

## THE MANAGEMENT OF THROMBOSIS IN THE ANTIPHOSPHOLIPID-ANTIBODY SYNDROME

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**Abstract Background.** The antiphospholipid-antibody syndrome is a thrombophilic disorder in which venous or arterial thrombosis, or both, may occur in patients with antiphospholipid antibodies. The optimal treatment of these patients is unclear. We assessed the efficacy of warfarin, low-dose aspirin, or both in the secondary prevention of thrombosis in patients with the syndrome.

**Methods.** One hundred forty-seven patients (124 [84 percent] of whom were female) with the antiphospholipid-antibody syndrome and a history of thrombosis were studied retrospectively. The syndrome was primary in 62 patients and was associated with systemic lupus erythematosus in 66 patients and lupus-like disease in 19. Each patient's history was reviewed.

**Results.** One hundred one patients (69 percent) had a total of 186 recurrences of thrombosis. The median time between the initial thrombosis and the first recurrence was 12 months (range, 0.5 to 144 months). Treatment with high-intensity warfarin (producing an interna-

tional normalized ratio of  $\geq 3$ ) with or without low-dose aspirin (75 mg per day) was significantly more effective ( $P < 0.001$  by the log-rank test) than treatment with low-intensity warfarin (producing an international normalized ratio of  $< 3$ ) with or without low-dose aspirin or treatment with aspirin alone in preventing further thrombotic events (recurrence rates per patient-year, 0.013, 0.23, and 0.18, respectively). The rate of recurrence of thrombosis was highest (1.30 per patient-year) during the first six months after the cessation of warfarin therapy. Complications involving bleeding occurred in 29 patients during warfarin therapy and were severe in 7 (0.071 and 0.017 occurrence per patient-year, respectively).

**Conclusions.** The risk of recurrent thrombosis in patients with the antiphospholipid-antibody syndrome is high. Long-term anticoagulation therapy in which the international normalized ratio is maintained at or above 3 is advisable in these patients. (N Engl J Med 1995;332:993-7.)

THE antiphospholipid-antibody syndrome is a thrombophilic disorder in which venous or arterial thrombosis, or both, may occur.<sup>1</sup> The serologic markers of the syndrome are antiphospholipid antibodies (anticardiolipin antibodies, the lupus anticoagulant, or both).

The antiphospholipid-antibody syndrome often occurs in systemic lupus erythematosus, but the majority of patients with the syndrome do not meet the criteria for that disease.<sup>2</sup> Thus, the combination of recurrent thrombosis and antiphospholipid antibodies in patients without features of lupus is called the primary antiphospholipid syndrome.<sup>3-5</sup> Other important features of the syndrome are thrombocytopenia and recurrent spontaneous abortion.

Thrombosis, the main complication of the antiphospholipid-antibody syndrome, can affect vessels of all sizes; the consistent histopathological lesion is a bland thrombus without inflammation.<sup>6</sup> The antiphospholipid antibodies persist for years, possibly for a lifetime. Thus, one of the key clinical questions is what causes the sudden development of thrombosis in these patients.<sup>7</sup>

Preventing thrombosis in the antiphospholipid-antibody syndrome is important, but there is no consensus about the duration and extent of prophylactic antithrombotic treatments.<sup>8</sup> Controlled therapeutic trials have been difficult to perform<sup>9</sup> because of the limited number of eligible patients available for study at a single center and the need for long-term follow-up. Therefore, the results of only a few small, retrospective

studies of antithrombotic treatment of the antiphospholipid-antibody syndrome have been published.<sup>10-14</sup> We assessed the efficacy of warfarin, low-dose aspirin, or both in preventing recurrent thrombosis in patients with the antiphospholipid-antibody syndrome seen in our unit since 1983.

### METHODS

#### Patients

During the 10 years from December 1983 through December 1993, 183 patients with the antiphospholipid-antibody syndrome were referred to the lupus clinic at St. Thomas's Hospital. They included 28 patients whose initial thrombosis occurred before December 1983 and in whom the syndrome was diagnosed retrospectively. Referrals to this clinic were predominantly from other hospitals throughout the United Kingdom. Although 21 patients were initially seen at Hammersmith Hospital between 1983 and 1985, they have been followed at St. Thomas' Hospital since July 1985. All the patients met the diagnostic criteria for the antiphospholipid-antibody syndrome.<sup>15</sup> Inclusion in this study required positive tests for lupus anticoagulant, anticardiolipin antibodies, or both and a history of thrombosis (venous, arterial, or both).

We excluded 36 patients from the study for the following reasons: a history of thrombosis but a follow-up of less than one year (3 patients); loss to follow-up (8 patients); the antiphospholipid-antibody syndrome manifested only by recurrent fetal loss (with or without accompanying thrombocytopenia), with no history of thrombosis (18 patients); thrombocytopenia but no history of vascular occlusion (5 patients); and antiphospholipid antibodies and thrombosis undocumented by objective tests (2 patients).

Table 1 gives details about the 147 patients (124 female and 23 male) who were included in the study. They were classified into three groups. The first group included patients with the antiphospholipid-antibody syndrome who met four or more of the criteria established by the American Rheumatism Association for the classification of systemic lupus erythematosus; this group included 66 patients (56 female and 10 male) with a median age of 32 years (range, 14 to 62). The second group included patients with the antiphospholipid-antibody syndrome who met one to three of the criteria for systemic lupus erythematosus; this group was considered to have "lupus-like" disease and included 19 patients (18 female and 1 male) with a median age of 33 years (range, 20 to 47). The third group included patients who had no evidence of an underlying collagen vascular disease and in whom tests for antibodies against double-stranded DNA and

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Table 1. Characteristics of the Study Patients.\*

VARIABLE	VALUE
Patients — no. (%)	147 (100)
Women	124 (84)
Men	23 (16)
Age in yr — median (range)	
All patients	32 (14–66)
Women	32 (14–66)
Men	31 (15–62)
Months of APS — median (range)	84 (12–180)
Months from initial thrombosis to first recurrence — median (range)	12 (0.5–144)
	<i>no. of patients/ no. studied (%)</i>
Initial thrombosis	
First event venous	80/147 (54)
Deep venous thrombosis	61/80 (76)
Pulmonary embolism	7/80 (9)
Both	12/80 (15)
First event arterial	67/147 (46)
Stroke	32/67 (48)
Transient ischemic attack	24/67 (36)
Other	11/67 (16)
Recurrence	
Any	101/147 (69)
Arterial only	53/101 (52)
Venous only	40/101 (40)
Both	8/101 (8)
Positive anticardiolipin-antibody test†	
All isotypes	122/147 (83)
Low	32/122 (26)
Medium	47/122 (39)
High	43/122 (35)
IgG isotype	113/122 (93)
Low	30/113 (27)
Medium	44/113 (39)
High	39/113 (35)
IgM isotype	38/122 (31)
Low	17/38 (45)
Medium	15/38 (39)
High	6/38 (16)
Positive lupus-anticoagulant test	97/128 (76)
False positive syphilis test‡	23/87 (26)
Thrombocytopenia	28/147 (19)
Primary APS	62/147 (42)
APS plus systemic lupus erythematosus	66/147 (45)
APS plus lupus-like disease	19/147 (13)

\*APS denotes antiphospholipid-antibody syndrome.

†The degree of positivity was scored as low (5 to 20 IgG or IgM phospholipid units), medium (>20 to 60 units), or high (>60 units), as described in the Methods section.

‡Denotes a biologic false positive serologic test for syphilis.

extractable nuclear antigen were negative; this group was considered to have the primary antiphospholipid-antibody syndrome and included 62 patients (50 female and 12 male) with a median age of 35 years (range, 18 to 66).

A three-page questionnaire was used in interviewing each patient. Particular attention was paid to any previous occurrence of thrombotic events, additional risk factors for thrombosis (blood pressure >140/90 mm Hg, smoking of >10 cigarettes daily, pregnancy or puerperium, diabetes mellitus and hyperlipidemia as defined by a fasting serum total cholesterol concentration >250 mg per deciliter [6.5 mmol per liter] and a fasting serum tryglyceride concentration >220 mg per deciliter [2.5 mmol per liter]), antithrombotic treatments received, and immunosuppressive therapy prescribed (corticosteroids, azathioprine, or cyclophosphamide). All the data from each patient were entered into a computerized registry.

### Antithrombotic Treatment

For purposes of this analysis, antithrombotic treatments were subdivided into the following categories: none, indicating no treatment with aspirin or warfarin; aspirin, indicating low-dose aspirin (75 mg daily) prescribed as the only antithrombotic drug; and warfarin, indicating warfarin therapy categorized according to the level of intensity of the international normalized ratio (with low intensity defined

by an international normalized ratio of <3.0 and high intensity by an international normalized ratio of  $\geq 3$ ). The warfarin groups were further subdivided according to whether there was concomitant use of aspirin. "Recent cessation of warfarin" indicates that no more than six months had elapsed since the cessation of warfarin therapy but that the patient might have received aspirin in this period. The patients were treated according to the clinical judgment of their physicians (either the referring physicians or those on our own team). Many patients received different treatments at different times. Our clinic and the primary care physicians communicated closely, and all changes of therapy were discussed with the referring doctors.

Pregnant patients were included only if they received low-dose aspirin as the only treatment. If such patients received heparin, the period during which this treatment was administered was excluded from the analysis.

### Diagnosis of Thrombotic Events

Only patients with objectively verified thrombotic events were included in this study. Deep venous thrombosis was diagnosed by venography or ultrasonography; pulmonary embolism by radionuclide lung scanning or angiography; thrombosis in intracerebral vessels by computed tomographic scanning, magnetic resonance imaging, or angiography; and retinal thrombosis by ophthalmologic examination. Peripheral- or mesenteric-artery thrombosis was documented by arteriography or thrombectomy or at surgery. The diagnosis of myocardial infarction required an acute clinical presentation with typical electrocardiographic features and an elevated creatine kinase MB fraction. A diagnosis of cerebral transient ischemic attack required neurologic symptoms or signs lasting less than 24 hours in a patient who met the criteria for the classification of cerebrovascular disease of the National Institute of Neurological Disorders and Stroke.<sup>16</sup> The diagnosis of amaurosis fugax was established when sudden monocular blindness lasted less than 24 hours.

### Laboratory Methods

The presence or absence of lupus anticoagulant was confirmed by the method of Exner et al.<sup>17</sup> until July 1992, when our laboratory began using the dilute Russell's viper-venom time.<sup>18</sup> The lupus-anticoagulant test was not performed while patients were receiving anticoagulant therapy. Anticardiolipin antibodies (the IgG and IgM isotypes) were measured in all patients with a standardized enzyme-linked immunosorbent assay.<sup>19</sup> The results were expressed in IgG and IgM phospholipid units according to the recommendations of the 1986 workshop on standardization of the anticardiolipin test.<sup>20</sup> They were reported as negative (<5 units), low but positive (5 to 20 units), moderately positive (>20 to 60 units), or highly positive (>60 units). Prothrombin-time tests to monitor warfarin therapy were performed with various thromboplastins, and the results were expressed as international normalized ratios.

Serum samples were tested at a dilution of 1:10 for antinuclear antibodies by indirect immunofluorescence on mouse liver and kidney sections. Positive samples were further tested on HEp-2 cells for patterns of antinuclear antibodies and on *Crithidia luciliae* for double-stranded DNA antibodies. Antibodies against extractable nuclear antigen were analyzed by counterimmunoelectrophoresis in which rabbit kidney and human spleen were used as a substrate.

### Statistical Analysis

The total follow-up time for the patients receiving each treatment was calculated, and treatment-specific rates of recurrent thrombosis were obtained. The follow-up time for each patient was divided into periods that began with either an occurrence of thrombosis or a change of treatment and ended with either an occurrence of thrombosis or a censoring event (i.e., a change of treatment, the end of the study, or death). Each rate was compared with that of the "no treatment" category by a goodness-of-fit test based on the Poisson heterogeneity test, to allow for differing lengths of follow-up; rates are given relative to that of the "no treatment" category, with 95 percent confidence intervals.<sup>21</sup>

Thrombosis-free survival rates were calculated by the Kaplan-Meier method<sup>22</sup> for individual periods of treatment throughout follow-up and were compared by the log-rank test. Proportional-hazards regression analysis<sup>23</sup> with the Wald significance test was then

used to examine the combined effect of the treatments (modeled as time-dependent factors) and characteristics of patients on thrombosis-free survival after the initial thrombosis. The results are presented as hazard ratios with 95 percent confidence intervals and P values.

## RESULTS

### Patients

Table 1 shows the main characteristics of the patients in this study. The total follow-up of these patients after their first thrombotic events was 946.9 patient-years; for individual patients, the median follow-up was 6.0 years (range, 1.0 to 21.5). One hundred one patients (69 percent) had recurrent thrombotic events (a total of 186 episodes). The first thrombotic event was a venous thrombosis in 57 patients. These patients had 105 subsequent thrombotic events, 69 of which (66 percent) were venous and 36 of which (34 percent) were arterial. In the remaining 44 patients, the first thrombotic event was an arterial thrombosis, and there were 81 recurrences, 75 of which (93 percent) were arterial and 6 of which (7 percent) were venous. When all consecutive pairs of thromboses in the same patient were analyzed, an arterial thrombosis was followed by an arterial thrombosis in 89 of 96 cases (93 percent), and a venous thrombosis was followed by a venous thrombosis in 68 of 90 cases (76 percent). The median duration of follow-up after the first thrombotic event was 82 months (range, 12 to 258) in the 101 patients with recurrences and 60 months (range, 12 to 129) in the 46 patients with a single thrombotic episode.

### Predisposing Factors

One hundred twelve patients (76 percent) had risk factors for thrombosis at the time of their first thrombotic event. Table 2 shows the association of various factors with the interval to the first recurrence of thrombosis. The only factor that influenced this interval significantly was treatment with antithrombotic agents ( $P < 0.001$ ). There were apparent associations with the original diagnosis ( $P = 0.017$ ) and the presence or absence of diabetes ( $P = 0.016$ ), but after Bonferroni's adjustment for multiple comparisons these associations were no longer significant. To avoid the problem of dependency in calculating the time free of thrombosis when a patient had several thromboses, only the time to the first recurrence was used in this analysis.

### Antithrombotic Treatments and Follow-up

Table 3 summarizes the data on the antithrombotic treatments and recurrences of thrombosis. The effects of the various treatments can be compared with the proportional-hazards analysis of survival in Table 2. No recurrences were noted during the 39.8 patient-years of treatment with high-intensity warfarin plus low-dose aspirin (a lower rate of recurrence than that of the untreated patients,  $P < 0.001$ ). The first 6 months after the cessation of warfarin therapy (16.2 patient-years) were associated with the highest rate of recurrence: 1.30 thrombotic events per year, a higher rate than that of the untreated patients ( $P < 0.001$ ). The me-

Table 2. Proportional-Hazards Analysis of Associations with the Time to the First Recurrence of Thrombosis among the 147 Study Patients.\*

VARIABLE	NO. OF PATIENTS†	HAZARD RATIO (95% CI)	P VALUE
<b>Antithrombotic treatment</b>			
None		1.00	<0.001
Aspirin only		0.93 (0.51–1.68)	
Warfarin (INR, <3) with or without aspirin		0.32 (0.15–0.70)	
Warfarin (INR, ≥3) with or without aspirin		0.06 (0.01–0.45)	
During 6 mo after cessation of any warfarin treatment		2.34 (1.11–4.94)	
<b>Age (yr)</b>			
<30	52	1.00	0.659
30–39	59	1.03 (0.62–1.72)	
≥40	36	1.30 (0.72–2.35)	
<b>Sex</b>			
Female	124	1.00	0.204
Male	23	1.49 (0.80–2.77)	
<b>Diagnosis</b>			
Primary APS	62	1.00	0.017
APS with SLE	66	0.66 (0.39–1.12)	
APS with lupus-like disease	19	1.98 (0.99–3.95)	
<b>Anticardiolipin antibodies</b>			
Negative	25	1.00	0.377
Low	32	0.66 (0.30–1.42)	
Medium	47	0.59 (0.29–1.19)	
High	43	0.87 (0.44–1.74)	
<b>Lupus-anticoagulant test</b>			
Negative	31	1.00	0.053
Positive	97	0.60 (0.33–1.10)	
Not known	19		
<b>Pregnancy or puerperium</b>			
No	141	1.00	0.595
Yes	6	1.28 (0.51–3.23)	
<b>Hypertension</b>			
Absent	111	1.00	0.677
Present	36	1.13 (0.64–2.00)	
<b>Hyperlipidemia</b>			
No	132	1.00	0.180
Yes	11	0.94 (0.32–2.76)	
Not known	4		
<b>Diabetes</b>			
No	145	1.00	0.016
Yes	2	6.56 (1.43–30.16)	
<b>Nephrotic syndrome</b>			
No	141	1.00	0.960
Yes	6	0.96 (0.19–4.81)	
<b>Corticosteroids</b>			
No	83	1.00	0.282
Yes	64	1.32 (0.79–2.21)	
<b>Azathioprine</b>			
No	119	1.00	0.412
Yes	28	1.18 (0.62–2.25)	
<b>Cyclophosphamide</b>			
No	135	1.00	0.607
Yes	12	0.61 (0.22–1.70)	
<b>Period of treatment</b>			
Up to 1985		1.00	0.666
1986–1989		1.30 (0.74–2.29)	
1990–1993		1.20 (0.65–2.21)	

\*CI denotes confidence interval, INR international normalized ratio, APS antiphospholipid-antibody syndrome, and SLE systemic lupus erythematosus.

†The number of patients in each category of antithrombotic treatment and each period of treatment is not given because these data were analyzed as time-dependent variables in the model.

dian time to the first such recurrence after the cessation of warfarin was 2 months (range, 0.5 to 6).

Figure 1 shows thrombosis-free intervals during individual periods of treatment, as calculated by the Kaplan–Meier method. For patients given high-intensity warfarin therapy (international normalized ratio, ≥3) with or without aspirin, the probability that there would be no new thrombotic event over a five-year pe-

Table 3. Comparison of the Antithrombotic Treatments Used in the Study.\*

TREATMENT†	NO. OF PATIENTS RECEIVING TREATMENT AT ANY TIME	PATIENT-YEARS OF FOLLOW-UP	RECURRENT EVENTS	EVENTS PER YEAR OF FOLLOW-UP	RELATIVE RISK (95% CI)‡	P VALUE‡
<i>all (venous/arterial)</i>						
None	84	280.6	80 (34/46)	0.29	1.00	—
Aspirin	70	240.3	43 (5/38)	0.18	0.63 (0.43–0.92)	0.013
Warfarin						
Any treatment	104	409.8	42 (16/26)	0.10	0.36 (0.24–0.53)	<0.001
INR, <3	67	141.3	32 (14/18)	0.23	0.79 (0.51–1.21)	0.270
With aspirin	14	31.4	7 (0/7)	0.22	0.78 (0.30–1.69)	0.531
INR, ≥3	64	197.3	3 (2/1)	0.015	0.05 (0.01–0.16)	<0.001
With aspirin	17	39.8	0 (0/0)	0	0.00 (0.00–0.33)	<0.001
During 6 mo after cessation of any warfarin treatment	39	16.2	21 (20/1)	1.30	4.55 (2.67–7.43)	<0.001
All	147	946.9	186 (75/111)	0.20	—	<0.001§

\*CI denotes confidence interval, and INR international normalized ratio.

†As compared with no treatment.

‡Denotes the regimen in effect at the time of the thrombotic recurrence.

§For the overall variation among treatments in the rate of recurrent thrombosis.

riod was 90 percent. Among patients who were treated with low-dose aspirin alone or with low-intensity warfarin therapy (international normalized ratio, <3), there was no difference between those who had an initial venous thrombosis and those who had an initial arterial thrombosis (data not shown). This analysis could not be performed for the other treatments because there were insufficient numbers of patients with initial arterial thromboses.

The possibility that there was a systematic, long-

term change in the rate of thrombosis was assessed by including the period of treatment (up to 1985, 1986 to 1989, and 1990 to 1993) as a factor in the proportional-hazards analysis (Table 2), but no such effect was found.

Nonfatal complications involving bleeding occurred in 29 patients during warfarin treatment (0.071 occurrence per patient-year; 95 percent confidence interval, 0.047 to 0.102). All these patients had international normalized ratios of 3 or higher at the time of the episodes of bleeding; seven (24 percent) were also receiving low-dose aspirin. In 22 of the 29 patients, the bleeding was mild and was easily controlled by reducing the dose of warfarin. Severe bleeding occurred in the remaining seven patients (hemoperitoneum and menorrhagia in two each, and pericapsular kidney hemorrhage, subdural hemorrhage, and ovarian hemorrhage in one each) (0.017 occurrence per patient-year; 95 percent confidence interval, 0.007 to 0.035). In four of the seven patients with severe bleeding warfarin therapy was started again, and no further episodes of bleeding were noted during the follow-up period.

Five patients died during the follow-up period, one each from stroke, widespread thrombosis, sepsis, multiorgan failure, and cancer.

## DISCUSSION

Antiphospholipid antibodies have been linked to a strong tendency toward venous and arterial thrombosis. In many patients the antiphospholipid-antibody syndrome not only causes serious disease, but also proves difficult to treat. There is now strong evidence that the thromboses in this syndrome tend to recur, and thus require prophylactic therapy.<sup>10,11,24,25</sup> However, no prospective clinical trials of treatment or prophylaxis against thrombosis in patients with antiphospholipid antibodies have been reported so far.<sup>26</sup> In this study, we found that high-intensity oral anticoagulants (producing an international normalized ratio of ≥3) with or without low-dose aspirin are an effective prophylaxis against both venous and arterial thrombosis in most of our patients with the antiphospholipid-antibody syndrome.

The cessation of warfarin therapy in patients with

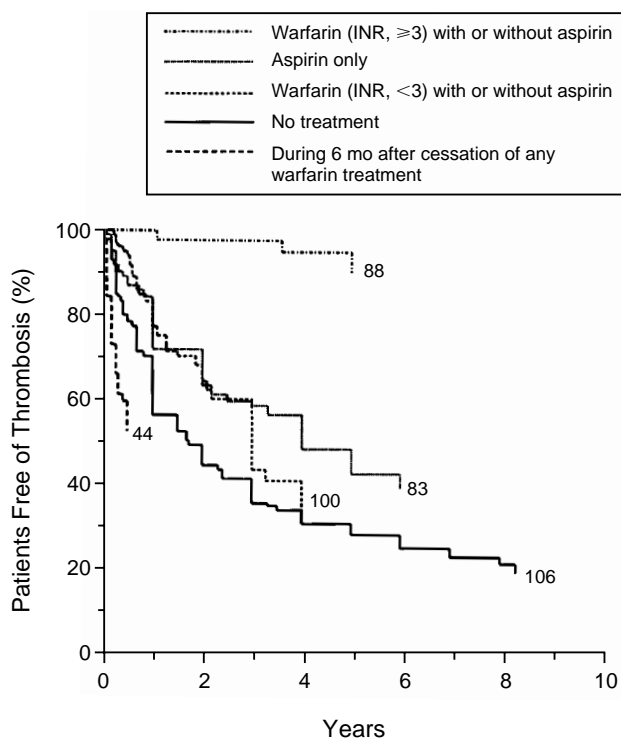


Figure 1. Kaplan-Meier Analysis of the Interval from Each Episode of Thrombosis or Change in Treatment to the Next Episode of Thrombosis or Censoring Event in the Same Patient, Throughout the Follow-up Period, According to Antithrombotic Treatment.

The total number of such intervals for the patients while they were receiving each treatment is shown after each curve. INR denotes international normalized ratio.

antiphospholipid-antibody-associated thromboses carries a high risk of recurrent thrombosis.<sup>24</sup> In a retrospective study of 19 patients with antiphospholipid antibodies and venous thromboembolic episodes, Derksen et al.<sup>11</sup> showed that the probability of having no recurrence of these episodes over an eight-year period was 100 percent among patients receiving oral anticoagulant agents (and thereby maintaining an international normalized ratio between 2.5 and 4.0), as compared with 22 percent among patients who stopped warfarin therapy. Our study confirms these observations. Thrombosis recurred in nearly 70 percent of our patients. By contrast, Rosove and Brewer<sup>10</sup> reported a recurrence rate of 53 percent in a five-year follow-up of 70 patients. This difference in rates may reflect the longer follow-up in our study. We found the highest rate of recurrence (1.30 thrombotic events per year) during the first six months after the discontinuation of warfarin therapy. This, together with the high probability of recurrent thrombosis in patients who were not treated with oral anticoagulants, suggests that patients with the antiphospholipid-antibody syndrome require long-term warfarin therapy. The benefits of long-term anticoagulation should, however, be balanced against the risks of bleeding. In our series, 29 patients had complications involving bleeding (0.071 complication per patient-year), and in 7 (0.017 complication per patient-year) the bleeding was severe, suggesting that the benefits of warfarin in the antiphospholipid-antibody syndrome are greater than the risks. The risk of bleeding compares favorably with the risk of bleeding associated with long-term oral anticoagulation therapy in other conditions.<sup>27-29</sup>

Aspirin is widely used as an antiplatelet agent. In our patients receiving low-dose aspirin, the unadjusted rate of thrombosis was lower than the rate in untreated patients (Table 3). However, after adjustment for other risk factors for thrombosis this effect was no longer statistically significant (Table 2). Thus, we had no evidence that low-dose aspirin prevented recurrences of thrombosis, a finding similar to that of Rosove and Brewer.<sup>10</sup>

Low-intensity oral anticoagulation therapy has aroused increasing interest in view of its safety and efficacy.<sup>30-32</sup> However, our study and other smaller studies<sup>10,11,13,14</sup> show that even a "normal" intensity of anticoagulation (producing an international normalized ratio of 2 to 3) in patients with the antiphospholipid-antibody syndrome did not prevent thrombotic events. We believe, therefore, that it is appropriate to maintain an international normalized ratio of greater than 3 in patients with this disorder.

In conclusion, this study demonstrates that the risk of recurrent thrombosis is high in patients with the antiphospholipid-antibody syndrome. Patients with thromboses associated with antiphospholipid antibodies should receive long-term anticoagulation therapy, with or without low-dose aspirin, in which an international normalized ratio of 3 or above is maintained. Controlled prospective studies dealing with the secondary prevention of thromboses in the antiphospholipid-antibody syndrome are urgently needed.

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