Newer Antiphospholipid Antibodies Predict Adverse Outcomes in Patients With Acute Coronary Syndrome

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Key Words: Antiphospholipid antibodies; Anti-β2-glycoprotein I; Oxidized low-density lipoprotein; Coronary artery disease

Abstract

Antiphospholipid antibodies (aPLs) have been implicated in atherogenesis. We studied 344 patients with acute coronary syndromes; approximately 40% were aPL+ in 1 or more tests and 60% aPL−. In 215 patients, coronary artery disease (CAD) was angiographically documented, with 43.7% positive for aPL vs 34.9% of patients without CAD positive for aPLs. Anti–β2-glycoprotein I (β2GPI; 54%) and anti–oxidized low-density lipoprotein (oxLDL)/β2GPI (48%) were most frequent, accounting for 87% of all aPL+ CAD cases. aPLs correlated with severity of CAD (P = .012). Adverse events occurred in 16.7% of patients with CAD, more frequently in patients who were aPL+ (P = .0006; relative risk, 2.9; 95% confidence interval, 1.5-5.6). Patients who were aPL+ with severe CAD had more adverse events than patients who were aPL− with severe CAD (P = .005) and aPL+ patients undergoing revascularization procedures (P = .001). Vascular events occurred in 21.7% of aPL+ patients compared with 7.1% of aPL− patients (P = .005). Anti-β2GPI and anti-oxLDL/β2GPI were associated with CAD severity and adverse outcomes.

Numerous serologic markers of inflammation and coagulation have been prognostically associated with coronary artery disease (CAD) progression, events, and outcomes.1-7 The usefulness of many of these markers in the routine management of patients is controversial,8 and their routine measurements are not recommended. Antiphospholipid antibodies (aPLs) have recently joined the arena of potential markers of importance in the assessment of patients with acute coronary syndromes, but not without controversy. aPLs have been positively associated with increased risk of ischemic stroke and myocardial infarction (MI) and with the presence of CAD.9 An association with adverse events (AEs) and outcomes especially in young patients, angioplasties, and coronary artery bypass has been reported,10-20 although negative associations have also been noted.21-24

Previous studies have revealed an association between atherosclerosis and aPLs, especially with antibodies to β2-glycoprotein I (β2GPI), a phospholipid-binding plasma protein.25,26 β2GPI is thought to be the antigenic target of aPLs relevant in antibody-mediated thrombotic diseases. This association was initially identified from clinical observations that patients having systemic lupus erythematosus and antiphospholipid syndrome experienced premature and advanced atherosclerotic cardiovascular complications, not fully explained by the disease itself or by the classic risk factors.27,28 The association has been strengthened by the detection of β2GPI in human atherosclerotic lesions, colocalized with CD4+/CD8+ lymphocytes and monocyte-derived cells.29 The proximity of these elements suggests an autoimmune reaction that would promote atherogenesis.30 Furthermore, anti-β2GPI antibodies accelerate in vitro macrophage uptake and intracellular accumulation of oxidized low-density lipoprotein.
lipoprotein (oxLDL) in the presence of β2GPI, providing a possible pathogenic role of aPLs in atherosclerosis.

The importance of aPLs as prognostic factors in CAD rests in their usefulness as markers of a potentially treatable illness mediated by antibodies that inherently cause more clotting associated with protracted thrombin generation. There is, however, some controversy about aPL tests themselves, including which aPL assay to use (anticardiolipin [aCL] vs anti-β2GPI or anti-oxLDL complexes).

In the present study, we evaluated the association of aPLs with CAD severity and adverse outcomes in patients with acute coronary syndromes. Patients with chest pain admitted to an acute care facility to rule out acute coronary syndromes were prospectively tested at the onset of symptoms and before any coronary intervention for multiple types of commonly used aPLs and isotypes, including antibodies to oxidized LDL complexes (oxLDL/β2GPI). Our results show that aPLs (anti-β2GPI and the recently described anti-oxLDL/β2GPI antibodies) occurred in patients with acute coronary syndromes and were strongly associated with the severity of CAD and adverse outcomes. These antibodies were the most frequently found, supporting the concept of an immune proatherogenic role of aPLs in CAD.

Materials and Methods

Study Design and Participants

This was a prospective, one-center study performed at Saint Mary’s Hospital, Waterbury, CT, designed to investi-
gate the association of aPLs with CAD severity and adverse outcomes in patients with acute coronary syndromes. The study protocol was approved by the St. Mary’s Hospital Institutional Review Board, and before study enrollment, all patients signed informed consent accepting their participation in the study. Randomly selected patients, men and women between the ages of 18 and 75 years with chest pain and sus-
pected coronary syndromes admitted to our acute care institu-
tion from October 2005 to November 2007 were eligible to participate. Of 395 eligible patients, 51 did not meet study criteria or were lost to follow-up; 344 patients fulfilling the admission criteria were entered into the study.

Before diagnostic and therapeutic procedures, admission serum samples from each patient were collected and stored frozen at −70°C for later analysis. All patients underwent the standard diagnostic workup and treatment for chest pain and acute coronary syndrome. Evaluations included cardiac stress testing and imaging, cardiac catheterizations, and procedures including angioplasty, stenting, and coronary artery bypass. Demographic information and history, including risk factors for CAD, were collected at study entry. Family histories for aPL-related events were obtained, predefining such events as premature MI, stroke (age <60 years), or recurrent fetal loss (>2 miscarriages). Patients were followed up to hospital discharge by their cardiologist/investigator and postdischarge by telephone to track clinical events. Mean follow-up for outcomes was 24 months. All patients received standard-of-care therapy after discharge, including dual antiplatelet therapy after angioplasty and single antiplatelet treatment after coronary artery bypass. Clinical and laboratory investigators remained blinded to each other’s data throughout the study.

CAD Classification

We evaluated the extent (severity) of CAD following a graded catheterization system we devised based on previous reports by others. Patients with normal stress imaging testing were graded as “0,” assuming normal coronaries and recognizing that a small percentage of the patients may have significant CAD or have nonobstructive CAD. For all other patients, the following grading system was used: I, normal coronaries; II, mild disease with 10% to 50% stenosis in 1, 2, or 3 branches; III, moderate disease with 50% to 80% stenosis in 1, 2, or 3 branches; IV, moderate to severe disease with 80% to 100% stenosis in 1, 2, or 3 branches and first cardiac event, angiogram, and/or intervention; V, severe, recurrent disease implying previous cardiac events, stenting, or bypass in 1, 2, or 3 branches and requiring diagnostic angiogram and/or therapeutic interventions; and VI, severe, recurrent disease implying previous cardiac events and/or stenting or bypass but not requiring angiographic evaluation or amenable to additional procedures during hospitalization.

Outcomes

Adverse vascular events (AVEs) were recorded, includ-
ing the need for revascularization owing to angioplasty failure, stent occlusion, or new coronary vascular occlusion; coronary artery bypass failure; MI; other major cardiovascular events; and no-cardiac vascular events. AEs included deaths plus AVE. In addition, AVEs and AEs were calculated for the CAD population, patients with the most advanced degree of CAD, and patients having revascularization procedures.

aPL Measurements

Serum levels of aPLs were measured by commercially available enzyme-linked immunosorbent assay test kits (Corgenix, Broomfield, CO), following the manufacturer instructions. IgG, IgM, and IgA isotype testing was performed for aCL, anti-β2GPI, and antiphosphatidylserine (aPS) antibodies. IgG and IgM isotypes were measured on antiprothrombin (aPT) and anti-oxidized LDL/β2GPI complexes (anti-AtherOx, Corgenix) antibodies. The prevalence of these aPLs in the general healthy population reported by the manufacturer is as follows: aCL: IgG, 3%; IgM, 4%; and
IgA, 5%; aPS: IgG, 4%; IgM, 4%; and IgA, 5%; anti-β2GPI: IgG, less than 1%; IgM, 7%; and IgA, 4%; aPT: IgG, 5%; and IgM, 3%; and anti-oxLDL/β2GPI: IgG, 7%; and IgA, 4%.

Statistical Analysis

Results of cardiac catheterization were used to classify patients into CAD– (grades 0-I) and CAD+ (grades II-VI). Patients with grades 0 or I were used as control subjects for statistical comparisons. Results of the aPL assays were classified as positive or negative according to the manufacturer cut-off values and instructions. Patients were classified as aPL+ if the results of one or more assays were positive. Statistical analysis of the data included t tests to compare continuous data, χ² tests to compare categorical data, and the analysis of means for proportions to compare multiple proportions. P values for significant findings are less than .05.

Results

Baseline Characteristics

We evaluated 344 patients with mean follow-up of 24 months. Table 1 summarizes the demographics of these study patients by CAD state; 215 CAD+ patients (62.5%) have documented CAD (grades II-VI), and all others (129 [37.5%]) are considered CAD–. Independent statistical tests for differences in the 2 groups showed that the CAD+ group included more men, was older, and had a higher incidence of dyslipidemia, statin use, and diabetes mellitus than the CAD– patients. The P values obtained for the aforementioned tests are small enough to be significant even if one were to consider a correction for performing multiple hypothesis tests.

Overall, 139 patients (40.4%) were aPL+ in 1 or more tests, and 205 (59.6%) were aPL– by all tests. Of the aPL+ patients, 95 (68.3%) were also CAD+ as compared with 115 (56.1%) of aPL– patients (P = .105; χ² for independence). Table 2 summarizes the demographics of the 215 CAD+ patients by the presence, aPL+, or absence, aPL–, of aPLs. The presence of family history of aPL-related events was more likely for aPL+ patients, and hyperlipidemia was less likely for aPL+ patients.

The distribution of the severity of CAD by aPL status is summarized in Figure 1. The proportion of aPL+ patients tended to increase with severity (34.9% of patients with grade 0-I CAD compared with 45.6% of patients with grade V-VI CAD; P = .05). Furthermore, the proportion of patients specifically positive for anti-β2GPI and/or anti-oxLDL/β2GPI significantly increased with the severity of CAD (26.3% of patients with grade 0-I CAD compared with 42.1% of patients with grade V-VI CAD; P = .012). Most of the patients positive for aCL, aPS, and aPT had grade 0 or I CAD.

aPL Distribution

Anti-β2GPI was the most frequent aPL type, occurring in 51 (54%) of the 94 aPL+ patients with CAD Table 3. The frequency of anti-oxLDL/β2GPI was second, found in 45 (48%) of the patients. Together, these aPLs accounted for 87% of all aPL+ patients with CAD. aCL was infrequently found in 6 (6%) of aPL+ patients with CAD. IgM isotypes predominated in all assays, except for anti-oxLDL/β2GPI, in which IgG and IgM were both frequently found.
Adverse Events

AEs occurred in 36 of 215 patients with documented CAD Figure 1, with 25 events occurring in 94 aPL+ patients (27%) and 11 events in 121 aPL– patients (9.1%) (P = .0006). The risk of an AE for aPL+ patients with CAD is at least 1.5 times greater than for aPL– patients with CAD (mean relative risk, 2.9; 95% confidence interval [CI],

Table 2
Demographics of 215 Study Patients With Coronary Artery Disease According to aPL Status*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>aPL– (n = 121)</th>
<th>aPL+ (n = 94)</th>
<th>P†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD) age (y)</td>
<td>61.0 (12.3)</td>
<td>63.7 (11.2)</td>
<td>.0999</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>80 (66.1)</td>
<td>52 (55)</td>
<td>.1067</td>
</tr>
<tr>
<td>African American</td>
<td>99 (81.8)</td>
<td>78 (83)</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>11 (9.1)</td>
<td>4 (4)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>9 (7.4)</td>
<td>12 (13)</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>2 (1.7)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>27 (22.3)</td>
<td>25 (27)</td>
<td>.4671</td>
</tr>
<tr>
<td>Family history (antiphospholipid antibodies)‡</td>
<td>56 (46.3)</td>
<td>60 (64)</td>
<td>.0104</td>
</tr>
<tr>
<td>Hyperlipidemia§</td>
<td>82 (67.8)</td>
<td>54 (57)</td>
<td>.0231</td>
</tr>
<tr>
<td>Statins</td>
<td>76 (62.8)</td>
<td>67 (71)</td>
<td>.1550</td>
</tr>
<tr>
<td>Diabetes</td>
<td>49 (40.5)</td>
<td>32 (34)</td>
<td>.3277</td>
</tr>
</tbody>
</table>

aPL, antiphospholipid antibody.
* Data are given as number (percentage) unless otherwise indicated.
† P value based on a t test for continuous data and Pearson χ2 test for nominal data.
‡ Assuming that “unknown” history is negative.
§ Elevated total cholesterol level (>200 mg/dL [5.18 mmol/L]) or dyslipidemic state (abnormal level of high-density lipoprotein, low-density lipoprotein, and/or triglycerides) for which therapy was started.

Table 3
Prevalence by Counts and Percentages of aPLs in 94 aPL+ Patients With Coronary Artery Disease*

<table>
<thead>
<tr>
<th>aPL Antibody</th>
<th>All Isotypes (n = 94)</th>
<th>IgG</th>
<th>IgM</th>
<th>IgA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti–β2GPI</td>
<td>51 (64)</td>
<td>3/51, 6 (1)</td>
<td>34/51, 67 (7)</td>
<td>20/51, 39 (4)</td>
</tr>
<tr>
<td>Anti–oxLDLβ2GPI</td>
<td>45 (48)</td>
<td>2/45, 64 (7)</td>
<td>23/45, 51 (8)</td>
<td>ND</td>
</tr>
<tr>
<td>aPS</td>
<td>11 (12)</td>
<td>4/11, 36 (4)</td>
<td>7/11, 64 (4)</td>
<td>0/11, 0 (5)</td>
</tr>
<tr>
<td>aPT</td>
<td>11 (12)</td>
<td>1/11, 9 (5)</td>
<td>10/11, 91 (3)</td>
<td>ND</td>
</tr>
<tr>
<td>aCL</td>
<td>6 (6)</td>
<td>1/6, 17 (3)</td>
<td>4/6, 67 (4)</td>
<td>2/6, 33 (5)</td>
</tr>
</tbody>
</table>

aCL, anticardiolipin antibody; aPL, antiphospholipid antibody; aPS, antiphosphatidylserine antibody; aPT, antiprothrombin antibody; β2GPI, β2-glycoprotein I; ND, not done; oxLDL, oxidized low-density lipoprotein.
* Patients may be positive for one or more antibodies and for one or more isotypes of each antibody. Data for all isotypes are given as number (percentage); data for IgG, IgM, and IgA are given as prevalence, percentage positive (expected percentage positive for the general healthy population).
1.5-5.6). Of 36 AEs, 8 (22%) were deaths. Causes of death were multifactorial and occurred equally in aPL+ and aPL− groups (5 and 3, respectively).

All AVEs (cardiac and noncardiac) occurred in patients with moderate to severe CAD (grade III-VI), documented in 205 patients, 92 of whom (44.9%) were aPL+ and 113 of whom (55.1%) were aPL−. Overall, AVEs occurred in 20 (22%) of 92 aPL+ patients compared with 8 (7.1%) of 113 aPL− patients (P = .005). A total of 5 AVEs were noncardiac events (4 cerebrovascular, 1 pulmonary embolism). All occurred in aPL+ patients.

From this group, a similar proportion of aPL+ and aPL− patients, 60 (65%) of 92 and 72 (63.7%) of 113, respectively, underwent clinical procedures (ie, stenting, angioplasty, bypass). Significantly more AVEs occurred in aPL+ patients having procedures (17/60 [28%]) compared with aPL− patients having procedures (7/72 [10%]) (P = .001).

Further analysis focused on AEs in patients with the most advanced catheterization findings (grade IV, V, or VI; n = 189). Table 4 summarizes the observed frequency of AEs and AVEs, independent of interventions, by aPL state and CAD grade. Patients with advanced recurrent disease (grade V) who were aPL+, had a 44% rate (12/27) of AVEs compared with 11% (4/36) in the aPL− group (P = .007).

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Other Findings

Family histories of aPL-related events for the entire patient population occurred more frequently (P = .003) in aPL+ patients (86/139 [61.9%]) than in aPL− patients (93/205 [45.4%]). In patients with CAD, family histories of an aPL-related event also occurred more frequently in aPL+ patients (P = .01; Table 2).

**Discussion**

Our data support previous studies that suggested a predictive role of aPLs in the prognosis of CAD.10,13-18 We found that anti-β2GPI and anti-oxLDL/β2GPI antibodies were the most frequent and relevant aPLs in patients with acute coronary syndromes, consistent with current concepts on the immune pathogenesis of atherosclerosis.27 aPLs have been associated with CAD12,37 and acute MI, especially in young patients,11,13,20,38 occurring more frequently in patients with recurrent coronary events,10 restenosis after angioplasty,17,18 and coronary graft failure.15 In our study, the patients who were most at risk for AEs were specifically aPL+ patients with more severe CAD and revascularizations. The presence of aPLs in patients with established recurrent CAD syndromes (grades V and VI) was a poor prognostic factor, with more than 40% of aPL+ patients in these groups developing AEs.

<table>
<thead>
<tr>
<th>CAD Grade</th>
<th>aPL+</th>
<th>aPL−</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV</td>
<td>7/51 (14)</td>
<td>4/60 (7)</td>
<td>.357</td>
</tr>
<tr>
<td>V</td>
<td>12/27 (44)</td>
<td>4/36 (11)</td>
<td>.007</td>
</tr>
<tr>
<td>VI</td>
<td>1/8 (13)</td>
<td>0/7 (0)</td>
<td>.005</td>
</tr>
<tr>
<td>IV-VI</td>
<td>20/86 (23)</td>
<td>8/103 (7.8)</td>
<td>.001</td>
</tr>
<tr>
<td>aPL+</td>
<td>10/51 (20)</td>
<td>4/60 (7)</td>
<td>.333</td>
</tr>
<tr>
<td>aPL−</td>
<td>13/27 (48)</td>
<td>6/36 (17)</td>
<td>.016</td>
</tr>
<tr>
<td>aPL+</td>
<td>2/8 (25)</td>
<td>0/7 (0)</td>
<td>.001</td>
</tr>
<tr>
<td>aPL−</td>
<td>25/86 (29)</td>
<td>10/103 (9.7)</td>
<td>.001</td>
</tr>
</tbody>
</table>

Table 4 Prevalence by Counts and Percentages of Adverse Events in Patients With Severe CAD (>80% Stenosis)*

* Data are given as number/total (percentage). Nine patients died; 7 of the 9 patients had CAD severity grades of IV through VI. Two deaths in aPL− groups occurred in patients with grade I and grade III CAD severity. All deaths were multifactorial.

$^*$ P value based on the Pearson χ² test for nominal data.
The severity of CAD in our patients seemed to be related to aPL+ status (Figure 1), reaching significance especially when anti-β2GPI and/or anti-oxLDL/β2GPI antibodies were considered and analyzed (P = .012). There was no correlation between aPLs and standard cardiovascular risk factors such as smoking, hypertension, and diabetes (Table 2), as seen in a previous study.11 A negative association existed between hyperlipidemia and aPL+ status, with aPL+ patients with CAD less likely to have hyperlipidemia compared with their aPL− counterparts. Except for family histories, also more common in aPL+ patients with CAD, other risk factors occurred equally in both groups.

With continued controversies on the significance of particular aPL assays,31,34 we performed tests for multiple types of aPLs, including those that have been considered proatherogenic. Although classic aPLs (ie, aCL and lupus anticoagulants) have been traditionally associated with the antiphospholipid syndrome,30-44 more refined concepts have integrated inflammatory, coagulation, and autoimmune mechanisms in atherosclerotic cardiovascular diseases. Newer classes of aPLs (ie, anti-β2GPI and anti-oxLDL/β2GPI) in association with oxLDL have been proposed to participate in development and progression of atherosclerotic plaques.7,45-48 β2GPI, a ubiquitous phospholipid-binding plasma protein, is thought to be the antigenic target of aPLs relevant in antibody-mediated thrombotic diseases. Antibodies to β2GPI have been found to increase coagulation by humoral mechanisms (via the coagulation cascade and plasminogen system) and by increasing platelet adhesiveness, which may enhance acute events in CAD. Anti-β2GPI antibodies may also have a role in coronary disease via mechanisms of atherosclerotic plaque production itself. The binding of anti-β2GPI with oxLDL to form oxLDL/β2GPI immunoreactive complexes promotes the intracellular accumulation of oxLDL in macrophages, enhancing foam cell formation and rupture.31 Immunoreactivity against β2GPI and oxLDL has now been demonstrated histologically in atherosclerotic plaque.29,49 The demonstration that elevated serum levels of oxLDL are associated with the severity of angiographically proven CAD6 enhances the concept of CAD as an autoimmune entity in which antibodies (ie, anti-β2GPI and anti-oxLDL/β2GPI) promote the progression of atherosclerotic plaque, ruptured plaque, and acute arterial thrombosis.

The relative infrequency of aCLs in our patients with CAD correlates well with studies evaluating aPLs in patients without underlying autoimmune disease. A study on patients with cardiovascular disease found fewer than 2.6% of patients positive for aCLs, whereas 36% were positive for anti-β2GPI. The IgA isotype predominated.37 Others have also found IgA anti-β2GPI to be important in nonautoimmune patients with thrombosis50 and MI.19 The demonstration of predominantly IgM anti-β2GPI in our study could be because our patients had more acute events and were studied earlier, although IgA isotypes also occurred frequently. Studies have suggested that IgM isotypes may be more important in arterial events, whereas IgG isotypes may be more important in venous disease.51 Meroni et al58 reported that anti-β2GPI antibodies were a significant risk factor for MI in young premenopausal women independent of other risk factors. After adjusting for smoking and hypertension, IgM anti-β2GPI was a stronger risk factor for MI (odds ratio, 3.68; 95% CI, 1.69-8.02) than IgG (odds ratio, 2.47; 95% CI, 1.81-3.38), and Neville et al52 recently demonstrated that aPLs independently predict new vascular events and discriminate between people with and without events in the first 2 years of follow-up, suggesting that aPLs are associated with short-term risk of developing new and recurrent vascular events.

The presence of aPLs in our study population without CAD is also of concern. These patients, however, do not represent a healthy control group. All had chest pain syndromes, and many had multiple cardiac risk factors, including positive family histories. We also recognize that a small percentage of patients with normal stress testing (grade 0) may have CAD, possibly biasing our results slightly. Patients positive for aPLs in our study were more likely than aPL− patients to have a family member with aPL-related events such as premature strokes, MI, or recurrent miscarriage, consistent with a potential familial nature of aPLs53-57 and possibly one of the unexplained risk factors for clustering of CAD in relatives of patients with premature MI.58

We believe that the data from our study and from other studies10-20 support the potential importance and prognostic implications of aPL testing in patients with acute coronary syndrome. As the search for newer biomarkers for cardiovascular disease increases,59,60 their use may add to standard risk assessment61 and treatment outcomes. Whether testing for aPLs, especially antibodies to β2GPI and oxLDL/β2GPI, will strengthen the bridge between diagnostic, prognostic, and treatment modalities for CAD and its complications warrants larger prospective studies.

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References


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