

# D-Dimer Level and the Risk for Thrombosis in Systemic Lupus Erythematosus

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**Background and objectives:** Patients who have systemic lupus erythematosus (SLE) and manifest antiphospholipid antibodies (APA) are at increased risk for thrombosis; however, it is difficult to predict who will clot. This study tested the hypothesis that peak D-dimer level measured routinely during follow-up identifies whether a hypercoagulable state is developing and, therefore, the patient is at increased risk for thrombosis.

**Design, setting, participants, & measurements:** One hundred consecutive patients who had SLE with recurrent activity (71% renal SLE) and were evaluated for or enrolled in the Ohio SLE Study were studied. D-dimer testing was done annually and usually at SLE flare or other serious illness. When D-dimer was elevated, evaluation for thrombosis (large vessel, small vessel, or Libman-Sacks) was undertaken. Mean follow-up was  $37.5 \pm 15$  SD months.

**Results:** Of those with peak D-dimer  $<0.5 \mu\text{g/ml}$  ( $n = 46$ ), 0% thrombosed, 33% had APA. Of those with peak D-dimer  $0.5$  to  $2.0 \mu\text{g/ml}$  ( $n = 19$ ), 6% thrombosed, 44% had APA. Of those with peak D-dimer  $>2.0 \mu\text{g/ml}$  ( $n = 36$ ), 42% thrombosed, 76% had APA. The most common causes of elevated D-dimer in the absence of demonstrable thrombosis were SLE flare and systemic infection. D-dimer levels were usually elevated for several months before thrombosis.

**Conclusions:** Patients with SLE and normal D-dimer levels are at low risk for thrombosis, irrespective of APA status. Those with persistent unexplained elevated D-dimer levels, particularly when  $>2.0 \mu\text{g/ml}$ , are at high risk for thrombosis.

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**T**hrombosis is an important manifestation of human systemic lupus erythematosus (SLE). Virtually any organ can be involved. The thrombosis can occur in large or small vessels (1–3) or can involve the cardiac valves (Libman-Sacks) (4,5). When large-vessel thrombosis occurs, usually it involves the deep veins (DVT) of the lower extremities (2). Large-vessel thrombosis can also involve arteries as a consequence of thromboembolism (*e.g.*, from thrombi on the mitral or aortic valve in those with Libman-Sacks, “paradoxical embolism” through an atrial-septal defect) (6). Arterial thrombosis can also occur *in situ*, apparently as successive layers of clot accumulate until the lumen is stenosed or completely occluded (7).

When small-vessel thrombosis occurs and the predominant site is arteriolar, the usual manifestation is a thrombotic microangiopathic hemolytic anemia (1,8). The lung can also be involved in small-vessel thrombosis. This process is independent of DVT and pulmonary embolism (9,10). At autopsy, these cases show noninflammatory fibrin microthrombi in pulmonary vessels (10–16). This thrombotic process in its mildest form may represent the unexplained reversible hypoxia of SLE

flare (10,17). In its more severe and chronic form, it may manifest as restrictive lung disease that can progress to severe pulmonary hypertension (8–11,15). The small-vessel thrombotic lung disease of SLE may be analogous to that seen in primary pulmonary hypertension (18). Small-vessel thrombosis in SLE can also affect the kidney with a characteristic arteriopathy that shows, side by side, acute thromboses and chronic vascular lesions. The latter include arterial fibrous intimal hyperplasia, arteriosclerosis, and organized thromboses with or without recanalization (19).

The most common risk factors for thrombosis in SLE are antiphospholipid antibodies (APA), including anticardiolipin antibodies (ACL; IgG or IgM) or the lupus anticoagulant (LAC) (2). Collectively, these are referred to as APA. The clotting disorder associated with APA is referred to as the antiphospholipid syndrome (2). ACL is present in approximately 39% and LAC in approximately 22% of patients with SLE. These estimates are the median of the reported values described in a systematic review of the literature (2). ACL in high titer ( $>5$  SD above the mean; *e.g.*, IgG ACL  $>40$  GPL units) (20–22) increases the risk for clotting by approximately two-fold; LAC increases clotting risk approximately six-fold (23). The absolute risk for clotting in untreated patients who have SLE with ACL, LAC, or both has not been well established (24); however, in patients who had SLE with APA and previously thrombosed but were not currently receiving anticoagulation therapy, the risk for recurrent thrombosis was 19 to 29 per 100 patient-years (24).

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When thrombosis occurs in patients with SLE and APA, long-term warfarin therapy, perhaps for a lifetime, is generally recommended (2,23,25–27). Less clear is how to treat patients who have SLE and APA but have not yet thrombosed (20,24). This study tested the hypothesis that periodic measurement of D-dimers can identify whether the patient with SLE is becoming hypercoagulable and, therefore, is at increased risk for thrombosis regardless of their ACL/LAC status.

D-dimer is a cross-linked peptide derived from fibrin thrombus (28). *In vivo*, fibrin clot normally undergoes fibrinolysis by plasmin, which releases D-dimer as a specific fibrin-splitting product. Thus, D-dimers are elevated in patients who have formed clots. Elevated D-dimer can also be present in those who are forming and degrading fibrin at an abnormally high rate but who do not have evidence of a clinically significant clot. In such patients, elevated D-dimers have been used to predict the risk for recurrent DVT (29–31), pulmonary embolus (32), myocardial infarction (33), progression of primary pulmonary hypertension (18), or death in patients with peripheral arterial disease (34). Normal D-dimer levels have also been used to exclude clinically significant clot burden to exclude DVT or pulmonary embolism (35–37). The association of D-dimer level and risk for clotting has not been reported in patients with SLE. This work addresses that unmet need.

## Materials and Methods

### Study Population

This D-dimer study was a prospective study of 100 consecutive patients who had SLE and were evaluated for or followed in the Ohio SLE Study (OSS). All met at least four World Health Organization criteria for classification of SLE. The OSS is a detailed, prospective, longitudinal study of patients with recurrently active SLE. Approximately two thirds had major renal manifestations, and approximately one third had major nonrenal manifestations. The goal of the OSS was to identify genetic and clinical risk factors for SLE flare (38–44).

### Study Protocol

The OSS testing matrix involved extensive bimonthly clinical and research testing (39), including annual testing for D-dimer, ACL, and LAC. D-dimer testing was often repeated between the annual testing intervals if the patient's clinical status changed (*e.g.*, SLE flare or other major illness). For patients who were evaluated for but not enrolled in the OSS (seven of the 100 patients of this study), the baseline and follow-up clinical testing panel was similar to that of the OSS protocol but was carried out at 3- to 4-mo intervals. The finding of an elevated D-dimer or physical findings suggesting venous or arterial thrombus, initiated testing for clotting. The assessment for clotting events proceeded as follows.

**Assessment for Large-Vessel Thrombosis.** DVT was assessed by duplex venous scan of the lower extremities. When acute pulmonary embolus was suspected, computed axial tomography angiographic contrast-enhanced chest scan was undertaken. For those with suspected central nervous system clotting, a gadolinium-enhanced magnetic resonance angiogram was done. Arterial clotting was assessed by magnetic resonance angiography of the relevant vascular bed or by coronary artery angiography.

**Assessment for Small-Vessel Thrombosis.** This included the following: (1) Testing for thrombotic microangiopathic hemolytic anemia (thrombocytopenia, schistocytes, reticulocytosis, and increased serum lactic dehydrogenase). (2) Testing for hypoxia in those with unexplained new-onset dyspnea. This was done by finger tip oximeter to assess for desaturation (<94% hemoglobin saturation at rest with a further decrease after walking 100 ft at a moderate pace). When abnormal, evaluation for pulmonary embolus was undertaken (see previous paragraph). When that testing was negative, the patient was referred to a pulmonologist. (3) Testing for the renal arteriopathy of the antiphospholipid syndrome. This was done by kidney biopsy in those with an unexplained progressive increase in serum creatinine not associated with heavy proteinuria (*e.g.*, 24-h urine protein/creatinine ratio >1.0) (45).

**Assessment for Libman-Sacks Endocarditis.** For those with a new-onset cardiac murmur or evidence of arterial thromboembolism, transesophageal echocardiography was done to search for Libman-Sacks endocarditis (4).

### Analytical Methods

All assays were performed in the clinical laboratories of the Ohio State University Medical Center hospitals on the day that the specimens were obtained. D-dimer levels were measured using a quantitative D-dimer kit from Diagnostica Stago (Asnieres, France).

Anticardiolipin levels (IgG and IgM) were determined using the ELISA kits from INOVA Diagnostics (San Diego, CA). Workup for LAC was performed according to the guidelines from Subcommittee on Lupus Anticoagulants/Antiphospholipid Antibodies of the ISTH (46).

### Statistical Analysis

Values are shown as means  $\pm$  SD. The statistical tests used are shown in relationship to the data. The statistical calculations were performed using the software program InStat (GraphPad Software, San Diego, CA).

## Results

Table 1 shows the clinical characteristics of the 100 study patients stratified according to their peak D-dimer during follow-up. None of the differences among the strata was different except for a trend for greater SLE flare rate according to the higher peak D-dimer level.

Next we assessed whether peak D-dimer routinely measured during follow-up could identify those at increased risk for thrombosis. As shown in Table 2, of those with peak D-dimer <0.5  $\mu\text{g/ml}$  during study follow-up, none had identifiable thrombotic events. By contrast, of those whose peak D-dimer during follow-up was  $\geq 0.5 \mu\text{g/ml}$ , 15 experienced thrombotic events; 14 of those events occurred in those whose peak D-dimer was >2.0  $\mu\text{g/ml}$ .

To assess whether ascertainment bias influenced stratification of patients according to peak D-dimer (Table 2), we determined the frequency of D-dimer testing in each of the strata shown in Table 2. Excluded were the D-dimer measures made after the diagnosis of thrombosis. This analysis showed that the mean number of D-dimer measurements  $\pm 1$  SD per patient in the D-dimer stratum <0.5  $\mu\text{g/ml}$  was  $1.7 \pm 1.0$ , in stratum 0.5 to 2.0  $\mu\text{g/ml}$  was  $1.9 \pm 2.3$ , and in the stratum >2.0  $\mu\text{g/ml}$  was  $5.2 \pm 5.0$ . Testing frequency was significantly higher in the cohort with D-dimer >2.0  $\mu\text{g/ml}$  ( $P = 0.001$  by ANOVA). The

Table 1. Baseline clinical characteristics of the 100 patients with SLE according to peak D-dimer levels<sup>a</sup>

Characteristics	Peak D-Dimer ( $\mu\text{g/ml}$ )		
	<0.5	0.5 to 2.0	>2.0
<i>n</i>	45	19	36
Age	35.6	32.9	32.3
% Female	84	100	97
Race (black/white/other)	9/35/1	11/7/1	18/17/1
% renal SLE	69	68	75
Scr (mg/dl)	0.99	1.22	0.98
P/C	0.93	1.97	1.82
Hb (g/dl)	12.70	11.90	11.60
WBC count (/mm <sup>3</sup> )	6.50	7.98	6.90
Platelet count ( $\times 10^{-3}$ )	256	294	286
% Patients receiving			
prednisone	64	84	72
immunosuppressant <sup>b</sup>	51	63	72
aspirin (81 mg/d)	22	37	33
hydroxychloroquine (200 mg twice daily)	33	47	47
% WHO III/IV <sup>c</sup>	47	26	58
% WHO V <sup>c</sup>	20	37	14
Flare rate (mean/yr) <sup>d</sup>	0.38	0.45	0.89

<sup>a</sup>The clinical laboratory results are the measures taken at baseline. The therapies are those prescribed during follow-up. Hb, hemoglobin; P/C, 24-h urine protein/creatinine ratio; Scr, serum creatinine; SLE, systemic lupus erythematosus; WBC, white blood cell.

<sup>b</sup>Azathioprine, mycophenolate, methotrexate, or cyclophosphamide.

<sup>c</sup>Percentage of patients according to World Health Organization kidney biopsy class.

<sup>d</sup>Mean SLE flare rate for each D-dimer group,  $P = 0.014$  by nonparametric ANOVA. None of the other differences among the D-dimer strata was significant.

Table 2. Relationship between peak DD measured during study follow-up and the onset of clotting events during study follow-up<sup>a</sup>

DD Range ( $\mu\text{g/ml}$ ) <sup>b</sup>	<i>n</i>	DD (Mean $\pm$ SD)	No. of Patients with Clotting (%) <sup>c</sup>	LAC/ACL (%)	Renal SLE (%) <sup>d</sup>
<0.5	45	0.29 $\pm$ 0.08	0 (0)	33	69
0.5 to 2.0	19	0.92 $\pm$ 0.48	1 (6)	44	68
>2.0	36	7.65 $\pm$ 6.17	14 (42) <sup>e</sup>	74 <sup>e</sup>	75

<sup>a</sup>ACL, anticardiolipin antibodies; DD, D-dimer; LAC, lupus anticoagulant.

<sup>b</sup>Normal <0.5.

<sup>c</sup>To calculate the percent of patients who clotted during follow-up in each of the DD ranges, the patients who had clotted previously were excluded because they were receiving warfarin therapy and were protected from clotting. In the DD range <0.5, seven were excluded; in the DD range 0.5 to 2.0, one was excluded; and in the DD range >2.0, three were excluded.

<sup>d</sup>Percentage of each DD range cohort that had past or present major renal manifestations as defined by Ohio SLE Study (OSS; see the Materials and Methods section).

<sup>e</sup> $P < 0.001$  by Fisher exact test compared with the cohorts with lower peak DD.

greater D-dimer testing frequency in those with D-dimer >2.0  $\mu\text{g/ml}$  is the result of their more severe SLE, which led to more frequent nonprotocol testing.

We estimated the likelihood that a patient in the cohort with peak D-dimer >2.0  $\mu\text{g/ml}$  would be mistakenly stratified in the normal D-dimer stratum (<0.5  $\mu\text{g/ml}$ ) if the patient had been tested on only one occasion. This was done by determining the frequency of D-dimer <0.5  $\mu\text{g/ml}$  in the cohort with peak D-dimer >2.0  $\mu\text{g/ml}$ . D-dimer levels that were normal were

not counted when the normal value was obtained after the start of warfarin therapy. This analysis showed that in the cohort with peak D-dimer >2.0  $\mu\text{g/ml}$ , normal D-dimer levels were documented in only 20 (8.1%) of 246 instances.

In the D-dimer stratum <0.5  $\mu\text{g/ml}$ , mean follow-up was 35.3  $\pm$  12.5 mo; in the stratum 0.5 to 2.0  $\mu\text{g/ml}$ , mean follow-up was 36.6  $\pm$  20 mo; and in stratum >2.0  $\mu\text{g/ml}$ , mean follow-up was 45.2  $\pm$  13.5 mo ( $P < 0.01$  versus the other two strata by Kruskal-Wallis ANOVA). The mean number of D-dimer mea-

tures per patient was less than the mean number of years of study follow-up because after the third year of the OSS, the annual testing for D-dimer, ACL, and LAC was discontinued as a cost-saving measure; however, the D-dimer, LAC, and ACL testing was continued for clinical indications (see the Materials and Methods section).

Figure 1 shows the sequential D-dimer levels before identification of the thrombotic event in each of the 15 patients who thrombosed during study follow-up. As shown, generally the elevated D-dimer levels were consistently present and well in advance of the recognition of the thrombotic event.

Table 3 provides detail regarding each of the 15 patients shown in Figure 1. As shown, seven (46%) of 15 manifested LAC, 10 (67%) of 15 manifested elevated ACL, and three of (20%) 15 had neither LAC nor ACL. Abnormal ACL or LAC was present either intermittently or not at all. For example, Columns 6, 7, and 8 of Table 3 show that usually LAC, ACL IgG, and ACL IgM were normal/negative, even when the tests were performed within 6 mo of the clotting event. By contrast, D-dimer levels were abnormal on almost all occasions before the clotting event (Figure 1).

Figure 2 shows the sequential changes in D-dimer level in the 19 patients who had peak D-dimer >2.0 µg/ml and did not experience thrombosis during study follow-up. Excluded were the three patients who were receiving warfarin therapy because of a previous thrombotic event. In these patients, elevated D-dimers were seen only when the international normalized ratio was subtherapeutic. D-dimer trends for the clotters (Figure 1) were not significantly different from those of the non-clotters (Figure 2). The Figure 2 cohort also resembles the Figure 1 cohort, with respect to ACL/LAC status: Six (32%) of 19 manifested LAC, 12 (63%) of 19 manifested ACL (IgG or IgM), and five (26%) of 19 manifested neither LAC nor ACL.

Table 4 shows the sensitivity and specificity for predicting a clotting event using as predictors peak D-dimer level >2.0 µg/ml, abnormal ACL level or LAC at any time during follow-

up, or the combination of these variables. As shown, D-dimer >2.0 µg/ml alone was at least as sensitive and specific in predicting clotting events as ACL/LAC status. We suggest, however, that in “real time” patient treatment, ACL/LAC status is not as useful as D-dimer measurement in assessing thrombotic risk because ACL/LAC testing is frequently negative, even when measured within 6 mo of the thrombotic event. By contrast, D-dimer levels were consistently abnormal before the clotting event.

In this study, the two most common causes of D-dimer elevation, in the absence of an identifiable clotting event, were SLE flare and systemic infection. Of the patients described in Table 3, only patients 2, 5, and 7 had overtly active SLE at the time of their clotting event. Preliminary analysis showed that by univariate testing, the following were significantly associated with elevated D-dimer: The presence of anti-double-stranded DNA antibody ( $P < 0.001$ ), higher erythrocyte sedimentation rate ( $P = 0.023$ ), C-reactive protein ( $P < 0.001$ ), platelet count ( $P < 0.001$ ), 24-h urine protein/creatinine ratio ( $P = 0.01$ ), and lower C4 ( $P = 0.026$ ) and hemoglobin level ( $P < 0.001$ ). By multivariate analysis, elevated D-dimer was associated higher C-reactive protein ( $P < 0.0001$ ), higher proteinuria ( $P < 0.0001$ ), and lower C4 ( $P = 0.0032$ ). A detailed analysis of the risk factors for elevated D-dimer in SLE will be the subject of a separate report.

To assess whether therapy with drugs that are thought to mitigate the hypercoagulable state might prevent thrombosis (47), we determined the use of aspirin, hydroxychloroquine, and statins in the 2 mo before the diagnosis of the thrombotic events in the 15 patients described in Table 3. The results are as follows: None of the three drugs ( $n = 3$ ), low-dosage aspirin only ( $n = 1$ ), statins only ( $n = 1$ ), hydroxychloroquine only ( $n = 3$ ), aspirin + hydroxychloroquine ( $n = 5$ ), aspirin + statin ( $n = 1$ ), and aspirin + hydroxychloroquine + statin ( $n = 1$ ). Thus, the use of these drugs singly or in combination did not prevent clotting.

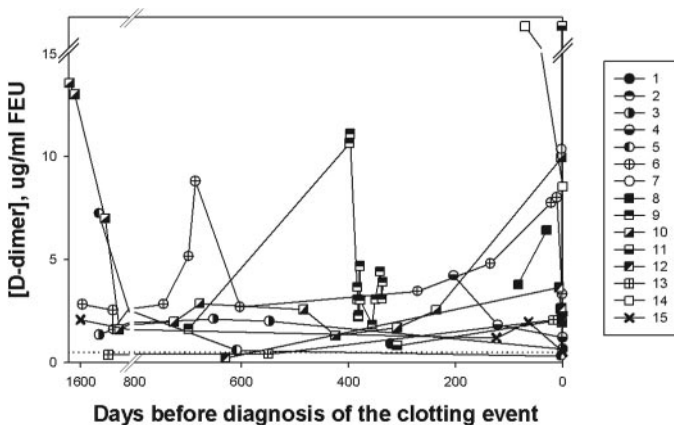


Figure 1. Sequential changes in D-dimer levels before the diagnosis of the clotting event in the 15 patients who experienced clotting during study follow-up. Each patient is represented by a different symbol, which also has the assigned number that corresponds to the patients described in Table 3.

## Discussion

This study was a prospective, longitudinal study of the relationship between plasma D-dimer levels and thrombotic events in 100 consecutive patients with recurrently active SLE. Each was tested at baseline and then annually for D-dimers, LAC, and anticardiolipin antibody.

We found that abnormally elevated D-dimer levels, particularly peak values >2.0 µg/ml, identified a group at high risk for thrombosis. During study follow-up, 42% developed thrombosis. By contrast, in the cohort with peak D-dimer <0.5 µg/ml, none developed thrombosis. Of those with peak D-dimer between 0.5 and 2.0 µg/ml (mean 0.92 µg/ml) during study follow-up, 6% developed thrombosis.

ACL/LAC status also identified those at increased risk for thrombosis; however, this line of testing was not useful in identifying when the patient was becoming hypercoagulable. For example, ACL/LAC status usually was not abnormal in the 6 mo before the thrombotic event. By contrast, D-dimer testing

Table 3. Association of coagulation parameters with the specific type of clotting events in the patients shown in Figure 1<sup>a</sup>

Patient	Age (yr)	Gender	Race	SLE Type	LAC (No. Done/No. Abnormal)	ACL IgG (No. Done/No. Abnormal/Peak) <sup>b</sup>	ACL IgM (No. Done/No. Abnormal/Peak) <sup>c</sup>	LE Duplex Scan <sup>d</sup>	CLT Type/Outcome
1	21	F	White	Renal	3/2 <sup>e</sup>	1/1/29 <sup>f</sup>	1/1/14 <sup>f</sup>	1/0	Unexplained chronic hypoxic lung disease. Stable on warfarin. This was the only patient who had peak D-dimer <2.0 μg/ml (0.9 μg/ml) and clotted.
2	24	F	White	Nonrenal	2/0 <sup>f</sup>	1/1/26 <sup>g</sup>	1/1/16 <sup>g</sup>	0/0	Severe MAPS. Died 3 mo later of unrecognized catastrophic APS (CAPS) while visiting another city.
3	27	F	Black	Renal	1/0 <sup>g</sup>	4/2/23 <sup>e</sup>	4/1/15 <sup>e</sup>	1/0	Pulmonary embolus. Stable on warfarin.
4	51	F	White	Nonrenal	3/0 <sup>g</sup>	4/0/6 <sup>g</sup>	4/0/11 <sup>g</sup>	4/0	Unexplained chronic hypoxic lung disease. Lost to follow-up.
5	24	F	Black	Renal	4/1 <sup>g</sup>	4/0/<5 <sup>g</sup>	4/0/4<5 <sup>g</sup>	4/0	Severe MAPS. Stable on warfarin. Has progressed to ESRD from severe chronic WHO class IV/V GN.
6	24	F	Black	Renal	4/3 <sup>g</sup>	4/0/9 <sup>g</sup>	4/1/16 <sup>g</sup>	1/0	Acute left anterior descending coronary artery thrombosis. No Libman-Sacks. Coronary angiogram showed minimal plaque disease in nonthrombosed arteries. Clotting attributed to "disappearing artery disease."
7	20	F	White	Renal	4/1 <sup>e</sup>	4/0/6 <sup>g</sup>	4/0/6 <sup>g</sup>	0/0	MAPS. Stable on warfarin.
8	49	F	Black	Renal	4/0 <sup>f</sup>	5/2/20 <sup>e</sup>	5/0/9 <sup>g</sup>	2/0	Unexplained chronic hypoxic lung disease. Stable on warfarin.
9	27	F	White	Nonrenal	2/0 <sup>f</sup>	3/0/7 <sup>g</sup>	2/0/10 <sup>f</sup>	3/0	TMHA (MAPS?). Stable on warfarin.
10	26	F	Black	Renal	5/0 <sup>g</sup>	5/1/17 <sup>e</sup>	5/1/27 <sup>g</sup>	8/0	CAPS (brain, lung, kidney). Survived. Stable on warfarin.
11	32	F	Black	Renal	2/1 <sup>e</sup>	3/1/16 <sup>e</sup>	3/0/1 <sup>g</sup>	0/0	CAPS with brain, lung, liver, and kidney involvement. Transferred to our hospital for plasma exchange. Died shortly thereafter.
12	32	F	White	Renal	1/0 <sup>f</sup>	1/0/<5 <sup>e</sup>	1/0/<5 <sup>f</sup>	1/0	Thrombotic splenic artery occlusion. No Libman-Sacks.
13	24	F	White	Renal	7/6 <sup>e</sup>	8/1/13 <sup>g</sup>	8/0 <sup>g</sup>	1/0	Thrombosis cleared, and patient stable on warfarin
14	21	F	White	Renal	0/0 <sup>f</sup>	1/1/126 <sup>e</sup>	1/1/50 <sup>e</sup>	1/0	Libman-Sacks with brain emboli. Left facial paresis and parasthesia cleared on warfarin. Patient stable.
15	50	F	Black	Nonrenal	4/2 <sup>f</sup>	3/2/27 <sup>f</sup>	3/0/0 <sup>f</sup>	1/0	Severe MAPS. Cleared and stable on warfarin. Severe histoplasmosis of lung may have been MAPS trigger.

<sup>a</sup>APS, antiphospholipid syndrome; CAPS, catastrophic antiphospholipid syndrome; CLT, clotting; GN, glomerulonephritis; MAPS, microangiopathic antiphospholipid syndrome; TMHA, thrombotic microangiopathic hemolytic anemia.

<sup>b</sup>GPL units; normal 0 to 15.

<sup>c</sup>GPM units; normal 0.0 to 12.5.

<sup>d</sup>Number of lower extremity duplex scans for venous thrombosis done in response to an elevated D-dimer/number of scans that were abnormal.

<sup>e</sup>Test was done within 6 mo of CTL and was abnormal.

<sup>f</sup>Test not done within 6 mo before CTL.

<sup>g</sup>Test was done within 6 mo of CTL and was normal/negative.

Libman-Sacks with brain emboli. Left facial paresis and parasthesia cleared on warfarin. Patient stable.

Severe MAPS. Cleared and stable on warfarin. Severe histoplasmosis of lung may have been MAPS trigger.

Libman-Sacks with toe emboli. Kidney biopsy showed vascular changes consistent with the arteriopathy of APS. Stable on warfarin.

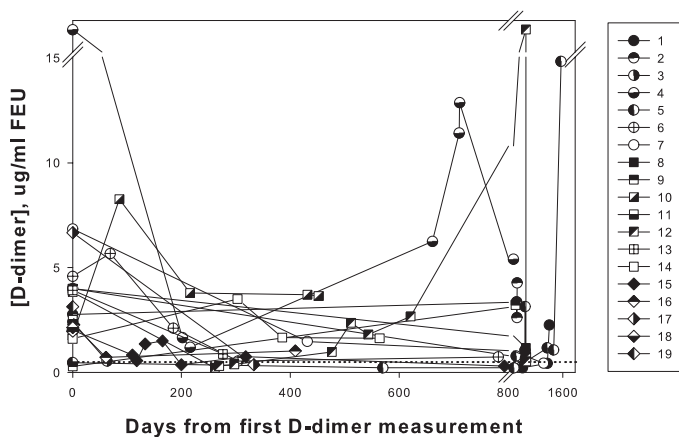


Figure 2. Sequential changes in D-dimer levels in the 19 patients who had D-dimer levels >2.0 μg/ml and did not experience clotting either before or during study follow-up. All D-dimer measurements during study follow-up are shown. Each patient is indicated by a different symbol.

showed abnormal results at almost all testings before the thrombotic event (Figure 1). Thus, although ACL/LAC testing identifies those at increased risk for clotting, it does not identify whether the patient has become hypercoagulable. D-dimer testing, however, does identify the emergence of hypercoagulability. Also, the combination of D-dimer >2.0 μg/ml and positive LAC/ACL was 100% sensitive for clotting and had a 100% negative predictive value. Thus, clearly there is a role for both types of testing; however, for empiric longitudinal testing for coagulation risk, D-dimer may be preferred over LAC/ACL. Also, D-dimer testing is less expensive than LAC/ACL testing.

A limitation of this study is that, in the cohort with D-dimer levels >2.0 μg/ml, neither the level of D-dimer elevation nor its pattern differentiated those who clotted (Figure 1) from those who did not clot (Figure 2). We suggest, however, that if the D-dimer levels had been taken at more frequent intervals (e.g., bimonthly), then we might have observed a progressive rise in D-dimer levels before the onset of the thrombotic event. This interpretation is based on comparison of Figure 1 with Figure 2.

With regard to ascertainment bias, we suggest that it is unlikely that more frequent testing would have changed the major conclusions of this work. Specifically, with regard to ascertainment of the thrombotic episodes, it is unlikely that such episodes were overlooked because they are clinically obvious and sustained events. With regard to ascertainment of

peak D-dimer level, we suggest that that was determined with reasonable accuracy despite more frequent D-dimer testing in the cohort with D-dimer >2.0 μg/ml. That is, those with D-dimers >2.0 μg/ml showed abnormal D-dimer on almost all occasions (see Figures 1 and 2). Thus, it is unlikely that those with persistently normal D-dimers would be mistakenly included in the cohort with high peak D-dimers. By this same line of reasoning, it is unlikely that the cohort with peak D-dimer <0.5 would mistakenly include those with persistent D-dimer levels >2.0 μg/ml. In light of this, we suggest that the risk stratification for thrombosis according to peak D-dimer level as shown in Table 2 was determined with reasonable accuracy.

The cohort with D-dimer <0.5 experienced SLE flare and infections, but neither elevated D-dimer nor thrombosis was detected during follow-up. We speculate that this cohort may be less susceptible to the development of a hypercoagulable state. It should be noted, however, that seven patients in this cohort were receiving warfarin therapy because of a previous thrombosis. Thus, this speculation does not extend to these patients.

This work also attempted to delineate when a thrombotic event was likely to occur after the onset of D-dimer elevation. This effort, however, encountered limitations. For example, we were unable to determine precisely the onset of the clotting events that are insidious in onset such as that of idiopathic hypoxic lung disease, arterial stenosis, Libman-Sacks endocarditis, and the renal arteriopathy of the antiphospholipid syndrome. For the purposes of this study, we arbitrarily defined the date of the thrombotic event as the date when the diagnosis of thrombosis was made; however, in many of these patients, the clotting event likely was under way for several months or more before the diagnosis was made. Conversely, for thrombotic events that have a decisive onset (microangiopathic antiphospholipid syndrome, catastrophic antiphospholipid syndrome, pulmonary embolus, or DVT), it should be possible to estimate accurately the interval between the onset of the hypercoagulable state and the onset of the thrombotic event. Unfortunately, of the six thrombotic events of this study with decisive onset (patients 3, 5, 7, 9, 10, and 14), only patient 14 had D-dimers measured at >1 wk but <6 mo before the onset of the thrombotic event. Patient 14 showed high D-dimers approximately 1.5 mo before the onset of microangiopathic antiphospholipid syndrome. By comparison, the studies of D-dimer in recurrent DVT in patients without SLE showed that the D-

Table 4. Sensitivity, specificity, PPV, and NPV of predicting a clotting event using as predictors peak DD, ACL, LAC, and the combination of peak DD >2 and ACL/LAC status<sup>a</sup>

Predictor	Sensitivity	Specificity	PPV	NPV
DD > 2 versus DD ≤ 2	0.93	0.74	0.42	0.98
+ ACL/LAC versus -ACL/LAC	0.87	0.61	0.33	0.95
DD > 2 and + ACL/LAC versus DD ≤ 2 and -ACL/LAC	1.00	0.78	0.50	1.00

<sup>a</sup>NPV, negative predictive value; PPV, positive predictive value. None of the differences was statistically significant.

dimers became decisively elevated ( $>1.0 \mu\text{g/ml}$ ) approximately 2 to 5 mo before the onset of DVT (30,31).

The cardiovascular risks associated with ACL and LAC (2,48) might be more reliably assessed by periodic D-dimer measurement. In support of this notion is the strong statistical association that we found between D-dimer level and inflammatory parameters. This association suggests that thrombosis causes inflammation and/or inflammation causes clotting. Either way, the presence of persistent D-dimer level may more clearly identify the patient who have SLE and are at increased risk for the cardiovascular events that are associated with the antiphospholipid syndrome.

## Conclusions

Clearly much more work needs to be done to understand fully the relationship between elevated D-dimers and the risk for thrombosis in SLE. Nevertheless, this work provides a plausible basis for the following preliminary recommendations: (1) Periodic D-dimer measurements can be justified in patients with recurrent SLE disease; (2) if D-dimers are elevated (particularly when  $>1.0 \mu\text{g/ml}$ ), then evaluation for clotting is appropriate; and (3) if no clotting is found, then close follow-up and the routine use of aspirin, antimalarials, and statins, which are thought to mitigate the clotting process in SLE (47), may be appropriate. Aspirin alone, however, may not be sufficient (49).

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## Disclosures

None.

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