37]  |
| Sastry 2006          | 1                   | 86             | 0          | 101         | 2.44 [0.05, 118.24] |
| Linnemann 2008       | 0                   | 31             | 20         | 817         | 0.00 [0.00, 22.28]  |
| Biswas 2009          | 4                   | 120            | 0          | 120         | 12.53 [0.50, 314.65]|
| Romdhane 2011        | 2                   | 20             | 3          | 54          | 1.56 [0.15, 15.41]  |
| Fawadito 2012        | 0                   | 340            | 0          | 272         | 0.00 [0.00, 150.76] |
| Chatterjee 2013      | 6                   | 52             | 1          | 52          | 6.03 [0.61, 60.61]  |
| Pahu 2016            | 1                   | 363            | 14         | 9648        | 1.05 [0.07, 16.74]  |
| Zimba 2017           | 5                   | 52             | 0          | 52          | 18.73 [0.72, 487.16]|

Overall Effect ($I^2$ = 86%)

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

| Study                | Experimental Events | Control Events | Odds Ratio | OR [95% CI] |
|----------------------|---------------------|----------------|------------|-------------|
| Mayer 1993           | 20                  | 94             | 19         | 94          | 1.06 [0.28, 4.01]   |
| D’Amico 1998         | 2                   | 31             | 0          | 124         | 20.39 [0.76, 546.78]|
| De Lucia 1999        | 3                   | 50             | 1          | 100         | 5.06 [0.43, 59.48]  |
| Hankey 2001          | 2                   | 219            | 2          | 205         | 0.72 [0.07, 7.44]   |
| Karttunen 2003       | 1                   | 57             | 0          | 104         | 3.39 [0.07, 159.13] |
| Chee 2003            | 22                  | 104            | 3          | 35          | 2.98 [0.53, 16.65]  |
| Jernard-Dunne 2003   | 4                   | 130            | 2          | 130         | 1.75 [0.23, 13.61]  |
| Kanakus 2005         | 1                   | 21             | 0          | 81          | 8.27 [0.16, 429.75] |
| Mochan 2005          | 11                  | 33             | 12         | 33          | 0.86 [0.19, 3.98]   |
| Sastry 2006          | 1                   | 86             | 1          | 101         | 0.70 [0.03, 16.98]  |
| Linnemann 2008       | 1                   | 30             | 28         | 788         | 0.56 [0.04, 8.76]   |
| Biswas 2009          | 6                   | 120            | 0          | 120         | 18.63 [0.90, 384.93]|
| Romdhane 2011        | 6                   | 20             | 2          | 54          | 10.89 [1.42, 83.54] |
| Fawadito 2012        | 0                   | 340            | 0          | 272         | 0.00 [0.00, 110.39] |
| Chatterjee 2013      | 15                  | 52             | 1          | 52          | 20.25 [2.09, 196.69]|
| Pahu 2016            | 2                   | 364            | 9          | 3788        | 1.72 [0.22, 13.23]  |
| Zimba 2017           | 22                  | 52             | 18         | 52          | 1.30 [0.35, 5.44]   |

Overall Effect ($I^2$ = 8.8%)
Figure S10. Forest plot showing pooled odds ratio for antithrombin deficiency.

| Study                | Experimental Events | Control Events | Odds Ratio | OR [90% CI]     |
|----------------------|---------------------|----------------|------------|-----------------|
| De Lucia 1999        | 0 50 0 100          |                |            | 0.00 [0.00, 207.73] |
| Hankey 2001          | 11 219 8 205        |                |            | 1.26 [0.29, 5.47] |
| Karttunen 2003       | 1 57 2 104          |                |            | 0.53 [0.03, 10.85] |
| Chen 2003            | 1 104 1 35          |                |            | 0.20 [0.01, 5.23] |
| Jerrard-Dunne 2003   | 0 130 0 130         |                |            | 0.00 [0.00, 104.22] |
| Karakus 2005         | 1 21 0 81           |                |            | 8.10 [0.16, 423.33] |
| Saxty 2006           | 3 86 0 101          |                |            | 11.39 [0.39, 334.20] |
| Linnemann 2008       | 1 40 29 983         |                |            | 0.51 [0.03, 7.76] |
| Romdhane 2011        | 7 26 5 54           |                |            | 5.26 [0.91, 30.24] |
| Favaretto 2012       | 0 340 0 272         |                |            | 0.00 [0.00, 109.91] |
| Chatterjee 2013      | 0 52 0 52           |                |            | 0.00 [0.00, 77.88] |
| Pahus 2016           | 0 288 16 989        |                |            | 0.00 [0.00, 119.42] |
| Overall Effect (I² = 88.8%) |               |                |            | 1.21 [0.50, 2.67] |
Figure S11. Subgroup Analyses: Factor V Leiden.

| Study                          | Experimental Events | Control Events | Odds Ratio | OR [95% CI] |
|-------------------------------|---------------------|----------------|------------|-------------|
| Patients with PFO            | 4                   | 57             | 164        | 6.49 [0.61, 69.10] |
| Pezzi 2005                    | 6                   | 163            | 5          | 1.11 [0.21, 5.82] |
| Wypasek 2009                  | 9                   | 100            | 5          | 1.96 [0.40, 9.70] |
| Favaretto 2012                | 16                  | 340            | 14         | 0.91 [0.24, 3.47] |
| Overall Effect [95% CI]       |                     |                |            | 1.44 [0.86, 2.35] |
| Young Patients                | 0                   | 40             | 16         | 0.00 [0.00, 11.86] |
| Longishoom 2001               | 1                   | 20             | 2          | 0.32 [0.02, 6.87] |
| Hämström 1998                 | 5                   | 31             | 4          | 5.33 [0.87, 32.47] |
| D'Amico 1998                  | 5                   | 153            | 8          | 0.85 [0.17, 4.25] |
| Versteeg 2000                 | 3                   | 100            | 10         | 0.49 [0.10, 2.37] |
| Lopușescu 2001                | 2                   | 49             | 5          | 1.91 [0.22, 16.33] |
| Aznar 2004                    | 3                   | 21             | 4          | 2.85 [0.38, 21.20] |
| Karakus 2005                  | 6                   | 163            | 5          | 1.22 [0.56, 2.69] |
| Pezzi 2005                    | 4                   | 115            | 10         | 0.55 [0.10, 2.91] |
| Stroiter 2005                 | 14                  | 179            | 42         | 1.41 [0.39, 5.11] |
| Sastri 2006                   | 4                   | 101            | 8          | 0.44 [0.08, 2.41] |
| Martini 2006                  | 6                   | 105            | 7          | 2.30 [0.47, 11.33] |
| Pezzi 2007                    | 5                   | 108            | 6          | 1.56 [0.29, 8.33] |
| Sn 2008                       | 0                   | 97             | 0          | 0.00 [0.00, 120.47] |
| Blewax 2009                   | 10                  | 120            | 1          | 9.55 [1.04, 88.54] |
| Hexher 2012                   | 7                   | 41             | 22         | 2.31 [0.53, 10.06] |
| Supanc 2014                   | 14                  | 155            | 5          | 2.81 [0.61, 13.06] |
| Ranefuk 2015                  | 7                   | 51             | 4          | 2.52 [0.45, 14.00] |
| Pahus 2016                    | 15                  | 207            | 282        | 1.05 [0.30, 3.67] |
| Andraus 2017                  | 6                   | 120            | 2          | 2.86 [0.40, 20.42] |
| Kumar 2017                    | 9                   | 250            | 5          | 1.75 [0.36, 8.50] |
| Overall Effect [95% CI]       |                     |                |            | 1.46 [0.87, 2.40] |

Figure S12. Subgroup Analyses: Prothrombin G20210A Mutation.

| Study                          | Experimental Events | Control Events | Odds Ratio | OR [95% CI] |
|-------------------------------|---------------------|----------------|------------|-------------|
| Patients with PFO            | 2                   | 57             | 0          | 9.76 [0.31, 302.83] |
| Pezzi 2005                    | 9                   | 163            | 3          | 2.92 [0.02, 16.34] |
| Wypasek 2009                  | 1                   | 100            | 1          | 0.58 [0.02, 14.17] |
| Favaretto 2012                | 29                  | 340            | 9          | 2.77 [0.70, 10.48] |
| Overall Effect [95% CI]       |                     |                |            | 2.62 [1.11, 6.16] |
| Young Patients                | 8                   | 125            | 5          | 1.70 [0.34, 8.45] |
| Berchi 2007                   | 1                   | 41             | 6          | 0.97 [0.06, 14.71] |
| Hämström 1998                 | 2                   | 20             | 0          | 8.14 [0.21, 323.14] |
| Versteeg 2000                 | 7                   | 153            | 5          | 2.02 [0.40, 10.32] |
| Egan 2000                     | 0                   | 42             | 13         | 0.00 [0.00, 51.54] |
| Lopușescu 2001                | 2                   | 100            | 5          | 0.74 [0.09, 6.15] |
| Aznar 2004                    | 4                   | 49             | 7          | 3.24 [0.57, 18.29] |
| Karakus 2005                  | 1                   | 21             | 1          | 2.15 [0.08, 61.67] |
| Pezzi 2007                    | 9                   | 163            | 3          | 2.89 [0.51, 16.26] |
| Rubatto 2005                  | 8                   | 115            | 10         | 1.23 [0.28, 5.49] |
| Stroiter 2005                 | 5                   | 188            | 18         | 1.62 [0.22, 7.41] |
| Sastri 2006                   | 2                   | 101            | 0          | 5.86 [0.19, 183.48] |
| Martini 2006                  | 5                   | 105            | 15         | 0.86 [0.18, 4.03] |
| Pezzi 2007                    | 10                  | 108            | 3          | 6.96 [1.22, 39.79] |
| Blewax 2009                   | 0                   | 120            | 0          | 0.00 [0.00, 68.17] |
| Hexher 2012                   | 1                   | 38             | 10         | 0.44 [0.03, 4.95] |
| Chatterjee 2013               | 0                   | 52             | 0          | 0.00 [0.09, 126.45] |
| Supanc 2014                   | 7                   | 155            | 2          | 3.28 [0.49, 22.00] |
| Jang 2015                     | 14                  | 397            | 6          | 2.50 [0.57, 10.65] |
| Ranefuk 2015                  | 7                   | 51             | 4          | 2.54 [0.46, 14.16] |
| Pahus 2016                    | 3                   | 92             | 1377       | 1.30 [0.24, 6.87] |
| Overall Effect [95% CI]       |                     |                |            | 1.70 [1.26, 2.34] |

Cryptogenic Stroke            | 5                   | 20             | 0          | 7.54 [0.22, 262.62] |
| Kartunen 2003                 | 2                   | 57             | 0          | 9.24 [0.33, 268.34] |
| Aznar 2004                    | 4                   | 49             | 7          | 2.21 [0.06, 65.25] |
| Karakus 2005                  | 1                   | 21             | 1          | 0.43 [0.07, 2.55] |
| Belvis 2008                   | 3                   | 89             | 13         | 2.70 [0.70, 10.50] |
| Favaretto 2012                | 29                  | 340            | 9          | 0.42 [0.03, 4.69] |
| Hexher 2012                   | 1                   | 38             | 10         | 1.85 [0.67, 5.39] |
**Figure S13. Subgroup Analyses: Protein C Deficiency.**

| Study                  | Experimental Events | Control Events | Odds Ratio | OR [95% CI] |
|------------------------|---------------------|----------------|------------|-------------|
| **Patients with PFO**  |                     |                |            |             |
| Karttunen 2003         | 0                   | 57             | 0          | 0.00 [0.00, 120.55] |
| Overall Effect ($I^2 = 0\%$) | 0       |                |            |             |
| **Young Patients**     |                     |                |            |             |
| D'Amico 1998           | 0                   | 31             | 0          | 0.00 [0.00, 460.01] |
| Jernard-Dunne 2003     | 6                   | 130            | 2          | 2.88 [0.41, 20.39] |
| Karakus 2005           | 1                   | 21             | 1          | 2.15 [0.08, 56.46] |
| Sastry 2006            | 1                   | 86             | 0          | 2.26 [0.05, 110.13] |
| Biswas 2009            | 4                   | 120            | 0          | 11.41 [0.47, 275.00] |
| Romdhane 2011          | 2                   | 20             | 3          | 1.54 [0.15, 15.79] |
| Chatterjee 2013        | 6                   | 52             | 1          | 5.06 [0.62, 57.44] |
| Pahus 2016             | 1                   | 363            | 14         | 1.04 [0.06, 18.17] |
| Overall Effect ($I^2 = 0\%$) | 0       |                |            |             |

**Cryptogenic Stroke**

| Study                  | Experimental Events | Control Events | Odds Ratio | OR [95% CI] |
|------------------------|---------------------|----------------|------------|-------------|
| Karttunen 2003         | 0                   | 57             | 0          | 0.00 [0.00, 267.25] |
| Karakus 2005           | 1                   | 21             | 1          | 2.39 [0.10, 58.50] |
| Favaretto 2012         | 0                   | 340            | 0          | 0.00 [0.00, 141.22] |
| Overall Effect ($I^2 = 37.5\%$) | 0       |                |            |             |

**Figure S14. Subgroup Analyses: Protein S Deficiency.**

| Study                  | Experimental Events | Control Events | Odds Ratio | OR [95% CI] |
|------------------------|---------------------|----------------|------------|-------------|
| **Patients with PFO**  |                     |                |            |             |
| Karttunen 2003         | 1                   | 57             | 0          | 3.52 [0.08, 164.01] |
| Overall Effect ($I^2 = 0\%$) | 3       |                |            |             |
| **Young Patients**     |                     |                |            |             |
| D'Amico 1998           | 2                   | 31             | 0          | 20.70 [0.70, 608.34] |
| Jernard-Dunne 2003     | 4                   | 130            | 2          | 1.79 [0.23, 14.07] |
| Karakus 2005           | 1                   | 21             | 0          | 8.24 [0.15, 440.50] |
| Sastry 2006            | 1                   | 86             | 1          | 0.68 [0.03, 17.40] |
| Biswas 2009            | 6                   | 120            | 0          | 18.92 [0.86, 416.75] |
| Romdhane 2011          | 6                   | 20             | 2          | 10.75 [1.40, 82.33] |
| Chatterjee 2013        | 15                  | 52             | 1          | 20.28 [2.05, 201.01] |
| Pahus 2016             | 2                   | 364            | 9          | 1.76 [0.23, 13.41] |
| Overall Effect ($I^2 = 5.9\%$) | 5       |                |            |             |

**Cryptogenic Stroke**

| Study                  | Experimental Events | Control Events | Odds Ratio | OR [95% CI] |
|------------------------|---------------------|----------------|------------|-------------|
| Karttunen 2003         | 1                   | 57             | 0          | 3.71 [0.07, 193.71] |
| Karakus 2005           | 1                   | 21             | 0          | 7.32 [0.15, 368.60] |
| Favaretto 2012         | 0                   | 340            | 0          | 0.00 [0.00, 86.15] |
| Overall Effect ($I^2 = 0\%$) | 2       |                |            |             |
Figure S15. Subgroup Analyses: Antithrombin Deficiency.

| Study                  | Experimental Events | Control Events | Odds Ratio | OR [95% CI] |
|------------------------|---------------------|----------------|------------|-------------|
| Patients with PFO     |                     |                |            |             |
| Karttunen 2003        | 1                   | 57             | 2          | 104         | 0.53 [0.02, 12.19] |
| Overall Effect [I² = 8%] |                     |                |            |             | 6.53 [0.83, 10.62] |
| Young Patients        |                     |                |            |             |
| Jerrard-Dunne 2003    | 0                   | 130            | 0          | 130         | 0.00 [0.00, 173.68] |
| Karakus 2005          | 1                   | 21             | 0          | 81          | 8.14 [0.18, 373.91] |
| Sastri 2006           | 3                   | 86             | 0          | 101         | 10.62 [0.39, 288.48] |
| Romdhane 2011         | 7                   | 20             | 5          | 54          | 5.23 [0.92, 29.79] |
| Chatterjee 2013       | 0                   | 52             | 0          | 52          | 0.00 [0.00, 230.43] |
| Palhus 2016           | 0                   | 288            | 16         | 9669        | 0.00 [0.00, 103.67] |
| Overall Effect [I² = 8%] |                     |                |            |             | 2.49 [0.83, 7.47] |
| Cryptogenic Stroke    |                     |                |            |             |
| Karttunen 2003        | 1                   | 67             | 2          | 104         | 0.54 [0.03, 11.44] |
| Karakus 2005          | 1                   | 21             | 0          | 81          | 8.60 [0.17, 423.72] |
| Favaribbs 2012        | 0                   | 340            | 0          | 272         | 0.00 [0.00, 52.57] |
| Overall Effect [I² = 9.8%] |                     |                |            |             | 0.99 [0.13, 7.61] |
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