Anticardiolipin Antibodies and Risk of Ischemic Stroke and Transient Ischemic Attack

The Framingham Cohort and Offspring Study

Vallabh Janardhan, MD; Philip A. Wolf, MD; Carlos S. Kase, MD; Joseph M. Massaro, PhD; Ralph B. D’Agostino, PhD; Carl Franzblau, PhD; Peter W.F. Wilson, MD

Background and Purpose—The role of anticardiolipin antibodies (aCLs) as novel risk factors for ischemic stroke and transient ischemic attacks (TIAs) has been a matter of debate. Prior cohort studies included only selected subjects, mostly men. We related serum concentrations of aCLs to incident first ischemic stroke/TIA among men and women in the Framingham Heart Study cohort and offspring.

Methods—There were a total of 2712 women (mean age, 59.3 years) and 2262 men (mean age, 58.3 years) free of stroke/TIA at the time of their baseline examinations. An enzyme immunoassay was used to measure aCLs. Optical density of the sample serum compared with the reference serum was defined as the aCL screening ratio (aCL SR). Analyses were based on sex-specific aCL SR quartiles and individual ratios.

Results—During the 11-year follow-up, 222 ischemic strokes/TIAs occurred. In multivariate analysis, after adjustment for age, prior cardiovascular disease, systolic blood pressure, diabetes, smoking, C-reactive protein, and total and high-density lipoprotein cholesterol levels, an aCL SR of 0.4 (78% of sample) was significantly associated with an increased risk of ischemic stroke/TIA for women (hazard ratio [HR], 2.6; 95% confidence interval [CI], 1.3 to 5.4; absolute risk, 3.2%; 95% CI, 2.2 to 4.3) but not in men (HR, 1.3; 95% CI, 0.7 to 2.4; absolute risk, 4.5%; 95% CI, 3.0 to 6.0). Similar results were obtained when the higher 3 aCL SR quartiles were compared with the lowest.

Conclusions—Elevated serum concentrations of aCLs, independently of other cardiovascular risk factors, significantly predict the risk of future ischemic stroke and TIA in women but not in men. (Stroke. 2004;35:GGG-GGG.)

Key Words: antibodies, anticardiolipin ■ antibodies, antiphospholipid ■ cerebral ischemia, transient ■ risk factors ■ stroke, ischemic

Antiphospholipid antibodies (aPAs) are a heterogeneous group of immunoglobulins directed against negatively charged phospholipids (such as cardiolipin, phosphatidyl serine, phosphatidyl inositol), phospholipid-protein complexes, or plasma proteins (such as B2-glycoprotein I). Anticardiolipin antibodies (aCLs) have been the most widely studied of the aPAs. Although aCLs were initially identified as serodiagnostic markers for syphilis and subsequently noted to be present in patients with systemic lupus erythematosus (SLE), they have become a subject of great interest because of their presence in healthy individuals and their association with arterial/venous thrombosis and recurrent spontaneous abortions in an autoimmune syndrome called the antiphospholipid syndrome.

The role of aCLs as novel risk factors for thrombotic events, especially ischemic stroke and transient ischemic attacks (TIAs), remains a matter of debate. Several prospective studies have suggested that aCLs are not significant risk factors for stroke/TIA, although a more recent cohort study has shown that aCLs are independent risk factors for stroke.

To address the issue of aCL and risk of first ischemic stroke or TIA, the serum concentration of aCL was measured in members of the Framingham Heart Study original cohort in 1980 and offspring in 1991. Baseline serum concentrations of aCLs were related to incident first ischemic stroke or TIA in these subjects during an 11-year follow-up period. The prevalence of aCLs in this population-based cohort and the relationship of aCLs to known cerebrovascular risk factors were also addressed.

Subjects and Methods

Subjects and Definition of Clinical Outcome

The Framingham Heart Study was begun in 1948 to identify risk factors for cardiovascular disease (CVD) and to evaluate the conse-
quences of CVD in a longitudinal community-based population sample. Study design, response rates, and completeness of follow-up have been reported elsewhere. In the present study, we related aCL levels at examination 16 (1980) in the original cohort and examination 5 (1991) in the offspring cohort to ischemic stroke or TIA incidence during follow-up. At the time of the baseline examinations, nonfasting blood specimens were obtained from 562 men and 815 women of the original cohort and from 1700 men and 1897 women of the offspring cohort who were free of stroke or TIA, and the serum aliquots were stored at $-20^\circ \text{C}$ until mid-1997. Subjects were followed up over an 11-year period for the development of incident ischemic stroke or TIA. Events were entered as TIs in the database only when there were no subsequent strokes in these subjects during follow-up. The criteria for defining ischemic stroke and TIA in the subjects have been discussed previously.

**Assessment of the Risk Factors**

In addition to aCL screening ratio (aCL SR), other baseline covariates assessed for the present analysis included age, sex, prior CVD, systolic blood pressure, diabetes, cigarette smoking, plasma C-reactive protein (CRP), and total and high-density lipoprotein (HDL) cholesterol levels. Diabetes was defined as use of insulin preparations or oral hypoglycemic agents or any recorded blood glucose level of $\geq 126 \text{ mg/dL}$. Definitions for the other baseline covariates and methods of assessment have been discussed previously.

**Laboratory Procedures**

Serum concentrations of aCLs were measured with a commercial anticardiolipin enzyme-linked immunoassay (ELISA) kit (Hemagen Diagnostics). Briefly, a stabilized preparation of diphosphatidyl glycerol (cardiolipin) coated onto the surface of the microplate wells served as the antigen. Each patient sample was diluted (1:51 dilution). Calibrator serum, controls, and diluted patient samples were placed into microplate wells that were incubated for 30 minutes at room temperature and then washed. The microplate wells were incubated for another 10 minutes with goat anti-human antibodies labeled with horseradish peroxidase. The horseradish peroxidase–conjugated antibody preparation would detect human IgG, IgM, and/or IgA. If results were positive, a stable 3-part complex was formed. This complex consisted of horseradish peroxidase–conjugated anti-human antibody bound to human aCL, which was bound to cardiolipin stabilized on the surface of the microplate wells. This complex was detected by adding a chromogenic substrate. The enzymatic reaction was stopped by the addition of a stopping agent.

**Figure 1.** Prevalence of aCL positivity increases with age among men and women in the Framingham Cohort and Offspring Study.
solution. The degree of color development in each well is proportional to the concentration of aCL in each serum sample. The optical density (OD) of the patient sample was quantified in an ELISA plate reader at a wavelength of 450 nm.

In the present study, the OD of the patient sample serum (measured with ELISA) compared with the OD of the reference serum used for this kit had an aCL level of 15 GPL/MPL/APL units and was standardized to the Antiphospholipid Standardization Laboratory Standards, the “Harris Standards.”

On the basis of the manufacturer’s instructions (Hemagen Diagnostics), an arbitrary cutoff was used to define aCL positivity, namely an aCL SR of >1.0 (ie, OD of patient serum sample is higher than that of the reference sample).

Statistical Analyses
Analyses were performed separately for men and women by use of sex-specific quartiles (quartiles 1 to 4 [Q1 to Q4]) of aCL SR (men: Q1=0.00 to 0.429, Q2=0.430 to 0.609, Q3=0.610 to 0.899, and Q4=0.9 to 11.9; women: Q1=0.00 to 0.430, Q2=0.430 to 0.606, Q3=0.607 to 0.870, and Q4=0.871 to 11.0).

Unadjusted, bivariate (adjusted for age), and multivariate (adjusted for age, prior CVD, systolic blood pressure, diabetes, cigarette smoking, plasma CRP, and total and HDL cholesterol) hazard ratio (HR) estimates (with 95% confidence intervals [CIs]) for aCL SR quartiles were generated by Cox proportional-hazards modeling with aCL SR quartiles as the independent variable. These HRs were derived by using the lowest quartile (Q1) as the referent group. Similar analyses were performed for each aCL SR starting from ≥0.1.

Results
Study participant characteristics were recorded at the time of the baseline examinations in the original cohort and offspring (Table 1). The original cohort (n=1377) and offspring (n=3597) were followed up for 11 years (mean follow-up: cohort, 9.6 years; offspring, 7.2 years). During this time, first cerebrovascular events (ischemic stroke or TIA) occurred in 4.5% (222 of 4974) of the study participants in the original cohort and offspring combined; 116 of the 222 ischemic strokes/TIAs occurred in women. In the original cohort, first cerebrovascular events (ischemic stroke or TIA) occurred in 11.3% of the study participants (155 of 1377); 88 of the 155 ischemic strokes/TIAs occurred in women. In the offspring, first cerebrovascular events (ischemic stroke or TIA) occurred in 1.9% of the study participants (67 of 3597); 28 of the 67 ischemic strokes/TIAs occurred in women. The prevalence of aCL positivity in the Framingham original cohort and offspring combined was 19.7% in men (446 of 2262) and 17.6% in women (476 of 2712). The prevalence of aCL positivity increased with age in men and women (Figure 1) and was higher in subjects with first ischemic stroke or TIA (Figure 2). The relative risks of first ischemic stroke or TIA with increasing quartiles of baseline aCL SR are shown in Table 2. The highest quartiles (Q4) in men (aCL SR range, 0.9 to 11.9) and women (aCL SR range, 0.871 to 11.0) included all patients who were aCL positive (aCL SR >1.0). When the relative risk and absolute risk of ischemic stroke or TIA for aCL SR from 0.1 to 1.0 were analyzed, a threshold effect (aCL SR cutoff ≥0.4) rather than a dose-response relationship was noted (Tables 3 and 4). In the present study (cohort and offspring combined), the risk of ischemic stroke/TIA (aCL SR >0.4) also increased with the duration of follow-up in men and women (data not shown).

![Figure 2. Prevalence of aCL positivity among men and women, with and without first incident ischemic stroke or TIA (original cohort and offspring combined), in the Framingham Cohort and Offspring Study.](image-url)

**Figure 2.** Prevalence of aCL positivity among men and women, with and without first incident ischemic stroke or TIA (original cohort and offspring combined), in the Framingham Cohort and Offspring Study.

**TABLE 2. Relative Risk of Incident Ischemic Stroke or TIA in the Original Cohort and Offspring Combined According to Serum Concentration of aCL**

<table>
<thead>
<tr>
<th>Adjustment</th>
<th>Q1 HR†</th>
<th>Q1 HR (95% CI)</th>
<th>P</th>
<th>Q2 HR (95% CI)</th>
<th>P</th>
<th>Q3 HR (95% CI)</th>
<th>P</th>
<th>Q4 HR (95% CI)</th>
<th>P</th>
<th>Q2, Q3, Q4* P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>1.0</td>
<td>1.4 (0.7–2.7)</td>
<td>0.341</td>
<td>1.8 (0.9–3.3)</td>
<td>0.085</td>
<td>2.1 (1.1–3.9)</td>
<td>0.018</td>
<td>1.8 (1.0–3.1)</td>
<td>0.051</td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>1.0</td>
<td>2.1 (1.0–4.0)</td>
<td>0.038</td>
<td>2.4 (1.2–4.6)</td>
<td>0.011</td>
<td>2.9 (1.5–5.4)</td>
<td>0.001</td>
<td>2.4 (1.3–4.4)</td>
<td>0.004</td>
<td></td>
</tr>
<tr>
<td>Age adjusted</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>1.0</td>
<td>1.2 (0.6–2.3)</td>
<td>0.659</td>
<td>1.3 (0.7–2.4)</td>
<td>0.483</td>
<td>1.4 (0.7–2.6)</td>
<td>0.298</td>
<td>1.3 (0.7–2.3)</td>
<td>0.401</td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>1.0</td>
<td>1.8 (0.9–3.6)</td>
<td>0.080</td>
<td>1.9 (1.0–3.8)</td>
<td>0.050</td>
<td>1.8 (1.0–3.5)</td>
<td>0.065</td>
<td>1.9 (1.0–3.4)</td>
<td>0.041</td>
<td></td>
</tr>
<tr>
<td>Multivariate</td>
<td></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>1.0</td>
<td>1.2 (0.6–2.4)</td>
<td>0.626</td>
<td>1.3 (0.7–2.5)</td>
<td>0.428</td>
<td>1.4 (0.8–2.7)</td>
<td>0.277</td>
<td>1.3 (0.7–2.3)</td>
<td>0.357</td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>1.0</td>
<td>2.0 (1.0–3.9)</td>
<td>0.056</td>
<td>1.9 (1.0–3.8)</td>
<td>0.054</td>
<td>1.9 (1.0–3.6)</td>
<td>0.058</td>
<td>1.9 (1.1–3.5)</td>
<td>0.035</td>
<td></td>
</tr>
</tbody>
</table>

†In calculation of HRs, Q1 was used as referent (HR=1), and other quartiles were compared to Q1.

*Compared with Q1.
Similar trends were obtained when the original cohort and offspring were analyzed separately (data not shown). The mean age for menopause in the Framingham original cohort and offspring was 52.5 years. Given the increased risk of ischemic stroke/TIA in women, we dichotomized women in the Framingham original cohort and offspring by age into ≥55 years of age (postmenopausal, n = 1724; 63.6%) and <55 years (premenopausal and perimenopausal, n = 988; 36.4%). In women <55 years of age, the unadjusted relative risk of first ischemic stroke/TIA was increased with aCL SR in Q3 (HR, 2.0; 95% CI, 0.2 to 22.2) and Q4 (HR, 3.0; 95% CI, 0.3 to 28.8) compared with those in Q1, but the results did not reach statistical significance. The unadjusted relative risk of first ischemic stroke or TIA was also increased in postmenopausal women with aCL SR in Q3 (HR, 2.0; 95% CI, 1.1 to 3.6; P = 0.024) and Q4 (HR, 1.9; 95% CI, 1.1 to 3.5; P = 0.031) compared with those in Q1. After multivariate adjustment, although not statistically significant, similar trends of increased risk remained.

Age was significantly associated with each increasing aCL SR quartile in both men (P < 0.001) and women (P < 0.001) (data not shown). Systolic blood pressure was significantly associated with each increasing aCL SR quartile in both men (P = 0.007) and women (P < 0.001) (data not shown). Presence of diabetes was also significantly associated with each increasing aCL SR quartile in both men (P = 0.0096) and women (P = 0.0001) (data not shown). Smoking status (P = 0.0001), serum total cholesterol levels (P = 0.045), and HDL cholesterol levels (P = 0.0114) were also significantly associated with each increasing aCL SR quartile, especially in women (data not shown). Plasma CRP concentration was significantly associated with each increasing aCL SR quartile in both men (Q1, 3.8 ± 6.8 μg/mL; Q2, 3.6 ± 5.6 μg/mL; Q3, 4.4 ± 7.2 μg/mL; Q4, 5.4 ± 7.8 μg/mL [mean ± SD]; P < 0.001) and women (Q1, 4.1 ± 6.6 μg/mL; Q2, 5.1 ± 11.9 μg/mL; Q3, 5.5 ± 10.8 μg/mL; Q4, 6.7 ± 15.4 μg/mL; P < 0.001).

### Discussion

aCLs have become a subject of great interest because they have also been shown to be present in healthy individuals. The prevalence of aCL ranges from 1% to 7% in young individuals to as high as 12% to 50% in healthy elders. In this large population-based cohort with long-term follow-up, we showed that the prevalence of aCL in subjects free of stroke or TIA is 19.7% in men and 17.6% in women and that the prevalence of aCL positivity increases with age in men and women. To the best of our knowledge, this is the first prospective population-based cohort study that has shown aCL to be an independent risk factor for ischemic stroke and TIA in women. We have also found aCL to be associated with other cardiovascular risk factors such as age, systolic blood pressure, diabetes, and plasma CRP.

Although some studies have suggested a dose-response relationship between aCL titers and stroke risk, the largest case-control study and a recent prospective study have suggested a threshold effect. In the present study, after multivariate adjustment, there was no evidence of a dose-response relationship, but a threshold effect was noted, and women with aCL SR > 0.4 had a significantly increased risk of incident first ischemic stroke or TIA (HR, 2.6; 95% CI, 1.3 to 5.4), with an absolute risk of 3.2% and an average yearly risk of 0.3%. Experimental studies on normal mice have shown an increased induction of aCLs in female compared

### Table 3: Relative Risk of Incident Ischemic Stroke or TIA in the Original Cohort and Offspring Combined According to Serum Concentration of aCL (Cutoff)

<table>
<thead>
<tr>
<th>aCL SR Cutoff (≥0.4)</th>
<th>Unadjusted</th>
<th>Age Adjusted</th>
<th>Multivariate Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men, n = 1754 (77.5%)*</td>
<td>1.8 (1.0–3.4)</td>
<td>1.3 (0.7–2.5)</td>
<td>1.3 (0.7–2.4)</td>
</tr>
<tr>
<td>Women, n = 2138 (78.8%)†</td>
<td>3.1 (1.5–6.5)</td>
<td>2.4 (1.2–5.0)</td>
<td>2.6 (1.3–5.4)</td>
</tr>
</tbody>
</table>

Multivariate adjustment was made for age, prior CVD, systolic blood pressure, diabetes, smoking, plasma CRP, and serum total and HDL cholesterol.

*Percentage of men with aCL SR > 0.4.
†Percentage of women with aCL SR > 0.4.

### Table 4: Absolute Risk of Incident Ischemic Stroke or TIA in the Original Cohort and Offspring Combined According to Serum Concentration of aCL (Cutoff)

<table>
<thead>
<tr>
<th>aCL SR Cutoff by Sex</th>
<th>Unadjusted</th>
<th>Age Adjusted</th>
<th>Multivariate Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>aCL SR ≤ 0.4, men, n = 508</td>
<td>4.5 (1.8–7.0)</td>
<td>4.3 (1.8–6.7)</td>
<td>3.4 (1.3–5.5)</td>
</tr>
<tr>
<td>aCL SR &gt; 0.4, men, n = 1754 (77.5%)†</td>
<td>8.0 (6.0–10.0)</td>
<td>5.7 (4.0–7.4)</td>
<td>4.5 (3.0–6.0)</td>
</tr>
<tr>
<td>aCL SR ≤ 0.4, women, n = 574</td>
<td>2.3 (0.7–3.9)</td>
<td>1.7 (0.5–2.8)</td>
<td>1.3 (0.3–2.2)</td>
</tr>
<tr>
<td>aCL SR &gt; 0.4, women, n = 2138 (78.8%)‡</td>
<td>7.1 (5.4–8.7)</td>
<td>4.0 (2.8–5.2)</td>
<td>3.2 (2.2–4.3)</td>
</tr>
</tbody>
</table>

Multivariate adjustment was made for age, prior CVD, systolic blood pressure, diabetes, smoking, plasma CRP, and serum total and HDL cholesterol.

*Percentage of men with aCL SR > 0.4.
†Percentage of women with aCL SR > 0.4.
‡Percentage of women with aCL SR > 0.4.

Absolute risk during 11-year follow-up (average yearly risk can be computed by dividing the absolute risk by 11).
with male mice. This finding is thought to be due to an estrogen effect in females rather than a suppressive effect from testosterone in males. This might partly explain the reason for the increased relative risk (HR) for ischemic stroke or TIA in women compared with men (significant) and in premenopausal and perimenopausal women compared with postmenopausal women (although not statistically significant because of the sample size of subjects <55 years of age) in this study.

aCL was associated with advancing age and total cholesterol in the Honolulu Heart Program. In the present study, similar results were obtained with regard to aCL and atherosclerotic risk factors such as advancing age (in both sexes), systolic blood pressure (in both sexes), and diabetes (in both sexes). aCL SR quartiles were also significantly associated with smoking status and serum total and HDL cholesterol levels in women. Plasma CRP is an independent novel risk factor for stroke and a marker for inflammation. In the present study, aCL SR quartiles were significantly associated with increasing plasma CRP concentration (in both sexes), suggesting that aCL and CRP may have similar mechanisms by which they promote vascular thrombosis.

One mechanism by which aCLs are associated with progression of atherothrombosis is their interaction with the endothelial cells. These cells have cell surface receptors called annexin II that can attract and bind to β2-glycoprotein I, which in turn can attract aPAs. This leads to endothelial cell activation, increased secretion of proinflammatory cytokines, release of tissue factor, and subsequent initiation of the coagulation cascade. These changes, along with endothelial dysfunction, eventually lead to a full-blown atheromatous lesion. It is unclear how long this process takes from induction of aCLs to development of a full-blown atheromatous lesion. In a recent prospective cohort study, the association between aCL and risk of stroke was strongest at 15 years of follow-up. Similar results were obtained in the present study, suggesting that there could be a time lag between induction of aCLs and subsequent stroke and possibly accounting in part for the fact that some subjects with aCL positivity developed ischemic strokes or TIAs while others did not.

Our findings of a high prevalence of aCLs in individuals free of stroke or TIA and the significantly increased risk of incident first ischemic stroke or TIA in women raise several issues. First, should subjects free of CVD be routinely screened for the presence of aCLs? Second, is there a role for prophylactic pharmacological therapy in these individuals as a means of primary prevention of stroke? In the Antiphospholipid Antibodies and Stroke Study (APASS), aPA positivity neither increased the risk of subsequent thromboembolic events nor generated a differential response to aspirin (325 mg/d) or adjusted-dose warfarin (target international normalized ratio ranged from 1.4 to 2.8) therapy (secondary prevention). Douketis et al. showed that low-intensity warfarin therapy (target international normalized ratio, 2.0 to 2.5) in patients with aPA and SLE is effective in suppressing coagulation activation and therefore may be effective in preventing thromboembolism (primary prevention). The results of the above study are being further addressed in a larger ongoing Canadian trial (PRECLUDE) that is evaluating the role of warfarin therapy (target international normalized ratio, 2.0 to 2.5) in the primary prevention of thromboembolism in SLE patients with aPA. At the present time, there is no proven therapy for the primary prevention of stroke or TIA in subjects with aCLs.

The present study has limitations. Our findings are based on a 1-time measurement of aCL, which may not fully and accurately reflect the status of the study subjects over the long follow-up period. Study participants were largely middle-aged to elderly men and women, which may limit the applicability of study results to younger men and women. The strengths of this study include the prospective population-based cohort study design with pre-event sampling of blood; large sample size; adequate duration of follow-up; use of a commercial aCL screening kit with standardized reference serum; statistical analyses adjusted for known cerebrovascular risk factors, including plasma CRP; and a study sample that is representative of the general population.

In conclusion, elevated serum concentrations of aCLs are independent risk markers for ischemic stroke and/or TIA in women. However, there currently is no specific proven therapy for prevention of ischemic stroke or TIA in subjects with aCL positivity.

**Acknowledgments**

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**References**


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