Antiphospholipid Antibodies and Venous Thromboembolism

By J.S. Ginsberg, P.S. Wells, P. Brill-Edwards, D. Donovan, K. Moffatt, M. Johnston, P. Stevens, and J. Hirsh

The clinical relevance of antiphospholipid antibodies (APLA) in patients without systemic lupus erythematosus who have venous thromboembolism (VTE) is unknown. Limited evidence suggests that there is an association between the presence of APLA and both initial and recurrent episodes of VTE and that patients with APLA and VTE are resistant to warfarin therapy. Unselected patients with a first episode of clinically suspected deep vein thrombosis or pulmonary embolism were evaluated with objective tests for VTE and with laboratory tests for APLA; the latter included tests for the lupus anticoagulant (LA) and anticardiolipin antibodies (ACLA). Patients with VTE were treated with anticoagulant therapy and observed during and after discontinuation of anticoagulants for symptomatic recurrence of VTE. There was a strong association between LA and VTE (odds ratio, 9.4; 95% confidence interval [CI], 2.1 to 46.2) and 9 of 65 (14%; 95% CI, 7% to 25%) patients with VTE had LA. There was no association between the presence of ACLA and VTE (odds ratio, 0.7; 95%CI, 0.3 to 1.7) because of the high frequency of positive ACLA assays in patients without VTE. None of the 16 patients with VTE and APLA developed recurrent VTE while receiving warfarin therapy. There was no difference in rates of recurrent VTE in patients with or without APLA after anticoagulant therapy was discontinued. The strong association between LA and VTE suggests that testing for LA in patients with VTE is useful. The measurement of ACLA in patients with VTE has no clinical usefulness because the results are abnormal in a high proportion of patients without VTE. Although the presence of APLA in patients with VTE was not associated with resistance to a conventional intensity of warfarin or an increased risk of recurrent VTE after discontinuation of warfarin, a larger study should address these issues in a subgroup of patients with VTE and LA.

ANTIPHOSPHOLIPID antibodies (APLA) are a heterogeneous group of antibodies that can be detected as lupus anticoagulants (LA) and anticardiolipin antibodies (ACLA).[1] It is generally assumed that an association exists between APLA and venous thromboembolism (VTE). This assumption is based primarily upon the results of cross-sectional studies of patients with systemic lupus erythematosus (SLE).[2-23] The results of studies in patients with SLE cannot be extrapolated to patients without SLE because the prevalence of APLA in patients with SLE is very high (30% to 50%) and patients with SLE have a high prevalence of VTE, even in the absence of APLA.[23] The evidence supporting an association between APLA and VTE in patients without SLE is weak and consists of case reports, case series, and one prospective nested case-control study.[4,5,7,9,15,19,20,24-30] The latter, a substudy of the Physician's Health Study, found an association between deep vein thrombosis (DVT)/pulmonary embolism (PE) and ACLA in healthy adult men.[24] Unfortunately, assays to measure the LA were not performed and the method(s) of diagnosing or excluding DVT and PE was not stated. In addition, a recent cross-sectional study of unselected patients with suspected DVT or PE showed no significant association between VTE and ACLA; tests for LA were not performed.[30]

Despite the lack of convincing evidence of an association between VTE and APLA in non-SLE patients, the presence of APLA influences the management approach used by many physicians. Thus, clinicians who believe that such an association exists and that patients with VTE and APLA are prone to recurrences prescribe long-term anticoagulants in non-SLE patients with VTE and APLA. In many centers, assays to measure APLA are performed routinely in screening patients for hypercoagulable states. Finally, based on the results of two retrospective studies that suggested that patients with APLA and VTE were resistant to usual intensities of warfarin, it has been recommended that such patients should be treated with warfarin therapy to achieve an international normalized ratio (INR) of 3.0 or more.[31,32] These practices are only justifiable if there is an association between APLA and VTE, if the prevalence of APLA in patients with VTE is sufficiently high to be clinically meaningful, and if the presence of APLA in patients with VTE is associated with a high rate of recurrence during conventional anticoagulant therapy and/or when anticoagulants are discontinued.

To address these issues, we performed a prospective cohort study of unselected outpatients with suspected DVT or PE. To determine whether there is an association between APLA and VTE in patients without SLE, all patients underwent objective tests for DVT or PE and laboratory tests for APLA. In addition, patients with VTE were treated with usual intensities and duration of anticoagulants and observed prospectively for recurrent VTE to determine whether non-SLE patients with VTE and APLA are prone to recurrence while receiving conventional intensities of warfarin and after discontinuing anticoagulants.

PATIENTS AND METHODS

Informed consent was obtained from all patients after the study had been explained. The study was approved by the Institutional Review Board of Chedoke-McMaster Hospitals.

Study population. Consecutive patients referred to the thromboembolism consultants at Chedoke-McMaster hospitals with clinically suspected PE or DVT between August 1992 and April 1994 were potentially eligible for the study. The following were exclusion crite-

From The Departments of Medicine and Laboratory Medicine, McMaster University, Hamilton, Ontario, Canada.

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Address reprint requests to J.S. Ginsberg, MD, McMaster University Medical Centre,1200 Main St W, HSC-3W11, Hamilton, Ontario, Canada L8N 3Z5.

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ria: previously diagnosed SLE, because the objective of this study was to elucidate an association between VTE and APLA in patients without SLE; and previous objectively documented DVT or PE, because this could constitute a group of patients that is likely to have a greater susceptibility to thromboembolic recurrence. All patients were seen by a consultant of the thromboembolism service and underwent an examination of patient history and a physical examination.

Investigations for PE and DVT. In patients with suspected PE, ventilation perfusion (V/Q) lung scanning was performed within 24 hours of presentation using a previously described technique.[33] Some patients were treated with overnight heparin therapy while awaiting investigations. The results of lung scanning were classified as normal (if the perfusion scan was normal), high probability (segmental or greater perfusion defects with normal ventilation), or non-high probability (all other patterns).[33] All patients also underwent bilateral impedance plethysmography (IPG) within 24 hours of presentation, which was performed and interpreted according to a previously described technique.[34] Patients with non-high probability scans and a normal initial IPG underwent serial IPG testing on days 2, 5, 7, 10, and 14; in patients whose IPG results remained normal, follow-up for 3 months for the presence or absence of VTE by clinical evaluation and repeat IPG was performed, whereas in patients whose IPG became abnormal, venography was performed to confirm the presence of DVT and anticoagulant therapy was initiated. The validity of this approach has been shown by clinical trial.[35] Five patients underwent pulmonary angiography at the request of attending physicians and were included in the study.

According to the results of the lung scanning, IPG, contrast venography (when applicable), and pulmonary angiography (when applicable) patients were classified as follows: (1) PE-positive when one of the following occurred: (a) positive pulmonary angiography, (b) high probability lung scan, or (c) non-high probability lung scan and either abnormal IPG (either at presentation or upon serial testing and confirmed by venography) or symptomatic venous thromboembolic event, verified by objective testing, within 3 months of presentation; or (2) PE-negative when one of the following occurred: (a) normal perfusion lung scan, (b) normal pulmonary angiography, or (c) non-high probability lung scan and normal serial IPG and absence of VTE within 3 months of follow-up.

In patients with suspected DVT, all episodes of DVT were confirmed by venous ultrasonography or contrast venography, whereas DVT was considered to be excluded only in patients having a normal venogram. Ascending contrast venography was performed using the Rabinov and Paulin technique[36] and DVT was considered to be present if a persistent intraluminal filling defect was identified in two or more views. In patients in whom contrast venography could not be performed on the day of presentation, venous ultrasound of the proximal veins of the symptomatic leg was performed.[37] If ultrasound was performed before venography and the results showed a definite thrombus in the popliteal or femoral vein, venography was not performed because the rate of true-positivity of a noncompressible venous segment on venous ultrasound is very high and only clear-cut results were accepted as positive.[37] However, if the ultrasound was normal, contrast venography was performed to determine whether the patient had calf DVT or proximal DVT that was not detected by ultrasound. Patients with suspected DVT were excluded from analysis if they had normal results from ultrasound and either no venography or inadequate venography.

Venous ultrasonography of the proximal veins was performed using an Accuson Model 128 with a 5 MHz linear array probe (Accuson, Mountain View, CA), as described previously.[37]

Management and follow-up of patients with VTE. All patients with DVT or PE were admitted to hospital and an intravenous infusion of heparin was initiated. The dose of heparin was adjusted to maintain an activated partial thromboplastin time of 60 to 85 seconds, a range that corresponds to a heparin level of 0.2 to 0.4 U/mL by protamine sulfate titration.[38] Warfarin was initiated on the day of or the day after admission and an INR of 2.0 to 3.0 was targeted. Heparin was discontinued after a minimum of 5 days and provided the INR was 2.0 or greater on two consecutive samples at least 24 hours apart. Patients were discharged home on warfarin therapy and the duration of warfarin was left to the discretion of the attending physicians.

All patients were carefully advised about symptoms of possible recurrent DVT and PE and were told to return to hospital immediately if such symptoms developed. All living patients were contacted by telephone in July 1994 to determine their clinical status and to inquire about symptoms or diagnosis of recurrent VTE. Patients with suspected recurrent DVT underwent repeat contrast venography and recurrence was diagnosed if a new intraluminal filling defect was seen. In patients with suspected recurrent PE, a lung scan was repeated and recurrence diagnosed if a new segmental defect in perfusion with normal ventilation was seen.

Laboratory methods. At the time of initial presentation, blood was drawn into a vacutainer tube (Becton Dickinson, Mountain View, CA) containing 0.105 mol/L buffered citrate. Plasma was immediately separated from cellular elements by centrifugation at 1,700*g* for 15 minutes at 4°C. To assure platelet-free plasma, the plasma was removed from the cells, placed into a clean tube, and centrifuged again for 5 minutes. The plasma was removed and frozen at −70°C until batch assays were performed.

To detect APLA, an enzyme-linked immunosorbent assay (ELISA) for ACLA and three different assays for LA were performed. A commercially available, standardized ELISA kit (Advanced Biological Products, Mississauga, Canada) was used to quantitate IgG ACLA; the standard of this kit was referenced against the International Preparation of the Phospholipid Standardization Laboratory, University of Louisville (Louisville, KY). A normal range was established and levels of ≥30 gamma phospholipid (GPL) units were considered to be abnormal; this cutoff is approximately 3 standard deviations (SD) greater than the mean of 50 controls. We also performed a secondary analysis using an a priori cut-point of 50 GPL units, which corresponds to 10 SD greater than the mean, a result that we considered to represent a high titer ACLA.

Three tests were used to detect the presence of LA: (1) dilute Russell viper venom time (DRVVT), (2) the dilute one-stage prothrombin time (DPT), and (3) the activated partial thromboplastin time (aPTT). The DRVVT was performed using commercially available screening and confirmatory tests (American Diagnostica, Greenwich, CT).[39] For the DPT and the aPTT, patient samples were run neat and in a 1:1 mix of normal pooled plasma consisting of plasma from 20 normal hospital personnel. The DPT was performed using a 1/500 dilution of rabbit brain thromboplastin (Dade Thromboplastin C) in a saline $CaCl_2$ mixture,[40] whereas the aPTT was performed using a commercially available reagent, PTT-LA (Diagnostica Stago, Guelph, Canada).[41] DPT and aPTT results for the 1:1 mix that were greater than the upper limit of normal (3 SD greater than the mean) were considered to be abnormal. If the DPT or aPTT was abnormal, the result was confirmed using an hexagonal phospholipid assay (Stagclot assay; Diagnostica Stago, Guelph, Canada). Briefly, this assay is performed by mixing test plasma and hexagonal phase phospholipid in one test tube and test plasma and buffer in another test tube. The tubes are incubated at 37°C for 9 minutes and normal plasma and aPTT reagent are added to both tubes. After 5 minutes of incubation, $CaC1_2$ is added to both tubes and the clotting times are measured. If an LA is present, the antibody will be neutralized by the addition of the hexagonal phase phospholipid and the clotting time will become normal, whereas the clotting time in the tube with

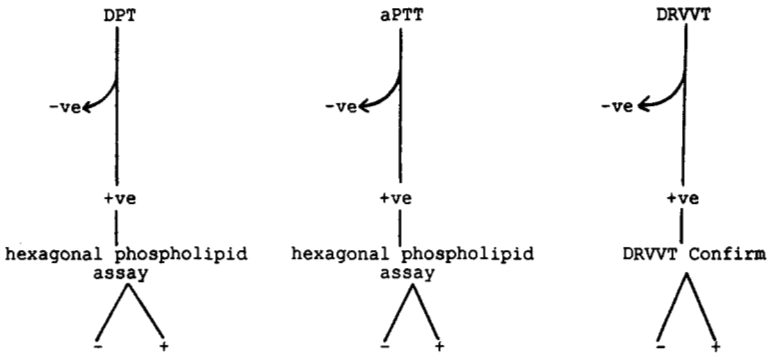

Fig 1. Summary of LA testing. Patients were classified as LA-positive if DPT and/or aPTT and hexagonal phospholipid assays were positive or DRVVT and its confirmatory test were positive. All other patients were classified as negative for LA.

buffer only will remain prolonged. A discrepancy of more than 8 seconds was considered to be positive for LA.

Results for the DRVVT, DPT, and aPTT were considered to be abnormal only if both screening and confirmatory tests were abnormal. A priori for the analysis, patients were categorized as positive for LA if one or more of the tests was abnormal and were categorized as negative for LA if all tests were normal (Fig 1).

Avoidance of bias and cointervention. The results of APLA were not disclosed to the physicians caring for the patients and their performance outside of the study setting was strongly discouraged. In addition, the aPTT reagent used in our institution is insensitive to LA and, therefore, the presence of LA could not be inferred by the presence of a prolonged baseline aPTT. Therefore, it is highly likely that the management of the patient population was performed without knowledge of the APLA status of the patients. The laboratory personnel performing the APLA assays were blinded to the clinical status of the patients.

Statistics. Data were organized into 2 × 2 contingency tables according to the DVT/PE status of the patients and the presence or absence of APLA. Odds ratios (OR) and the corresponding 95% confidence intervals (CI) were calculated where indicated using the statistical program Metstat (Suskin and Super, Cleveland, OH). An OR was considered to be statistically significant when the lower limit of the 95% CI was ≥1.0. Proportions were compared using the χ^2 test and, where indicated, 95% CI of proportions were calculated according to the binomial distribution. Event-free survival curves for patients with VTE who discontinued warfarin treatment were calculated using the Kaplan-Meier method and were compared using the Mantel-Haenszel test.[42] A P value of ≤.05 was considered to be statistically significant.

RESULTS

Two hundred fifty-six potentially eligible patients were evaluated during the study period, 115 with suspected DVT and 141 with suspected PE. All patients with suspected PE were included in the final analysis, whereas 12 patients with suspected DVT were excluded from the primary analysis because they did not have technically adequate venography. Therefore, 244 patients (158 women) with a mean age of 55 years (range, 17 to 89 years) were enrolled into the study and included in the final analysis: 141 with suspected PE and 103 with suspected DVT. Sixty-five (27%) of the patients were classified as VTE-positive (22 of 141 [16%] with PE and 43 of 103 [42%] with DVT). Of the VTE-positive patients, 36 of 65 (55%) were women, compared with 122 of 179 (68%) women in the VTE-negative group (P = .09).

Fifty-one of 244 patients (21%) had APLA. Of the patients with suspected PE, 28 of 119 (24%) PE-negative patients had APLA (25 with ACLA only and 3 with LA only) and 7 of 22 (32%) PE-positive patients had APLA (2 with ACLA only and 5 with LA only). Of the patients with suspected DVT, 7 of 60 (12%) DVT-negative patients had APLA (all with ACLA alone) and 9 of 43 (21%) DVT-positive patients had APLA (2 with LA alone, 5 with ACLA alone, and 2 with both LA and ACLA). Therefore, of the 51 patients with APLA, only 2 had both ACLA and LA, whereas the remaining 49 had either LA or ACLA. The titers of ACLA and VTE status of the patients are summarized in Table 1.

The associations between APLA and VTE are summarized in Tables 2, 3, and 4. A strong and statistically significant association is shown between the presence of LA and VTE, whereas no significant association is shown between the presence of ACLA and VTE. This difference is due to the fact that, although the frequency of LA positivity in VTE-positive patients is the same as the frequency of ACLA-positivity in VTE-positive patients (9 of 65 [14%]; 95%CI, 7% to 25%), a much higher proportion of VTE-negative patients have ACLA (32 of 179 [18%]) than have LA (3 of 179 [2%]).

Follow-up of VTE-positive patients. There were 16 patients with VTE who had APLA, 7 with ACLA alone, 7 with LA alone, and 2 with both ACLA and LA; none (0%; 95% CI, 0% to 21%) developed symptomatic recurrent VTE while receiving their initial heparin or warfarin, with a targeted INR of 2.0 to 3.0. Two of these patients died of metastatic cancer; 1 died while still receiving warfarin and 1 patient died 2 months after discontinuing warfarin treatment but had not developed recurrent VTE. Of the 14 patients who were alive at the termination of this study, 4 never discontinued warfarin treatment; 3 continued warfarin treatment as prophylaxis for DVT and 1 because of concomitant atrial fibrillation. Therefore, 11 patients discontinued warfa-

Table 1. Titers of ACLA in Study Population

ACLA Titer (GPL units)	VTE+	VTE−
<30	56	147
30-39	4	20
40-49	1	6
50-80	3	2
>80	1	4

Table 2. Contingency Tables of APLA Status in All Patients

	VTE			
	+	−	OR	95% CI
LA			9.4*	2.1-46.2
+	9	3		
−	56	176		
ACLA (GPL units)			0.7	0.3-1.7
≥30	9	32		
<30	56	147		
ACLA (GPL units)			1.9	0.4-7.9
≥50	4	6		
<50	61	173		
APLA			1.3	0.6-2.8
+†	16	35		
−‡	49	144		

* Results that are statistically significant.
† Either one or more LA tests abnormal and/or ACLA ≥30 GPL units.
‡ All LA tests negative and ACLA ≤30 GPL units.

rin treatment 6 weeks to 6 months (median, 3 months) after identification of their VTE and were followed-up for a mean of 8.7 ± 6.4 months; 2 (18%) developed recurrent VTE, both of whom had LA alone.

There were 49 patients with VTE who did not have APLA. Five of these patients died while receiving warfarin (4 of metastatic cancer and 1 of a nonhemorrhagic stroke) and 1 of these patients had developed recurrent VTE while receiving warfarin. Of the 44 patients who were alive at the termination of this study, 10 never discontinued warfarin treatment. Therefore, 34 patients discontinued warfarin treatment 6 weeks to 1 year after identification of their VTE and were followed-up for a mean of 8.5 ± 5.5 months; 6 (18%) developed recurrent VTE.

Figure 2 shows that there was no significant difference in the event-free survival curves of patients with VTE and APLA and patients with VTE and no APLA after discontinuing warfarin.

Table 3. Contingency Tables of APLA Status in Patients With Suspected PE

	PE			
	+	−	OR	95% CI
LA			11.4*	1.9-68.1
+	5	3		
−	17	116		
ACLA (GPL units)			0.4	0.0-1.9
≥30	2	25		
<30	20	94		
ACLA (GPL units)			1.4	0.4-14.3
≥50	1	4		
<50	21	115		
APLA			1.5	0.5-4.5
+†	7	28		
−‡	15	91		

* Results that are statistically significant.
† Either one or more LA tests abnormal and/or ACLA ≥30 GPL units.
‡ All LA tests negative and ACLA ≤30 GPL units.

Table 4. Contingency Tables of APLA Status in All Patients With Suspected DVT

	DVT			
	+	−	OR	95% CI
LA			13.8	0.9-65.0
+	4	0		
−	39	60		
ACLA (GPL units)			1.5	0.4-5.2
≥30	7	7		
<30	36	53		
ACLA (GPL units)			2.2	0.2-20.0
≥50	3	2		
<50	40	58		
APLA			2.0	0.6-6.7
+*	9	7		
−†	34	53		

* Either one or more LA tests abnormal and/or ACLA ≥30 GPL units.
† All LA tests negative and ACLA ≤30 GPL units.

DISCUSSION

This study of unselected patients with suspected DVT or PE shows that DVT and PE are strongly associated with the presence of LA and that the prevalence of LA is relatively high (14%; 95% CI, 7% to 25%) in patients with DVT or PE. The low prevalence of LA in patients without DVT or PE (3 of 179 [2%]) is consistent with the findings of other studies that reported the presence of LA in 2% of the general population.[43] On the other hand, we showed no association between DVT or PE and ACLA; the prevalence of ACLA was similar in patients with (9 of 65 [14%]) and without (32 of 179 [18%]) DVT or PE. If a higher cut-point for ACLA positivity is used, the OR increases to 1.9, a level that is still not statistically significant. We also showed that, in non-SLE patients with APLA, there is considerable discordance in LA and ACLA results. Although a high level of concordance has been reported between LA and ACLA results in

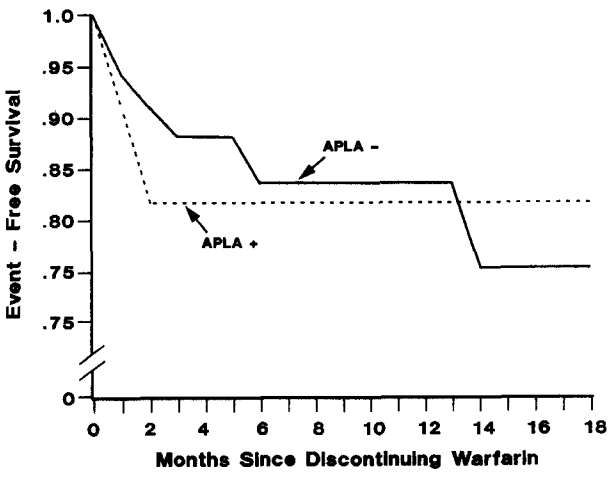

Fig 2. Graph of event-free survival in patients with (APLA+; n = 11) and without (APLA−; n = 34) APLA who discontinued warfarin therapy.

patients with SLE, our results are consistent with other studies that have also shown discordance in LA and ACLA results in patients without SLE.[44,45]

In the subgroup of 16 patients with APLA and VTE who were treated with conventional anticoagulant therapy consisting of an intravenous infusion of heparin for at least 5 days followed by warfarin therapy with a targeted INR of 2 to 3, none developed symptomatic recurrence during treatment. Therefore, our study does not support the recommendation that patients with APLA are resistant to conventional warfarin and, therefore, require a more intense target INR. Of the 11 patients with APLA and VTE who finished warfarin therapy, 2 developed recurrent VTE, a recurrence rate not significantly different than that of patients who had VTE but not APLA. However, the relatively small numbers of patients who discontinued warfarin therapy and the relatively short follow-up do not allow us to make definitive conclusions about whether patients with APLA and VTE have an increased risk of developing recurrent VTE when anticoagulants are discontinued. In particular, a larger number of patients with VTE and LA, which is strongly associated with an initial episode of VTE, should be observed to determine whether this subgroup has a high risk of recurrence.

It is important to address the validity and generalizability of our study, particularly in view of the lack of association between ACLA and DVT or PE and the high degree of discordance of LA and ACLA results in APLA-positive patients. Selection bias was avoided by enrolling consecutive outpatients presenting with suspected DVT or PE. The interpretation of the diagnostic tests for DVT and PE was performed without knowledge of the results of APLA testing and, similarly, the personnel performing APLA testing were unaware of the patient's diagnosis. DVT was diagnosed by either an abnormal venous ultrasound, which has a very high positive predictive value[36] or an abnormal venogram, the reference standard[35]; DVT was excluded only in those patients with a normal venogram. Our classification of patients with suspected PE may be limited because the gold-standard test, pulmonary angiography, was not performed in most patients. Normal lung scans reliably exclude PE, whereas high probability lung scans reliably diagnose PE.[32] However, our classification of patients with non-high lung scans, normal serial IPG, and absence of events in follow-up is less reliable because a very small proportion of patients with PE might be classified as not having PE. However, this would only invalidate our conclusions if a substantial proportion of patients that we misclassified as PE-negative had ACLA. This seems unlikely in view of the similarity of the results in patients with suspected DVT and patients with suspected PE. One potential limitation of our study is the fact that we did not measure levels of protein C, protein S, or antithrombin III or resistance to activated protein C. It is conceivable that the frequency of one of these abnormalities could be higher in the VTE-positive patients than in the VTE-negative patients and that such patients would be less likely to have APLA than patients without one of these abnormalities. However, this confounder should lead to an underestimation of the strength of the association of APLA and VTE and would not refute two of the key observations in our study, ie, the striking association of LA and VTE and the high frequency of ACLA in VTE-negative patients.

In view of the high frequency of abnormal ACLA in patients without VTE and the lack of association of ACLA-positivity with VTE, it is critical to exclude technical factors causing false-positive results. A recent study has shown that there are differences in positivity rates among different commercial kits for ACLA and that this may account for differences in rates of ACLA-positivity.[46] Other studies have reported rates of ACLA-positivity of 12% in VTE-negative controls and in elderly patients; these rates are not inconsistent with ours.[47,48]

Although 18% (32 of 179) of our patients without VTE were classified as positive for ACLA, only 6 of these (19%) had high-titer results ($\geq$50 GPL units). It is possible that nonthrombotic causes of inflammation cause transient, false-positive ACLA results in patients without VTE and that if tests had been repeated, patients with VTE would show persistently positive ACLA results, whereas patients without VTE would normalize their ACLA results. However, this hypothesis would need to be tested by performing serial tests for ACLA.

The plasma samples for ACLA assays were frozen at -70°C for up to 1 year before assay. Recent reports suggest that prolonged storage does not effect ACLA results.[49] The kits used in our study employ standard previously published methodologies and are similar to the kits that we used in showing a strong association between ACLA-positivity and both pregnancy loss and thromboembolism in patients with SLE. Although we were unable to show an association between ACLA-positivity and VTE using a cut-point of 30 GPL units (3 SD greater than the mean of 50 normals), there is the possibility of a type II error. However, the 95% CI suggest it is unlikely that the true OR is greater than 1.7 (the upper limit of the 95% CI). The OR increases when a higher cut-point is used, but not to a level that is statistically significant.

Previous studies by ourselves and others have shown that the presence of persistent APLA-positivity in patients with SLE is more strongly associated with pregnancy loss and thromboembolic complications than transient positivity or persistent negativity.[50-52] This study was not designed to address the issue of persistent positivity, but future studies should be performed to address the clinical relevance in patients without SLE.

To summarize, our study has shown an association between LA-positivity and VTE and a relatively high prevalence of LA-positivity in patients with VTE. There was a high rate of ACLA-positivity in patients without VTE that negated an association between ACLA-positivity and VTE. The presence of APLA in patients with VTE was not associated with resistance to a conventional intensity of warfarin nor did it identify a high-risk group for recurrent VTE; however, the relatively small numbers and short follow-up limit these conclusions. Future studies should be designed to address these issues and to determine the importance of persistent versus transient APLA positivity.

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