Primary Antiphospholipid Syndrome: A 5-Year Transesophageal Echocardiographic Followup Study

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ABSTRACT. ***Objective.*** To study valvular abnormalities in patients with primary antiphospholipid syndrome (APS) assessed by transesophageal echocardiography (TEE).

Methods. This was a 5-year followup study. Between 1995 and 1997, 29 consecutive patients with primary APS were studied by TEE. Twenty-four patients were evaluated in our institution and 5 were referred from elsewhere. Four patients had died, 12 patients had the 5-year followup TEE, and 8 failed to report for the study.

Results. In the first TEE, valve lesions were found in 17 patients (70.8%), myocardial infarction in 5 cases (29.4%), pulmonary hypertension in 4 (23.5%), and a calcified thrombus in the right atrium in one patient. Five-year followup TEE was performed in 12 patients. Valve lesions were unchanged in 3 cases, and in one of them a new apical akinesis of the left ventricle appeared. New valve lesions were detected in 3 patients. In 6 patients, the valve lesions had progressed and in 2, abnormalities of ventricular wall motion had appeared.

Conclusion. In this highly selected population of patients with primary APS, the predominant cardiac lesion was a noninfective valve lesion. Oral anticoagulant treatment and aspirin proved ineffective in terms of valvular lesion regression. Altogether, myocardial infarction occurred in 9 (37.5%) patients. All had coronary angiography and coronary arteries were normal in 6. (J Rheumatol 2004;31:2402–7)

Key Indexing Terms:
PRIMARY ANTIPHOSPHOLIPID SYNDROME
ECHOCARDIOGRAPHY
VALVE LESIONS
ISCHEMIC HEART DISEASE

Antiphospholipid syndrome (APS) is defined by clinical features such as vascular thromboses, recurrent pregnancy loss, and thrombocytopenia in association with the presence of circulating antiphospholipid antibodies[1]. It is considered the most common acquired hypercoagulability state and a major cause of pregnancy morbidity. The heart is a major target organ in APS. Within the cardiac manifestations, valvular involvement is the most common, as reported in several transthoracic and transesophageal echocardiographic studies[2-4]. The prevalence of valvular lesions varies between 30% and 76%, and the left-side valves are the most frequently involved[2-5]. Histopathologic studies of the affected valves have revealed superficial and intravalvular fibrin deposits, vascular proliferation, fibroblastic infiltrate, intravalvular capillary thrombosis, fibrosis, and calcification[6]. Moreover, in valves from patients with APS, markers of endothelial cell activation are upregulated whereas inflammatory exudate is scant[7]. There is also prominent deposition of immunoglobulins, including anticardiolipin antibodies (aCL), and complement components, suggesting a possible association between antibody deposits and endothelial cell activation[8].

To our knowledge, there are only 2 isolated cases reported in which echocardiographic followup demonstrated the dissappearance of valvular vegetations after treatment with oral anticoagulants (warfarin)[9,10]. However, in a transesophageal echocardiographic (TEE) followup study in 13 patients one year after oral anticoagulant and/or antiplatelet treatment had been started, no modification of valve lesions was found in 6 patients and new lesions had appeared in the remaining 7 patients[3].

We describe the evolution of valvular abnormalities observed by TEE in patients with primary APS 5 years after treatment with acenocoumarin and acetylsalicylic acid.

MATERIALS AND METHODS

Between 1995 and 1997, the Departments of Rheumatology and Echocardiography of the Instituto Nacional de Cardiología Ignacio Chávez studied 29 consecutive patients with primary APS who fulfilled the Sapporo criteria for classification of APS[11]; 22 patients were women and 7 were men. Mean age of patients was 35.4 ± 10.65 years. All patients gave informed consent before the first TEE study.

Of the 29 patients[3], 24 were first evaluated in our institution, and 5 were referred from elsewhere for a TEE. The latter patients were excluded from this investigation due to a lack of access to their clinical records and fol-

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lowup. Of our 24 patients, 8 did not attend for the followup TEE. Four of the patients had died, 2 from massive cerebral vascular accident, one from catastrophic APS, and one from gastric carcinoma. The remaining 12 patients are the subject of this report.

Echocardiographic study. All patients were ambulatory. After a 6-hour fasting period, TEE was performed in the left lateral decubitus with a commercial ultrasound unit (Sonos 5500, Hewlett-Packard, Andover, MA, USA) equipped with a multiplane transducer. The oropharynx was anesthetized with 10% xylocaine spray, and in patients with a history of cerebrovascular events, a peripheral vein was cannulated for contrast studies to investigate patent foramen ovale.

Echocardiographic measurements. Thickness, motion, and characteristics of the subvalvular apparatus were evaluated in the mitral, tricuspid, aortic, and pulmonary valves. All measurements were done on the horizontal and longitudinal planes. Calcification associated with thickening was defined as a region of high reflectance. A thickness > 5 mm for the mitral and tricuspid valves and > 3 mm for the aortic and pulmonary valves was considered abnormal. Valvular regurgitation and/or stenosis was evaluated by Doppler echocardiography. Mitral and tricuspid valve regurgitation was graded using the color and continuous Doppler jet and the area method[12]. Aortic and pulmonary regurgitation was graded according to the ratio between the width of the color jet and the diameter of the outflow tract. Stenosis of the aortic or mitral valve was determined by planimetry in intermediate planes between 35° and 50° and by the Doppler pressure half-time method at 0° and 90°, respectively.

Heart chamber diameter, ventricular wall movement, left ventricular function, presence of spontaneous contrast, intracavitary thrombosis, thickness and reflectance of the pericardium, and the presence of effusion were assessed. Studies were recorded on VHS tape for interpretation by 2 blinded expert echocardiographists. Results were reached by consensus.

Statistical analysis. Mean values and standard deviation (SD) were calculated for continuous variables. Comparisons between quantitative variables were made with the Student t test for grouped data. Comparisons between qualitative variables were made with the chi-square test with Yates' correction.

RESULTS

Twenty-four patients with primary APS were studied. Demographic data are shown in Table 1. The average time between the first and the followup TEE was 83.75 ± 7.78 months. Followup TEE after 5 years was performed in 12 patients (50%).

Findings in the first TEE. In the first TEE, valve lesions were found in 17 (70.8%) patients. Ten (58.8%) of these patients were in the NYHA functional class I and 7 (41.2%) in functional class II (3 cases) and III (4 cases) (Table 2). Among patients with valve lesions, other heart abnormalities were detected in 7 patients, including myocardial infarction in 5 and severe pulmonary hypertension in 2. Two of the patients with myocardial infarction also had pulmonary hypertension, and one of these also presented an irregular (2 × 3.6 cm diameter) calcification in the roof of the right atrium (Table 3).

Valve disease was not detected in 7 patients (24%). However, segmental alterations of left ventricular wall movement secondary to myocardial infarction (Figure 1), severe pulmonary hypertension with patent foramen ovale, and an aneurysm of the atrial septum with patent foramen ovale were found in one patient each (Table 3).

When the frequency of embolic events was examined, no significant difference was found between patients with and those without valve lesions. In patients with valve lesions, arterial and venous thrombosis were detected in 10, isolated arterial thrombosis in 6, and isolated venous thrombosis in one. It is noteworthy that of the total of 24 patients, the 4 who died had valve lesions, and in addition, 2 had myocardial infarction. In the group without valve lesions, venous and arterial thrombosis (3 cases) was detected as often as isolated arterial thrombosis (3 cases).

Coronary angiograms were performed in 9 of the initial 24 patients who had myocardial infarction and/or ventricular wall movement abnormalities. Normal coronary arteries were found in 6 patients. In the remaining 3 patients, in addition to APS, other risk factors for ischemic heart disease such as systemic hypertension, diabetes mellitus, and smoking were present. The coronary angiograms revealed 90% obstruction of the right coronary artery in one patient, and complete obstruction of the right coronary artery with thrombi as well as significant occlusion of the posterior descending artery in its origin in another patient. Stenosis of the left anterior descending artery of 80% in its medial segment was apparent in the third case.

Cardiac abnormalities detected in the followup TEE. All 12 patients had received acenocoumarin to maintain an international normalized ratio (INR) of 2.5 to 3.0. In addition, 10 had received acetylsalicylic acid 100 mg/day.

On the 5-year followup TEE, valve lesions were found in all 12 patients studied. In 3 patients lesions were unchanged, 3 patients had developed new valve lesions, and in 6 patients the valve lesions present in the initial study had not only progressed in size, but new lesions had appeared in other valves (Figures 2A, 2B). These new lesions were irregular nodules on the atrial face of the free edge of the mitral and

Table 1. Demographic data of 24 patients with primary antiphospholipid syndrome.

Variables	All Patients, n = 24	With Valve Disease, n =17	Without Valve Disease, n = 7	Patients with a Followup TEE, n = 12	Time Between 1st and 2nd TEE, mo
Age, yrs					
Mean	42.71 ± 11.23	41.00 ± 11.30	45.20 ± 11.30	42.60 ± 13.00	83.75 ± 7.78
Median	44.50	44.00	45.00	43.50	85.50
Range	24–68	24–68	33–60	24–68	69–96
Sex, M/F	6/18	4/13	2/5	4/8	
Average, %	25.0/75.0	23.5/76.5	28.6/71.4	33.3/66.7	

Table 2. Clinical cardiac characteristics of 24 patients with primary antiphospholipid syndrome.

Variables	All Patients (n = 24)	With Valve Disease (n =17)	Without Valve Disease (n = 7)	Patients with a Followup TEE, (n = 12)
Physical examination				
Normal, n (%)	11 (45.8)	4 (23.5)	7 (100)	3 (25.0)
Abnormal, n (%)	13 (54.2)	13 (76.5)	0	9 (75.0)
Cardiac rhythm				
Sinus rhythm, n (%)	21 (87.5)	14 (82.4)	7 (100)	11 (91.7)
Atrial fibrillation, n (%)	3 (22.5)	3 (17.6)	0	1 (8.3)
NYHA functional class				
I, n (%)	15 (62.5)	10 (58.8)	5 (71.4)	8 (66.6)
II, n (%)	4 (16.7)	3 (17.6)	1 (14.3)	2 (16.7)
III, n (%)	5 (20.8)	4 (23.6)	1 (14.3)	2 (16.7)

Table 3. Comparative transesophageal echocardiographic (TEE) findings in 12 patients with a 5-year followup TEE study.

Patient	Sex	Age, yrs	First Study	Second Study	Treatment
1	F	31	SN on AML + PML with mild MR	SN on AML + PML with mild MR, SN on RCAoL, LCAoL and ATL	AC + ASA
2	F	47	LN on AML + PML with moderate MR. Status post mitral valvuloplasty. SN on RCAoL	LN on AML + PML with severe MR and mild MreS.SN on RCAoL + LCAoL, SN on ATL with mild TR	AC + ASA
3	F	68	SN on AML	SN on AML	AC + ASA
4	F	30	SN on AML and LN on 2AoL with mild AR	SN on AML and LN on 2AoL with mild AR and moderate AS	AC + ASA
5	M	60	No valve lesions	SN with moderate-severe MR	AC + ASA
6	M	48	LN on AML + PML, LN on 2AoL with mild-moderate AR	LN on AML + PML with mild-moderate MR, LN on 2AoL with moderate AR	AC + ASA
7	F	42	LN on AML + PML with moderate MR	LN on AML + PML with moderate MR	AC + ASA
8	M	33	No valve lesions	SN on AML + PML SN on LCAol with mild AR, LN on ATL with moderate TR	AC + ASA
9	F	45	No valve lesions	SN on AML + PML, SN on RCAoL SN on ATL + PTL with mild TR, SN on PPL	AC
10	F	50	SN on AML + PML with mild MR, SN on 3AoL	SN on AML + PML with mild to moderate MR LN on AoL with mild AR	AC
11	M	34	SN on AML	SN on AML with mild MR, SN on ATL with mild TR	AC + ASA
12	F	24	LN on AML + PML, LN on NCAoL	LN on AML + PML, LN on NCAoL	AC + ASA

SN: small nodules; LN: large nodules; AML: anterior mitral leaflets; PML: posterior leaflet; MR: mitral regurgitation; MS: mitral stenosis, RCAoL: right coronary aortic leaflet; LCAoL: left coronary aortic leaflet; NCAoL: noncoronary aortic leaflet; 2AoL: bicuspid aortic leaflets with nodules; 3AoL: all 3 aortic leaflets; AR: aortic regurgitation, AS: aortic stenosis; ATL: anterior tricuspid leaflet; TR: tricuspid regurgitation; PPL: posterior pulmonary leaflet; AC: acenocoumarin; ASA: aspirin.

tricuspid valves and on the vascular face of the aortic and pulmonary valves (Table 3).

In the followup TEE, new left ventricular movement abnormalities, apical thrombosis, and pulmonary hypertension were found in some of the patients (Table 4).

Three patients developed myocardial infarction during the followup period (Table 4).

INR during the study. All patients had close anticoagulation monitoring during the study. In general, it was therapeutic (Table 5).

DISCUSSION

Involvement of cardiac valves is a well known feature of primary APS. Recognition of this association began with case reports describing "verrucous endocarditis" of the mitral valve in association with cerebral ischemic events in patients with lupus anticoagulants[13-15]. Chartash, *et al* reported the association between antiphospholipid antibodies and valvular disease in a group of patients with systemic lupus erythematosus with elevated aCL concentrations who had a history of stroke[16]. Recently, 2 TEE studies in patients with primary APS described a prevalence of valve lesions of 63% to 76%[3,4], and the prevalence of arterial thrombosis in one of these series was 58.7%[3]. In our study at a cardiology center, the prevalence of valve lesions in patients with primary APS was 70.8%, and arterial thrombosis was found in 94% of these patients. There is controversy in the literature whether oral anticoagulation or antiplatelet treatment con-

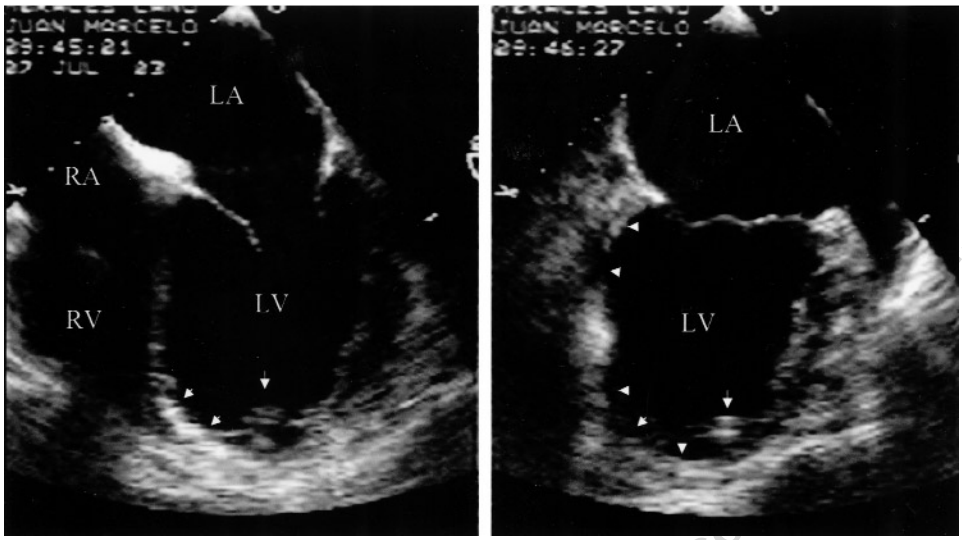

Figure 1. TEE images at 0° and 90° showing akinesis of the inferior wall of the left ventricle at its basal portion (arrowhead) and apical akinesis (arrowhead) with apical thrombus (arrow) in a patient with primary APS without valve disease. LA: left atrium, LV: left ventricle, RA: right atrium, RV: right ventricle.

Table 4. Other echocardiographic findings in the total group of 24 patients with primary APS. Patients 13, 14, 16, 17, and 18 are from the total group of 24 patients.

Patient	Age, yrs	Right Ventricular Cavities (RVC)	Systolic Pulmonary Pressure, mm/Hg	Myocardial Infarction Left Ventricle	Other
1+	31	Moderate enlargement	92	—	—
2+	47	Moderate enlargement	70	—	—
3+	68	Mild enlargement	53	Nontransmural inferolateral	—
4+	30	Normal	—	Anteroseptal and apical	Apical thrombus
5+	60	Normal	—	Posteroinferior	—
8+	33	Severe enlargement	87	—	PFO
10+*	50	Normal	—	Apical	Apical thrombus
11+*	34	Normal	—	Posteroinferior	—
13	33	Normal	—	Posteroinferior	—
14	50	Moderate enlargement and hypokinesia of RVC	98	Posteroinferior	Calcificated thrombus on RA
16*	24	Normal	—	Apical	Apical thrombus
17	26	Hypokinesia of RV anterior wall	—	Posteroinferior and apical	—
18	33	Normal	—	—	Aneurysm of atrial septum with PFO

* Wall motion abnormalities that appeared in the followup TEE. RV: right ventricle, PFO: patent foramen ovale, +: same number patients as in Table 3.

tributes to the disappearance of valvular lesions. In our previous one-year TEE followup study on 13 patients with primary APS, we found that noninfective valvular vegetations did not respond to anticoagulant and/or antiplatelet treatment[3].

In the current 5-year followup study, all patients had been using anticoagulant and 10 of them, in addition, received antiplatelet treatment. Valve lesions were unchanged in 3 patients and in one of them a left ventricular apex akinesis appeared. Interestingly, despite treatment, new valve lesions appeared in 3 patients, and in one of these patients posteroinferior left ventricle akinesis was also observed. Strikingly, in the remaining 6 patients, valve lesions had progressed. One of these patients also had anteroseptal and left ventricle apical hypokinesis, and 2 patients had abnormalities of left ventricular wall motion.

In this study, ischemic heart disease was detected in 9/24 patients (37.5%). Myocardial infarction occurred in 8 patients with valve disease and in one without. Six patients had myocardial infarction at the time of the first TEE, and in 3 a myocardial infarction occurred during the followup period. Coronary angiograms showed normal coronary arteries in 6 of the patients, suggesting the possibility of embolic events. In the remaining 3 cases the cause of the infarction was probably mixed, because these patients had traditional coronary risk factors and the coronary angiogram showed significant coronary artery obstruction.

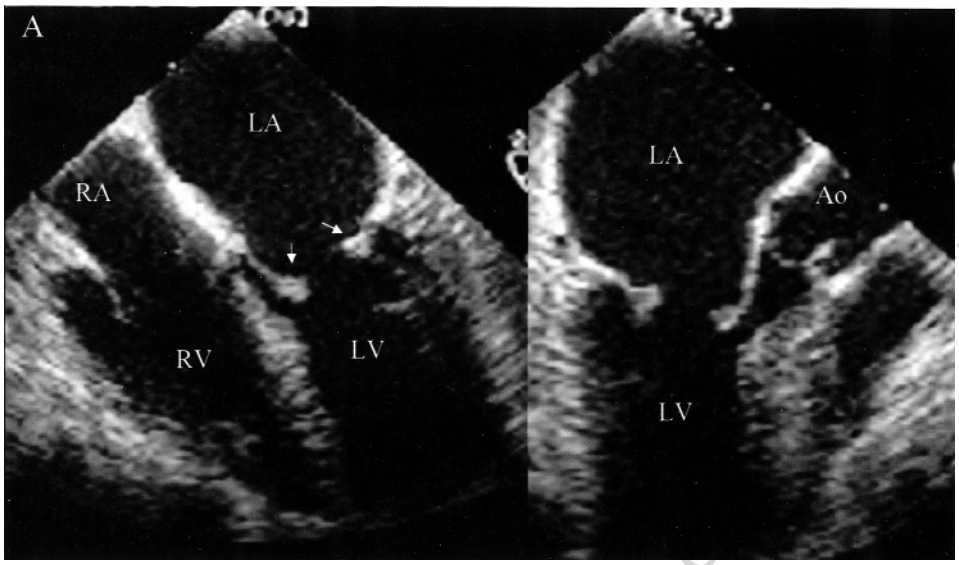

Figure 2A. Transesophageal views at 0° and 130° before anticoagulant and antiplatelet treatment. Irregular nodules are evident on the atrial side of the mitral valve leaflets (arrows). The aortic valve leaflets are normal. LA: left atrium, LV: left ventricle, RA: right atrium, RV: right ventricle.

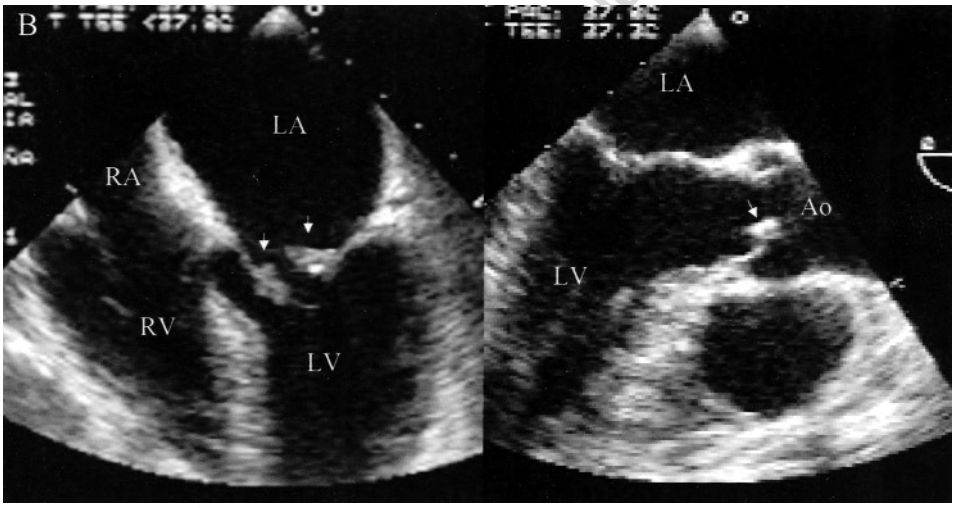

Figure 2B. Five years after anticoagulant and antiplatelet therapy the mitral valve leaflet nodules are increased (arrows) and new nodules have appeared on the free edge of the noncoronary aortic valve leaflet (arrow). Ao: aorta, LA: left atrium, LV: left ventricle, RA: right atrium, RV: right ventricle.

Table 5. International normalized ratio (INR) in 12 patients with a 5-year followup TEE study.

Patient	INR (at least 6 per year) Mean (range)
1	2.4 (1.7–3.8)
2	2.9 (1.6–3.8)
3	1.9 (1.4–2.1)
4	2.9 (1.8–4.3)
5	2.5 (1.8–3.5)
6	2.7 (1.2–3.8)
7	2.2 (1.1–4.7)
8	2.4 (1.3–4.5)
9	2.6 (1.2–4.5)
10	2.5 (1.1–3.7)
11	2.2 (2.1–2.3)
12	3.0 (1.9–4.9)

Hamsten, et al measured aCL concentrations in 62 survivors of acute myocardial infarction who were under age 45 years. They found that 21% had elevated aCL and that these patients had higher incidence of another cardiovascular event in the subsequent 5 years compared with patients with normal aCL level[17]. In a prospective cohort of 4081 healthy middle-aged men, Vaarala, et al found that the presence of a high aCL level was an independent risk factor for myocardial infarction or cardiac death[18]. However, other studies found no significant association between aPL and myocardial infarction[19-21] and did not find aPL to be a risk factor for subsequent cardiovascular thrombosis[22].

Moreover, antiphospholipid antibodies have been associated with the presence of thrombi within the chambers of the

heart[23]. We found this complication in 4 cases (16.6%), 3 in the left ventricle and one in the right atrium.

We emphasize that our patient population is highly selected in so far as our institution is a cardiology referral center. Nonetheless, we believe our data are of more than biological interest.

Our results confirm the notion that in primary APS the predominant cardiac lesion is a noninfective valvular lesion. This valvular damage increases mortality. Additionally, ischemic heart disease, a major complication in primary APS, has an additional impact on cardiovascular morbidity. The pathogenetic mechanisms leading to cardiovascular morbidity involve not only coronary thrombosis, but also atherosclerosis and possibly embolism. Therefore, myocardial infarction in patients with APS may occur despite normal coronary angiography findings.

Oral anticoagulation and aspirin failed to resolve valvular vegetations in a 5-year followup. Similarly, this treatment failed to prevent ischemic heart disease in our patients.

There is no evidence that treatment with corticosteroids can prevent valvular damage. Although a dramatic clinical and hemodynamic response has been reported in some cases[24], the basic disease process of APS is not inflammatory and it would be unwise to administer corticosteroids for the remaining years of the patient's life. Moreover, corticosteroids may facilitate healing of valvular vegetations, leading to scarring and deformity of the valves[2,25].

Additional treatment interventions currently under investigation may improve prognosis in this serious complication of APS[26].

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