Ethnic Differences in Markers of Thrombophilia: Implications for the Investigation of Ischemic Stroke in Multiethnic Populations: The South London Ethnicity and Stroke Study

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Background and Purpose—The role of hypercoagulable states in the pathogenesis of ischemic stroke in black subjects is not known, and data on normal reference ranges in black populations are lacking. This study estimated ethnic-specific reference ranges in a community population to determine the prevalence of thrombophilic states in a multiethnic stroke population.

Methods—Free protein S, protein C, antithrombin III, activated protein C resistance, IgG anticardiolipin antibodies, and lupus anticoagulant were determined in 130 consecutive ischemic stroke cases ≤65 years of age (50 black Caribbeans, 30 black Africans, 50 whites) and 130 community controls.

Results—Black African controls had significantly lower protein S (P<0.001) and protein C (P=0.049) and a trend toward lower antithrombin III (P=0.056) levels compared with white controls. Black Caribbean and African controls had higher diluted Russell’s viper venom time ratios compared with whites (P<0.001, P<0.001). Using ethnic-specific reference ranges, 8 controls (6.3%) and 11 cases (8.5%) had thrombophilia abnormalities (odds ratio [OR], 1.39; 95% confidence interval [CI], 0.54 to 3.57; P=0.50). ORs were 0.96 (95% CI, 0.18 to 4.99; P=0.96) for whites, 1.57 (95% CI, 0.41 to 5.94; P=0.51) for black Caribbeans, and 2.07 (95% CI, 0.18 to 24.2; P=0.95) for black Africans.

Conclusions—Failure to account for ethnic differences in the normal reference ranges for thrombophilia markers may lead to inappropriate diagnosis and investigation of hypercoagulable states in black individuals. Protein S and protein C deficiencies and lupus anticoagulant may contribute to stroke risk in a minority of black cases, but they are unlikely to be major contributors to the excess stroke risk seen in young individuals of African and African-Caribbean descent. (Stroke. 2003;34:1821-1827.)

Key Words: stroke ■ thrombosis

Hypercoagulable states may account for a small proportion of ischemic stroke, particularly in younger individuals, although recent studies suggest that in white populations, most positive thrombophilia screening tests are likely to be coincidental rather than causal. Individuals of African and African-Caribbean descent have a higher incidence of ischemic stroke compared with whites and present with stroke at a younger age. The prevalence of inherited thrombophilic states shows marked interethnic variation, and the role of thrombophilia in the pathogenesis of ischemic stroke in blacks is not known. Although the factor V Leiden mutation is rare in blacks, both protein S and C deficiencies and lupus anticoagulant have been reported to be more common in individuals of African descent presenting with ischemic stroke. However, data on normal reference ranges in the black community are lacking. If reference ranges are different in black individuals, the inappropriate use of ranges derived from white populations could lead to overdiagnosis of thrombophilia abnormalities as a cause of stroke in black individuals.

The aim of this study was to determine whether there are ethnic differences in values for thrombophilia assays in normal community controls of white, black Caribbean, and black African ethnicity. Normal reference ranges derived from these data were then used to determine whether prothrombotic states are risk factors for stroke in each ethnic group. We studied younger stroke patients (≤65 years) because the association between prothrombotic states and stroke appears to be more important in younger individuals.

Subjects and Methods
A total of 130 cases, consisting of 50 black Caribbeans, 30 black Africans, and 50 white Caucasians, were recruited from a consecu-
tive case series of patients ≥65 years of age presenting to 3 stroke services in adjacent geographical regions in South London with acute ischemic stroke confirmed by brain imaging. Twelve additional cases on anticoagulant therapy were excluded from the study because of known interactions with thrombophilia assays. None of these excluded cases had a known diagnosis of thrombophilia. During the same time period, the same number (n=130) of stroke-free community controls, matched 1:1 for sex, age ±5 years, and self-declared ethnicity, were recruited by sampling of 5 primary care lists in the same geographic area as the stroke cases.

Documented risk factors included age, sex, smoking status, hypertension, diabetes, and hypercholesterolemia. Smoking status was categorized as current (patient admission or ≥1 cigarette per day in the past 12 months), ex-, or never smoker. Hypertension was defined as pharmacological treatment for hypertension or systolic blood pressure ≥160 mm Hg and/or diastolic blood pressure ≥95 mm Hg persisting >7 days after the acute event (World Health Organization classification). Diabetes was defined as reported or medical record of either diet-controlled, oral hypoglycemic-controlled, or insulin-treated diabetes. Hyperlipidemia was defined as pharmacological treatment for hypertension or obesity was defined as a body mass index of ≥27.

Details were corroborated with patient’s medical records. Informed consent was obtained from all subjects, and the local research ethics committee approved the study.

Thrombophilia Screening

Serum and citrated plasma samples were collected at presentation, centrifuged, and stored at −80°C before analysis. In all cases, with abnormal thrombophilia results, screening was repeated at ≥3 months after the acute stroke event to exclude an acute-phase response, and results of the repeated testing were used in the final data analysis. Samples were defrosted once only and analyzed for free protein S, protein C, antithrombin III, activated protein C resistance (APCR), IgG anticardiolipin antibodies, and lupus anticoagulant. Free protein S was determined by use of an automated latex ligand agglutination immunoassay with results reported in percent normality (IL Coagulation Systems). Protein C was quantified with a synthetic chromogenic substrate after incubation of plasma with a protein C activator (IL Coagulation Systems). Antithrombin III levels were determined by chromogenic assay after incubation of plasma with factor Xa in the presence of an excess of heparin (IL Coagulation Systems). APCR (in factor V–deficient plasma) was determined with the activated partial thromboplastin time–based Coatest (Chromogenix). Lupus anticoagulant was determined with the diluted Russell’s viper venom test (DRVVT) and the recombinant thromboplastin inhibition test (RTI), and abnormal results were confirmed using DRVVT with platelet phospholipid correction (IL Coagulation Systems). IgG anticardiolipin antibodies were evaluated with a commercially available enzyme-linked immunosorbent assay (Pharmacia & Upjohn Ltd).

Statistical Analysis

Data were analyzed with SPSS version 10.0. Differences between groups were tested with analysis of variance (ANOVA) with posthoc Bonferroni correction for continuous variables and binary logistic regression analysis for categorical variables. Univariate and multivariate analyses controlling for vascular risk factors were performed. Results from the control population were used to establish normal reference ranges, ie, ±2 SD, for the 3 ethnic groups. The proportion of cases falling outside these reference ranges was then calculated for each ethnic group, and odds ratios (ORs) for thrombophilia abnormalities in cases compared with controls were calculated through binary logistic regression analysis.

Results

Ethnic Differences in Thrombophilia Markers in Stroke-Free Community Controls

The thrombophilia marker levels approximated normal distributions. The Figure shows mean levels of thrombophilia markers according to ethnicity for the community control population. Significant ethnic differences in the normal reference ranges were seen for a number of the thrombophilia markers (the Figure). The black African control group had significantly lower protein S levels compared with either the black Caribbean (P=0.014) or the white (P<0.001) group. Protein C levels were also lower in the black African compared with the white group (P=0.049), and there was a nonsignificant trend toward lower antithrombin III levels (P=0.056). APCR did not differ between the 3 ethnic groups (P=0.265). Both black Caribbean and black African controls had higher DRVVT (P=0.001 and P<0.001 for both) and RTI ratios (P=0.032 and P<0.001, respectively) compared with whites. No relationships were found between thrombophilia markers and age, sex, hypertension, diabetes, hypercholesterolemia, or obesity in any of the 3 ethnic groups, and additional adjustment for these vascular risk factors did not alter the significance of the observed ethnic differences. For protein S, protein C, DRVVT, and RTI, black Caribbeans had intermediate levels between the those of the white and African groups. For all of these measures, the black African group showed the greater thrombophilic tendencies. None of the white or African controls and only 1 Caribbean control had raised IgG anticardiolipin (>16 IU/mL).

Clinical Importance of Defining Ethnicity-Specific Reference Ranges

To determine the potential clinical relevance of the observed differences in normal reference ranges, the proportion of black community control subjects who would be classified as having an abnormal thrombophilia screen on the basis of the laboratory reference ranges for whites was calculated. With these cutoffs, 7 black African controls (23.3%) and 4 black Caribbean controls (8%) would meet the criteria for either protein S or protein C deficiency compared with 2 control whites (4%) (P=0.021 for black African versus white). In addition, 4 black African controls (13.3%) and 9 black Caribbean controls (18%) would fit at least 1 criterion for the presence of lupus anticoagulant compared with 1 white control (2%) (P=0.036 for black versus white ethnicity). For any thrombophilia, 11 black African controls (36.7%) and 13 black Caribbean controls (26%) would test positive using the reference ranges for whites (P=0.013 for black Caribbean versus white, P=0.001 for black African versus white).

Prevalence of Thrombophilia in Stroke Cases

Demographic and risk factor profiles for cases and controls according to ethnic group are given in Table 1. The 3 control groups were matched for age and sex. Compared with whites, the black Caribbean and African subjects were more likely to be hypertensive, were more obese, and were less likely to be current smokers.

The distribution of stroke subtypes among the cases was as follows: large-vessel atherosclerosis, 13%; cardioembolism, 13%; lacunar stroke, 37%; and stroke of undetermined origin, 35%. Two cases had carotid artery dissection, both with normal thrombophilia screens, and 1 case had a cerebral venous thrombosis, also with a normal thrombophilia screen.
Data from the community control population were used to define normal reference ranges specific for each ethnic group. With these ±2-SD cutoff values, the prevalence of abnormal thrombophilia screens according to ethnic group was determined for the stroke cases. ORs and 95% confidence intervals (CIs) for the presence of thrombophilia screening abnormalities in cases compared with controls were calculated overall and for each ethnic group using binary logistic regression analysis.

The prevalence of abnormal results for cases and controls is presented in Table 2. The overall prevalence of any thrombophilia abnormality using the ethnicity-specific reference ranges was 6.3% in controls and 8.5% in stroke cases (OR, 1.39; 95% CI, 0.54 to 3.57; \( P = 0.50 \)). The presence of any abnormality in thrombophilia screening was not a significant risk factor for stroke in any of the 3 ethnic groups (OR, 0.96; 95% CI, 0.18 to 4.99; \( P = 0.96 \) for whites; OR, 1.57; 95% CI, 0.41 to 5.94; \( P = 0.51 \) for black Caribbeans; OR, 2.07; 95% CI, 0.18 to 24.2; \( P = 0.55 \) for black Africans). Similarly, mean levels of thrombophilia assays did not differ significantly between cases and ethnically matched controls. When only subjects <50 years of age were considered, the

### TABLE 1. Demographic and Risk Factor Profiles for Cases and Controls According to Ethnic Group

<table>
<thead>
<tr>
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<th>Whites</th>
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<th>Black Caribbean</th>
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<td>25 (50)</td>
<td>30 (60)</td>
<td>25 (50)</td>
<td>32 (64)</td>
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<td>53 (7)</td>
<td>56 (6)</td>
<td>57 (9)</td>
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<td>Hypertension, n (%)</td>
<td>14 (29)</td>
<td>19 (38)</td>
<td>22 (44)</td>
<td>38 (76)*</td>
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<td>20 (67)</td>
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<td>4 (8)</td>
<td>7 (14)</td>
<td>6 (12)</td>
<td>19 (38)*</td>
<td>3 (10)</td>
<td>8 (28)</td>
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<td>27 (53)</td>
<td>31 (66)</td>
<td>14 (29)</td>
<td>21 (46)</td>
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<td>Obesity, n (%)</td>
<td>17 (35)</td>
<td>20 (53)</td>
<td>31 (62)</td>
<td>26 (59)</td>
<td>18 (60)</td>
<td>19 (76)</td>
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<td>Current smoker, n (%)</td>
<td>16 (26)</td>
<td>33 (67)*</td>
<td>13 (26)</td>
<td>18 (36)</td>
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*\( P < 0.05 \) for cases vs controls. Differences between groups were tested with ANOVA with posthoc Bonferroni analysis for continuous variables and logistic regression analysis for categorical variables.
OR for any thrombophilia was higher (2.92; 95% CI, 0.52 to 16.4) compared with the overall group but remained statistically nonsignificant ($P=0.21$).

A low free protein S level was the most commonly observed abnormality in black cases, accounting for 2 of the 6 abnormal cases in black Caribbeans and both black African cases with abnormalities but none of the white cases (Table 2). Low protein C was the next-most-common abnormality, affecting 4 of the 6 abnormal cases in black Caribbeans (with 1 case of combined low protein C and protein S) and 2 of the 3 abnormal white cases. One black Caribbean and 1 white stroke case tested positive for lupus anticoagulant. None of the stroke cases had antithrombin III deficiency, APCR, or positive anticardiolipin antibodies.

**Discussion**

This study demonstrates significant ethnic differences in the normal reference ranges for markers of thrombophilia. Using the normal reference ranges determined from a white population, a significant proportion of healthy black community controls would be classified as having abnormal thrombophilia screening. When appropriate reference ranges were used, thrombophilia was not a significant risk factor for stroke either overall or in any of the 3 ethnic groups studied. Failure to account for these differences may lead to incorrect diagnoses of hypercoagulable states in blacks presenting with ischemic stroke.

Although thrombophilia was excluded as a major cause of ischemic stroke in the overall stroke population, a larger study in specific groups would be required to determine whether they account for a small proportion of strokes. The ORs for the presence of thrombophilia abnormalities were higher in both black groups compared with whites, but the study was underpowered to detect a small effect. From the observed ORs, we estimate that a sample size of 600 cases and 600 controls would be required to effectively exclude thrombophilia as a risk factor for stroke in a black population. The data suggest that hypercoagulable states contribute to stroke risk in, at most, a small minority of black cases. Previous studies in white populations have suggested that thrombophilia, if a risk factor at all, may be a risk factor only in young stroke cases.\textsuperscript{10,12} To maximize any age effect, we chose to recruit only subjects $\leq 65$ years of age; therefore, the role of thrombophilia in older blacks is likely to be even less. Restricting the study to younger patients may accentuate the role of thrombophilia because conventional vascular risk factors are more prevalent in older patients. Consistent with this hypothesis, when only subjects $\leq 50$ years of age were considered, the OR for any thrombophilia was higher compared with the overall group but remained statistically nonsignificant.

<table>
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<tr>
<th></th>
<th>Controls, n (%)</th>
<th>Cases, n (%)</th>
<th>OR (95% CI)</th>
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<tr>
<td>Overall</td>
<td>8 (6.3)</td>
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<td>1.39 (0.54–3.57)</td>
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<td>3 (6.3)</td>
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<td>0.96 (0.18–4.99)</td>
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<td>4 (8.0)</td>
<td>6 (12)</td>
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<td>2 (6.7)</td>
<td>2.07 (0.18–24.2)</td>
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<tr>
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<td>Overall</td>
<td>2 (1.6)</td>
<td>4 (3.1)</td>
<td>2.00 (0.36–11.1)</td>
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<td>2 (6.7)</td>
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<td><strong>Low protein C</strong></td>
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<td>Overall</td>
<td>2 (1.6)</td>
<td>6 (4.6)</td>
<td>3.05 (0.60–15.39)</td>
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<td><strong>Low antithrombin III</strong></td>
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<td><strong>APCR</strong></td>
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<tr>
<td>Overall</td>
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<td>0.26</td>
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<td><strong>Lupus anticoagulant</strong></td>
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<td>Overall</td>
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<td>2.23 (0.20–24.90)</td>
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<td><strong>Anticardiolipin Abys</strong></td>
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<td>Black Caribbean</td>
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A number of inherited and acquired abnormalities in blood coagulation have been implicated in the pathogenesis of venous thromboembolism. Associations with ischemic stroke are less clear, and data relating to hypercoagulable states in black stroke populations are scarce. In a small number of studies, protein S and C deficiencies and lupus anticoagulant have been reported to be more common in individuals of African descent presenting with ischemic stroke. Although protein S and C deficiencies also constituted the most commonly observed abnormalities in our black stroke populations, previous studies may have overestimated the impact of these factors by failing to account for ethnic differences in the normal reference ranges for these assays.

The free protein S and protein C assays used in this study were quantitative antigenic assays. The antigenic assay detects common forms of quantitative protein S and protein C deficiencies but will not detect the rare qualitative (type II) abnormalities, which are characterized by normal total and free antigen levels and low APCR cofactor activity. Therefore, this study may have missed a small number of cases with the rare quantitative forms of protein S or protein C deficiency.

Published data on the prevalence of thrombophilic states in stroke vary widely, ranging from 0% to 23%, depending on the screening methodology used. Some of this apparent heterogeneity may be explained by the different ethnic makeup of the populations studied. In addition, a number of factors need to be considered when the results of thrombophilia tests in stroke patients are interpreted. For instance, it is well recognized that the acute-phase response may affect functional thrombophilia assays, resulting in false-positive tests. After acute ischemic stroke, levels of protein S, protein C, and antithrombin III may be transiently suppressed. To overcome this problem, a diagnosis of thrombophilia was made only when repeated testing ≥3 months after the stroke event confirmed an abnormality. Subjects on oral contraceptives and warfarin were excluded from this study because warfarin is known to decrease levels of the vitamin K–dependent factors protein C and protein S and to interfere with APCR and lupus anticoagulant screening tests. Other physiological and pharmacological factors such as liver disease, the oral contraceptive pill, and some vascular risk factors may also affect thrombophilia assays.

The observed ethnic differences in community control subjects were not explained by the different prevalences of vascular risk factors in the 3 groups. The influence of other environmental and/or cultural factors may be important determinants of thrombophilia markers. For example, Mochan et al found a high prevalence of protein S deficiency in a case series of HIV-positive black Africans presenting with stroke, suggesting that HIV infection may be associated with protein S deficiency. However, they acknowledged that a study including HIV-negative controls is required to confirm this association. For ethical reasons, we were unable to test for HIV in all our samples. In addition to environmental influences, it is likely that these differences are at least in part genetically determined. For example, functional genetic variants in the protein S gene have been identified that influence protein S levels, although the frequency of these variants in different ethnic groups has not been reported. As-yet-unrecognized genetic variants in the protein S and protein C genes may be important determinants of normal levels of these proteins. For protein S, protein C, and lupus anticoagulant screening tests, black Caribbeans had intermediate levels between the Caucasian and African groups, which may reflect the genetic admixture in this population. Consistent with the reported lower frequency of the factor V Leiden mutation in black populations, none of the black subjects in this study tested positive on APCR screening. Interestingly, we found no ethnic differences in APCR. It has previously been suggested that APCR in nonwhite ethnic groups may be caused by other, as-yet-undiscovered mechanisms. Another possible explanation is the limited sensitivity of the APCR assay as a screening test. We did not screen for the prothrombin 20210 mutation, although previous studies have also shown that the prevalence of this mutation in black populations (<0.2%) is considerably lower than in whites (1% to 2%).

In summary, there are ethnic differences in normal reference ranges for a number of thrombophilia markers. When appropriate reference ranges were used, thrombophilia was not a significant risk factor for stroke either overall or in any of the 3 ethnic groups studied. Protein S and protein C deficiencies and lupus anticoagulant may contribute to stroke risk in a minority of black cases, but they are unlikely to be major contributors to the excess stroke risk seen in young individuals of African and African Caribbean descent.

Acknowledgments
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References


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**Editorial Comment**

**Routine Thrombophilia Testing in Stroke Patients Is Unjustified**

The whole area of laboratory screening for thrombophilias in stroke patients is shrouded in uncertainty as to which (if any) patients to screen, what laboratory tests to order, how to interpret the results, and when to change therapy. To answer these questions, it is important to define the conditions and to consider their prevalence in the community and in patients with venous thromboembolism (VTE) and stroke; the likely attributable risk of stroke for each, if any, of the thrombophilias; the costs of the laboratory tests for thrombophilias; and the effectiveness of the results of testing in optimizing patient management and outcome.

**What Are the Thrombophilias?**

There is no internationally accepted definition of thrombophilia, but the term is commonly used to describe disorders of the hemostatic mechanisms that are likely to predispose to thrombosis. Thrombophilia may be inherited (deficiency of protein C, protein S, or antithrombin; activated protein C resistance resulting from the factor V Leiden mutation; the prothrombin gene [20210 G/A] mutation; and dysfibrinogenemia), acquired (lupus anticoagulant [LA] and anticardiolipin [ACL] antibodies), or mixed or unknown (high levels of coagulation factor VIII, IX, or XI; high levels of thrombin activatable fibrinolysis inhibitor).

**How Common Are the Thrombophilias?**

At least 1 thrombophilic disorder is present in approximately 10% to 15% of the white Western European population, and as highlighted in the study by Jerrard-Dunne et al in this issue of Stroke, the distribution of blood concentrations of coagulation proteins, and thus diagnostic criteria and prevalence of thrombophilias, varies among other well-defined ethnic groups such as black Caribbeans and black Africans. Similarly, the prevalences of factor V Leiden and the 20210 G/A prothrombin gene mutation are common among healthy whites but extremely rare among Asians and Africans.
ischemic stroke, but there was a nonsignificant trend toward a higher prevalence of any thrombophilia in 8 of the 45 cases (20.5%; 95% CI, 8 to 32) of ischemic strokes caused by cardiogenic embolism. Although the estimates are very imprecise because of the small sample size, it is biologically plausible that thrombophilia may predispose to “red” fibrin thrombi in areas of relative stasis of blood such as veins and heart chambers compared with the predominant “white” platelet thrombi that occur in areas of high shear stress in arteries. Our study was underpowered to reliably identify or exclude a modest, but important, association between a particular inherited thrombophilic disorder (eg, protein C deficiency) and a particular etiological stroke subtype (eg, cardiogenic embolism).

What is the Likely Attributable Risk of Stroke for the Thrombophilias?

The data of Jerrard-Dunne et al and others suggest that the attributable risk of inherited thrombophilia for ischemic stroke is likely to be low overall and perhaps even nonexistent in some ethnic groups such as individuals of African and African-Caribbean descent. However, it may be higher and of clinical relevance for particular ethnic groups, particular types of thrombophilia (eg, the acquired thrombophilias, LA or ACL), and particular etiological subtypes of stroke such as thromboembolism from an area of stasis in the veins (via a right-to-left shunt, eg, patent foramen ovale) or heart chambers (eg, atrial fibrillation). Much larger studies than previously undertaken are required to answer this question.

What Are the Costs of the Laboratory Tests for Thrombophilias?

The cost of a battery of tests to investigate inherited coagulation defects, activated protein C resistance, ACL, and LA in 1 patient at Duke Hospital (Durham, NC) is US $1014; inherited thrombophilia at University College Hospital (London, UK) is Euros 500 (US $500); and inherited or acquired thrombophilia at Royal Perth Hospital (Australia) is Aus $313.50 (US $200).

What Is the Effectiveness of the Laboratory Tests in Optimizing Patient Management and Outcome?

At present, the finding of a positive test for ≥1 thrombophilic disorders using ethnic-specific reference ranges does not prove that it is relevant to the cause, because there is a 5% to 15% chance that the result is coincidental, as seen in community controls. Furthermore, there is no clear evidence to suggest the clinical circumstances under which a positive result is more likely to be causal (eg, unexplained stroke, young stroke, cardiogenic stroke). And even if larger studies do establish a causal association between ≥1 thrombophilias (eg, LA) and a subtype of ischemic stroke (eg, small-vessel disease), it is not certain how the finding of a positive test result (eg, LA positive) should change management; for example, there have been no randomized trials comparing anticoagulation with antiplatelet therapy in these patients. If our hypothesis proves correct and the acquired thrombophilias play a contributory role in a minority of patients with ischemic stroke caused by thromboembolism from the veins or cardiac chambers, many of the patients are likely to be anticoagulated long term anyway, regardless of the presence or absence of a thrombophilia.

We believe that outside a research setting, there is no justification for incurring the substantial costs of routine thrombophilia screening in patients with ischemic stroke in the absence of reliable data linking any or all of the thrombophilias to the origin of any subtype of ischemic stroke or to a favorable response to a particular intervention. Further research should focus on the possible role of acquired thrombophilias (LA, ACL) in the pathogenesis of specific etiological subtypes of ischemic stroke (embolism from or via the heart, perhaps small-vessel disease) and the response of etiologically relevant thrombophilias to different antithrombotic regimens. The article by Jerrard-Dunne et al highlights the importance of accounting for ethnic differences in the pursuit of answers to these questions.

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Ethnic Differences in Markers of Thrombophilia: Implications for the Investigation of Ischemic Stroke in Multiethnic Populations: The South London Ethnicity and Stroke Study
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