Testing for Inherited Thrombophilias in Arterial Stroke  
Can It Cause More Harm Than Good?  

Jane G. Morris, MD; Swaraj Singh, MD; Marc Fisher, MD

Background and Purpose—Despite a paucity of evidence supporting a true association of ischemic stroke and the inherited thrombophilias, it is common practice for many neurologists to order these tests as part of the work-up of ischemic stroke, especially in young patients. Treatment with oral anticoagulation is often used in patients with positive results for the inherited thrombophilias.

Methods—We reviewed the literature focusing on case-control studies of the 5 most commonly inherited disorders of coagulation: protein C deficiency, protein S deficiency, antithrombin deficiency, and the factor V Leiden and prothrombin gene mutations in patients with stroke. We also analyzed the available data on stroke patients with inherited thrombophilia and patent foramen ovale.

Results—Multiple case-control studies have not convincingly shown an association of the inherited thrombophilias with ischemic stroke, even in young patients and patients with patent foramen ovale.

Conclusion—If there is an association between the inherited thrombophilias and arterial stroke, then it is a weak one, likely enhanced by other prothrombotic risk factors. The consequences of ordering these tests and attributing causality to an arterial event can result in significant costs to the health care system and pose a potential risk to patients, because this may lead to inappropriate use of long-term oral anticoagulants, exposing patients to harm without a clearly defined benefit.

Key Words: blood coagulation disorders ■ inherited ■ foramen ovale ■ patent ■ stroke ■ thrombophilia

Patients with inherited thrombophilias are known to be at increased risk for venous thromboembolism (VTE), but a causal relationship with arterial thrombosis has not been clearly established. The data supporting thrombophilias as a cause of arterial stroke are limited predominantly to case reports and uncontrolled studies with mixed results from meta-analyses. Case-control studies do not consistently support an association of these disorders with stroke. Despite many authorities stating that these tests should not be ordered routinely in the work-up of ischemic stroke,1–3 many books and articles continue to perpetuate the need to order these tests as part of the stroke work-up, especially in the young.4,5 We review the current literature on the inherited thrombophilias in ischemic arterial stroke, present a cost and risk-benefit analysis, and suggest when testing should be considered.

Materials and Methods

The PubMed and Ovid Medline databases from 1950 to present were searched using “stroke” combined with the following key words: “thrombophilia,” “protein C deficiency,” “protein S deficiency,” “antithrombin III deficiency,” “factor V Leiden,” and “prothrombin gene mutation.” Additional searches with these terms and “patent foramen ovale” were also performed. Limits of human and English language were imposed, although if abstracts could be obtained in other factors; however, race should be considered before testing.
because their prevalence is highly race-dependent. Worldwide prevalence estimates of FVL range from 5% to 8% in European whites to 0% in blacks and Asians.6 The prevalence of PTM among whites is ~0.7% to 6.5%, slightly less common in Northern Europeans (1.7%) compared with Southern Europeans (3.0%), and is extremely rare in nonwhite populations.6 The treatment of VTE in all of the inherited thrombophilias is similar. Acute VTE is treated with heparin or low-molecular-weight heparin and then warfarin with a target international normalized ratio of 2.0 to 3.0 for at least 6 months. Several factors, including age, family history, the site and severity of thrombosis, recurrent thrombosis, and the presence of other provoking factors, go into the decision to continue oral anticoagulation, possibly for life.7

The treatment of an ischemic stroke patient who is found to have an inherited thrombophilia is less clear. To our knowledge, there are no randomized trials regarding the efficacy of anticoagulation for stroke prevention in the setting of an inherited thrombophilia. However, 1 prospective observational study comparing cryptogenic stroke patients with and without thrombophilia demonstrated no significant difference in recurrence rates of stroke or TIA, and anticoagulation use did not influence outcomes.8 It is generally accepted that most ischemic stroke patients should not be administered heparin or low-molecular-weight heparin in the acute phase because of concerns for hemorrhagic transformation of the infarction. Oral anticoagulation is not recommended for asymptomatic carriers of these defects. Therefore, asserting that a stroke was a symptom of an inherited thrombophilia may result in the initiation of anticoagulation, when the result may have been incidental.

**Case-Control Studies of PC, PS, and AT in Ischemic Arterial Stroke**

We identified 6 case-control studies of PC, PS, and/or AT deficiency in ischemic stroke that included at least 50 cases.9–14 Most were in young patients (younger than 55 years old) and none showed any relationship between these deficiencies and stroke (Table 1).

Although most studies were performed in whites, 1 study produced interesting results on the ethnic differences in markers of thrombophilia. In this study, the levels of PC, PS, AT, and activated PC resistance were similar. Acute VTE is treated with heparin or low-molecular-weight heparin in the acute phase.

We identified 16 case-control studies that examined FVL or PTM in ischemic stroke patients younger than age 60 that enrolled at least 50 cases (Table 2). For consistency, we did not include data on activated PC resistance alone. The majority of these studies do not support any association between the inherited thrombophilias and stroke. The method of patient recruitment helps to explain the heterogeneity in results. Margaglione et al12 found an association between FVL and stroke (14.9% vs 4.2%) but not PTM and stroke (5.0% vs 4.2%), whereas De Stefano et al13 reported an association between PTM (12.5% vs 2.5%), but not with FVL and stroke (5.5% vs 2.5%). Both of these studies are clear outliers when compared to prevalence rates in other studies, and both studied patients who had been referred to a laboratory for thrombophilia testing. Additionally, there were statistically significant differences in cases and controls regarding personal history of VTE (7.4% vs 1.4%; P<0.0001) and family history of VTE (7.9% vs 4.2%; P<0.05) in patients studied by Margaglione et al.12 We feel that the method of recruitment affected the results of these studies and that studies using unselected patients admitted to a hospital9,13,20,23,26,27 more accurately reflect the patient population seen by most neurologists.

Subgroup analyses performed in some studies have led to conflicting results. Nabavi et al21 examined the prevalence of FVL in young stroke survivors by review of medical records and stroke data banks. Whereas the overall difference between cases and controls was not significant, the FVL mutation occurred in significantly more cryptogenic stroke patients. They also found nonsignificant trends in patients with a right-to-left cardiac shunt, a positive personal history of VTE, a positive family history of VTE, and age younger than 25 years. An association of inherited thrombophilias and cryptogenic strokes has been reported elsewhere,22 but other studies stratified by stroke subtype did not find this association.12,19–21,26 Lalouschek et al23 found higher prevalence of PTM in men and of FVL in women who smoke. This higher rate of the PTM in men was likely attributable to the lower (1%) prevalence of the PTM in the control population because this finding never has been reported in any other

### Table 1. Case-Control Studies of PC, PS, and AT in Patient With Ischemic Stroke

<table>
<thead>
<tr>
<th>Reference</th>
<th>Age</th>
<th>N Cases and Controls</th>
<th>Thrombophilia Test</th>
<th>% Identified in Cases</th>
<th>% Identified in Controls</th>
<th>Statistical Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sastri (2006)9</td>
<td>16–39</td>
<td>101</td>
<td>PC, PS, AT</td>
<td>7.9</td>
<td>8.9</td>
<td>NS</td>
</tr>
<tr>
<td>Jerrard-Dunn (2003)10</td>
<td>≤65</td>
<td>130</td>
<td>PS, PC, AT</td>
<td>8.5*</td>
<td>6.3*</td>
<td>NS</td>
</tr>
<tr>
<td>Hankey (2001)11</td>
<td>Mean 66</td>
<td>219</td>
<td>PS, PC, AT</td>
<td>7.3</td>
<td>6.8</td>
<td>NS</td>
</tr>
<tr>
<td>Margaglione (1999)12</td>
<td>3–50</td>
<td>202</td>
<td>PC, PS, AT</td>
<td>0</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>De Stefano (1998)13</td>
<td>2–50</td>
<td>72</td>
<td>PC, PS, AT</td>
<td>1.4</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>Mayer (1993)14</td>
<td>&gt;39</td>
<td>94</td>
<td>PS</td>
<td>21</td>
<td>20</td>
<td>NS</td>
</tr>
</tbody>
</table>

*AT indicates antithrombin deficiency; NS, not significant; PC, protein C deficiency; PS, protein S deficiency.

*Using ethnicity-specific reference ranges.

**Case-Control Studies of FVL and PTM in Ischemic Arterial Stroke**

Several well-designed, prospective, case-control studies have provided good evidence that there is no association between FVL or PTM and ischemic stroke in older patients.11,13,14 These data eliminate the need to test for inherited thrombophilias in patients older than age 60 years.

We identified 16 case-control studies that examined FVL or PTM in ischemic stroke patients younger than age 60 that enrolled at least 50 cases (Table 2). For consistency, we did not include data on activated PC resistance alone. The majority of these studies do not support any association between the inherited thrombophilias and stroke. The method of patient recruitment helps to explain the heterogeneity in results. Margaglione et al12 found an association between FVL and stroke (14.9% vs 4.2%) but not PTM and stroke (5.0% vs 4.2%), whereas De Stefano et al13 reported an association between PTM (12.5% vs 2.5%), but not with FVL and stroke (5.5% vs 2.5%). Both of these studies are clear outliers when compared to prevalence rates in other studies, and both studied patients who had been referred to a laboratory for thrombophilia testing. Additionally, there were statistically significant differences in cases and controls regarding personal history of VTE (7.4% vs 1.4%; P<0.0001) and family history of VTE (7.9% vs 4.2%; P<0.05) in patients studied by Margaglione et al.12 We feel that the method of recruitment affected the results of these studies and that studies using unselected patients admitted to a hospital9,13,20,23,26,27 more accurately reflect the patient population seen by most neurologists.

Subgroup analyses performed in some studies have led to conflicting results. Nabavi et al21 examined the prevalence of FVL in young stroke survivors by review of medical records and stroke data banks. Whereas the overall difference between cases and controls was not significant, the FVL mutation occurred in significantly more cryptogenic stroke patients. They also found nonsignificant trends in patients with a right-to-left cardiac shunt, a positive personal history of VTE, a positive family history of VTE, and age younger than 25 years. An association of inherited thrombophilias and cryptogenic strokes has been reported elsewhere,22 but other studies stratified by stroke subtype did not find this association.12,19–21,26 Lalouschek et al23 found higher prevalence of PTM in men and of FVL in women who smoke. This higher rate of the PTM in men was likely attributable to the lower (1%) prevalence of the PTM in the control population because this finding never has been reported in any other
series. Increased stroke risk with thrombophilas associated with female gender, 18,19 oral contraceptive use, 9,18 smoking, 12,18,19 and migraine 9,30 have been reported, yet others have found no association with gender, 20,21,24 oral contraceptive use, 13,19,23 smoking, 31 or atrial fibrillation. 32 Meta-analyses have reported an association of FVL and PTM with arterial strokes, 33,34 an association of FVL but not PTM with ischemic stroke, 35 and that FVL is not associated with ischemic stroke. 36 These analyses included studies that were small, included patients who were recruited by referral to a laboratory for evaluation of thrombophilia, 12,13,29 include children, 12,13,20,28,29 and had controls that were unmatched or poorly defined, 13,25,26,28–30 making any conclusions from these meta-analyses suspect.

Inherited Thrombophilia and Patent Foramen Ovale

Without limitation to the number of subjects, we identified 9 case-control studies examining the relationship of the inherited thrombophilias, patent foramen ovale (PFO), and stroke 21,24,37–43 (Table 3). Sastry et al 9 collected data on both PFO and thrombophilia in ischemic stroke but did not evaluate them in relation to each other. These studies also produced conflicting results, with some studies suggesting an association between PTM or FVL and PFO, 24,41–43 and others finding no relation. 21,37–40 None of the studies that examined PC, PS, or AT found any association of these deficiencies with PFO and stroke. 37–40,42

No study has evaluated the utility of warfarin vs antiplatelets for patients with PFO and thrombophilia. One small study of 72 patients referred for PFO closure found no difference in recurrent stroke at 6 months in patients with or without thrombophilia. 44

### Cost and Risk-Benefit Analysis

The cost of ordering an inherited thrombophilia work-up in our institution is close to $1000. Many insurance companies do not cover some or all of these tests, leaving the patient or the hospital to pay for the costs.
The cost of warfarin includes the cost of the drug, the cost of monitoring, and the cost of bleeding complications. Menzin et al\textsuperscript{47} estimated that the direct cost for anticoagulation services was \$2800 to \$5800 per patient per year. In 2005, Fanikos et al\textsuperscript{47} published the actual costs of treating patients with major bleeding complications per patient administered warfarin was \$64,446. Prolonged exposure to warfarin increases the chances of multiple minor bleeding complications, which would increase the cost substantially. Meanwhile, the benefit of anticoagulation in this population is unknown. At this point, it is unclear how much newer drugs, such as direct thrombin inhibitors, will cost or change this risk-benefit ratio.

### Discussion

These studies provide convincing evidence that testing for the inherited thrombophilias should not be performed routinely in patients with ischemic stroke, even in the young. No case-control studies of PC, PS, or AT showed an association of these deficiencies and stroke. Multiple case-control studies have demonstrated no association between FVL or PTM and ischemic stroke in patients older than age 60. Case-control studies of FVL and PTM performed in unselected younger patients do not support an association of these disorders and stroke, and meta-analyses are unconvincing because of the inclusion of suboptimal data. Patients who do not have a white ancestor should not be tested for FVL or PTM, and the levels of PC and PS should be interpreted with caution because they may have ethnic variability that could lead to an erroneous diagnosis in patients of African descent. It is unclear if PFO in association with an inherited thrombophilia in the absence of an identified deep venous thrombosis should alter management of either the thrombophilia or the PFO. We suggest that cryptogenic stroke patients found to have PFO should be evaluated for deep venous thrombosis in the legs and the pelvic veins. We would consider ordering a thrombophilic work-up in patients with a positive family or personal history of VTE, especially if unprovoked, or if other clinical features suggest paradoxical embolism. The decision

### Table 3. Case-Control Studies of the Inherited Thrombophilias and PFO in Patients With Ischemic Stroke

<table>
<thead>
<tr>
<th>Reference</th>
<th>Age</th>
<th>N Cases and Controls</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Offelli (2007)\textsuperscript{37}</td>
<td>(\leq 55)</td>
<td>76 PFO(+) cryptogenic stroke (76) age- and gender-matched</td>
<td>Tested for PC, PS, AT, FVL, and PTM; found no association</td>
</tr>
<tr>
<td>Palmieri (2007)\textsuperscript{38}</td>
<td>38±9</td>
<td>29 cryptogenic stroke/TIA 30 healthy volunteers</td>
<td>Tested for PC, PS, AT, FVL, and PTM; thrombophilia was not associated with PFO but was associated with ASA</td>
</tr>
<tr>
<td>Belvis (2007)\textsuperscript{39\textblacksquare}</td>
<td>&lt;55</td>
<td>17 PFO(+) cryptogenic stroke 22 PFO(−) cryptogenic stroke</td>
<td>Tested for PC, PS, FVL, and PTM; found no association</td>
</tr>
<tr>
<td>Carod-Artal (2006)\textsuperscript{40\textblacksquare}</td>
<td>15–45</td>
<td>42 PFO(+) ischemic stroke 88 PFO(−) ischemic stroke</td>
<td>Tested for PC, PS, AT, and FLV; found no association</td>
</tr>
<tr>
<td>Lichy (2003)\textsuperscript{41}</td>
<td>Mean 53.4</td>
<td>220 PFO(+) cryptogenic stroke 196 stroke of known source 362 healthy, from same region</td>
<td>PTM, but not FVL, was associated with cryptogenic stroke (5% v. 1.4%) but not stroke attributable to other causes</td>
</tr>
<tr>
<td>Karttunen (2003)\textsuperscript{42}</td>
<td>15–60</td>
<td>58 PFO(+) cryptogenic stroke 104 community-based controls</td>
<td>FVL (7%) and PTM (4%) were more common in PFO(+) cryptogenic stroke than controls (1%) ((P=0.008))</td>
</tr>
<tr>
<td>Pezzini (2003)\textsuperscript{43}</td>
<td>&lt;45</td>
<td>125 first-ever ischemic stroke</td>
<td>No association with cases and controls irrespective of PFO; PTM was associated with PFO(+) cases vs PFO(−) cases (11% vs 1.1%)</td>
</tr>
<tr>
<td>Austin (2002)\textsuperscript{44}</td>
<td>18–50</td>
<td>67 cryptogenic stroke 149 age- and gender-matched 79 noncryptogenic stroke 1 had PFO(+)</td>
<td>2 of 20 subjects (10%) were PFO(+) and FVL(+) 7 of the remaining 126 PFO(−) subjects (6%) were FVL(+) this was not statistically significant</td>
</tr>
<tr>
<td>Nabavi (1998)\textsuperscript{45}</td>
<td>14–45</td>
<td>225 TIA or ischemic stroke 200 healthy white subjects</td>
<td>36% of cases were PFO(+) 53% (8/15) FVL(+) cases were also PFO(+) whereas 35% (66/190) of FVL(−) cases were PFO(−) (P=0.15)</td>
</tr>
</tbody>
</table>

ASA indicates atrial septal aneurysm; AT, antithrombin deficiency; FVL, factor V Leiden; PC, protein C deficiency; PFO, patent foramen ovale; PS, protein S deficiency; PTM, prothrombin gene mutation; (+), present; (−), absent.

*Abstract only.
to anticoagulate or proceed with PFO closure needs to be
individualized.

There are no absolute indications for testing for inherited
thrombophilias in patients with ischemic stroke. We recom-
mend that testing for inherited thrombophilias should be no
different in the stroke population than in any other popula-
tion, ie, accepted clinical features that suggest the need for a
thrombophilic work-up per WHO recommendations: history
of an unprovoked VTE, VTE in an unusual location, family
history of a VTE, thrombosis at a young age (younger than
45), and frequent thrombotic recurrences. Any future at-
tempts to understand the relationship of the inherited throm-
bophilias and stroke must include details of the patient’s
personal and family history of VTE, attention to the timing
and circumstances of testing, performance of confirmatory
testing for PC, PS, and AT, have a well-matched control
group, and collect data not only on incidence of stroke but
also on treatment options and outcome.

The simple act of ordering these tests under the presump-
tion that they can cause arterial strokes is not without risk.
The assertion of causality could lead to the use of long-term
oral anticoagulation, exposing a patient to risk without proven
benefit.

Conclusion

Multiple large case-control studies have not convincingly
shown an association of the inherited thrombophilias with
ischemic stroke, even in young patients and patients with
PFO. If there is an association between these genetic abnor-
malities and ischemic stroke, then it is a weak one, likely
enhanced by other prothrombotic risk factors. The conse-
quences of ordering these tests and attributing causality to an
arterial event can be substantial regarding safety and cost.

Disclosures

Dr Fisher served as an associate editor of Stroke and is now
the Editor-in-Chief of Stroke. He receives compensation for this. He also
has received research support from Wyeth Pharmaceuticals (now
Pfizer), Syngis, and Guerbet. He consults for BioClinica, FerrerWyeth,
OleA Medical, Mistubishi Pharma USA, Daichi Sankyo Pharma,
Takeda Pharmaceuticals, Syngis, BrainGate, and Coaxia. He serves
or has served on steering committees for Photothera, Servier, and
CoAxia. He has equity positions in BrainGate and Photothera. None of
these relations has any impact on this study.

References

1. Markus HS, Hambly H. Neurology and the blood: haematological abnor-
malities in ischaemic stroke. J Neurol Neurosurg Psychiatry. 1998;64:
150–159.
2. Bushnell CD, Goldstein LB. Diagnostic testing for coagulopathies in
3. Rahemtullah A, Van Cott EM. Hypercoagulation testing in ischemic
Lippincott Williams & Wilkins; 2004.
7. Inherited thrombophilia: memorandum from a joint WHO/International
Society on Thrombosis and Haemostasis meeting. Bull World Health Org.
8. Weber R, Goertler M, Benemann J, Diener HC, Weimar C, German Stroke Study Collaboration. Prognosis after cryptogenic cerebral isch-
McCullom C. Young Adult Myocardial Infarction and Ischemic Stroke: theole of paradoxical embolism and thrombophilia (The YAMIS Study).
Wolfe CD, Markus HS. Ethnic differences in markers of thrombophilia:
implications for the investigation of ischemic stroke in multiethnic pop-
ulations: the South London Ethnicity and Stroke Study. Stroke. 2003;34:
1821–1826.
11. Hankey GJ, Eikelboom JW, van Boekelmeer FM, Loffthouse E, Staples N,
Baker RI. Inherited thrombophilia in ischemic stroke and its pathogenic
12. Marigliano M, D’Andrea G, Giuliani N, Brancaccio V, De Lucia D,
Grandone E, De Stefano V, Tonali PA, Di Minno G. Inherited pro-
thrombotic conditions and premature ischemic stroke: sex difference in
13. De Stefano V, Chiussolo P, Paciaroni K, Casorrelli I, Rossi E, Molinari M,
Servidei S, Tonali PA, Leone G. Prothrombin G20210A mutant genotype
is a risk factor for cerebrovascular ischemic disease in young patients.
deficiency in acute ischemic stroke. A case-control study. Stroke. 1993;
24:222–227.
15. Cushman M, Rosendaal FR, Psaty BM, Cook EF, Valliere J, Kuller LH,
Tracy RP. Factor V Leiden is not a risk factor for arterial vascular disease
in the elderly: results from the Cardiovascular Health Study. Thromb
16. Ridker PM, Hennekens CH, Lindpaintner K, Stampfer MJ, Eisenberg PR,
Miletich JP. Mutation in the gene coding for coagulation factor V and the
risk of myocardial infarction, stroke, and venous thrombosis in apparently
17. Ridker PM, Hennekens CH, Miletich JP. G20210A mutation in pro-
thrombin gene and risk of myocardial infarction, stroke, and venous
18. Slooter AJ, Rosendaal FR, Tanis BC, Kemmeren JM, van de Graaf Y,
Algra A. Prothrombotic conditions, oral contraceptives, and the risk of
Cheng S, Mannhalter C. Matched case-control study on factor V Leiden
and the prothrombin G20210A mutation in patients with ischemic stroke/
transient ischemic attack up to the age of 60 years. Stroke. 2005;36:
1405–1409.
20. Madonna P, de Stefano V, Coppola A, Cirillo F, Cerbone AM, Orefice F,
Di Minno G. Hyperhomocysteinemia and other inherited prothrombotic
conditions in young adults with a history of ischemic stroke. Stroke.
WC, Genetics and Stroke in the Young Study Group. Cryptogenic stroke
in relation to genetic variation in clotting factors and other genetic
polymorphisms among young men and women. Stroke. 2002;33:
2762–2767.
22. Lopaciuk S, Bykowska K, Kwiecinski H, Mickiewicz A, Czlonkowska
A, Mendel T, Kuczyznska-Zardzewialy A, Szelagowska D, Windyga J,
Schroeder W, Herrmann FH, Jedrzejowska H, Factor V Leiden, pro-
thrombin gene G20210A variant, and methylenetetrahydrofolate reductase
C677T genotype in young adults with ischemic stroke. Clin Appl Thromb
23. Voetsch B, Damasceno BP, Camargo EC, Massaro A, Bacheschi LA,
Scaff M, Annichino-Bizzacchi JM, Arruda VR. Inherited thrombophilia
as a risk factor for the development of ischemic stroke in young adults.
DW, Kessler C, Assmann G, Ringelstein EB. Prevalence of factor V
Leiden mutation in young adults with cerebral ischemia: a case-control
25. Longstreth WT Jr, Rosendaal FR, Siscovick DS, Vos HL, Schwartz SM,
Psaty BM, Raghunathan TE, Koepsell TD, Reitsma PH. Risk of stroke in
young women and two prothrombotic mutations: Factor V Leiden and
the prothrombin G20210A mutation in patients with ischemic stroke.
due to 20210 G→A prothrombin polymorphism and cerebral ischemia in


Testing for Inherited Thrombophilias in Arterial Stroke: Can It Cause More Harm Than Good?
Jane G. Morris, Swaraj Singh and Marc Fisher

Stroke. 2010;41:2985-2990; originally published online October 14, 2010;
doi: 10.1161/STROKEAHA.110.595199

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/41/12/2985