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. (Stroke. 2010;41:00-00.)

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 English they were included. All results were searched for relevant data and divided into case reports, case series, case-control studies, meta-analyses, and review articles. References were mined for other relevant articles. Although all available abstracts and articles were reviewed, this article focuses on case-control trials performed in adults (age older than 18 years). The scope of this article is limited to these hypercoagulable markers and other tests, such as antiphospholipid antibodies, homocysteine, and the methyltetrahydrofolate reductase gene mutation, are not discussed.

Background
The inherited thrombophilias include protein C (PC) deficiency, proteins S (PS) deficiency, antithrombin (AT) deficiency, factor V Leiden (FVL), and the prothrombin G20210A gene mutation (PTM). All are inherited through autosomal-dominant transmission and all have been associated with an increased risk of VTE; however, none has convincingly been demonstrated to be risk factors for arterial thrombosis.1–3 Homozygosity for these defects significantly enhances the risk of thrombosis; however, homozygotes are rare and the bulk of the data presented here comes from heterozygotes.

Before assuming hereditary deficiencies of PC, PS, and AT, acquired deficiencies must be ruled out. A patient’s comorbid medical conditions, medications, and timing from the thrombosis must be taken into account, because these factors may affect the results. An extensive review of the conditions that affected these assays is reported elsewhere.3

FVL and PTM are genetic tests and therefore are not affected by other factors; however, race should be considered before testing because their prevalence is highly race-dependent. Worldwide prev-
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.

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.

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. 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. Most were in young patients (younger than 55 years old) and none showed any relationship between these deficiencies and stroke (Table 1).

<table>
<thead>
<tr>
<th>Reference</th>
<th>Age</th>
<th>N Cases and Controls</th>
<th>Thrombophilia Tested</th>
<th>% Identified in Cases</th>
<th>% Identified in Controls</th>
<th>Statistical Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sastry (2006)</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)</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)</td>
<td>Mean</td>
<td>219</td>
<td>PC, PS, AT</td>
<td>7.3</td>
<td>6.8</td>
<td>NS</td>
</tr>
<tr>
<td>Margaglione (1999)</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)</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)</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.

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 compared between whites and blacks of either Caribbean or African descent. The reference range of PC, PS, AT, and 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 al 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 al 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. We feel that the method of recruitment affected the results of these studies and that studies using unselected patients admitted to a hospital more accurately reflect the patient population seen by most neurologists.

Subgroup analyses performed in some studies have led to conflicting results. Nabi et al 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, but other studies stratified by stroke subtype did not find this association. Lalouchek et al 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 low (1%) prevalence of the PTM in the control population because this finding never has been reported in any other population.
Increased stroke risk with thrombophilias associated with female gender,18,19 oral contraceptive use,9,18 smoking,12,18,19 and migraine9,30 have been reported, yet others have found no association with gender,20,21,24 oral contraceptive use,13,19,23 smoking,12,31 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 stroke21,24,37–43 (Table 3). Sastry et al9 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 estimated that the direct cost for anticoagulation services was $205 to $305 per patient per year (2003 values). Based on MediCare reimbursement for 2004, Auerbach et al reported the average cost of bleeding complications per patient-administered warfarin was $2530 for minor bleeding and $5034 for major bleeding. Using these estimates, the average annual cost of oral anticoagulation ranges from $2800 to $8000 per patient per year. In 2005, Fanikos et al published the actual costs of treating patients with major hemorrhages attributable to warfarin, which ranged from $3192 to $64,446.

The major risk of warfarin therapy is excessive bleeding. A review of the literature reported average annual bleeding rates of fatal, major, and major or minor bleeding are 0.6%, 3.0%, and 9.6% respectively. Prolonged exposure to warfarin increases the chances of a bleeding complication, an important consideration given that most patients undergoing a thrombophilia work-up are young.

Assuming a life expectancy of 80 years, a mean warfarin cost of $12 per month and a mean monitoring cost of $255 per year, a 35-year-old person’s estimated cost of warfarin therapy and monitoring over a lifetime would be $120,000, excluding costs from bleeding complications. Over the next 45 years, this person has a 2.7% chance of a fatal bleed, a 13.5% of a major bleed, and a 100% chance 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.

### 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)</td>
<td>≤55</td>
<td>76 PFO(+) cryptogenic stroke</td>
<td>Tested for PC, PS, AT, FVL, and PTM; found no association</td>
</tr>
<tr>
<td></td>
<td></td>
<td>76 age- and gender-matched</td>
<td></td>
</tr>
<tr>
<td>Palmieri (2007)</td>
<td>38 ± 9</td>
<td>29 cryptogenic stroke/TIA</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></td>
<td></td>
<td>30 healthy volunteers</td>
<td></td>
</tr>
<tr>
<td>Belvis (2007)</td>
<td>&lt;55</td>
<td>17 PFO(+) cryptogenic stroke</td>
<td>Tested for PC, PS, FVL, and PTM; found no association</td>
</tr>
<tr>
<td></td>
<td></td>
<td>22 PFO(−) cryptogenic stroke</td>
<td></td>
</tr>
<tr>
<td>Carod-Artal (2006)</td>
<td>15–45</td>
<td>42 PFO(+) ischemic stroke</td>
<td>Tested for PC, PS, AT, and FVL; found no association</td>
</tr>
<tr>
<td></td>
<td></td>
<td>88 PFO(−) ischemic stroke</td>
<td></td>
</tr>
<tr>
<td>Lichy (2003)</td>
<td>Mean 53.4</td>
<td>220 PFO(+) cryptogenic stroke</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></td>
<td></td>
<td>196 stroke of known source</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>362 healthy, from same region</td>
<td></td>
</tr>
<tr>
<td>Karttunen (2003)</td>
<td>15–60</td>
<td>58 PFO(+) cryptogenic stroke</td>
<td>FVL (7%) and PTM (4%) were more common in PFO(+) cryptogenic stroke than controls (1%) (P=0.008)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>104 community-based controls</td>
<td></td>
</tr>
<tr>
<td>Pezzini (2003)</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></td>
<td></td>
<td>Divided into:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>36 PFO(+) and 89 PFO(−)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>149 age- and gender-matched</td>
<td></td>
</tr>
<tr>
<td>Austin (2002)</td>
<td>18–50</td>
<td>67 cryptogenic stroke</td>
<td>2 of 20 subjects (10%) were PFO(+) and FVL(+) vs PTO(−) and FVL(−); this was not statistically significant</td>
</tr>
<tr>
<td></td>
<td></td>
<td>−19 had PFO(+)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>79 noncryptogenic stroke</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>−1 had PFO(+)</td>
<td></td>
</tr>
<tr>
<td>Nabavi (1998)</td>
<td>14–45</td>
<td>225 TIA or ischemic stroke</td>
<td>36% of cases were PFO(+) whereas 53% (8/15) FVL(+) were also PFO(+) (P=0.15)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>−205 were evaluated for PFO</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>200 healthy white subjects</td>
<td></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.

### 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
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 recommend that testing for inherited thrombophilias should be no different in the stroke population than in any other population, 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 attempts to understand the relationship of the inherited thrombophilias 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 presumption 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 abnormalities and ischemic 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 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, Ferrer-Wyeth, Otea Medical, Mistubishi Pharma USA, Daichi Sankyo Pharma, Takeda Pharmaceuticals, Syngis, BrainGate, and Covidiene. He serves or has served on steering committees for Photothera, Servier, and CoAxia. He has equity positions in Brainsgate and Photothera. None of these relations has any impact on this study.

References


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