Diagnostic Testing for Coagulopathies in Patients With Ischemic Stroke

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Background—Hypercoagulable states are a recognized, albeit uncommon, etiology of ischemic stroke. It is unclear how often the results of specialized coagulation tests affect management. Using data compiled from a systematic review of available studies, we employed quantitative methodology to assess the diagnostic yield of coagulation tests for identification of coagulopathies in ischemic stroke patients.

Summary of Review—We performed a MEDLINE search to identify controlled studies published during 1966–1999 that reported the prevalence of deficiencies of protein C, protein S, antithrombin III, plasminogen, activated protein C resistance (APCR)/factor V Leiden mutation (FVL), anticardiolipin antibodies (ACL), or lupus anticoagulant (LA) in patients with ischemic stroke. The cumulative prevalence rates (pretest probabilities) and positive likelihood ratios for all studies and for those including only patients aged ≤50 years were used to calculate posttest probabilities for each coagulopathy, reflecting diagnostic yield. The cumulative pretest probabilities of coagulation defects in ischemic stroke patients are as follows: LA, 3% (8% for those aged ≤50 years); ACL, 17% (21% for those aged ≤50 years); APCR/FVL, 7% (11% for those aged ≤50 years); and prothrombin mutation, 4.5% (5.7% for those aged ≤50 years). The posttest probabilities of ACL, LA, and APCR increased with increasing pretest probability, the specificity of the tests, and features of the patients’ history and clinical presentation.

Conclusions—The pretest probabilities of coagulation defects in ischemic stroke patients are low. The diagnostic yield of coagulation tests may be increased by using tests with the highest specificities and by targeting patients with clinical or historical features that increase pretest probability. Consideration of these data might lead to more rational ordering of tests and an associated cost savings. (Stroke. 2000;31:3067–3078.)

Key Words: cerebral infarction ■ coagulation ■ decision analysis ■ diagnosis

The etiology of ischemic stroke remains undetermined in nearly 40% of patients despite extensive evaluations. The recognition that hypercoagulable states are sometimes found in ischemic stroke patients has led to testing for these rare conditions. Coagulopathies related to protein C (PC), protein S (PS), antithrombin III (ATIII), or plasminogen deficiencies, activated protein C resistance (APCR), prothrombin gene mutation, anticardiolipin antibodies (ACL), or lupus anticoagulant (LA) can be evaluated with various coagulation testing strategies. Rational use and interpretation of this array of tests can be daunting for noncoagulation specialists.

Before ordering any diagnostic test, the physician should first consider its diagnostic yield (ie, the physician should consider whether the results add to the evaluation, potentially altering therapy and improving patient outcome). The diagnostic yield is a direct reflection of the positive predictive value or posttest probability of the test. This is defined as the proportion of patients with positive tests that have the diagnosis (in this case, a coagulopathy). To calculate this estimate, the pretest probability (prevalence of the disease in the target population) and the positive likelihood ratio (LR), which is based on the sensitivity and specificity of the test, must be determined. Although topic reviews have been published previously, this type of diagnostic yield assessment has not been systematically applied to coagulation testing in ischemic stroke patients.

The aim of this review is to compile the available data necessary to estimate posttest probabilities for coagulation tests in general ischemic stroke patients and to indicate where these data are lacking. Separate probabilities are estimated for younger patients who have been traditionally considered at higher risk for coagulopathies. To accomplish these aims, the currently available diagnostic tests as well as the physiological or pharmacological factors that may interfere with their interpretation are critically reviewed. Next, the reported prevalence rates and odds ratios (ORs) from controlled studies of inherited and acquired coagulopathies in these populations are summarized. Positive LRs are then calculated with the use of assessments of the sensitivities and specific-
ities of the tests. The prevalence rates and LRs are subsequently used for estimation of the posttest probabilities for different subpopulations of patients. On the basis of these data, we suggest a scheme for coagulation testing that should prove useful to physicians evaluating ischemic stroke patients.

Methods

Publications reporting the prevalence of coagulopathies in patients with ischemic stroke (case-control, cross-sectional, or prospective cohort studies) and the use of specific diagnostic tests for coagulopathies, including sensitivity and specificity measurements, were systematically identified. Sources included MEDLINE (limited to English language and human studies), cited references from publications, letters to the editor, and abstracts published between January 1966 and December 1999. Studies of coronary heart disease, case series, case reports, and other studies lacking controls were excluded. If the numbers of ischemic stroke cases and controls were not stated, the latter were calculated with the use of a standard formula. The cumulative prevalence for APCR, prothrombin mutation, ACL, and LA was calculated by dividing the total number of ischemic stroke cases with the coagulation defect by the total number of ischemic stroke cases. Cumulative prevalence rates were calculated for patients aged ≤50 years and for all age ranges. These prevalence rates, in addition to the LRs, provided data for calculation of the posttest probability estimates described below.

Whenever possible, the sensitivity and specificity for an individual diagnostic test used were to calculate the positive likelihood ratio (LR+) = Sensitivity/(1 − Specificity), expressed as a percentage). This result was then used to calculate the posttest probability for the corresponding diagnostic test (Pretest Odds = Probability/(1 − Probability), where probability is equal to the prevalence of the disease in the target population; Posttest Odds = Pretest Odds × LR for Desired Result; Posttest Probability = Posttest Odds/(Odds + 1)).

Results

Coagulation Tests: Factors Affecting Interpretation

Table 1 lists the coagulation tests and the influence of various physiological, pharmacological, and hematologic factors on these tests. Although 2 different tests may be influenced by the same factor, the relative degree of influence is not indicated in this table.

Protein C, Protein S, ATIII, and Plasminogen Deficiencies

Hereditary coagulation defects are evaluated in a similar fashion by screening functional assays, followed by quantitative assays. However, accurate diagnosis of these defects is quite complex, since the functional assays are influenced by acute thrombosis or acute phase reactants. As a result, if the tests are to be performed, patients should be tested at least 3 months after an acute thrombotic event and have no ongoing active illness that may artificially affect the studies. In addition, many other medical conditions and medications can potentially influence the test results (Table 1). Abnormal tests must be repeated and confirmed with the appropriate functional or quantitative assays. If a patient’s family history is suspicious for venous thrombosis, then family members should be considered for testing, because PC, PS, and ATIII deficiencies have autosomal dominant patterns of inheritance.

Activated Protein C Resistance

In approximately 95% of patients with APCR, the condition is due to the factor V Leiden (FVL) mutation. This is diagnosed with a screening assay for APCR followed by polymerase chain reaction (PCR) for the FVL mutation or by PCR alone. Screening for APCR can be accomplished with the original or modified activated partial thromboplastin time ratio (preduction of patient plasma with factor V–depleted plasma). The most commonly reported APCR ratio cutoff is 2.1, but the ratio is determined by the individual laboratory performing the test. The original APCR screening test can be influenced by multiple physiological, pharmacological, and hematologic factors (Table 1). If the APCR is abnormal and a hereditary diagnosis is suspected, ethnic variations in the prevalence of FVL mutation should be considered.

Prothrombin Gene Mutation

The only test available for detection of the prothrombin gene mutation is the PCR test for the guanine-to-arginine mutation at position 20210 of the 3′-untranslated region of this gene. The mechanism of hypercoagulability due to the mutation is still not known but is thought to be related to increased amounts of thrombin formation once thrombin generation is triggered. Plasma prothrombin levels have been correlated with the mutation in homozygous and heterozygous individuals, but to our knowledge, prothrombin levels have not been evaluated for sensitivity or specificity in comparison to the genetic test.

Lupus Anticoagulant

The laboratory criteria for establishing a diagnosis of LA have recently been revised. Laboratory diagnosis of LA is complex because multiple LA tests measuring different types of phospholipids are available. The heterogeneity of these tests was demonstrated in a study reporting sensitivities of 62% to 100%, depending on the cutoff value chosen. Therefore, at least 2 different screening assays should be negative before the diagnosis is excluded (eg, activated partial thromboplastin time and direct Russell viper venom time). The results are also dependent on the reagents used, with both the tests and the reagents varying among laboratories. Table 1 also lists factors that may influence LA screening test results. Of note, LA test results can still be interpreted in warfarin-treated patients, provided that mixing studies are performed (Thomas Ortel, MD, oral communication, March 2000).

Anticardiolipin Antibodies

The standard screening assay for measuring ACL is based on an enzyme-linked immunosorbent assay (ELISA). The ACL ELISA can be false-positive in the setting of infection, hypergammaglobulinemia, rheumatoid factor, and heat treatment of serum samples (Table 1). In addition, titers increase with increasing age and multiparity (Table 1). Unlike LA, which is based on a functional assay, the ACL ELISA is not influenced by concurrent anticoagulation with heparin. In the diagnostic evaluation of antiphospholipid (APL) syndrome, both LA and ACL should be obtained, because patients may have either one or both tests positive at the same time.
Prevalence Rates of Coagulopathies in Ischemic Stroke Patients

Given this background of limitations in test interpretation, a total of 107 studies of coagulopathies in ischemic stroke patients were identified. Fourteen case reports and 38 case series were excluded on the basis of the listed criteria; therefore, 55 controlled studies were included in the analysis of prevalence rates, ORs, and pretest and posttest probabilities. Five studies providing sensitivities and specificities of ACL, LA, and APCR were used to calculate positive LRs and posttest probabilities.

Hereditary Coagulation Defects

Only 4 case-control studies of the prevalence of hereditary deficiencies of PC, PS, and ATIII in ischemic stroke were

<table>
<thead>
<tr>
<th>TABLE 1. Physiological, Pharmacological, and Hematologic Factors Altering Coagulation Test Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physiological</td>
</tr>
</tbody>
</table>
| Acute thrombosis | Decrease | Decrease | Decrease | Decrease | ... | ...
| Ischemic stroke | ... | Decrease | Decrease | ... | ...
| DVT/PE | Decrease | Decrease | Decrease | Decrease | ... | ...
| Liver disease | Decrease | Decrease | Decrease | ... | ...
| Nephrotic syndrome | Decrease | Decrease | Decrease | ... | ...
| DIC | Decrease | Decrease | Decrease | ... | ...
| Severe trauma | ... | ... | Decrease | ... | ...
| Sepsis | ... | ... | Decrease | ... | ...
| Postoperative period | Decrease | ... | ... | ... | ...
| Acute respiratory distress | Decrease | ... | ... | ... | ...
| Malnutrition | ... | ... | Decrease | ... | ...
| Malignancy | ... | ... | Decrease | ... | ...
| Infections | ... | ... | ... | Positive | Positive |
| Diabetes | Increase | Decrease | Decrease | ... | ...
| Ischemic heart disease | Increase | ... | ... | ... | ...
| Aging | Decrease | ... | Decrease | Decrease | ... | Increased positivity
| Female sex | ... | ... | ... | ... | ...
| Pregnancy | Decrease | Decrease | Decrease | ... | ...
| Multiparity | ... | ... | ... | ... | Increased positivity
| Menopause | ... | ... | Increase | ... | ...
| Rheumatoid factor | ... | ... | ... | ... | False-positive
| Hypergammaglobulinemia | ... | ... | ... | ... | False-positive
| Smoking | Decrease | ... | ... | ... | ...
| Hypercholesterolemia | Increase | ... | Increase | ... | ...
| Hypertriglyceridemia | Increase | ... | ... | ... | ...
| Fibrinogen | Increase | ... | Increase | ... | ...
| Pharmacological | Oral contraceptives | Decrease | Decrease | Decrease | ... | ...
| Warfarin | Decrease | ... | Decrease | ... | False-positive | ...
| Heparin | ... | ... | Decrease | ... | False-positive | ...
| L-Asparaginase | ... | ... | Decrease | ... | ...
| Hematologic | Elevated factor VIII | ... | ... | ... | Decrease | False-positive | ...
| Elevated PC, plasminogen, or ATIII | ... | ... | ... | Decrease | ...
| Low PS | ... | ... | ... | Decrease | ...
| APCR | ... | Decrease | ... | ... | ...
| Positive LA/ACL | ... | ... | ... | Decrease | ...
| Specific factor inhibitors | ... | ... | ... | False-positive | ...
| Presence of platelets | ... | ... | ... | False-negative | ...

DVT indicates deep venous thrombosis; PE, pulmonary embolism; and DIC, disseminated intravascular coagulation. Data from references 3–5, 9–16, 18, 19, 29.
identified, ranging from 0% to 21% (Table 2).31–34 Case-series studies reported prevalence rates of 0% to 23%.32,35–40 Hereditary fibrinolytic defects such as plasminogen deficiency have a reported prevalence of 0% to 2.7% in case-control and case-series studies of ischemic stroke patients aged <45 years.32,35,37,39 These data do not permit calculation of cumulative prevalence rates.

**Activated Protein C Resistance/Factor V Leiden Mutation**

Data related to APCR prevalence range from 0% to 38% in studies of ischemic stroke (Appendix 1).41–46,49–68 However, of the 31 studies measuring APCR and/or FVL mutation, 5 studies (2 studies of APCR49,68 and 3 studies of FVL43,51,61) found significantly increased odds in ischemic stroke patients compared with controls (Appendix 1).

The 5 studies that showed a significant association between ischemic stroke and APCR/FVL all had features that limit generalization to unselected ischemic stroke populations.43,51,59,61,68 These limitations include cases identified with obsolete APCR assays that have been modified since elucidation of the genetic mutation,68 highly selected patients with transient ischemic attack only,61 patients aged 0 to 10 years,51 young adults with stroke referred for thrombophilic workup,43 and use of the modified APCR assay without confirmation with PCR for FVL.49

Evidence against an association between FVL and ischemic stroke comes from 2 well-designed prospective studies. The Physicians’ Health Study followed subjects over many years recording the incidence of venous thrombosis, ischemic stroke, and myocardial infarction. A nested case-control study of this cohort, matched for age, smoking habits, and other traditional stroke risk factors32,45,49,56 or a history of thromboembolism.64 Others included patients with only minor stroke or transient ischemic attack43 or transient ischemic attack alone.61 Although the OR appears to be increased in patients aged <50 years (OR, 3.1; Table 3), patients within this younger group were also highly selected.52,45,49,61

**Prothrombin Gene Mutation**

The prevalence of prothrombin gene mutation in ischemic stroke patients varied from 1% to 12.5% (Appendix 1).6 Of the 13 relevant studies, 2 found a significant association with ischemic stroke (Appendix 1)45,69; however, the patients were highly selected. One of the studies included patients with first stroke before age 50 years, with no history of hypertension, diabetes, hypercholesterolemia, or hypertriglyceridemia, and no age-matched controls.45 The other study included a selected population of patients with prior myocardial infarction who subsequently had venous or arterial events. The controls were consecutive newborns and not age matched.69 In contrast to these studies with highly selected patients, the majority of the case-control studies identified (Appendix 1) showed no association between the prothrombin mutation and ischemic stroke. The cumulative prevalence of this mutation was 5.7% in studies of those aged ≤50 years and 4.5% in

### Table 2. Prevalence of PC, PS, ATIII, and Plasminogen Deficiencies in Ischemic Stroke

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Study Design</th>
<th>Age, Range or Mean±SD, y</th>
<th>Total No. Stroke Pts</th>
<th>Patients With Coagulopathies</th>
<th>Type</th>
<th>Cases, n (%)</th>
<th>Controls, n (%)</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>De Lucia/199831</td>
<td>Case-control</td>
<td>65±13</td>
<td>50</td>
<td></td>
<td>PC</td>
<td>2 (4)</td>
<td>1 (1)</td>
<td>4.1 (0.37–47)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Tosetto/199732</td>
<td>Case-control</td>
<td>17 to 45</td>
<td>23</td>
<td></td>
<td>PS</td>
<td>3 (6)</td>
<td>1 (1)</td>
<td>6.3 (0.64–62)</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Mayer/199343</td>
<td>Case-control</td>
<td>&gt;40</td>
<td>188</td>
<td></td>
<td>PC</td>
<td>0</td>
<td>0</td>
<td>0.0282</td>
<td></td>
</tr>
<tr>
<td>Emerudn/199044</td>
<td>Case-control</td>
<td>36 to 83</td>
<td>45</td>
<td></td>
<td>PS</td>
<td>40 (21)</td>
<td>20</td>
<td>1.1 (0.5–2.2)</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ATIII</td>
<td>0</td>
<td>0</td>
<td>0.285</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Plasminogen</td>
<td>0</td>
<td>0</td>
<td>0.625</td>
<td></td>
</tr>
</tbody>
</table>

| Pts indicates patients; NS, not significant or P>0.05. |
| *Actual P values using data from study were NS. |

### Table 3. Cumulative ORs for APCR, Prothrombin Mutation, ACL, and LA

<table>
<thead>
<tr>
<th>Type of Coagulopathy</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>APCR/FVL</td>
<td>3.1 (2.3–4.1)</td>
</tr>
<tr>
<td>FII (prothrombin)</td>
<td>1.9 (1.3–3.0)</td>
</tr>
<tr>
<td>ACL</td>
<td>5.8 (2.6–12.7)</td>
</tr>
<tr>
<td>LA</td>
<td>2.1 (0.6–7.3)</td>
</tr>
</tbody>
</table>

OR (95% CI): Odds Ratio (95% Confidence Interval)
TABLE 4. Pretest and Posttest Probabilities for ACL, LA, and APCR

<table>
<thead>
<tr>
<th></th>
<th>Pretest Probability</th>
<th>Posttest Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age ≤50 y</td>
<td>All Ages</td>
</tr>
<tr>
<td>ACL standard ELISA (screen) (^{102})</td>
<td>21%</td>
<td>17%</td>
</tr>
<tr>
<td>APL ELISA kit (confirm) (^{103})</td>
<td>21%</td>
<td>17%</td>
</tr>
<tr>
<td>LA DVW test + DVW confirm kit (American Diagnostica) (^{49})</td>
<td>8%</td>
<td>3%</td>
</tr>
<tr>
<td>APCR ratio &lt;1.57 (^{19})</td>
<td>11%</td>
<td>7%</td>
</tr>
<tr>
<td>APCR normalized ratio &lt;0.85 (^{16})</td>
<td>11%</td>
<td>7%</td>
</tr>
<tr>
<td>APCR modified ratio &lt;2.1 (^{16})</td>
<td>11%</td>
<td>7%</td>
</tr>
<tr>
<td>Coatest APC</td>
<td>11%</td>
<td>7%</td>
</tr>
</tbody>
</table>

DVW indicates direct viper venom; SA, spontaneous abortion. Coatest APC is a trademark.

Comparisons among ACL prevalence studies are fraught with difficulty for at least 3 reasons. First, neither the ACL ELISA test \(^{94}\) nor the selection of a cutoff value for a positive test has been standardized among laboratories. \(^{95}\) The significance of IgM titers is also unclear because they may be elevated in diseases other than stroke. \(^{80}\) Second, the diagnosis of ACL or LA positivity must be confirmed with repeated testing \(^{87,88}\) since another important feature of ACL and LA is that the titers can fluctuate over time. \(^{96,97}\) Only 2 studies \(^{87,88}\) mentioned confirmation of abnormal titers. Third, in addition to the widely recognized groups of patients with either SLE-associated or primary APL syndrome, there appears to be a third category of patients with ACL in the setting of multiple atherosclerotic risk factors. \(^{78}\) Prospective studies are needed to ascertain the significance of fluctuations of antibodies over time and the prognosis of further arterial events in this latter group. \(^{78}\)

The cumulative prevalence rates of ACL and LA in patients of all ages and in those aged ≤50 years are listed in Table 4. These rates for ACL in ischemic stroke patients were relatively high (all ages, 17%; aged ≤50 years, 21%), with an increased odds of ischemic stroke with ACL (Tables 3 and 4). \(^{77,78,80,81,83,86} \)

**Estimation of Posttest Probabilities**

With allowances for the limitations reviewed in the previous sections, Table 4 lists the calculated posttest probabilities for specific coagulopathies and available coagulation tests based on the indicated pretest probabilities, sensitivities, specificities, and positive LR+. \(^{18,19,98}\) Of note, for the combined LA screening and confirmatory tests, the sensitivity was 67% and the specificity was 100%, resulting in a LR+ approaching infinity. \(^{99}\) Therefore, an arbitrary value of 1000 was used for this calculation. Table 4 also shows that the pretest probabilities for ACL and APCR, but not LA, increased by 4% in patients aged ≤50 years and that the highest posttest probabilities resulted from tests with the highest specificities. Because of the paucity of data on the prevalence of deficiencies of PC, PS, ATIII, and plasminogen in ischemic stroke, combined with a lack of sensitivity and specificity data for...
these coagulation tests, pretest and posttest probabilities could not be calculated.

### Coagulation Tests and Clinical Decision Making in Patients With Ischemic Stroke

Using data from controlled studies, we calculated cumulative prevalence rates (pretest probabilities) that ranged from 3% to 21% (Table 4). A diagnostic test is typically most helpful with a pretest probability in the range of 40% to 60%. This represents a situation in which the clinician is undecided about the diagnosis, and the diagnostic test will aid in decisions concerning further testing or lead to a change in treatment. However, the posttest probability decreases as the pretest probability decreases. Because none of the coagulopathies had a cumulative pretest probability greater than approximately 20%, unselected use of coagulation tests is unlikely to lead to a change in diagnostic or treatment strategies.

Given this limitation, a proposed scheme based on the calculated pretest and posttest probabilities in conjunction with patient-related factors for each coagulopathy is given in the Figure. Because data are lacking for estimating pretest (and therefore posttest) probabilities for the hereditary coagulation defects in ischemic stroke patients, the left column lists the general features of these disorders. The testing strategy for these potential coagulopathies is based on evidence not from controlled trials but from the practical issues related to coagulation testing as recommended by coagulation experts. The middle and right columns include the cumulative pretest probabilities and associated common features for ACL/LA (primary or SLE-associated APL syndrome) and APCR/FVL/prothrombin (FII) mutations, respectively.

### Discussion

This systematic review of the literature shows that the prevalence of inherited deficiencies of PC, PS, ATIII, or plasminogen is low in unselected ischemic stroke patients. The prevalence of mutations of FVL or prothrombin genes in ischemic stroke patients is also low, but there may be an association between these deficiencies and ischemic stroke in younger patients. Before one reaches definitive conclusions...
of any association between these 2 mutations and ischemic stroke, additional well-designed prospective studies are required. The prevalence ranges reported for APL antibodies in ischemic stroke patients were quite variable, with more than half of the controlled studies showing a significant association with ischemic stroke. However, concurrent atherosclerotic risk factors make the significance of this association difficult to interpret, and further prospective clinical trials are needed to assess the risk of recurrent stroke in these patients. The posttest probabilities for ACL, LA, and APCR detection are related to the corresponding pretest probabilities and the specificities of the screening tests (Table 4).

Despite the systematic nature of this review, combining heterogeneous studies, ie, those with varying patient populations, leads to limitations in interpretation of the results. Including only studies of unselected ischemic stroke patients would have provided conclusions that are more generalizable. However, combining available prevalence studies of both selected and unselected patients provides larger numbers for calculating the estimates, and many clinicians select patients in a similar manner when justifying further testing.

Another limitation is that the sensitivity and specificity measurements, crucial for the calculation of posttest probabilities, were available for only a few diagnostic studies. Most of these studies did not meet the methodological standards considered necessary for diagnostic test research. Documentation of the spectrum of patients tested is an important methodological consideration, and the studies of ACL and LA diagnostic tests were limited to patients with secondary APL syndrome in the setting of SLE or to patients with primary APL syndrome. To our knowledge, these measurements have not been performed in unselected populations of seropositive patients with other atherosclerotic risk factors for ischemic stroke. Adequate sample size is another methodological standard, and 2 studies of ACL/LA tests made assessments using only a small number of patients. The results of studies with ≤30 patients will often produce sensitivity and specificity measurements with wide CIs and poorer test accuracy. Test reproducibility is a very important methodological consideration, and this is a significant problem in the diagnostic testing for ACL. Although the cited studies used an average of multiple test results from the same laboratory, the potential for interlaboratory variability was not addressed.

Information that could potentially increase the pretest probability includes clinical or historical factors, physical examination findings, and other diagnostic test results. Because of the low prevalence of coagulopathies in the general population of stroke patients, these factors formed the basis for development of the scheme for coagulation testing shown in the Figure. For example, the pretest probability of a positive LA and/or ACL may be 40% to 60% in a 30-year-old woman admitted with an ischemic stroke who has a history of miscarriages and marantic endocarditis (3 features of the APL syndrome; Figure). In contrast, the pretest probability of LA and/or ACL may be only 20% in a 65-year-old woman with an ischemic stroke who has 1 or 2 traditional stroke risk factors. The screening ELISA produces a better yield for the 30-year-old woman with 3 features of APL syndrome because these historical features increase her pretest probability, thereby resulting in a posttest probability of 60% (Table 4).

Deciding on a pretest probability estimate for an individual patient is difficult, but studies have shown that this skill can be improved with clinical experience in the target disorder or with the use of nomograms or computerized algorithms. Another useful method is to choose a range of pretest probabilities and calculate a posttest probability for the middle, upper, and lower ranges. This type of sensitivity analysis can help the clinician to appreciate the spectrum in which the coagulation test might be useful. Once the decision is made to pursue the diagnosis, selecting a test with a high specificity will result in a high posttest probability. The diagnostic yield in this situation is optimized by the use of the quantitative approach of pretest and posttest probabilities.

Conclusion

Because of the lack of strong evidence supporting an association between most coagulopathies and ischemic stroke in general populations of patients, the difficulty with interpretation of these tests in the setting of an acute ischemic stroke, and the methodological problems with the reviewed prevalence studies, our conclusion is that coagulation tests are often of little value in the evaluation of general patients with ischemic stroke. On the basis of the current data, the low diagnostic yield necessitates careful consideration before these tests are obtained. Additional prospective, controlled studies of unselected ischemic stroke patients are needed to better assess the roles of hereditary coagulation defects, APCR/FVL, prothrombin gene mutation, and ACL/LA in the etiology of ischemic stroke. The suggested scheme developed on the basis of the results of this comprehensive literature review should be further validated in prospective studies.
### Appendix 1

**TABLE 5. Prevalence of APCR and Prothrombin Mutation in Ischemic Stroke**

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Study Design</th>
<th>Age, Range or Mean ± SD, y</th>
<th>Total No. Stroke Pts</th>
<th>Test Type</th>
<th>Cases, n (%)</th>
<th>Controls, n (%)</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lalouschek/1999</td>
<td>Case-control</td>
<td>28 to 89</td>
<td>81</td>
<td>FVL</td>
<td>10 (12.3)</td>
<td>4 (4.9)</td>
<td>2.75 (0.83–9.17)</td>
<td>0.09</td>
</tr>
<tr>
<td>McColl/1999</td>
<td>Case-control</td>
<td>2 mo to 14 y</td>
<td>37</td>
<td>FVL</td>
<td>2 (5.7)</td>
<td>5 (2.2)</td>
<td>2.5 (0.5–13.5)</td>
<td>NS</td>
</tr>
<tr>
<td>Margaglione/1999</td>
<td>Case-control</td>
<td>3 to 50</td>
<td>202</td>
<td>FVL</td>
<td>30 (14.9)</td>
<td>43 (4.2)</td>
<td>2.56 (1.28–5.14)</td>
<td>0.0081</td>
</tr>
<tr>
<td>Mohanty/1999</td>
<td>Case-control</td>
<td>4 to 42</td>
<td>37†</td>
<td>FVL</td>
<td>2 (5.7)</td>
<td>5 (2.2)</td>
<td>2.5 (0.5–13.5)</td>
<td>NS</td>
</tr>
<tr>
<td>Cushman/1998</td>
<td>Case-control</td>
<td>3.6 ± 7.8</td>
<td>20</td>
<td>FVL</td>
<td>3 (15)</td>
<td>2 (10)</td>
<td>0.77 (0.15–3.9)</td>
<td>NS</td>
</tr>
<tr>
<td>Halbmayer/1998</td>
<td>Case-control</td>
<td>38 to 44</td>
<td>104</td>
<td>FVL</td>
<td>8 (8)</td>
<td>8 (8)</td>
<td>1.0 (0.25–3.9)</td>
<td>NS</td>
</tr>
<tr>
<td>Nabi/1998</td>
<td>Case-control</td>
<td>&lt;45</td>
<td>225</td>
<td>FVL</td>
<td>11 (5)</td>
<td>11 (5)</td>
<td>1.0 (0.25–3.9)</td>
<td>NS</td>
</tr>
<tr>
<td>Zenz/1998</td>
<td>Case-control</td>
<td>5 to 10</td>
<td>33</td>
<td>FVL</td>
<td>6 (18)</td>
<td>7 (18)</td>
<td>1.0 (0.25–3.9)</td>
<td>NS</td>
</tr>
<tr>
<td>Arruda/1997</td>
<td>Cross-section</td>
<td>17 to 56</td>
<td>70</td>
<td>FVL</td>
<td>6 (12)</td>
<td>5 (12)</td>
<td>2.56 (1.28–5.14)</td>
<td>0.0081</td>
</tr>
<tr>
<td>Bentolia/1997</td>
<td>Case-control</td>
<td>18 to 49</td>
<td>125</td>
<td>FVL</td>
<td>8 (6.4)</td>
<td>5 (3.7)</td>
<td>1.8 (0.56–5.54)</td>
<td>NS</td>
</tr>
<tr>
<td>Corral/1997</td>
<td>Case-control</td>
<td>24 to 88</td>
<td>104</td>
<td>FVL</td>
<td>1 (1)</td>
<td>2 (1.9)</td>
<td>0.5 (0.04–5.5)</td>
<td>NS</td>
</tr>
<tr>
<td>Halbmayer/1997</td>
<td>Case-control</td>
<td>45 ± 11</td>
<td>112†</td>
<td>FVL</td>
<td>8 (7)</td>
<td>6 (5)</td>
<td>0.83 (0.28–2.51)</td>
<td>NS</td>
</tr>
<tr>
<td>Ferraresi/1997</td>
<td>Case-control</td>
<td>Unknown</td>
<td>105</td>
<td>FVL</td>
<td>2 (2)</td>
<td>3 (3)</td>
<td>0.77 (0.14–4.3)</td>
<td>NS</td>
</tr>
<tr>
<td>Iniesta/1997</td>
<td>Case-control</td>
<td>27 to 88</td>
<td>125</td>
<td>FVL</td>
<td>4 (3.2)</td>
<td>3 (3.2)</td>
<td>0.82 (0.25–3.4)</td>
<td>NS</td>
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<tr>
<td>Martinelli/1997</td>
<td>Case-control</td>
<td>43 ± 13</td>
<td>155</td>
<td>FVL</td>
<td>5 (3.2)</td>
<td>2 (1.3)</td>
<td>2.5 (0.35–13.4)</td>
<td>NS</td>
</tr>
<tr>
<td>Rigoli/1997</td>
<td>Case-control</td>
<td>66.3</td>
<td>321†</td>
<td>FVL</td>
<td>17 (5.3)</td>
<td>14 (3.3)</td>
<td>1.7 (0.35–13.4)</td>
<td>NS</td>
</tr>
<tr>
<td>Sanchez/1997</td>
<td>Case-control</td>
<td>6 to 61</td>
<td>66†</td>
<td>FVL</td>
<td>7 (3)</td>
<td>5 (3.2)</td>
<td>1.72 (0.39–7.52)</td>
<td>0.3589</td>
</tr>
<tr>
<td>Tosetto/1997</td>
<td>Case-control</td>
<td>17 to 45</td>
<td>23</td>
<td>FVL</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1.0 (0.5–2.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Press/1996</td>
<td>Case-control</td>
<td>64 ± 9</td>
<td>161†</td>
<td>FVL</td>
<td>4 (2.5)</td>
<td>2 (0.8)</td>
<td>1.0 (0.25–3.9)</td>
<td>NS</td>
</tr>
<tr>
<td>Albucher/1996</td>
<td>Case-control</td>
<td>18 to 45</td>
<td>30†</td>
<td>FVL</td>
<td>3 (10)</td>
<td>1 (3.2)</td>
<td>2.5 (0.35–13.4)</td>
<td>NS</td>
</tr>
<tr>
<td>Fisher/1996</td>
<td>Case-control</td>
<td>57 ± 11</td>
<td>63</td>
<td>FVL</td>
<td>5 (7.5)</td>
<td>3 (4.5)</td>
<td>1.72 (0.39–7.52)</td>
<td>0.3589</td>
</tr>
<tr>
<td>van der Bom/1996</td>
<td>Cross-section</td>
<td>&gt;55</td>
<td>107</td>
<td>APCR</td>
<td>6 (9.5)</td>
<td>5 (7.5)</td>
<td>1.1 (0.6–2.3)</td>
<td>NS</td>
</tr>
<tr>
<td>De Lucia/1996</td>
<td>Case-control</td>
<td>20 to 45</td>
<td>50</td>
<td>APCR</td>
<td>6 (9.5)</td>
<td>5 (7.5)</td>
<td>1.1 (0.6–2.3)</td>
<td>NS</td>
</tr>
<tr>
<td>Landi/1996</td>
<td>Case-control</td>
<td>5 to 44</td>
<td>95</td>
<td>APCR</td>
<td>6 (9.5)</td>
<td>5 (7.5)</td>
<td>1.1 (0.6–2.3)</td>
<td>NS</td>
</tr>
<tr>
<td>Catto/1993</td>
<td>Case-control</td>
<td>65 to 80</td>
<td>386†</td>
<td>FVL</td>
<td>16 (4.1)</td>
<td>14 (5.7)</td>
<td>0.72 (0.34–1.5)</td>
<td>NS</td>
</tr>
<tr>
<td>Ticiti/1995</td>
<td>Case-control</td>
<td>18 to 84</td>
<td>209</td>
<td>APCR</td>
<td>9 (3.3)</td>
<td>2 (0.8)</td>
<td>1.0 (0.4–2.8)</td>
<td>NS</td>
</tr>
<tr>
<td>Kontul/1996</td>
<td>Case-control</td>
<td>40 to 84</td>
<td>209</td>
<td>APCR</td>
<td>5 (5.5)</td>
<td>9 (6.5)</td>
<td>1.5 (0.8–2.9)</td>
<td>NS</td>
</tr>
<tr>
<td>Cushman/1994</td>
<td>Case-control</td>
<td>&lt;55</td>
<td>15†</td>
<td>APCR</td>
<td>6 (9.5)</td>
<td>5 (7.5)</td>
<td>1.1 (0.6–2.3)</td>
<td>NS</td>
</tr>
<tr>
<td>Halbmayer/1993</td>
<td>Case-control</td>
<td>47 ± 13</td>
<td>30†</td>
<td>APCR</td>
<td>6 (9.5)</td>
<td>5 (7.5)</td>
<td>1.1 (0.6–2.3)</td>
<td>NS</td>
</tr>
</tbody>
</table>

APC-F: indicates APC assay specific for FVL mutation; FII, prothrombin mutation. APCR: Total patients (pts), n = 3439; cases, n = 233; cumulative prevalence rate = 6.8%; total pts aged <50, n = 978; cases, n = 104; cumulative prevalence rate = 10.6%. Prothrombin mutation: Total pts, n = 1215; cases, n = 55; cumulative prevalence rate = 4.5%; total pts aged <50, n = 560; cases, n = 32; cumulative prevalence rate = 5.7%.

*Excluded patients with hypertension, diabetes, hypercholesterolemia, or “traditional stroke risk factors.”
†No genetic testing.
§No genetic testing.
||Cerebrovascular disease, not all patients with ischemic stroke.
Appendix 2

TABLE 6. Prevalence of APL Antibodies in Ischemic Stroke

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Study Design</th>
<th>Age, Range or Mean±SD, y</th>
<th>Total No. Stroke Pts</th>
<th>Test Type</th>
<th>Cases, n (%)</th>
<th>Controls, n (%)</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tuhrin/1999</td>
<td>Case-control</td>
<td>72±11</td>
<td>524*</td>
<td>ACL</td>
<td>180 (34)</td>
<td>111 (11)</td>
<td>4.0 (3.0–5.5)</td>
<td>Not given</td>
</tr>
<tr>
<td>Metz/1998</td>
<td>Case-control</td>
<td>29 to 91</td>
<td>151</td>
<td>ACL</td>
<td>12 (8)</td>
<td>9 (8.3)</td>
<td>0.8 (0.4–1.2)</td>
<td>NS</td>
</tr>
<tr>
<td>D’Olhaberriague/1998</td>
<td>Case-control</td>
<td>64±14</td>
<td>300*</td>
<td>ACL</td>
<td>78 (26)</td>
<td>25 (17)</td>
<td>1.17 (1.04–2.83)</td>
<td>0.029</td>
</tr>
<tr>
<td>Nagaraja/1997</td>
<td>Case-control</td>
<td>&lt;40</td>
<td>60</td>
<td>ACL</td>
<td>14 (23)</td>
<td>2 (3)</td>
<td>8.83 (1.9–40.8)</td>
<td>0.002</td>
</tr>
<tr>
<td>Camerlingo/1995</td>
<td>Cross-section</td>
<td>26 to 88</td>
<td>100</td>
<td>ACL</td>
<td>26 (26)</td>
<td>0 (0)</td>
<td>. . .</td>
<td>0.007</td>
</tr>
<tr>
<td>Muir/1994</td>
<td>Case-control</td>
<td>25 to 96</td>
<td>262*</td>
<td>ACL</td>
<td>33 (13)</td>
<td>18 (8)</td>
<td>1.67 (0.91–3.05)</td>
<td>NS</td>
</tr>
<tr>
<td>APASS/1993</td>
<td>Cross-section</td>
<td>25 to 93</td>
<td>248</td>
<td>ACL</td>
<td>24 (9.7)</td>
<td>11 (4.3)</td>
<td>2.31 (1.09–3.08)</td>
<td>0.024</td>
</tr>
<tr>
<td>de Jong/1993</td>
<td>Case-control</td>
<td>22 to 52</td>
<td>44</td>
<td>ACL IgG</td>
<td>1 (2.3)</td>
<td>3 (6.5)</td>
<td>0.3 (0.03–3.3)</td>
<td>NS</td>
</tr>
<tr>
<td>Ginsburg/1992</td>
<td>Nested case-control</td>
<td>40 to 84</td>
<td>100</td>
<td>ACL</td>
<td>18 (14)</td>
<td>14 (14)</td>
<td>1.35 (0.6–3.08)</td>
<td>NS</td>
</tr>
<tr>
<td>Nencini/1992</td>
<td>Prospective cohort</td>
<td>15 to 44</td>
<td>55*</td>
<td>ACL</td>
<td>6 (11)</td>
<td>1 (2)</td>
<td>6.7 (0.78–57.9)</td>
<td>0.054</td>
</tr>
<tr>
<td>Muir/1994</td>
<td>Case-control</td>
<td>25 to 96</td>
<td>262*</td>
<td>ACL</td>
<td>33 (13)</td>
<td>18 (8)</td>
<td>1.67 (0.91–3.05)</td>
<td>NS</td>
</tr>
<tr>
<td>APASS/1993</td>
<td>Cross-section</td>
<td>25 to 93</td>
<td>248</td>
<td>ACL</td>
<td>24 (9.7)</td>
<td>11 (4.3)</td>
<td>2.31 (1.09–3.08)</td>
<td>0.024</td>
</tr>
<tr>
<td>de Jong/1993</td>
<td>Case-control</td>
<td>22 to 52</td>
<td>44</td>
<td>ACL IgG</td>
<td>1 (2.3)</td>
<td>3 (6.5)</td>
<td>0.3 (0.03–3.3)</td>
<td>NS</td>
</tr>
<tr>
<td>Ginsburg/1992</td>
<td>Nested case-control</td>
<td>40 to 84</td>
<td>100</td>
<td>ACL</td>
<td>18 (14)</td>
<td>14 (14)</td>
<td>1.35 (0.6–3.08)</td>
<td>NS</td>
</tr>
<tr>
<td>Nencini/1992</td>
<td>Prospective cohort</td>
<td>15 to 44</td>
<td>55*</td>
<td>ACL</td>
<td>6 (11)</td>
<td>1 (2)</td>
<td>6.7 (0.78–57.9)</td>
<td>0.054</td>
</tr>
<tr>
<td>Sletnes/1992</td>
<td>Prospective cohort</td>
<td>32 to 75</td>
<td>595#**</td>
<td>ACL IgG</td>
<td>44 (7.4)</td>
<td>7 (4.4)</td>
<td>0.95 (0.7–1.29)</td>
<td>NS</td>
</tr>
<tr>
<td>Hess/1991</td>
<td>Cross-section</td>
<td>58±12</td>
<td>110</td>
<td>ACL IgG</td>
<td>9 (8.2)</td>
<td>2 (1.6)</td>
<td>5.3 (1.13–25.3)</td>
<td>0.018</td>
</tr>
<tr>
<td>Chavarraty/1991</td>
<td>Prospective cohort</td>
<td>60 to 94</td>
<td>100</td>
<td>ACL</td>
<td>21 (21)</td>
<td>0 (0)</td>
<td>. . .</td>
<td>Not given</td>
</tr>
<tr>
<td>Montalban/1991</td>
<td>Case-control</td>
<td>14 to 88</td>
<td>146</td>
<td>ACL</td>
<td>6 (4.1)</td>
<td>0 (0)</td>
<td>. . .</td>
<td>Not given</td>
</tr>
<tr>
<td>Brey/1990</td>
<td>Case-control</td>
<td>&lt;50</td>
<td>46</td>
<td>ACL or LA†</td>
<td>21 (45.6)</td>
<td>2 (7.7)</td>
<td>10.1 (2.1–47.7)</td>
<td>Not given</td>
</tr>
</tbody>
</table>

NS indicates not significant or P>0.05. ACL: Total patients (pts), n=2841; ACL cases, n=493; cumulative prevalence rate=17.4%; total patients aged ≥50, n=205; cases, n=42; cumulative prevalence=20.5%. LA: Total pts, n=496; LA cases, n=24; cumulative prevalence rate=4.8%; total pts aged ≥50, n=99; LA cases, n=8; cumulative prevalence rate=8.1%.

*Unmatched controls.
†OR adjusted for age and stroke risk factors.
‡LA not confirmed.
§Controls had other neurological diseases.
‖ACL/LA measured ≤6 hours of onset of ischemic stroke.
¶Plasma collected in 1982 and stored at 60°C.
§Controls had other neurological diseases.
**Placebo group of Warfarin Reinfarction Study.

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References


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Cheryl D. Bushnell and Larry B. Goldstein

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