Antiphosphatidylserine Antibodies and Clinical Outcomes in Patients With Acute Ischemic Stroke

Xiaoqing Bu, MD*; Hao Peng, MD, PhD*; Chongke Zhong, MD; Tan Xu, MD, PhD; Tian Xu, MD, PhD; Yanbo Peng, MD, PhD; Chung-Shiuan Chen, MS; Jinchao Wang, MD; Zhong Ju, MD, PhD; Qunwei Li, MD; Deqin Geng, MD; Yingxian Sun, MD, PhD; Dongsheng Zhang, MD; Jintao Zhang, MD; Jing Chen, MD, MS; Yonghong Zhang, MD, PhD; Jiang He, MD, PhD

Background and Purpose—Antiphosphatidylserine antibodies (aPS) have been associated with the risk of ischemic stroke. However, it remains unclear whether aPS will influence clinical outcomes in patients with acute ischemic stroke.

Methods—A total of 3013 patients with acute ischemic stroke recruited from 26 hospitals across China from August 2009 to May 2013 were included in the study. The primary outcome was a combination of death and major disability (modified Rankin Scale score ≥3) at 3 months after stroke. Secondary outcomes included death, major disability, recurrent stroke, and vascular events.

Results—Composite outcome of death and major disability rates were 29.1% versus 23.9% in aPS-positive and aPS-negative groups. Compared with aPS-negative, adjusted odds ratios or hazard ratios (95% confidence interval) associated with aPS-positive were 1.35 (1.07–1.71), 1.63 (0.99–2.69), and 1.25 (0.98–1.59) for composite outcome of death or major disability, death, and major disability, respectively. For 1 interquartile range increase of aPS, the adjusted odds ratios or hazard ratios were 1.10 (1.01–1.20), 1.19 (1.05–1.35), and 1.05 (0.96–1.14), respectively. Adding aPS status to a model containing conventional risk factors improved risk prediction for composite outcome of death or major disability (net reclassification improvement index=11.3%, P=0.006; integrated discrimination improvement=0.2%, P=0.04). There was no significant association between aPS and risks of recurrent stroke and vascular events.

Conclusions—We found that positive aPS increased risks of death or major disability at 3 months after an acute ischemic stroke, suggesting that aPS might be a prognostic marker for ischemic stroke. (Stroke. 2016;47:2742-2748. DOI: 10.1161/STROKEAHA.116.013827.)

Key Words: antibodies, antiphospholipid • biomarkers • prognosis • stroke

Stroke is the leading cause of death and disabilities worldwide.1 Biomarkers to identify patients at high risk of poor clinical outcomes would assist the selection of patients for aggressive monitoring and therapeutic interventions. Antiphospholipid antibodies (aPLs) are a heterogeneous family of antibodies to phospholipids and phospholipid-binding proteins.2 The presence of these antibodies is the laboratory feature of antiphospholipid syndrome, an autoimmune disorder characterized by susceptibility to vascular thromboembolism or fetal loss.3 Anticardiolipin antibodies (aCL) and lupus anticoagulant antibodies were the most frequently studied members and had been associated with an increased risk of recurrent thrombo-occlusive events and death after stroke in some but not in all studies.4,5 Recently, studies suggest that antibodies directed against phosphatidylserine (antiphosphatidylserine antibodies [aPS]) may be a useful marker for the syndrome.6,11 Population-based studies showed an independent association of aPS with ischemic...
stroke. However, it remains unclear whether aPS will influence stroke outcomes. We aimed to examine the association of aPS with clinical outcomes in a large cohort of patients with acute ischemic stroke.

Methods

Participants
This study was drawn from the CATIS (China Antihypertensive Trial in Acute Ischemic Stroke), a randomized clinical trial conducted in 26 hospitals across China from August 2009 to May 2013. The CATIS design was described in detail elsewhere. In brief, a total of 4071 patients aged ≥22 years who had first-ever ischemic stroke confirmed by computed tomography or magnetic resonance imaging of the brain within 48 hours of symptom onset, and with a systolic blood pressure (BP) between 140 and <220 mmHg were recruited. Patients were randomly assigned to receive antihypertensive treatment (aimed at lowering systolic BP by 10%–25% within 24 hours after randomization, achieving BP <140/90 mmHg within 7 days, and maintaining this level during hospitalization) or to control group (no antihypertensive medications during hospitalization). Patients with a systolic BP ≥220 or diastolic BP ≥120 mmHg, severe heart failure, acute myocardial infarction or unstable angina, atrial fibrillation, aortic dissection, cerebrovascular stenosis, or resistant hypertension; those in a state of delirium during hospitalization) or to control group (no antihypertensive medications during hospitalization). Patients with a systolic BP ≥220 or diastolic BP ≥120 mmHg, severe heart failure, acute myocardial infarction or unstable angina, atrial fibrillation, aortic dissection, cerebrovascular stenosis, or resistant hypertension; those in a deep coma; and those treated with intravenous thrombolytic therapy were excluded. For present study, 1058 participants were excluded because they did not offer blood samples, or collected samples were hemolyzed in storage or transport, or failed to measure aPLs. Finally, 3013 participants were included in analysis. The study was approved by the Institutional Review Boards at Soochow University in China and Tulane University in the United States. Written consent was obtained from all study participants.

Measurements
Demographic characteristics and medical history were collected. Stroke severity was assessed using the National Institutes of Health Stroke Scale (NIHSS) by trained neurologists at baseline. Ischemic stroke was classified as large artery atherosclerosis (embolus/thrombosis), cardiac embolism (embolic), and small artery occlusion lacunar according to the symptoms and imaging data. Three BP measurements were conducted by trained nurses at baseline according to a common protocol adapted from procedures recommended by the American Heart Association.

Fasting blood samples were collected after at least 8 hours of fasting within 24 hours after admission. All blood samples were stored −80°C until test. Specimens were tested for aPS and aCL using the following ELISA kits: QUANTA Lite ACA IgG III (third generation) and QUANTA Lite Phosphatidylserine IgG. All ELISA assays were manufactured by INOVA Diagnostics, San Diego, CA. Results were reported in standard units (GPL for IgG-aCL and GPS for IgG-aPS). One GPL or GPS unit is equivalent to 1 ug/mL. Cutoff value for positive was IgG-aPS ≥11 GPL.

Outcome Assessment
The participants were followed up in person at month 3 by trained neurologists and nurses unaware of treatment assignment. The primary outcome was a combination of death and major disability (modified Rankin Scale score, 3–6). Secondary outcomes were death, major disability, recurrent fatal and nonfatal stroke, and vascular events (eg, vascular deaths, nonfatal stroke, nonfatal myocardial infarction, hospitalized and treated angina, hospitalized and treated congestive heart failure, and hospitalized and treated peripheral arterial disease). All deaths were confirmed by death certificates. Hospital data were abstracted for recurrent stroke and vascular events. The outcome assessment committee, blinded to treatment assignment, reviewed and adjudicated recurrent stroke and vascular events based on the criteria established in the ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial).

Statistical Analysis
All participants were categorized into 2 groups: aPS positive and aPS negative. Baseline characteristics were compared between the 2 groups using χ² tests, Student t tests, or Wilcoxon rank-sum tests as appropriate. Logistic regression and Cox proportional hazards models were used to analyze the association between aPS and study outcomes when appropriate. Ordinal logistic regression was used to estimate the association of aPS with a 1-U higher modified Rankin Scale score. Evidence of treatment-by-aPS interactions for each outcome was investigated by adding an interaction term (aPS×treatment) in the statistical models. Spline regression models were used to examine the shape of the association between aPS and outcomes by fitting a restricted cubic spline function with 4 knots (5th, 35th, 65th, and 95th percentiles). In the multivariable models, we adjusted for age, sex, baseline NIHSS scores (>4 versus ≤4, a conventional threshold for mild or minor stroke or as a continuous variable), time from stroke onset to hospitalization, systolic BP, smoking, drinking, diabetes mellitus, ischemic stroke subtypes, antihypertensive intervention, and baseline aCL levels. Net reclassification index and integrated discrimination improvement were calculated to evaluate the predictive value of adding aPS to conventional risk factors. All analyses were performed using SAS statistical software (version 9.3; Cary, NC). Two-tailed P<0.05 was considered to be statistically significant.

Results
Most baseline characteristics were balanced between participants who were assessed for aPS and those not assessed (Table I in the online-only Data Supplement). Of the 3013 assessed patients, 651 (21.6%) were classified as aPS positive and 2362 (78.4%) as aPS negative (Table I). Compared with aPS-negative patients, aPS-positive patients tended to be older, smokers, and drinkers, have higher levels of aPS and aCL, and higher frequencies of NIHSS >4. Other variables were similar between the 2 comparison groups (all P>0.05).

Within 3 months, 15 patients were lost to follow-up, 751 had a composite outcome of death or major disability (83 died), 53 developed a recurrent stroke, and 84 experienced vascular events (Table 2). Patients with positive aPS had higher risks of composite outcome of death or major disability, death, and major disability. After adjustment for possible confounders and baseline aCL, odds ratios or hazard ratios (95% confidence interval [CI]) associated with positive aPS were 1.35 (1.07–1.71), 1.63 (0.99–2.69), and 1.25 (0.98–1.59) for composite outcome of death or major disability, death, and major disability, respectively (Table 2, multivariable model 2). Ordinal logistic regression analyses did not find an independent association between aPS positivity and odds of a 1-U higher modified Rankin Scale score (Table 2). There were no significant associations between aPS status and recurrent stroke and vascular events. The results remained similar when NIHSS was further adjusted as a continuous variable (Table 2, multivariable model 3). Subgroup analyses found no significant heterogeneity for the primary outcome across trial arms and pathogenic stroke subtypes (Table II in the online-only Supplement Data). Statistical tests for interactions between aPS status and antihypertensive treatment on each study outcome were not significant (all P>0.05).

On continuous analyses, 1 interquartile range increase of aPS was associated with 10% and 19% increment in risks for composite outcome of death or major disability (adjusted odds ratio, 1.10 [95% CI, 1.01–1.20]) and death (adjusted hazard ratio, 1.19 [95% CI, 1.05–1.35]; Table 2, multivariable
The results remained statistically significant for composite outcome of death or major disability when NIHSS was adjusted as a continuous variable (Table 2, multivariable model 3). We did not find any evidence of interactions between aPS and antihypertensive intervention on all study outcomes (all \( P > 0.05 \)).

Multivariable spline regression models suggested a linear association between aPS titers and risks of composite outcome of death or major disability (\( P \) for linearity=0.03) and death (\( P \) for linearity=0.02; Figure). Serum aPS had no association with major disability, recurrent stroke, and vascular events (Figure; Figure I in the online-only Supplement Data).

Adding aPS to a logistic regression model consisting of conventional risk factors and aCL significantly improved risk prediction for composite outcome of death or major disability (Table 3). Adding aPS status (positive versus negative) to the conventional model improved category-free net reclassification index of 10.9\% (\( P = 0.006 \)) and integrated discrimination improvement was 0.2\% (\( P = 0.06 \)).

We also examined the association between aCL and clinical outcomes in patients with acute ischemic stroke (Table III in the online-only Data Supplement). Neither positive aCL (\( \geq 20 \) GPL) nor interquartile range of aCL increased risks of composite outcome of death or major disability, death, major disability, recurrent stroke, and vascular events (all \( P > 0.10 \)).

### Discussion

Our study found a significant association of baseline positive aPS with risks of composite outcome of death or major disability within 3 months after an acute ischemic stroke. This association was independent of established risk factors for stroke prognosis and baseline aCL levels. We also observed a linear association between aPS titers and risks of composite outcome of death or major disability. Furthermore, adding aPS to conventional risk factors improved risk prediction for the primary outcome. These findings indicated that aPS...
might be a valuable marker in prediction of stroke outcomes in patients with acute ischemic stroke.

Data from cohort studies on the association of aPS with death and disability after stroke are scarce. A small, prospective cohort study conducted in 410 ischemic stroke patients reported a significant association between positive aPS and death at 90 days, with an odds ratio of 1.77 (95% CI, 1.34–1.69), but not between aCL and study outcomes.22 Another retrospective cohort study conducted in 167 patients with TIA found that aPS were significantly associated with a composite outcome of stroke or death within 90 days (odds ratio, 16.3 [95% CI, 2.3–116.7]), and the association persisted after adjustment for covariates.23

Table 2. Odds Ratios or Hazard Ratios (95% Confidence Interval) of Clinical Outcomes According to aPS Status and 1 Interquartile Range

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>aPS Negative (n=2362)</th>
<th>aPS Positive (n=651)</th>
<th>Unadjusted Model</th>
<th>Multivariable Model 1</th>
<th>Multivariable Model 2</th>
<th>Multivariable Model 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR or HR (95% CI)</td>
<td>P Value</td>
<td>OR or HR (95% CI)</td>
<td>P Value</td>
<td>OR or HR (95% CI)</td>
<td>P Value</td>
</tr>
<tr>
<td>Death and major disability, n (%)*</td>
<td>562 (23.9)</td>
<td>189 (29.1)</td>
<td>1.30 (1.07–1.58)</td>
<td>0.008</td>
<td>1.24 (1.00–1.54)</td>
<td>0.05</td>
</tr>
<tr>
<td>Modified Rankin Scale, n (%)</td>
<td>0 (no symptoms)</td>
<td>434 (18.5)</td>
<td>121 (18.6)</td>
<td>1.81 (1.01–1.38)†</td>
<td>0.04</td>
<td>1.07 (0.92–1.26)†</td>
</tr>
<tr>
<td></td>
<td>1 (no significant disability)</td>
<td>811 (34.5)</td>
<td>198 (30.5)</td>
<td>2 (slight disability)</td>
<td>541 (23.0)</td>
<td>142 (21.9)</td>
</tr>
<tr>
<td>Death, n (%)</td>
<td>562 (23.9)</td>
<td>189 (29.1)</td>
<td>1.30 (1.07–1.58)</td>
<td>0.008</td>
<td>1.24 (1.00–1.54)</td>
<td>0.05</td>
</tr>
<tr>
<td>Major disability, n (%)</td>
<td>506 (21.6)</td>
<td>162 (24.9)</td>
<td>1.21 (0.99–1.48)</td>
<td>0.07</td>
<td>1.15 (0.92–1.43)</td>
<td>0.23</td>
</tr>
<tr>
<td>Recurrent stroke, n (%)</td>
<td>45 (1.9)</td>
<td>9 (1.4)</td>
<td>0.76 (0.37–1.56)</td>
<td>0.46</td>
<td>0.75 (0.36–1.54)</td>
<td>0.43</td>
</tr>
<tr>
<td>Vascular events,† n (%)</td>
<td>64 (2.7)</td>
<td>20 (3.1)</td>
<td>1.12 (0.67–1.87)</td>
<td>0.67</td>
<td>1.03 (0.61–1.73)</td>
<td>0.91</td>
</tr>
<tr>
<td>Per interquartile range</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death and major disability*</td>
<td>...</td>
<td>...</td>
<td>1.07 (1.01–1.14)</td>
<td>0.02</td>
<td>1.04 (0.98–1.12)</td>
<td>0.22</td>
</tr>
<tr>
<td>Ordinal modified Rankin Scale</td>
<td>...</td>
<td>...</td>
<td>1.07 (1.02–1.13)†</td>
<td>0.004</td>
<td>1.04 (0.99–1.09)†</td>
<td>0.23</td>
</tr>
<tr>
<td>Death</td>
<td>...</td>
<td>...</td>
<td>1.18 (1.08–1.30)</td>
<td>0.001</td>
<td>1.15 (1.04–1.27)</td>
<td>0.008</td>
</tr>
<tr>
<td>Major disability</td>
<td>...</td>
<td>...</td>
<td>1.04 (0.98–1.11)</td>
<td>0.21</td>
<td>1.01 (0.94–1.08)</td>
<td>0.86</td>
</tr>
<tr>
<td>Recurrent stroke</td>
<td>...</td>
<td>...</td>
<td>0.98 (0.79–1.22)</td>
<td>0.86</td>
<td>0.97 (0.78–1.21)</td>
<td>0.80</td>
</tr>
<tr>
<td>Vascular events†</td>
<td>...</td>
<td>...</td>
<td>1.07 (0.93–1.23)</td>
<td>0.35</td>
<td>1.04 (0.91–1.21)</td>
<td>0.55</td>
</tr>
</tbody>
</table>

Multivariable model 1: adjusted for age, sex, baseline NIHSS scores (>4 versus ≤4), time from onset to hospitalization, systolic blood pressure at entry, smoking, drinking, ischemic stroke subtypes, diabetes mellitus, antihypertensive intervention versus control. Model 2: model 1 plus anticardiolipin antibodies; model 3: model 2 with NIHSS adjusted as a continuous variable. aPS indicates antiphosphatidylserine antibodies; CI, confidence interval; HR, hazard ratio; OR, odds ratio; and NIHSS, National Institutes of Health Stroke Scale.

*Modified Rankin Scale score of 3–6.
†Include vascular deaths, nonfatal stroke, nonfatal myocardial infarction, hospitalized and treated angina, hospitalized and treated congestive heart failure, and hospitalized and treated peripheral arterial disease.
‡Odds of a 1-U higher modified Rankin Scale score.
The relationship between aPLs and recurrent stroke remains debatable. Early studies showed an increased recurrent stroke risk associated with aPLs, but later studies that included larger numbers of patients failed to find such an association.8,26 The Antiphospholipid Antibodies and Stroke Study (n=1770), a prospective cohort study, reported that immunoreactivity to either aCL or lupus anticoagulant antibodies at the time of a first ischemic stroke did not influence the risk of subsequent thrombo-occlusive events over the following 2 years.8 Our study examined aPS and aCL not lupus anticoagulant antibodies. Neither aPS nor aCL increased risks of recurrent stroke or vascular events.

The present study found a significant association of positive aPS with composite outcome of death or major disability, and the association seems to be stronger for death than for other outcomes. Because most deaths (67.5%) in this study were caused by the index stroke, positive aPS might deteriorate stroke progression to death. We also found a linear association between aPS levels and composite outcome of death or major disability, suggesting that there might exist a dose-dependent relationship between aPS titers and poor stroke outcomes. The precise mechanism by which aPS influence stroke outcomes is unclear. Several potential pathophysiological mechanisms have been proposed, including neurological toxicity, endothelial dysfunction, hypercoagulable state, complement activation, thrombotic condition, and accelerated atherosclerosis.27–30

Our results were not materially affected by the adjustment of baseline aCL, suggesting that the association of aPL with stroke outcomes might be underestimated if aPS were not considered.31 Although the clinical significance of other noncardiolipin aPLs, including aPS has not yet been demonstrated convincingly, if these noncardiolipin antibodies are associated with increased stroke risk and poor stroke prognosis,13,32 the significance of aPLs in stroke may be even greater.

### Table 3. Reclassification and Discrimination Statistics for Clinical Outcomes by Serum Antiphosphatidylserine Antibodies Among Patients With Acute Ischemic Stroke

<table>
<thead>
<tr>
<th></th>
<th>NRI (Category Free), %</th>
<th>NRI (Category), %*</th>
<th>IDI, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estimate (95% CI)</td>
<td>P Value</td>
<td>Estimate (95% CI)</td>
</tr>
<tr>
<td>Death and major disability†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conventional model‡</td>
<td>10.9 (3.8 to 17.9)</td>
<td>0.002</td>
<td>1.8 (0.6 to 3.1)</td>
</tr>
<tr>
<td>Conventional model+aPS positive</td>
<td>11.3 (3.2 to 19.3)</td>
<td>0.006</td>
<td>0.8 (−0.3 to 1.9)</td>
</tr>
<tr>
<td>Death</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conventional model‡</td>
<td>21.3 (0.9 to 41.7)</td>
<td>0.04</td>
<td>3.8 (−2.4 to 10.0)</td>
</tr>
<tr>
<td>Conventional model+aPS positive</td>
<td>15.8 (−5.9 to 37.4)</td>
<td>0.15</td>
<td>3.8 (−1.4 to 9.1)</td>
</tr>
<tr>
<td>Major disability</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conventional model‡</td>
<td>8.1 (0.8 to 15.4)</td>
<td>0.03</td>
<td>1.5 (0.2 to 2.7)</td>
</tr>
<tr>
<td>Conventional model+aPS positive</td>
<td>4.9 (−3.5 to 13.3)</td>
<td>0.25</td>
<td>0.8 (−0.2 to 1.7)</td>
</tr>
</tbody>
</table>

aPS indicates antiphosphatidylserine antibodies; CI, confidence interval; IDI, integrated discrimination index; and NRI, net reclassification improvement.

*Patients were divided into 3 categories for the risk classification: <5%, 5% to 15%, and >15%.

†Modified Rankin Scale score of 3–6.

‡Conventional model included age, sex, National Institutes of Health Stroke Scale scores, time from stroke onset to hospital, systolic blood pressure, current smoking, current drinking, ischemic stroke subtypes, diabetes mellitus, and anticardiolipin antibodies.
patients with antiphospholipid syndrome, the consensus is to
treat those who develop thrombosis with long-term oral anti-
coagulation therapy and to prevent obstetric manifestations by
use of aspirin and heparin.33,34 We did not find that positive
aPS increased risks of stroke recurrence and vascular events,
but found a significant association of aPS with death or major
disability. Therefore, specifically designed observational stud-
ies or clinical trials may be considered to examine whether
anticoagulation therapy after stroke decreases the risk of death
or major disability in patients with positive aPS.

Our study has some strengths. First, this is a large observa-
tional study from a randomized clinical trial with strict quality
controls in data collection and outcome assessment. Second,
we adjusted for baseline aCL and other important risk fac-
tors in analyzing the association of aPS with study outcomes.
Some limitations should be discussed here. First, this study is
a post hoc analysis of CATIS; therefore, a selection bias may
unavoidably be present. However, baseline characteristics of
participants in this study were similar to those from the China
National Stroke Registry, indicating that the selection bias
may be minimal. Second, aPS were tested only at baseline, we
were unable to examine the association between changes in
aPS and stroke outcomes in patients with acute ischemic stroke
although aPS were not found to increase over time in the first
week after stroke.36 Finally, a functional test of phospholipid-
dependent clotting was not performed as part of the study to
discriminate antiphospholipid syndrome among ischemic stroke
patients.

Conclusions
We found that positive aPS increased risks of death or major
disability at 3 months after an acute ischemic stroke. Adding
aPS to conventional risk factors slightly improved risk predic-
tion for death or major disability in patients with acute isch-
emic stroke.

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None.

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Antiphosphatidylserine antibodies and clinical outcomes in patients with acute ischemic stroke
Supplemental Table I. Baseline characteristics between antiphosphatidylserine antibodies assayed and not-assayed groups

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<thead>
<tr>
<th>Characteristics</th>
<th>Assayed (n=3013)</th>
<th>Not-assayed (n=1058)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>62.6 (10.9)</td>
<td>62.2 (10.9)</td>
<td>0.34</td>
</tr>
<tr>
<td>Male</td>
<td>1920 (63.7)</td>
<td>684 (64.7)</td>
<td>0.59</td>
</tr>
<tr>
<td>Time from onset to hospitalization, hours*</td>
<td>10.0 (4.3-24.0)</td>
<td>10.2 (5.0-24.0)</td>
<td>0.26</td>
</tr>
<tr>
<td>Admission NIHSS scores*</td>
<td>5 (3-8)</td>
<td>4 (2-7)</td>
<td>0.06</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>165.7 (16.7)</td>
<td>167.3 (17.4)</td>
<td>0.007</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>96.0 (11.0)</td>
<td>98.6 (11.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fasting plasma glucose, mmol/L</td>
<td>5.8 (5.1-7.2)</td>
<td>5.7 (5.0-7.2)</td>
<td>0.25</td>
</tr>
<tr>
<td>Disease history</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>2367 (78.6)</td>
<td>842 (79.6)</td>
<td>0.48</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>221 (7.3)</td>
<td>56 (5.3)</td>
<td>0.02</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>540 (17.9)</td>
<td>179 (16.9)</td>
<td>0.46</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>321 (10.7)</td>
<td>123 (11.6)</td>
<td>0.38</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>24.9 (3.1)</td>
<td>25.1 (3.3)</td>
<td>0.15</td>
</tr>
<tr>
<td>Current cigarette smoking</td>
<td>1105 (36.7)</td>
<td>380 (35.9)</td>
<td>0.66</td>
</tr>
<tr>
<td>Current alcohol drinking</td>
<td>911 (30.2)</td>
<td>342 (32.3)</td>
<td>0.21</td>
</tr>
<tr>
<td>Ischemic stroke subtype†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombotic</td>
<td>2324 (77.1)</td>
<td>846 (80.0)</td>
<td>0.06</td>
</tr>
<tr>
<td>Embolic</td>
<td>156 (5.2)</td>
<td>46 (4.4)</td>
<td>0.28</td>
</tr>
<tr>
<td>Lacunar</td>
<td>604 (20.1)</td>
<td>198 (18.7)</td>
<td>0.35</td>
</tr>
<tr>
<td>Antihypertensive intervention</td>
<td>1509 (50.1)</td>
<td>529 (50.0)</td>
<td>0.96</td>
</tr>
</tbody>
</table>

Data were presented as mean (SD) or no. (%) unless otherwise noted. NIHSS indicates National Institutes of Health Stroke Scale (scores range from 0 to 42).

* Data were presented as median (interquartile range).

† 12 patients with both thrombotic and embolic subtypes; 93 patients with thrombotic and lacunar subtypes; 6 patients with embolic and lacunar subtypes; 1 patient with all 3 subtypes.
Supplemental Table II. Odds ratios of death or major disability associated with positive antiphosphatidylserine antibody (aPS) according to trial arms and stroke etiology

<table>
<thead>
<tr>
<th>Subgroups</th>
<th>aPS-positive</th>
<th>aPS-negative</th>
<th>Adjusted OR* (95% CI)</th>
<th>P for heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Events (%)</td>
<td>Total</td>
<td>Events (%)</td>
</tr>
<tr>
<td><strong>Trial arms</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antihypertensive treatment</td>
<td>1502</td>
<td>91 (28.4)</td>
<td>1182</td>
<td>289 (24.5)</td>
</tr>
<tr>
<td>Control</td>
<td>330</td>
<td>98 (29.7)</td>
<td>1116</td>
<td>273 (23.4)</td>
</tr>
<tr>
<td><strong>Stroke etiology</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombotic</td>
<td>475</td>
<td>145 (30.5)</td>
<td>1765</td>
<td>446 (25.3)</td>
</tr>
<tr>
<td>Embolic</td>
<td>35</td>
<td>21 (60.0)</td>
<td>107</td>
<td>45 (42.1)</td>
</tr>
<tr>
<td>Lacunar</td>
<td>121</td>
<td>23 (19.0)</td>
<td>414</td>
<td>57 (13.8)</td>
</tr>
</tbody>
</table>

*Adjusted for age, sex, baseline NIHSS scores (>4 vs. ≤4), time from stroke onset to hospital, systolic blood pressure at entry, current smoking, current drinking, ischemic stroke subtypes, history of diabetes mellitus, antihypertensive treatment vs control, and anticardiolipin antibody.
Supplemental Table III. Odds ratios or hazard ratios of clinical outcomes according to aCL status and one interquartile range

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Unadjusted Model</th>
<th></th>
<th>Multivariable Model 1</th>
<th></th>
<th>Multivariable Model 2</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR or HR (95% CI)</td>
<td>P value</td>
<td>OR or HR (95% CI)</td>
<td>P value</td>
<td>OR or HR (95% CI)</td>
<td>P value</td>
</tr>
<tr>
<td>Status (positive vs. negative)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death and major disability*</td>
<td>1.12 (0.66-1.91)</td>
<td>0.68</td>
<td>0.92 (0.51-1.65)</td>
<td>0.78</td>
<td>0.78 (0.40-1.51)</td>
<td>0.45</td>
</tr>
<tr>
<td>Death</td>
<td>1.81 (0.57-5.72)</td>
<td>0.32</td>
<td>1.59 (0.50-5.04)</td>
<td>0.43</td>
<td>1.51 (0.47-4.83)</td>
<td>0.49</td>
</tr>
<tr>
<td>Major disability</td>
<td>1.04 (0.59-1.82)</td>
<td>0.90</td>
<td>0.86 (0.47-1.57)</td>
<td>0.61</td>
<td>0.78 (0.41-1.48)</td>
<td>0.44</td>
</tr>
<tr>
<td>Recurrent stroke</td>
<td>1.84 (0.45-7.56)</td>
<td>0.40</td>
<td>1.81 (0.44-7.45)</td>
<td>0.41</td>
<td>1.81 (0.44-7.45)</td>
<td>0.41</td>
</tr>
<tr>
<td>Vascular events†, No. (%)</td>
<td>1.19 (0.29-4.83)</td>
<td>0.81</td>
<td>1.13 (0.28-4.62)</td>
<td>0.86</td>
<td>1.12 (0.27-4.56)</td>
<td>0.88</td>
</tr>
<tr>
<td>Per interquartile range</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death and major disability*</td>
<td>1.00 (0.95-1.05)</td>
<td>0.98</td>
<td>0.97 (0.91-1.03)</td>
<td>0.32</td>
<td>0.96 (0.89-1.02)</td>
<td>0.19</td>
</tr>
<tr>
<td>Death</td>
<td>1.05 (0.96-1.16)</td>
<td>0.30</td>
<td>1.03 (0.92-1.16)</td>
<td>0.59</td>
<td>1.04 (0.92-1.17)</td>
<td>0.55</td>
</tr>
<tr>
<td>Major disability</td>
<td>0.99 (0.94-1.05)</td>
<td>0.71</td>
<td>0.96 (0.90-1.03)</td>
<td>0.23</td>
<td>0.96 (0.90-1.02)</td>
<td>0.18</td>
</tr>
<tr>
<td>Recurrent stroke</td>
<td>1.06 (0.95-1.19)</td>
<td>0.33</td>
<td>1.05 (0.94-1.18)</td>
<td>0.41</td>
<td>1.05 (0.94-1.18)</td>
<td>0.41</td>
</tr>
<tr>
<td>Vascular events†, No. (%)</td>
<td>1.05 (0.96-1.16)</td>
<td>0.30</td>
<td>1.04 (0.94-1.15)</td>
<td>0.45</td>
<td>1.04 (0.94-1.15)</td>
<td>0.46</td>
</tr>
</tbody>
</table>

aCL indicates anticardiolipin antibodies; cutoff value for positive was ≥20 U/mL.

*Modified Rankin Scale score of 3 or greater.
†Includes vascular deaths, non-fatal stroke, non-fatal myocardial infarction, hospitalized and treated angina, hospitalized and treated congestive heart failure, and hospitalized and treated peripheral arterial disease.

Multivariable Model 1: adjusted for age, sex, baseline NIHSS scores (>4 vs. ≤4), time from stroke onset to hospital, systolic blood pressure at entry, current smoking, current drinking, ischemic stroke subtypes, history of diabetes mellitus, antihypertensive intervention vs control; Model 2: model 1 with NIHSS adjusted as a continuous variable.
Supplemental Figure I. Association of antiphosphatidylserine antibody with hazard ratios of recurrent stroke and vascular events

Multiple spline regression analyses of hazard ratios (solid line) and their 95% confidence intervals (dotted line) of recurrent stroke and vascular events associated with baseline IgG antiphosphatidylserine antibody among 3013 patients with acute ischemic stroke. Panel A: Recurrent stroke; Panel B: Vascular events.