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High Antiphospholipid Antibody Levels are Associated with Statin Use and May Reflect Chronic Endothelial Damage in Non-Autoimmune Thrombosis: cross-sectional study

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Abstract

Objective—Persistently elevated antiphospholipid antibodies (aPL Ab) and positive lupus anticoagulant (LAC) are associated with an increased risk of thrombosis. Our objective was to explore whether aPL Ab and/or LAC positivity were associated with the traditional risk factors for thrombosis or with medication use in patients without autoimmune diseases hospitalized with arterial or venous thrombosis.

Design—Cross-sectional study

Setting—Montefiore Medical Center, a large urban tertiary care center

Patients—Two hundred and seventy patients (93 with deep vein thrombosis (DVT) or pulmonary embolism (PE), and 177 with non-hemorrhagic stroke (CVA)) admitted between January 2006 and December 2010 with a discharge diagnosis of either DVT, PE or CVA, who had LAC and aPL Abs measured within six months from their index admission. We excluded patients with lupus or antiphospholipid syndrome.

Main Outcome Measures—The main dependant variable was aPL Ab ≥ 40 units (aPL Ab+) and/or LAC+. Independent variables: traditional thrombosis risk factors, statin use, aspirin use, and warfarin use.

Results—Thirty one (11%) patients were LAC+ and/or aPL Ab+ (aPL/LAC+). None of the traditional risk factors at the time of DVT/PE/CVA was associated with aPL/LAC+. Current statin use was associated with an OR of 3.2 (95% CI 1.3, 7.9, $p = 0.01$) of aPL/LAC+, adjusted for age, ethnicity and gender. Aspirin or warfarin use was not associated with aPL Ab levels.

Conclusion—If statin therapy reflects the history of prior hyperlipidemia, high levels of aPL Abs may be a marker for prior endothelial damage caused by hyperlipidemia.

Keywords

Antiphospholipid antibodies; statins; endothelial damage; thrombosis

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INTRODUCTION

Antiphospholipid antibodies (aPL Abs) is a heterogeneous family of antibodies that target phospholipids or phospholipid-binding proteins, and lupus anticoagulant (LAC) is a qualitative functional assay measuring phospholipid-dependent coagulation abnormalities in plasma [1]. Persistently high levels of aPL Abs and LAC positivity are associated with an increased risk of arterial and/or venous thrombosis in autoimmune diseases such as lupus and antiphospholipid syndrome [2, 3], although the exact mechanisms are under investigation. Several mechanisms have been proposed, including oxidant-mediated endothelial injury, dysregulation of coagulation pathways, and complement activation [1, 4]. According to the two-hit hypothesis, the presence of aPL Abs is necessary to create a prothrombotic state (1st hit). However, the presence of aPL Abs is not sufficient, and aPL Abs may persist for a long time before the 2nd hit results in the actual thrombotic event [5, 6]. However, not all aPL Abs are thrombogenic [7, 8], in fact, some individuals may have persistently high aPL levels, but they never develop thrombosis [9]. Currently, secondary prophylaxis is recommended for individuals with persistently high aPL Ab levels after a thrombotic event, although duration, methods and therapeutic targets are still a subject of a debate [7, 10, 11, 12].

As clinical decisions are made based on the levels and persistence of aPL Abs and/or LAC positivity, it is important to understand the factors that may influence aPL Ab levels. Several studies have shown that the majority of individuals with medium or high aPL levels (≥ 40 units) who had thrombotic events also had traditional risk factors for arterial or venous thrombosis, including smoking, hyperlipidemia, hypertension, high body mass index (BMI), high triglycerides, or type 2 diabetes [9, 13, 14, 15, 16]. Therefore, it is not well understood whether high levels of aPL Abs constitute an additional risk factor for thrombosis [17] in individuals without autoimmune diseases. It is possible that high aPL Ab levels and/or LAC positivity reflect the degree of the endothelial damage over time caused by traditional risk factors [1, 18], and, thus, confound the relationship between traditional risk factors and thrombosis.

Study Objective

To explore this important question, we conducted a cross-sectional study to investigate whether elevated aPL Ab levels and LAC positivity were associated with some of the traditional risk factors, including low-density lipoprotein (LDL) levels, high-density lipoprotein (HDL) levels, high triglycerides, hypertension, type 2 diabetes, BMI, and smoking in individuals without a known history of autoimmune diseases, hospitalized with a deep vein thrombosis (DVT), pulmonary embolism (PE), or non-hemorrhagic stroke (CVA). In addition, since some studies have shown that statin therapy and aspirin use may be associated with a decreased risk of thrombosis in aPL Ab positive individuals with mixed results [4, 19], and since warfarin therapy is the main treatment in antiphospholipid syndrome [11, 12], we evaluated whether statins, aspirin, or warfarin use was associated with aPL Ab levels and/or LAC positivity in the same group of patients (Figure 1).

METHODS

We identified all patients hospitalized between January 2006 and December 2010 at Montefiore Medical Center, the University Hospital for the Albert Einstein College of Medicine, a large urban tertiary care center in the Bronx, NY, with a primary ICD9 discharge diagnosis of acute DVT (453.40 – 453.42, 453.82) or PE (ICD9 415.1) (n = 1215) or non-hemorrhagic CVA (ICD9 434.*) (n = 2800). Of these 4015 identified, patients were included in our analysis if they had a comprehensive antiphospholipid panel measured

within 6 months after the thrombotic event occurred. This panel is routinely available at the Montefiore Immunodiagnostics Laboratory, and includes lupus anticoagulant (LAC), and 9 antiphospholipid antibody subtypes: anticardiolipin (aCL), anti-beta2 glycoprotein I (anti-b2GPI), and antiphosphatidylserine (aPS) IgG, IgM, and IgA.

All patients were identified from the Montefiore Electronic Record system using “Clinical Looking Glass,” a proprietary query tool. Clinical Looking Glass is a software application developed at MMC that allows clinicians and researchers to identify populations of interest from the MMC database, and to gather information about the laboratory data, medications, and demographics [20]. Race and ethnicity were defined based on self-report and included in the study because of a possible association between race/ethnicity and antiphospholipid antibody levels. All electronic charts were reviewed by a researcher (A.B.) who was unaware of the outcomes prior to reviewing the charts to confirm the diagnoses and to exclude patients with a known history of lupus or antiphospholipid syndrome.

APL Abs were tested using BIO-RAD EIA kits (BIO-RAD, Ca, USA). APL Ab positivity (aPL+) was defined as at least one aPL Ab IgG, IgM or IgA ≥ 40 units [13]. LAC was analyzed as positive or negative (LAC+/LAC-) by dilute Russell’s Viper Venom Time test (DRVVT). Triglycerides, HDL and LDL were analyzed as both continuous variables, and as dichotomous variables (high/low), based on the previously established cut-offs used for cardiovascular risk factors. High triglycerides were defined as ≥ 150 mg/dl, and high LDL levels were defined as > 130 mg/dl. Low HDL levels were defined as < 40 mg/dl for men, and < 50 mg/dl for women. [21].

Statistical analysis was performed using STATA 10.0 software package (StataCorp, College Station, Texas, USA). We used the student’s t-test (or its non-parametric alternative, Wilcoxon rank sum test) to evaluate the differences between distributions of continuous variables, and chi-square (or Fisher’s exact test when appropriate) to evaluate the association between categorical variables. Logistic regressions were performed with at least one aPL Ab ≥ 40 units and/or LAC positive as the main outcome variable (aPL/LAC+). Logistic regression models were used to assess for interactions, to adjust for confounding, and to test for statistical assumptions using the Hosmer-Lemeshow goodness-of-fit statistic [22] that tests for how well the model fits the data. Since this was an exploratory study, no adjustments were made for multiple comparisons. Differences were considered statistically significant for $p < 0.05$ (two-tailed).

Because of the retrospective nature of this study and as no identifying information was stored or used in the data analysis, we did not obtain informed consent from the patients. This project was approved by the Institutional Review Board at Albert Einstein College of Medicine/Montefiore Medical Center.

RESULTS

Of the patients with non-hemorrhagic CVA ($n=2800$), 190 (7%) had aPL Abs and LAC measured, and of the patients with DVT or PE (DVT/PE) ($n=1215$), 101 (8%) had aPL Abs and LAC measured. The results of the comparison of the CVA and DVT/PE patients with and without aPL Abs/LAC measured are summarized in Tables 1 and 2. CVA patients with aPL Abs/LAC measured were younger compared to CVA patients without aPL Abs/LAC measured, mean (SD), 51(12) years and 72(14) years, respectively ($p < 0.0001$). Forty two percent of CVA patients who had the aPL Abs/LAC measured were Hispanic, compared with only 33% of CVA patients without aPL Abs/LAC measured ($p = 0.025$). Twenty three percent in the CVA with aPL Abs/LAC measured were Caucasian, compared with 33% in the CVA without the aPL Abs/LAC measured ($p = 0.055$). Similarly, patients with DVT/PE

who had aPL Abs/LAC measured were younger compared with the DVT/PE patients who did not have aPL Abs/LAC measured, mean (SD) 52(16) years compared with 69(16) years, respectively ($p < 0.0001$). Forty seven percent of patients in the DVT/PE group with aPL Abs/LAC measured were women, compared with 63% of women in the DVT/PE without aPL Abs/LAC measured ($p = 0.004$). There were no ethnic or racial differences between DVT/PE with and without aPL Abs/LAC measured. DVT/PE and CVA groups with aPL Abs/LAC measured were similar with respect to age, gender and race/ethnicity.

Of the 291 patients with DVT/PE or CVA who had aPL Abs/LAC measured, 21 were excluded following chart reviews: SLE ($n=18$), primary antiphospholipid syndrome ($n=2$), and one patient had a suspected CVA, but was found to have a brain mass. Therefore, 270 patients, (177 non-hemorrhagic CVA and 93 DVT or PE), were included in the final analysis.

Of the 270 patients included in the study, 31 (11%) were aPL Ab+ and/or LAC+, 11/93 (12%) with DVT and 20/177 (11%) with CVA. Of the 31 aPL/LAC+, 7 were aPL Ab+ and LAC+, 12 were LAC+ and aPL Ab-, and 12 were LAC- and aPL Ab+. Three patients were aCL Ab+, anti-beta2GPI+, and LAC+. Among the 19 aPL Ab+ patients, 8 were aCL Ab+, 13 were anti-beta2GPI+, and 4 were aPS Ab+. There were no statistically significant differences between DVT/PE and CVA groups with respect to the frequency of various aPL subtypes or LAC positivity, although the numbers were small, and the results should be interpreted with caution.

Of the 31 aPL/LAC+ patients, 25 (81%) had at least one other known risk factor for thrombosis. The results of the bivariate comparison between aPL/LAC+, and aPL- and LAC- (aPL/LAC-) groups are shown in Table 3. There were no clinically or statistically significant differences in age, gender, ethnicity, the prevalence of type 2 diabetes, mean HDL, mean LDL, mean triglycerides, seasons, aspirin use, or history of hypertension. However, in the aPL/LAC+ group 12 (39%) were on statin therapy compared with 45 (19%) in the aPL/LAC- group ($p=0.011$). The unadjusted OR of aPL/LAC+ was 2.6 (95% CI 1.2, 5.8) among individuals on statins (Table 4).

The results of the multivariate analysis are shown in Table 4. In the multivariate analysis, statin use at the time of aPL Ab measurement was associated with an odds ratio (OR) of 3.2 (95% CI 1.3, 7.9) of aPL/LAC+, compared with no statin use, adjusted for age, ethnicity and gender ($p = 0.01$) in the entire study sample, Model 1. When the multivariate model was adjusted for BMI in 134 individuals for whom BMI information at the time of the index hospital admission was available, Model 2, BMI was a confounder but not an independent predictor, increasing the OR for statin from 3.2 to 8.1 (95% CI 1.9, 33.7, p -value 0.004). Furthermore, even among individuals with LDL < 130 mg/dl ($n=144$), Model 3, statin use was associated with increased odds of aPL/LAC+, OR 4.9 (95% CI 1.4, 17.0), adjusted for age, gender, and ethnicity ($p=0.012$). In the LDL $\geq$ 130 mg/dl group ($n=64$), the relationship between statins and aPL levels was not statistically significant, however, this was a relatively small sample size. Finally, when we performed multivariate analysis in the subgroup of 164 individuals with LDL $\geq$ 70 mg/dl, Model 4, using the LDL cut-off for coronary artery disease [21], statin use was associated with OR of 5.2 (95% CI 1.9, 14.5) of aPL/LAC+, compared with no statin use, adjusted for age, ethnicity and gender ($p=0.002$). The association between statin use and aPL/LAC+ was also significant when aPL positivity was defined as only anti-beta2 IgG/IgM or anticardiolipin IgG/IgM $\geq$ 40 units, OR 2.6 (95% CI 1.04, 6.3), adjusted for gender and ethnicity ($p=0.04$).

Statin use was associated with aPL+ alone in the bivariate and multivariate analysis, unadjusted OR 3.5 (95% CI 1.2, 11, $p = 0.003$). There was a borderline statistically

significant association between statin use and LAC positivity alone ($p=0.06$). Neither aspirin nor warfarin use was significantly associated with aPL Ab levels and/or LAC+.

Finally, to explore some of the potential biases related to the retrospective nature of this study, we performed further subgroup analyses. We limited our analysis to patients in whom the diagnoses of DVT, PE, or CVA were confirmed by appropriate imaging: a venous duplex for DVT, a ventilation/perfusion scan or a CT scan for PE, or magnetic resonance imaging for CVA. We excluded patients with the diagnoses of HIV ($n=10$), malignancy ($n=11$), or hepatitis C ($n=8$), as these conditions are known to be associated with elevated aPL levels. Furthermore, to minimize misclassification bias and to decrease heterogeneity, we performed a subgroup analysis including only patients who had a known history of hyperlipidemia or who had lipids measured within 30 days from the index admission. The results of all of the subgroup analyses were similar to the results obtained for the entire study cohort (not shown), suggesting that this was not simply a spurious association due to multiple comparisons.

DISCUSSION

The main objective of this study was to explore the relationship between elevated aPL Ab levels, medication use, and the presence of traditional risk factors for arterial/venous thrombosis (Figure 1). In this cross-sectional data analysis from a large, tertiary academic medical center we did not find any significant associations between aPL+ and/or LAC+ and age, smoking, history of hypertension, or history of Type 2 diabetes in patients hospitalized with a thrombotic event. The 11% frequency of aPL+ and/or LAC+ in this highly selected sample was only slightly higher than in the general population (5%), but lower than in lupus patients (30%) [23].

Interestingly, we found that statin use was associated with increased odds of elevated aPL Ab levels, even when adjusting for age, ethnicity, and gender. Since we did not have information about the duration and history of hyperlipidemia or its treatment in our study cohort, we could not evaluate whether there was an association between long-standing hyperlipidemia and aPL Ab/LAC+. Thus, there are 2 possible interpretations of our results discussed below.

Statin therapy is associated with increased aPL levels

Previous studies have shown that statins reverse the proinflammatory and prothrombotic effects of aPL Abs *in vitro* [24] and in mice [25], and that statins reduce proinflammatory and prothrombotic markers in patients with antiphospholipid antibody syndrome [26, 27]. Therefore, based on the results of our study, it would appear that the anti-inflammatory and antithrombotic actions of statins are independent of aPL levels. This finding would be important for designing future studies investigating the role of statins in aPL treatment [4], and for understanding the causal sequence among elevated lipids, statin treatment, elevated aPL levels and thrombotic events. Further studies are needed to determine whether or not aPL Abs associated with statin use are thrombogenic.

Alternatively, if statins serve as a proxy for the history of hyperlipidemia and/or a history of higher LDL values, it is possible that long-standing hyperlipidemia which triggers statin use in clinical practice [28] and not statin use per se, may be associated with higher aPL Abs. There is evidence that endothelial dysfunction and early arterial endothelial damage that would occur in chronic hyperlipidemia may contribute to the exposure of phospholipids to the outer cell surface, which, in turn, facilitates antibody formation and the interaction of the antibodies with the phospholipid bilayer [1], resulting in high levels of aPL Abs and or LAC+. Therefore, in some individuals aPL levels may reflect the degree and the duration of

endothelial damage caused by hyperlipidemia. This suggests that aPL Abs may have developed in individuals with hyperlipidemia before they were treated with statins, and persisted even after treatment with statins was initiated.

To test these hypotheses generated from our data analysis, we plan to conduct further studies measuring aPL levels before and after initiation/withdrawal of statin therapy. We did not have information about other measures of endothelial dysfunction, therefore, we plan future studies to look at a possible association between aPL Ab levels and various measures of endothelial dysfunction including high sensitivity C-reactive protein, fibrinogen, intimal medial thickening measured by carotid ultrasound, and coronary artery calcium scores measured by CT scan [29, 30]. Furthermore, we also plan to evaluate the relationship between statin use, thrombotic events and aPL Abs in lupus patients in a large lupus cohort at our center, to determine if there is a similar relationship between statin use in SLE patient with hyperlipidemia and aPL Abs.

Our study has several other potential limitations, mainly related to the retrospective nature of this analysis and the possibility for differential selection for aPL Ab/LAC testing. We could not determine the duration of aPL+ and/or LAC+, changes in aPL levels over time, or the direction of causality. Furthermore, aPL Abs may be transiently elevated after an acute event in some patients [2, 31]. Complete information on medication compliance, and family history was not available. BMI, erythrocyte sedimentation rate, and C-reactive protein information was available for only a small subset of patients; however, none of these markers of inflammation was independently associated with aPL+ and/or LAC+, although individuals with aPL/LAC+ appeared to have a borderline statistically significant association with higher C-reactive protein levels ($p=0.07$). However, because of the relatively small sample size and a possible selection bias, this information should be interpreted with caution. We plan future prospective studies to address some of these limitations.

Despite of the limitations discussed above, our study has several important strengths. We compared data for IgG, IgM, and IgA isotypes for the 3 aPL Ab subtypes (aCL, anti-b2GPI, and aPS), and LAC at the same time. The frequency of aPL and/or LAC positivity in our study is comparable to what was previously reported [32, 33]. However, this is one of the very few studies that reflects a real world experience from a large urban tertiary care center and describes the frequency of aPL/LAC and associated risk factors in a hospital-based population in the United States. Based on our literature review, the association between statin use and aPL levels has not been previously reported.

Conclusion

Statin use may be associated with elevated aPL levels independent of the thrombosis risk. More likely, high levels of aPL Abs may reflect long-standing endothelial damage caused by past hyperlipidemia. If confirmed in large prospective studies, this finding will have important implications for designing future epidemiologic and interventional studies investigating the role of medications in aPL+ and/or LAC+ individuals and for risk stratification of aPL+ and/or LAC+ individuals in clinical practice. Furthermore, as statin use is being extended to additional patient populations, such as normal LDL with elevated high sensitivity CRP [34] or with varying levels of coronary artery calcium scores [30], and with the expectation that statins may become available without a prescription, the clinical significance of these associations will become of even greater importance.

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REFERENCES

1. Levine JS, Branch DW, Rauch J. The antiphospholipid syndrome. *N Engl J Med*. 2002; 346:752–63. [PubMed: 11882732]
2. Miyakis S, Lockshin MD, Atsumi T, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). *J Thromb Haemost*. 2006; 4:295–306. [PubMed: 16420554]
3. Palomo I, Segovia F, Ortega C, et al. Antiphospholipid syndrome: a comprehensive review of a complex and multisystemic disease. *Clin Exp Rheumatol*. 2009; 27:668–77. [PubMed: 19772805]
4. Erkan D, Lockshin MD. New approaches for managing antiphospholipid syndrome. *Nat Clin Pract Rheumatol*. 2009; 5:160–70. [PubMed: 19252521]
5. Meroni PL, Riboldi P. Pathogenic mechanisms mediating antiphospholipid syndrome. *Curr Opin Rheumatol*. 2001; 13:377–82. [PubMed: 11604591]
6. Bordin G, Boldorini R, Meroni PL. The two hit hypothesis in the antiphospholipid syndrome: acute ischaemic heart involvement after valvular replacement despite anticoagulation in a patient with secondary APS. *Lupus*. 2003; 12:851–3. [PubMed: 14667102]
7. Barbhaiya M, Erkan D. Primary thrombosis prophylaxis in antiphospholipid antibody-positive patients: where do we stand? *Curr Rheumatol Rep*. 2011; 13:59–69. [PubMed: 21104348]
8. Galli M, Barbui T. Antiphospholipid antibodies and thrombosis: strength of association. *Hematol J*. 2003; 4:180–6. [PubMed: 12764350]
9. Erkan D, Lockshin MD. Antiphospholipid syndrome. *Curr Opin Rheumatol*. 2006; 18:242–8. [PubMed: 16582686]
10. Derksen RH, de Groot PG. Towards evidence-based treatment of thrombotic antiphospholipid syndrome. *Lupus*. 2010; 19:470–4. [PubMed: 20353990]
11. Petri M. Evidence-based management of thrombosis in the antiphospholipid antibody syndrome. *Curr Rheumatol Rep*. 2003; 5:370–3. [PubMed: 12967519]
12. Khamashta MA, Cuadrado MJ, Mujic F, et al. The management of thrombosis in the antiphospholipid-antibody syndrome. *N Engl J Med*. 1995; 332:993–7. [PubMed: 7885428]
13. Erkan D, Yazici Y, Peterson MG, et al. A cross-sectional study of clinical thrombotic risk factors and preventive treatments in antiphospholipid syndrome. *Rheumatology (Oxford)*. 2002; 41:924–9. [PubMed: 12154210]
14. Greco TP, Conti-Kelly AM, Matsuura E, et al. Antiphospholipid antibodies in patients with coronary artery disease: new cardiac risk factors? *Ann N Y Acad Sci*. 2007; 1108:466–74. [PubMed: 17894011]
15. Neville C, Rauch J, Kassis J, et al. Thromboembolic risk in patients with high titre anticardiolipin and multiple antiphospholipid antibodies. *Thromb Haemost*. 2003; 90:108–15. [PubMed: 12876633]
16. Ruffatti A, Del Ross T, Ciprian M, et al. Risk factors for a first thrombotic event in antiphospholipid antibody carriers. A multicentre, retrospective follow-up study. *Ann Rheum Dis*. 2009; 68:397–9. [PubMed: 18812393]
17. Roubey RA. Risky business: the interpretation, use, and abuse of antiphospholipid antibody tests in clinical practice. *Lupus*. 2010; 19:440–5. [PubMed: 20353985]
18. Marai I, Shechter M, Langevitz P, et al. Anti-cardiolipin antibodies and endothelial function in patients with coronary artery disease. *Am J Cardiol*. 2008; 101:1094–7. [PubMed: 18394439]
19. Erkan D, Harrison MJ, Levy R, et al. Aspirin for primary thrombosis prevention in the antiphospholipid syndrome: a randomized, double-blind, placebo-controlled trial in asymptomatic antiphospholipid antibody-positive individuals. *Arthritis Rheum*. 2007; 56:2382–91. [PubMed: 17599766]

20. Bellin E, Fletcher DD, Geberer N, et al. Democratizing Information Creation From Health Care Data for Quality Improvement, Research, and Education-The Montefiore Medical Center Experience. *Acad Med*. 2010
21. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP). Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA*. 2001; 285:2486–97. [PubMed: 11368702]
22. Lemeshow S, Hosmer DW Jr. A review of goodness of fit statistics for use in the development of logistic regression models. *Am J Epidemiol*. 1982; 115:92–106. [PubMed: 7055134]
23. Petri M. Epidemiology of the antiphospholipid antibody syndrome. *J Autoimmun*. 2000; 15:145–51. [PubMed: 10968901]
24. Ferrara DE, Swerlick R, Casper K, et al. Fluvastatin inhibits up-regulation of tissue factor expression by antiphospholipid antibodies on endothelial cells. *J Thromb Haemost*. 2004; 2:1558–63. [PubMed: 15333031]
25. Ferrara DE, Liu X, Espinola RG, et al. Inhibition of the thrombogenic and inflammatory properties of antiphospholipid antibodies by fluvastatin in an in vivo animal model. *Arthritis Rheum*. 2003; 48:3272–9. [PubMed: 14613293]
26. Ferrara DE, Pierangeli SS. Diverse effects of statins on endothelial cells? *Thromb Haemost*. 2005; 93:186–8. [PubMed: 15711729]
27. Jajoria P, Murthy V, Papalardo E, et al. Statins for the treatment of antiphospholipid syndrome? *Ann N Y Acad Sci*. 2009; 1173:736–45. [PubMed: 19758223]
28. Boden WE. Therapeutic implications of recent ATP III guidelines and the important role of combination therapy in total dyslipidemia management. *Curr Opin Cardiol*. 2003; 18:278–85. [PubMed: 12858126]
29. Corrado E, Rizzo M, Coppola G, et al. An update on the role of markers of inflammation in atherosclerosis. *J Atheroscler Thromb*. 2010; 17:1–11. [PubMed: 20032572]
30. Blaha MJ, Budoff MJ, DeFilippis AP, et al. Associations between C-reactive protein, coronary artery calcium, and cardiovascular events: implications for the JUPITER population from MESA, a population-based cohort study. *Lancet*. 2011; 378:684–92. [PubMed: 21856482]
31. Pengo V, Banzato A, Bison E, et al. Antiphospholipid syndrome: critical analysis of the diagnostic path. *Lupus*. 2010; 19:428–31. [PubMed: 20353982]
32. Coull BM, Levine SR, Brey RL. The role of antiphospholipid antibodies in stroke. *Neurol Clin*. 1992; 10:125–43. [PubMed: 1556999]
33. Ginsberg JS, Wells PS, Brill-Edwards P, et al. Antiphospholipid antibodies and venous thromboembolism. *Blood*. 1995; 86:3685–91. [PubMed: 7579334]
34. Ridker PM, Danielson E, Fonseca FA, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med*. 2008; 359:2195–207. [PubMed: 18997196]

KEY POINTS

- Persistently high levels of aPL Abs and LAC positivity are associated with an increased risk of arterial and/or venous thrombosis in autoimmune diseases such as lupus and antiphospholipid syndrome
- It is not well understood whether high levels of aPL Abs constitute an additional risk factor for thrombosis in individuals without autoimmune diseases.
- In our study we did not find an association between aPL/LAC+ and the presence of the traditional cardiovascular or thrombosis risk factors in individuals without autoimmune diseases who were admitted to the hospital with DVT, PE or CVA.
- We found that statin use was associated with increased odds of aPL/LAC+, even after adjusting for age, ethnicity and gender.
- If statins serve as a proxy for the history of hyperlipidemia, it is possible that long-standing hyperlipidemia, which triggers statin use in clinical practice, may be associated with higher antiphospholipid antibodies.
- If confirmed in prospective studies, this finding will have important implications for designing future epidemiologic and interventional studies investigating the role of medications in antiphospholipid antibody-positive individuals and for risk stratification of antiphospholipid antibody-positive individuals in clinical practice.

Figure 1.

The proposed relationship between thrombosis, aPL+ and/or LAC+, traditional risk factors for thrombosis, and medications

APL Ab and/or LAC positivity are considered to be independent risk factors for arterial and venous thrombosis. However, it is unknown if aPL Ab levels and/or LAC+ are associated with medications and with traditional risk factors for thrombosis in individuals without autoimmune diseases. The objective of our study was to explore these associations.

Table 1

Demographic characteristics of CVA patients with and without aPL Abs/LAC measured within 6 months

	aPL Abs/LAC N = 190	no aPL Abs/LAC N = 2610	Differences (95% CI)	p-value
Age, years, mean (SD)	51(12)	72(14)	21 (20, 24)	<0.0001
Gender n (%) female	91 (52)	1441 (55)	3 (−4, 10)	0.40
Race, n (%) Black	101 (56)	1284 (49)	−7 (−15, 2)	0.14
Ethnicity, n (%) Hispanics	76 (42)	865 (33)	−9 (−16, −1)	0.02

Table 2

Demographic characteristics of DVT patients with and without aPL Abs/LAC measured within 6 months

	aPL Abs/LAC N = 101	no aPL Abs/LAC N = 1114	Differences (95% CI)	p-value
Age, years, mean (SD)	52 (16)	69 (16)	17 (14, 20)	<0.0001
Gender n (%) female	45 (47)	706 (63)	16 (5, 25)	0.004
Race, n (%) Black	59 (62)	571 (51)	-11 (-22 0)	0.10
Ethnicity, n (%) Hispanics	29 (31)	370 (33)	2 (-8, 12)	0.71

Table 3

Bivariate analysis comparing aPL+ and/or LAC+ and aPL– and LAC– groups

	Total N = 270	aPL/LAC+ N = 31	aPL/LAC– N = 239	Differences (95% CI)	p-value
Age , mean (SD)	51(13)	54(14)	51(13)	–3 (–8, 3)	0.35
Gender, n (%) female	132 (49)	16 (52)	116 (49)	–3 (–22, 16)	0.75
Race, n (%) * Black	119 (59)	14 (56)	105 (59)	3 (–18, 24)	0.73
Ethnicity, n (%) ** Hispanics	95 (39)	9 (33)	86 (39)	6 (–14, 26)	0.56
T2DM n (%)	72 (27)	8 (26)	64 (28)	2 (–13, 16)	0.82
HDL, mg/dl, mean (SD) ***	47(14)	45(11)	47(14)	2 (–4, 8)	0.66
LDL, mg/dl, mean (SD) ***	112	121(57)	111(39)	–10 (–28, 8)	0.66
Triglycerides, mg/dl, mean (SD) ****	143 (95)	138 (54)	145 (97)	7 (–39, 52)	0.38
Statins, n (%)	57 (21)	12 (39)	45 (19)	–19 (–35, –4)	0.01
Aspirin use , n (%)	52 (20)	8 (27)	44 (19)	–7 (–23, 8)	0.35
History of HTN, n (%)	157 (60)	21 (68)	136 (59)	–9 (–27, 10)	0.34
Oral contraceptives, n (%)	9 (4)	0	9 (4)	4 (–3, 11)	0.31
Warfarin, n (%)	24 (9)	3 (10)	21 (9)	–1 (–11, 10)	0.90
Season, n(%) June- September	180 (67)	21 (68)	159 (67)	–1 (–19, 17)	0.89
Smoking, n (%)	47 (18)	5 (17)	42 (18)	1 (–14, 16)	0.35
BMI, kg/m ² , mean (SD) *****	30 (8)	28 (6)	30 (8)	2 (–3, 6)	0.51

* Race not available for 67 patients

** Ethnicity not available for 24 patients

*** HDL/LDL data not available for 62 patients

**** Triglycerides data not available for 104 patients

***** BMI not available for 124 patients

Table 4

Logistic regression models of the relationship between statin use and aPL+ and/or LAC+

	OR of aPL/LAC+ for statin users	95% CI	p-value
Unadjusted (n = 270)	2.6	1.2, 5.8	0.02
Model 1, adjusted for age, gender, ethnicity (n = 246)	3.2	1.3, 7.9	0.01
Model 2, same as above, adjusted for BMI (n = 134)	8.1	1.9, 33.7	0.004
Model 3, same as Model 1, restricted to LDL < 130 mg/dl (n = 144)	4.9	1.4, 17.0	0.01
Model 4, same as Model 1, restricted to LDL < 70 mg/dl (n = 164)	5.2	1.9, 14.5	0.002