# Antiphospholipid Antibodies and Incidence of Venous Thrombosis in a Cohort of Patients with Systemic Lupus Erythematosus

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***ABSTRACT***. ***Objective***. To study the relationship between antiphospholipid antibodies (aPL) and the incidence of venous thrombosis (VT) among patients with systemic lupus erythematosus (SLE).

***Methods***. The study population consisted of 678 patients with SLE enrolled in the Hopkins Lupus Cohort. Medical records were reviewed to identify the occurrence of VT prior to cohort entry. During cohort participation, VT was diagnosed by ultrasound or venography. Lupus anticoagulant [LAC, Russell viper venom time (RVVT) assay] and anticardiolipin (aCL, polyclonal assay) status of each subject was determined on a quarterly basis. The Kaplan-Meier approach was used to estimate probability of having a VT over time since SLE diagnosis. The association between the most recently measured values of LAC and aCL on the subsequent risk of VT was estimated using Cox proportional hazards models.

***Results***. Counting only first occurrences, the rate of VT was 5.1 cases per 1000 person-years. Of those with a mean RVVT greater than 37 s during followup, an estimated 42% will develop a VT within 20 years of SLE diagnosis [95% confidence interval (CI) 21% to 63%, $p < 0.0001$ compared to those with lower RVVT]. The immediate risk (hazard) of deep venous thrombosis increased 34% with each 5 second prolongation of the RVVT test, based on the most recent assessment of RVVT, controlling for gender and cholesterol [$p = 0.0022$, 95% CI 11% to 61%]. Of those with a mean polyclonal aCL greater than 2.3 units, 34% developed a VT within 20 years of SLE diagnosis (95% CI 11% to 57%, $p = 0.0097$ compared to those with lower aCL). The immediate risk (hazard) of deep venous thrombosis was not significantly associated with the most recent assessment of aCL.

***Conclusion***. This large prospective study indicates that patients with SLE are at substantial risk for VT over time. Both the presence of a LAC and of polyclonal aCL are associated with the risk of VT, but LAC is a better predictor of risk than is aCL. (J Rheumatol 2002:29:2531–6)

*Key Indexing Terms*:
ANTIPHOSPHOLIPID ANTIBODIES VENOUS THROMBOSIS ANTICARDIOLIPIN
SYSTEMIC LUPUS ERYTHEMATOSUS LUPUS ANTICOAGULANT

A history of thrombosis has been reported in 7.2% to 12% of patients with systemic lupus erythematosus (SLE)[1,2]. Further, the proportionate mortality from thrombosis in SLE has been found to be 26.7%[1]. Thus, the severity of thrombosis, coupled with its high frequency in the SLE population, makes it essential to be able to predict which subset of patients is most likely to develop a thrombotic event. This would facilitate improved targeting of prevention efforts, as well as provide insight into the etiology and pathophysiology of thrombosis in SLE.

A positive association between antiphospholipid antibodies (aPL) and thrombosis has been documented in multiple, predominantly retrospective, studies. In their review of 29 published series of SLE patients, Love, *et al*[3] found that among patients positive for lupus anticoagulant (LAC), 42% had a history of thromboembolic events, in contrast to 12% of patients who were negative for LAC. Likewise, among anticardiolipin (aCL) positive patients, 40% had thrombotic events, compared to 18% of the aCL negative patients. For both LAC and aCL, the positive associations with thrombosis were found to be statistically significant.

A recent metaanalysis of aPL and risk of deep venous thrombosis in SLE found that patients who are LAC positive were 6 times more likely to have a venous thrombosis (VT), and patients with aCL were 2 times more likely[4]. A subsequent metaanalysis of aPL and venous thrombosis in patients without underlying immunologic disease also concluded that LAC was a more specific associate of thrombosis than was aCL[5].

Retrospective studies may be subject to ascertainment

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bias, in that patients with a prior history of thrombosis may be more likely to have multiple assessments of potential risk factors such as aPL. These studies may also be subject to referral bias. Such biases might lead to artificially inflated risk estimates. In addition, retrospective studies often assess exposures at only one timepoint. However, aPL titers in some patients with SLE are known to fluctuate over time. Thus, the current prospective study was undertaken to generate risk estimates that are less likely to be biased, and that take into account the time-varying nature of aPL in SLE.

## MATERIALS AND METHODS

*Study population.* The Johns Hopkins Lupus Cohort, conceived in 1987, comprises patients with SLE receiving ongoing care at Johns Hopkins Hospital. This study has been approved on an annual basis by the Johns Hopkins Hospital Institutional Review Board. Informed, written consent is obtained from all subjects who agree to participate in the study. Subjects enrolled in the cohort have clinic visits at 3 month intervals, or more frequently if medically necessary. All patients meet the American College of Rheumatology classification criteria for SLE[6]. For every study visit, a physical examination and laboratory investigations are performed, including screening tests for LAC and anticardiolipin antibody.

*Ascertainment of occurrence of VT.* This study is based on the 678 patients in the cohort for whom information on VT was available, and who did not have VT before or at the time of diagnosis with SLE. Only deep venous thrombosis (not superficial thrombophlebitis) and/or pulmonary emboli were included. Other sites of VT did not occur during cohort followup. Only incident thrombotic events were included in the analysis, i.e., for patients who experienced multiple thromboses, only the first occurrence was included. For all patients, medical charts were reviewed to ascertain whether a VT occurred prior to cohort entry. Some of the patients were diagnosed with SLE long before entering the cohort. For other patients, a VT occurred while the patient was followed in the cohort. Deep venous thrombosis was confirmed by ultrasound or venogram. Pulmonary emboli were confirmed by high probability V/Q scan, spiral computed tomography, or arteriogram.

*Measurement of antiphospholipid antibodies*. The 2 independent variables of primary interest were LAC and aCL status. The modified automated Russell viper venom time (RVVT) test, as described elsewhere, was used to screen for LAC[7]. RVVT results of greater than 37 seconds were considered positive (or high) for dichotomized analyses. For clinical purposes, patients with a prolonged RVVT, at least once during followup, also had a mixing study, and platelet neutralization procedure to confirm the presence of LAC, using international criteria[8]. Screening for aCL was performed with a polyclonal ELISA, which detects IgG, IgM, and/or IgA isotypes. Anticardiolipin results of greater than 2.3 ELISA binding units were considered positive (or high), based upon previous cutoff determination using nonparametric methods[2]. This assay was previously validated by an international committee[9].

*Other variables*. The following known or suspected risk factors were also included in this study: age at diagnosis, years of education, gender, race (Caucasian or African-American), complement components C3 and C4, anti-dsDNA by *Crithidia luciliae* assay, serum cholesterol, blood pressure, prednisone dose, hydroxychloroquine use, smoking history (ever smoker vs never smoker), and renal damage (history of nephrotic syndrome and/or renal insufficiency). In addition, an analysis of disease activity (using the Physician's Global Assessment ascertained at each visit) was performed.

*Statistical analysis*. Survival analysis, using the Kaplan-Meier technique, was used to estimate the probability of having an incident VT over time since the diagnosis of SLE. The effect of various time invariant predictors on the probability of having a VT was assessed using log rank tests (to statistically compare the survival curves) and Cox proportional hazards models (to estimate hazard ratios). These analyses were based on all incident events and all time since diagnosis with SLE, including events and time that occurred before cohort entry. Patients were censored after the occurrence of an incident VT, and were thus excluded from the denominator in subsequent risk estimates.

The effect of time-varying predictors (such as cholesterol level, and aPL) on the probability of having an incident VT was estimated using Cox models, modeling the hazard at a given time as a function of the most recently measured values of the predictors. For example, if a patient's RVVT was measured at 0, 3, and 6 months after diagnosis with SLE, the patient's hazard for VT from 0 to 3 months was assumed to be a function of the RVVT level at time 0, the patient's hazard for RVVT from 3 to 6 months was assumed to be a function of the RVVT level at time 3, etc. These analyses were based on only the followup time and events that occurred during cohort participation since the values of the time-varying predictors were unknown prior to cohort entry. To include patients in the analysis whose predictors were not known prior to cohort entry, we followed the approach for "left truncated" data described by Tsai, *et al*[10].

## RESULTS

Characteristics of the 678 cohort patients at baseline (time of study entry) are presented in Table 1. The large majority of patients were female and most were diagnosed with SLE at between 20 and 39 years of age. Forty-six percent of the patients entered the cohort within 2 years of diagnosis. Followup in the cohort ranged from 0 to 14 years, with 44% observed in the cohort for more than 5 years.

Thirty-five of the study patients had a first VT after diagnosis with SLE. These 35 cases were used in the overall survival analysis and the analyses of time invariant predictors. Of these cases, 15 occurred during cohort participation. These 15 were used in the analyses of time-varying predictors. The dataset captured the first thrombotic event. Recurrences were not systematically studied. The estimated rate of first time venous thrombosis is 5.1 cases per 1000 person-years. Of the 35 study subjects who had a VT, 27 (77%) were female and 18 (51%) were Caucasian. Seven (20%) of the cases occurred within one year of diagnosis and 16 (46%) occurred within 5 years of diagnosis with SLE.

A Kaplan-Meier estimate of the probability of remaining VT-free as a function of time since diagnosis with SLE is presented in Figure 1. Based on this analysis it is estimated that 9% (95% CI, 6% to 13%) of the patients with SLE will develop a VT within 20 years of SLE diagnosis.

Of the 678 patients, we obtained one or more RVVT measurements from 373 study subjects. This included 31 of the VT cases and 14 of the prospectively observed VT cases. Some study subjects had more than 50 RVVT measurements, though most had fewer than 12. The subject-specific mean RVVT ranged from 12 to 77 s with 10% having a mean greater than 37 s (i.e., "high" or "positive").

We obtained one or more aCL measurements from 352 subjects. This included 28 of the VT cases and 12 of the prospectively observed VT cases. As with RVVT, some study subjects had more than 50 aCL measurements,

*Table 1.* Baseline characteristics of patients in the Johns Hopkins Lupus Cohort (n = 678).

| Categorical Variables | Number (%) |
|---|---|
| Gender | |
| Female | 629 (93) |
| Male | 48 (7) |
| Race | |
| African–American | 305 (45) |
| Caucasian | 365 (54) |
| Other | 6 (1) |
| Age at diagnosis, yrs | |
| < 20 | 123 (18) |
| 20–39 | 402 (60) |
| 40–59 | 130 (19) |
| 60 + | 23 (3) |
| Duration of SLE at cohort entry, yrs | |
| < 2 | 314 (46) |
| 2–5 | 133 (20) |
| > 5 | 231 (34) |
| Duration of followup in the cohort, yrs | |
| < 2 | 169 (25%) |
| 2–5 | 209 (31%) |
| > 5 | 300 (44%) |
| Education level | |
| < High school | 96 (14) |
| High school | 209 (31) |
| > High school | 330 (49) |
| Unknown | 43 (6) |
| History of smoking | 305 (45) |
| Ever anti-dsDNA positive active followup | 397 (59) |
| Ever RVVT > 37 during active followup* | 102 (27) |
| Ever aCL > 2.3 EBU during active followup** | 168 (48) |
| **Continuous Variables** | **Mean (SD)** |
| RVVT, s | 29.7 (7.8) |
| aCL, EBU | 1.7 (2.7) |
| anti-dsDNA, titer, Crithidia method | 62.6 (159) |
| Cholesterol, mg/dl | 201.5 (56.8) |
| Systolic blood pressure, mm Hg | 123.8 (19.4) |
| Diastolic blood pressure, mm Hg | 77.0 (12.6) |

* Based on only 373 patients for whom RVVT data were available. ** Based on only 352 patients for whom aCL data were available. RVVT: Russel viper venom time test for lupus anticoagulant; aCL: anticardiolipin, polyclonal assay; EBU: ELISA binding unit.

although the majority had less than 12. The subject-specific mean aCL ranged from 0 to 25 units with 13% having mean aCL greater than 2.3 (i.e., high or positive).

Of those with a high mean RVVT during followup, 12/38 (32%) had a VT at some time after diagnosis with lupus. In contrast, of those with a low mean RVVT during followup, 19/335 (6%) had a VT at some time after diagnosis with lupus. Figure 2 shows Kaplan-Meier estimates of the occurrence of VT after diagnosis with SLE for those with high (> 37 s) and low mean levels of RVVT observed during participation in the cohort. The differences between the 2 survival curves were statistically significant ($p < 0.0001$). It can be seen that among those with high RVVT measures during the cohort, an estimated 42% (95% CI 21% to 63%) will have a VT within 20 years after diagnosis with SLE.

Of those with a high mean aCL during followup, 8/45 (18%) had a VT at some time after diagnosis with lupus. In contrast, of those with a low mean aCL during followup, 20/307 (7%) had a VT at some time after diagnosis with lupus. Figure 3 shows Kaplan-Meier estimates of the occurrence of VT after diagnosis with SLE for those with high (> 2.3 units) and low mean levels of aCL observed during participation in the cohort. The differences between the 2 survival curves were statistically significant ($p = 0.0097$). It can be seen that among those with high aCL measures during the cohort, an estimated 34% (95% CI 11% to 57%) will have a VT within 20 years after diagnosis with SLE. In a sensitivity analysis, similar results were found using an aCL cut-off of 3.0 ($p = 0.0082$).

Table 2 shows the association between time invariant predictors and the risk of VT based on a series of Cox proportional hazards models (one model for each predictor). Some of the predictors are not truly time invariant (e.g., RVVT and aCL level), but these are summarized by taking their subject-specific mean during the cohort followup and treating it as a fixed characteristic of the patient for these analyses. From Table 2 it can be seen that male gender, mean RVVT during cohort observation, and having a mean aCL greater than 2.3 during cohort observation were all significantly associated with higher risk of VT. The Physician Global Assessment of lupus activity had a hazard ratio of 1.9 which did not achieve statistical significance.

RVVT and aCL are highly correlated. To assess whether high levels of aCL (i.e., mean > 2.3 during cohort) were still predictive of VT risk after controlling for high levels of RVVT (mean > 37 s) we included both in the same model. It was found that, after controlling for high RVVT, high aCL was no longer associated with VT risk. The hazard ratio estimate was 1.1 (95% CI 0.4 to 3.0, $p = 0.88$). In contrast, high RVVT was still significantly associated with VT risk (hazard ratio estimate 5.0, 95% CI 1.9 to 13.1, $p = 0.0009$). There was no significant interaction between the 2 variables.

Table 3 shows the estimated association between time-varying predictors and risk of VT where the hazard is modeled as a function of the most recent measurement of each predictor. It can be seen that the most recent measure of RVVT is significantly associated with the risk for VT. The most recent aCL was not statistically significantly associated with VT risk.

A multivariable model was fit to see whether the most recent RVVT value was significantly associated with VT risk after controlling for gender and the most recent cholesterol measure. The result was similar to the unadjusted result. Each 5 s increase in RVVT was associated with a 34% increase in the hazard for VT (95% CI 1.1 to 1.6, p =

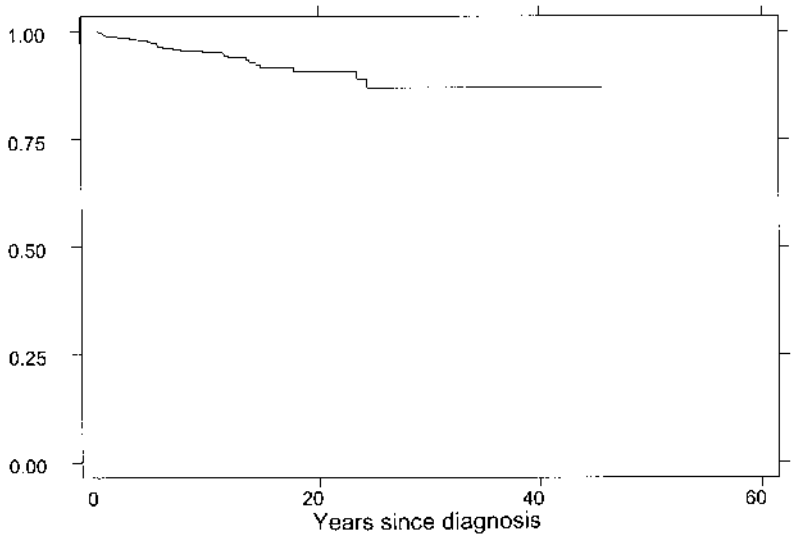


*Figure 1.* A Kaplan-Meier estimate of the probability of remaining VT-free as a function of time since diagnosis with SLE (based on the 35 occurrences of deep vein thrombosis observed retrospectively or prospectively).

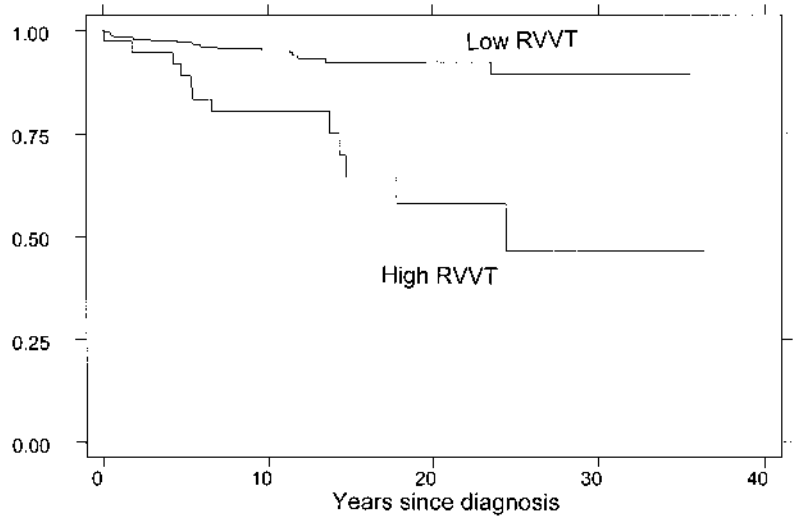


*Figure 2.* Kaplan-Meier curves in strata determined by mean Russell viper venom time (RVVT) during the cohort period (High RVVT indicates that the mean RVVT > 37 seconds, Low RVVT is ≤ 37 seconds). ($p < 0.0001$ for difference between the curves based on a log rank test.)

0.0022). Adding Physician Global Assessment to the model did not change the results with respect to RVVT.

## DISCUSSION

Results from the Cox proportional hazards modeling indicate that LAC is a risk factor for venous thrombosis in patients with SLE. This prospective analysis does not, however, support the premise that aCL is an independent risk factor for venous thrombosis. In consonance with findings from Triplett, *et al*[11], a synergistic relationship was not found between the 2 autoantibodies. Petri, *et al*[2] and Derksen, *et al*[12] have reported that LAC is a stronger predictor of thrombosis than aCL in the SLE population. However, lack of evidence in our study for an independent association between aCL and risk of venous thrombosis contrasts with findings from several retrospective studies. Various explanations may contribute to this discordance.

Many previous studies have not examined RVVT and aCL in the same model. Thus, reported associations between aCL and thrombosis may have been confounded by RVVT status. In our univariate analysis of aCL and RVVT as time invariant predictors of thrombosis, aCL appeared to be a significant predictor of thrombosis. However, when both RVVT and aCL were modeled together, only RVVT

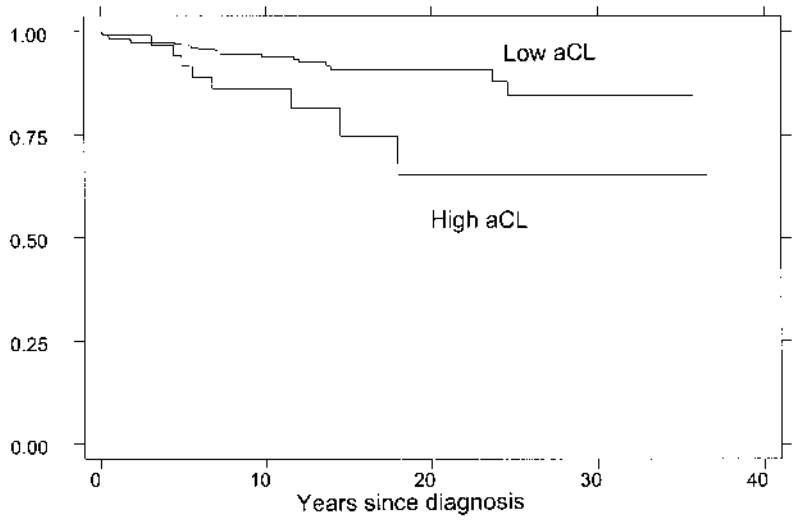


*Figure 3*. Kaplan-Meier curves in strata determined by mean anticardiolipin antibodies (aCL) during the cohort period (High aCL indicates that the mean aCL > 2.3 units, Low aCL is ≤ 2.3 units). ($p < 0.0097$ for difference between the curves based on a log rank test).

*Table 2*. Estimated effect of time-invariant predictors on the rate of deep venous thrombosis following SLE diagnosis. Estimates are based on a series of individual Cox proportional hazards models using all followup time (from diagnosis until end of followup).

| Predictor | Hazard Ratio | 95% CI | p |
|---|---|---|---|
| Gender, male vs female | 4.4 | 2.0, 9.6 | 0.0003 |
| Race, African-American vs Caucasian | 1.0 | 0.5, 1.9 | 0.95 |
| Age at diagnosis, per 5 yrs | 1.0 | 0.9, 1.2 | 0.78 |
| History of smoking, yes vs no | 0.9 | 0.5, 1.8 | 0.79 |
| Ever anti-dsDNA positive, *Crithidia* | 0.8 | 0.4, 1.7 | 0.64 |
| Mean RVVT during cohort observation, per 5 s increase* | 1.4 | 1.2, 1.6 | 0.0001 |
| Mean RVVT during cohort observation > 37 s, yes vs no* | 5.0 | 2.4, 10.4 | 0.0001 |
| Mean aCL during cohort observation, per 1 EBU increase** | 1.0 | 0.9, 1.2 | 0.37 |
| Mean aCL during cohort observation > 2.3 EBU, yes vs no** | 2.8 | 1.2, 6.4 | 0.013 |
| Physician's global assessment of disease activity, per 1 unit increase on a 0 to 3 visual analog scale | 1.9 | 0.95, 3.81 | 0.069 |

* Based on 373 patients for whom RVVT data were available. ** Based on 352 patients for whom aCL data were available.

*Table 3*. Estimated effect of time-varying predictors (measured during cohort followup) on the hazard rate of deep venous thrombosis following SLE diagnosis. Estimates are based on a series of individual Cox proportional hazards models using only followup that occurred while the patient was enrolled in the Johns Hopkins Lupus Cohort. The hazard was modeled as a function of the most recent measurement of each variable.

| Predictor | Hazard Ratio | 95% CI | p |
|---|---|---|---|
| RVVT, per 5 s | 1.30 | 1.10, 1.54 | 0.0025 |
| aCL, per EBU | 1.02 | 0.96, 1.08 | 0.62 |
| Anti-dsDNA, per unit increase in log-titer | 0.94 | 0.73, 1.23 | 0.66 |
| Systolic blood pressure, per 10 mm Hg increase | 1.15 | 0.90, 1.47 | 0.26 |
| Diastolic blood pressure, per 10 mm Hg increase | 1.15 | 0.76, 1.75 | 0.51 |
| Serum cholesterol, per 50 mg/dl increase | 1.95 | 1.34, 2.83 | 0.0005 |
| C3, per 30 mg/dl increase | 0.84 | 0.51, 1.40 | 0.48 |
| C4, per 10 mg/dl increase | 1.25 | 0.75, 2.07 | 0.39 |
| Prednisone, per 5 mg increase | 0.32 | 0.04, 2.81 | 0.31 |
| Plaquenil, using vs not | 0.65 | 0.18, 2.29 | 0.50 |

remained a significant predictor of venous thrombosis. This demonstrates the necessity of accounting for the correlation between RVVT and aCL when examining their relationship to thrombosis risk.

The aCL assay used in our study was polyclonal, detecting IgG, IgM, and IgA isotypes. It is now accepted that both IgM aCL[1] and IgA aCL[13] are associated with antiphospholipid syndrome, although IgG is the most important of the 3 isotypes. "Collapsing" 3 isotypes into 1 "polyclonal" variable would seem to increase, not decrease, the likelihood of finding a positive association.

One of the major weaknesses of past retrospective studies is that the temporality of the association of aPL and thrombosis in SLE could not be assessed. If the biological processes associated with thrombosis induced the acquisition of aPL, a spurious association would exist. For this reason, it is important to perform analyses that include values of aPL measured prior to an occurrence of VT, such as analyses summarized in Table 3. Many studies of aPL and thrombosis have not discerned between venous and arterial events. By pooling all thromboembolic events, the risk estimates obtained are not directly comparable to risk estimates for venous or arterial events alone. Thus, our study examined venous thrombotic events only.

Although hypercholesterolemia is a risk factor for atherosclerosis in SLE[12,14], it is not clear why it appeared as a risk factor for VT in this study. Hyperlipidemia is associated with renal insufficiency and nephrotic syndrome, which do affect venous thrombotic risk.

This is the first large, prospective study of aPL and VT in SLE in which aPL status was assessed quarterly. Because aPL status of the patients on enrollment to the Hopkins Lupus Center is usually not known, and because patients are not more likely to join the cohort because of high aPL or prior history of thrombosis, the biases that typically weaken retrospective studies have been avoided.

Prospective studies in the general population have shown that aCL is a risk factor for first VT[15] and recurrent VT[16]. However, screening for LAC appears to be a better prognostic predictor for VT than screening for aCL. The RVVT assay for the LAC used in this study appears to be more associated with antibodies to ß$_2$-glycoprotein I, one of the targets of some LAC and the target of aCL[17]. Anti-ß$_2$-glycoprotein I assays are not yet validated and were not available during the cohort study. However, there is a general consensus in retrospective studies that anti-ß$_2$-glycoprotein I is more highly associated with thrombosis than is anticardiolipin.

Further prospective studies of aPL and thrombosis in SLE should be performed in order to assess the consistency of findings across different study populations. Hopefully, these findings will lead to both prevention and treatment strategies targeted to SLE patients at highest risk.

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