Antiphospholipid Syndrome and the Kidney

formation can be regarded as part of the TMA spectrum. Zheng et al29 reported an association of the presence of glomerular microthrombi with detection of LAC and aβ2GPI in SLE patients. In the cohort of 124 LN patients studied by Zheng et al,29 serum complement C3 levels were lower, and C3 and C1q staining was more intense compared with patients without glomerular microthrombi. In a retrospective analysis of 114 renal biopsy specimens from lupus patients, Daugas et al19 showed that APSN occurred in 32% of patients in addition to and independently from lupus nephritis. APSN statistically was associated with aPL, mainly LAC and with extrarenal manifestations of APS, such as arterial thrombosis and obstetric fetal loss. In their cohort, no association between APSN and venous thrombosis was found. The investigators concluded that APSN was an independent risk factor favoring an increased prevalence of hypertension, an increased serum creatinine level, and an increased prevalence of interstitial fibrosis in SLE.19 Tektonidou et al18 studied the prevalence, clinical associations, and long-term outcomes of APSN. APSN was documented in approximately two thirds of SLE patients with secondary APS. The investigators concluded that LAC and/or aCL was associated with TMA, but not with LN, and hence that APS nephropathy occurred almost exclusively in patients with aPL, confirming the important role of aPL in the pathogenesis of APS nephropathy. In line with Daugas et al,19 they found an association with hypertension, increased serum creatinine levels, and histologic progression, all of which were associated with a poor renal outcome. aPL in Lupus Nephritis APS contributes significantly to the renal morbidity in patients with lupus nephritis.19,31 Moroni et al32 found that the presence of aPL in LN patients increased the risk of vascular and obstetric complications, and showed a strong association between aPL antibodies and prognosis in patients with LN. In their cohort of 111 patients, aPL antibody positivity, high plasma creatinine level at presentation, and chronicity index were independent predictors of chronic renal function deterioration. These results are in line with Pérez Velásquez et al,33 who examined a cohort of 600 patients with SLE. This group found not only that LAC and anticardiolipin were more prevalent, but also that more than half of patients with secondary APS had renal disease (56%) and 43% showed typical features of APS on renal biopsy. The significance of APSN is reflected in the longterm outcome of these patients. Tektonidou et al18 studied SLE patients (with or without aPL) to determine the prevalence and long-term outcome of APSN, as well as the histologic evolution of APSN lesions on serial kidney biopsy specimens. In their cohort of 151 patients, APSN was documented, in addition to and independently from lupus nephritis, in almost 40% of patients with aPL compared with only 3 of 70 (2.1%) patients without aPL, suggesting a critical role of aPL in the pathogenesis of APSN. Compared with patients without APSN, patients with APSN had a higher frequency of hypertension and increased serum creatinine levels at the time of kidney biopsy, and developed progression of histologic lesions, all of which were associated with a poor renal outcome.18 SLE, APS, and Pregnancy SLE commonly affects women during their childbearing years, and pregnancy is therefore an important topic. SLE has a tendency to flare during pregnancy and consequently may impact renal function with possible long-term consequences such as end-stage renal disease. Pregnancy counseling to ensure disease remission, close follow-up evaluation during pregnancy, and post-partum surveillance play a major role in improving pregnancy outcomes.34 The presence of aPL is a well-documented risk factor for pregnancy morbidity, including recurrent abortions, premature delivery, intrauterine growth restriction, and preeclampsia, and can be found in 25% of SLE pregnancies.35 Post-partum renal failure in association with the presence of aPL was described in the 1980s by Kincaid-Smith et al.36,37 A recent metaanalysis by Smyth et al35 confirmed a positive association between the presence of aPL and hypertension in pregnancy, premature birth, and recurrent miscarriages. A cohort of 1842 patients and 2751 pregnancies was examined. Maternal complications included lupus flare (25.6%), hypertension (16.3%), nephritis (16.1%), preeclampsia (7.6%), and eclampsia (0.8%). Fetal complications included spontaneous abortion (16.0%), stillbirth (3.6%), neonatal deaths (2.5%), and intrauterine growth restriction (12.7%), with a premature birth rate of 39.4%.35 Treatment The treatment of asymptomatic aPL carriers without

underlying autoimmune disease remains controversial. However, a recent consensus document emphasized that there is no role for primary thromboprophylaxis with low-titer aPL or intermittent aPL positivity (Table 4).38 In asymptomatic aPL carriers with underlying autoimmune conditions, especially SLE, primary thromboprophylaxis should be considered because this condition itself may be thought of as an additional risk factor for thrombosis. Therefore, primary thromboprophylaxis with low-dose aspirin (75-100 mg/day) could be considered in all patients with an underlying systemic autoimmune condition and persistent aPL at medium-high titers (IgM or IgG phospholipid units 4 40 GPL or MPL or 4 99th percentile). In patients with SLE specifically and persistently positive aPL, primary thromboprophylaxis including low-dose aspirin (75- 100 mg/day) and/or hydroxychloroquine (200-400 mg/day) is recommended. This suggestion is based on retrospective studies that have shown that hydroxychloroquine appears to protect SLE patients, especially those with aPL, against thrombosis.39 Although no study has investigated specifically whether the addition of antiplatelet agents offers additional protection, aspirin also may be considered in the setting of primary thromboprophylaxis.40 Given the general recommendation of hydroxychloroquine administration in most patients with SLE, the addition of low-dose aspirin should be decided on an individual basis. The addition of lowdose aspirin may be appropriate in selected cases, such as patients with a high-risk aPL profile (eg, triple positivity for lupus anticoagulant, aCL and aβ2GPI), other concomitant cardiovascular risk factors, and/or SLE patients with a history of obstetric APS. In patients with previous thrombosis (regardless of any underlying autoimmune disease) anticoagulation with a vitamin K antagonist (international normalized ratio, 2.0-3.0) is required as long-term secondary thromboprophylaxis.41,42 Patients with arterial events or cases of recurrent thrombotic events despite ongoing treatment may require high-intensity treatment (international normalized ratio, 3.0-4.0) with warfarin.43 With regard to the management of renal artery stenosis, treatment with antihypertensive drugs, antiaggregation agents, and anticoagulants have been reported to be effective. Sangle et al41 analyzed 14 hypertensive APS patients with renal artery stenosis who received oral anticoagulation for more than 1 year and reported the beneficial effects of their approach on blood pressure control and renal function. The treatment for APSN is based on anticoagulation. Steroids, hydroxycloroquine, and some immunosuppressive agents occasionally have been reported to reduce the titer of aPL, but their role in reducing the risk of thrombosis has not yet been proven. A few studies evaluating the role of immunosuppressants on primary APSN have reported favorable effects.42,44 The long-term use of intravenous immunoglobulin also has been reported in very selected cases of primary relapsing APS despite standard treatment.45 New oral anticoagulants such as dabigatran, apixaban, and rivaroxaban now are available. They have been shown to be effective in the management of venous thromboembolism and they do not require laboratory monitoring. Preliminary experience supporting the use of new oral anticoagulants in patients with APS were reported recently.46 A trial to assess the efficacy and safety of rivaroxaban in APS currently is underway.47 B-cell depletion with rituximab also has been suggested for selected cases of APS, mainly in the presence of severe thrombocytopenia.48 Recently, Erkan et al49 designed a 12-month, phase II pilot rituximab study, including adult aPL-positive patients with thrombocytopenia, cardiac valve disease, skin ulcer, aPL nephropathy, and/or cognitive dysfunction. A potential role of eculizumab, an anti-C5 antibody, in selected cases of APS also has been proposed. However, available evidence still is based on experimental APS models or anecdotal cases.50,51

Take Home Messages

The following points should be kept in mind. ı

 In patients affected by APS, both primary and associated with other autoimmune diseases such as SLE, the kidney is a major target organ. ı

 Renal involvement in APS is a well-recognized manifestation of the syndrome and is characterized by the occurrence of thrombosis, potentially involving any site of the kidney vasculature.

 In SLE, APSN can co-exist with LN. A biopsy is mandatory for a differential diagnosis. ı

 Because of the clinical and histologic similarities between APSN and other microangiopathies, an aPL test is useful to distinguish between possible causes. ı

 The presence of Lupus Anticoagulant and/or aCL in SLE patients can be considered a risk factor for poor renal outcome even in the absence of LN. ı

 CAPS must be considered in the differential diagnosis of APSN because it is associated with high mortality and must be treated aggressively. ı

 During pregnancy the presence of aPL is associated with a higher risk of morbidity including hypertension, nephritis, preeclampsia, and eclampsia. ı

 The use of hydroxychloroquine is recommended in patients with aPL associated with SLE even in the absence of APS.

 Low-dose aspirin can be useful in patients with a higher risk of thrombosis (eg, triple positivity for aPL). ı

 Therapeutic approaches for renal involvement in APS focuses on anticoagulation with long-term warfarin. ı

 Presently, there are not sufficient data regarding the use of new oral anticoagulants in patients with APSN. ı

 Rescue therapies, including intravenous immunoglobulins, rituximab, or eculizumab can be attempted in refractory cases.

REFERENCES 1. Miyakis S, Lockshin MD, Atsumi T, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). J Thromb Haemost. 2006;4:295-306.

2. Worrall JG, Snaith ML, Batchelor JR, et al. SLE: a rheumatological view. Analysis of the clinical features, serology and immunogenetics of 100 SLE patients during long-term followup. QJM. 1990;74:319-30.

3. Estes D, Christian CL. The natural history of systemic lupus erythematosus by prospective analysis. Medicine (Baltimore). 1971;50:85-95.

4. Rovin BH, Parikh SV. Lupus nephritis: the evolving role of novel therapeutics. Am J Kidney Dis. 2014;63:677-90.

5. Ruiz-Irastorza G, Crowther M, Branch W, et al. Antiphospholipid syndrome. Lancet. 2010;376:1498-509.

6. Cervera R, Serrano R, Pons-Estel GJ, et al. Morbidity and mortality in the antiphospholipid syndrome during a 10-year period: a multicentre prospective study of 1000 patients. Ann Rheum Dis. 2015;74:1011-8.
7. Stone S, Pijnenborg R, Vercruysse L, et al. The placental bed in pregnancies complicated by primary antiphospholipid syndrome. Placenta. 2006;27:457-67.

8. Cervera R, Tektonidou MG, Espinosa G, et al. Task Force on Catastrophic Antiphospholipid Syndrome (APS) and noncriteria APS manifestations (I): catastrophic APS, APS nephropathy and heart valve lesions. Lupus. 2011;20:165-73.

9. Stone S, Langford K, Nelson-Piercy C, et al. Antiphospholipid antibodies do not a syndrome make. Lupus. 2002;11:130-3.

10. Meroni PL, Borghi MO, Raschi E, et al. Pathogenesis of antiphospholipid syndrome: understanding the antibodies. Nat Rev Rheumatol. 2011;7:330-9.

11. Meroni PL, Riboldi R. Pathogenic mechanisms mediating antiphospholipid syndrome. Curr Opin Rheumatol. 2001;13:377-82.

12. Sciascia S, Cuadrado MJ, Khamashta M, et al. Renal involvement in antiphospholipid syndrome. Nat Rev Nephrol. 2014;10: 279-89.

13. Giannakopoulos B, Krilis SA. The pathogenesis of the antiphospholipid syndrome. N Engl J Med. 2013;368:1033-44.

14. Sciascia S, Sanna G, Murru V, et al. GAPSS: the Global AntiPhospholipid Syndrome Score. Rheumatology (Oxford). 2013; 52:1397-403.

15. Lie JT. Vasculitis in the antiphospholipid syndrome: culprit or consort? J Rheumatol. 1994;21:397-9.

16. Amigo MC, Garcia-Torres R, Robles M, et al. Renal involvement in primary antiphospholipid syndrome. J Rheumatol. 1992;19:1181-5.

17. Sinico RA, Cavazzana I, Nuzzo M, et al. Renal involvement in primary antiphospholipid syndrome: retrospective analysis of 160 patients. Clin J Am Soc Nephrol. 2010;5:1211-7.

18. Tektonidou MG, Sotsiou F, Nakopoulou L, et al. Antiphospholipid syndrome nephropathy in patients with systemic lupus erythematosus and antiphospholipid antibodies: prevalence, clinical associations, and long-term outcome. Arthritis Rheum. 2004;50:2569-79.

19. Daugas E, Nochy D, Huong DL, et al. Antiphospholipid syndrome nephropathy in systemic lupus erythematosus. J Am Soc Nephrol. 2002;13:42-52.

20. Uthman I, Khamashta M. Antiphospholipid syndrome and the kidneys. Semin Arthritis Rheum. 2006;35:360-7.

21. Griffiths MH, Papadaki L, Neild GH. The renal pathology of primary antiphospholipid syndrome: a distinctive form of endothelial injury. QJM. 2000;93:457-67.

22. Rankin EC, Nield GH, Isenberg DA. Deterioration of renal function in a patient with lupus. Ann Rheum Dis. 1994;53: 67-71.

23. Alchi B, Griffiths M, Jayne D. What nephrologists need to know about antiphospholipid syndrome. Nephrol Dial Transplant. 2010;25:3147-54.

24. Barbour T, Johnson S, Cohney S, et al. Thrombotic microangiopathy and associated renal disorders. Nephrol Dial Transplant. 2012;27:2673-85.

25. Bertolaccini ML, Amengual O, Andreoli L, et al. 14th International Congress on Antiphospholipid Antibodies Task Force. Report on antiphospholipid syndrome laboratory diagnostics and trends. Autoimmun Rev. 2014;13:917-30.

26. Asherson RA, Espinosa G, Cervera R, et al. Catastrophic antiphospholipid syndrome: proposed guidelines for diagnosis and treatment. J Clin Rheumatol. 2002;8:157-65.

27. Nochy D, Daugas E, Droz D, et al. The intrarenal vascular lesions associated with primary antiphospholipid syndrome. J Am Soc Nephrol. 1999;10:507-18.

28. Bhandari S, Harnden P, Brownjohn AM, et al. Association of anticardiolipin antibodies with intraglomerular thrombi and renal dysfunction in lupus nephritis. QJM. 1998;91:401-9.

29. Zheng H, Chen Y, Ao W, et al. Antiphospholipid antibody profiles in lupus nephritis with glomerular microthrombosis: a prospective study of 124 cases. Arthritis Res Ther. 2009;11: R93.

30. Miranda JM, Garcia-Torres R, Jara LJ, et al. Renal biopsy in systemic lupus erythematosus: significance of glomerular thrombosis. Analysis of 108 cases. Lupus. 1994;3:25-9.

31. Ruiz-Irastorza G, Egurbide MV, Ugalde J, et al. High impact of antiphospholipid syndrome on irreversible organ damage and survival of patients with systemic lupus erythematosus. Arch Intern Med. 2004;164:77-82.

32. Moroni G, Ventura D, Riva P, et al. Antiphospholipid antibodies are associated with an increased risk for chronic renal insufficiency in patients with lupus nephritis. Am J Kidney Dis. 2004;43:28-36.

33. Pérez Velásquez C, Isenberg D, Croca S. Secondary antiphospholipid syndrome nephropathy and lupus nephritis: a casecontrol study [abstract THU0308]. Ann Rheum Dis. 2013;72 (Suppl 3):270.

34. Kwok LW, Tam LS, Zhu T, et al. Predictors of maternal and fetal outcomes in pregnancies of patients with systemic lupus erythematosus. Lupus. 2011;20:829-36.

35. Smyth A, Oliveira GH, Lahr BD, et al. A systematic review and meta-analysis of pregnancy outcomes in patients with systemic lupus erythematosus and lupus nephritis. Clin J Am Soc Nephrol. 2010;5:2060-8.

36. Kincaid-Smith P, Fairley KF, Kloss M. Lupus anticoagulant associated with renal thrombotic microangiopathy and pregnancy-related renal failure. QJM. 1988;68:795-815.

37. Kincaid-Smith P. Post partum renal failure in systemic lupus erythematosus associated with circulating lupus anticoagulant and anticardiolipin antibody. Clin Nephrol. 1991;36:52

38. Ruiz-Irastorza G, Cuadrado MJ, Ruiz-Arruza I, et al. Evidencebased recommendations for the prevention and long-term management of thrombosis in antiphospholipid antibodypositive patients: report of a task force at the 13th International Congress on antiphospholipid antibodies. Lupus. 2011;20: 206-18.

39. Erkan D, Aguiar CL, Andrade D, et al. 14th International Congress on Antiphospholipid Antibodies Task Force Report on Antiphospholipid Syndrome Treatment Trends. Autoimmun Rev. 2014;13:685-96.

40. Tektonidou MG, Laskari K, Panagiotakos DB, et al. Risk factors for thrombosis and primary thrombosis prevention in patients with systemic lupus erythematosus with or without antiphospholipid antibodies. Arthritis Rheum. 2009;61:29-36.

41. Sangle SR, D'Cruz DP, Abbs IC, et al. Renal artery stenosis in hypertensive patients with antiphospholipid (Hughes) syndrome: outcome following anticoagulation. Rheumatology (Oxford). 2005;44:372-7.

42. Korkmaz C, Kabukcuoğlu S, Isiksoy S, et al. Renal involvement in primary antiphospholipid syndrome and its response to immunosuppressive therapy. Lupus. 2003;12:760-5.

43. Brodsky SV, Nadasdy T, Rovin BH, et al. Warfarin-related nephropathy occurs in patients with and without chronic kidney disease and is associated with an increased mortality rate. Kidney Int. 2011;80:181-9.

44. Sokunbi DO, Miller F, Wadhwa NK, et al. Reversible renal failure in the primary antiphospholipid syndrome–a report of two cases. J Am Soc Nephrol. 1993;4:28-35.

45. Sciascia S, Giachino O, Roccatello D. Prevention of thrombosis relapse in antiphospholipid syndrome patients refractory to conventional therapy using intravenous immunoglobulin. Clin Exp Rheumatol. 2012;30:409-13.

46. Sciascia S, Breen K, Hunt BJ. Rivaroxaban use in patients with antiphospholipid syndrome and previous venous thromboembolism. Blood Coagul Fibrinolysis. 2015;26:476-7.

47. Giles I, Khamashta M, D'Cruz D, et al. A new dawn of anticoagulation for patients with antiphospholipid syndrome? Lupus. 2012;21:1263-5.

48. Sciascia S, Naretto C, Rossi D, et al. Treatment-induced downregulation of antiphospholipid antibodies: effect of rituximab alone on clinical and laboratory features of antiphospholipid syndrome. Lupus. 2011;20:1106-8.

49. Erkan D, Vega J, Ramón G, et al. A pilot open-label phase II trial of rituximab for non-criteria manifestations of antiphospholipid syndrome. Arthritis Rheum. 2013;65:464-71.

50. Erkan D, Lockshin MD. New approaches for managing antiphospholipid syndrome. Nat Clin Pract Rheumatol. 2009;5:160-70.

51. Velik-Salchner C, Lederer W, Wiedermann F. Eculizumab and renal transplantation in a patient with catastrophic antiphospholipid syndrome: effect of heparin on complement activation. Lupus. 2011;20:772.

Figure 1. APS-associated nephropathy. (A) Hematoxylin-eosin stain. Intracapillary thrombi in the glomerulus on the left. The afferent arteriole is occluded entirely by a fibrin thrombus (black arrow). (B) Same stain. Fibrinoid necrosis and mucoid intimal edema in the intima of an arteriole (red arrow) with fragmented red blood cells. The interstitium around the arteriole is edematous. (C) Same stain. Thrombi occluding peritubular capillaries (black arrow). Interstitial edema, hemorrhage, and acute tubular injury might be present depending on the severity of the acute ischemic injury. (D) Large intravascular thrombus at the vascular pole of a glomerulus is red under trichrome staining (black arrow). (E) Direct immunofluorescence showing positive staining for fibrinogen in glomerular capillary lumina and at the vascular pole (white arrows). (F) At ultrastructural examination fibrin occludes the capillary lumen. Endothelial cells have lost fenestration and podocytes show extensive foot process effacement. (G) In chronic disease, double contours without interposition of electron dense immune complexes can be seen (white arrow). Platelets are seen in capillary lumina in both acute and chronic phases (black circle). Podocytes often are injured and show foot process effacement (black arrows). Figure reprinted with permission from Sciascia et al.1

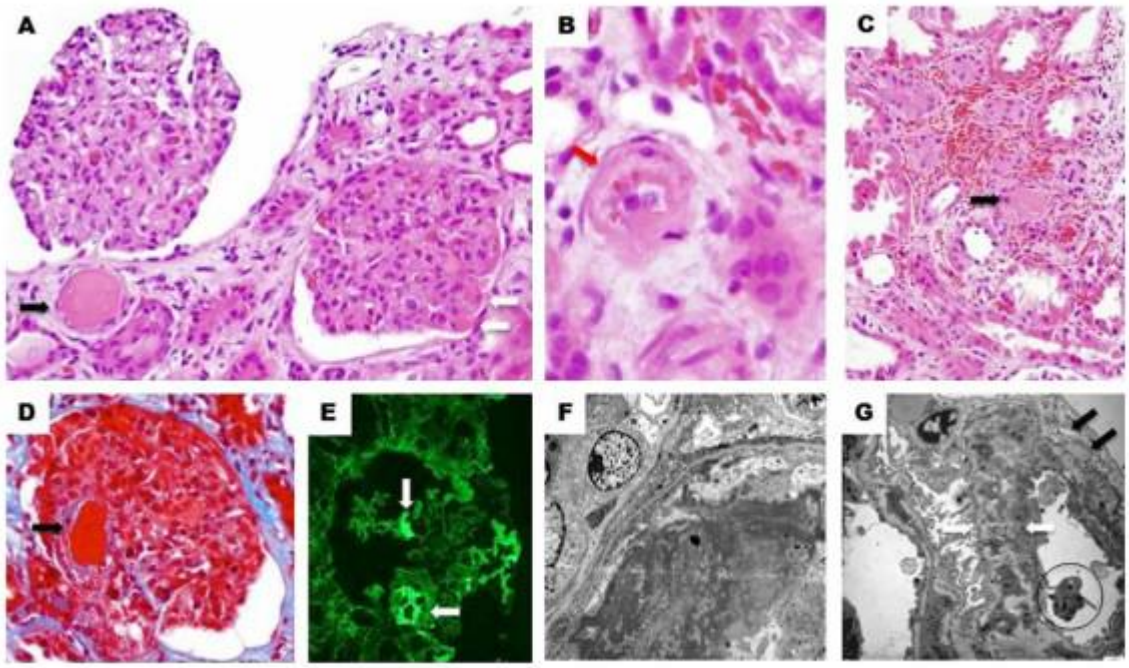

Table 1. Criteria for the Classification of Antiphospholipid Syndrome

Vascular thrombosis	Clinical criteria
One or more clinical episodes of arterial, venous, or small-vessel thrombosis, in any tissue or organ Thrombosis must be confirmed by objective validated criteria (ie, unequivocal findings of appropriate imaging studies or histopathology); for histopathologic confirmation, thrombosis should be present without significant evidence of inflammation in the vessel wall	
Pregnancy morbidity	
One or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation, with normal fetal morphology documented by ultrasound or by direct examination of the fetus, or One or more premature births of a morphologically normal neonate before the 34th week of gestation because of (1) eclampsia or severe preeclampsia defined according to standard definitions or (2) recognized features of placental failure or Three or more unexplained consecutive spontaneous abortions before the 10th week of gestation, with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded In studies of populations of patients who have more than one type of pregnancy morbidity, stratification of subjects according to this list is strongly encouraged	
Lupus anticoagulant present in plasma on 2 or more occasions at least 12 weeks apart and detected according to the guidelines of the International Society on Thrombosis and Hemostasis (Scientific Subcommittee on LA/phospholipid-dependent antibodies)	Laboratory criteria
Anticardiolipin antibody of IgG and/or IgM isotype in serum or plasma, present in medium or high titers (ie, >40 GPL or MPL, or >99th percentile), on 2 or more occasions, at least 12 weeks apart, measured by a standardized ELISA	
aβ2GPI antibody of IgG and/or IgM isotype in serum or plasma (in titers >99th percentile), present on 2 or more occasions, at least 12 weeks apart, measured by a standardized ELISA	

Definite antiphospholipid syndrome may be diagnosed if at least one of the clinical criteria and at least one of the laboratory criteria are met.
Abbreviation: ELISA, enzyme-linked immunosorbent assay; GPL, IIgG phospholipid units; MPL, IgM phospholipid units.

Table 2. Clinical Features of the Antiphospholipid Syndrome

Venous thrombosis: deep venous thrombosis	Major features
Arterial thrombosis: strokes, transient ischemic attacks, multi-infarct dementia, or myocardial infarction	
Pregnancy complications: recurrent pregnancy loss, intrauterine growth restriction, pre-eclampsia	
Thrombocytopenia	Associated clinical features
Leg ulcers, livedo reticularis, thrombophlebitis, and Sneddon's syndrome	
Budd–Chiari syndrome and pulmonary thromboembolism	
Heart valve lesions	
Transverse myelitis, chorea, and epilepsy	
Hemolytic anemia, Coombs' positivity, and Evans' syndrome	
Pulmonary hypertension	
Cognitive impairment	
Chronic headache	
Splinter hemorrhages	Other less common features
Labile hypertension and accelerated atherosclerosis	
Ischemic necrosis of bone	
Bone marrow necrosis	
Addison's disease	
Guillain–Barré syndrome and pseudomultiple sclerosis	
Amaurosis fugax	
Sensorineural hearing loss	
Renal artery and vein thrombosis and microangiopathy	
Retinal artery and vein thrombosis	
Digital gangrene	

Table 3. Renal Manifestations of Antiphospholipid Syndrome

APS nephropathy
Renal artery stenosis and thrombosis
Renal vein thrombosis
Renal infarction
Systemic hypertension
aPL-related glomerular microthrombosis in lupus nephritis
Catastrophic antiphospholipid syndrome

Table 4. Therapeutic Recommendations in Individuals With Antiphospholipid Antibodies

Strict control of cardiovascular risk factors should be accomplished in all individuals with a high-risk aPL profile,* irrespective of the presence of previous thrombosis, concomitant SLE, or additional APS features	General measures for aPL antibody carriers
All aPL carriers should receive thromboprophylaxis with the usual doses of LMWH in high-risk situations, such as surgery, prolonged immobilization, and puerperium	
In patients with SLE and positive lupus anticoagulant or isolated persistent anticardiolipin antibodies at medium-high titers, primary thromboprophylaxis with hydroxychloroquine ± low-dose aspirin is recommended	Primary thromboprophylaxis in SLE patients with antiphospholipid antibodies
In non-SLE individuals with aPL and no previous thrombosis, long-term primary thromboprophylaxis with low-dose aspirin is recommended in patients with a high-risk aPL profile, especially in the presence of other thrombotic risk factors	Primary thromboprophylaxis in aPL-positive individuals without SLE
Patients with either arterial or venous thrombosis and aPL who do not fulfill criteria for APS should be treated in the same manner as aPL-negative patients with similar thrombotic events	Secondary thromboprophylaxis
Patients with definite APS and a first venous event should receive oral anticoagulant therapy to a target INR of 2.0 to 3.0	
Patients with definite APS and arterial thrombosis should be treated with warfarin at an INR >3.0 or combined anti-aggregant–anticoagulant therapy (INR 2.0-3.0)	
The patient's bleeding risk should be estimated before prescribing high-intensity anticoagulant or combined anti-aggregant–anticoagulant therapy	
Non-SLE patients with a first noncardioembolic cerebral arterial event, with a low-risk aPL profile† and the presence of reversible trigger factors could be considered individual candidates for treatment with antiplatelet agents.	
Duration of treatment	
Indefinite antithrombotic therapy is recommended in patients with definite APS and thrombosis	
In cases of first venous event, low-risk aPL profile† and a known transient precipitating factor, anticoagulation could be limited to 3-6 months	
In patients with difficult management owing to recurrent thrombosis, fluctuating INR levels, major bleeding or at a high risk for major bleeding, alternative therapies could include long-term LMWH, hydroxychloroquine, or statins	Refractory and difficult cases
APS with poor obstetric outcomes	Antiphospholipid syndrome in pregnancy
Recurrent early (pre-embryonic or embryonic) miscarriage Low-dose aspirin alone, or plus: LMWH at thromboprophylactic doses	
Fetal death (>10 weeks' gestation) or prior early delivery (<34 weeks of gestation) caused by severe preeclampsia or placental insufficiency Low-dose aspirin, plus: LMWH at thromboprophylactic doses	
Women with previous thrombotic APS during pregnancy Low-dose aspirin, plus: LMWH	

INR, international normalized ratio; LMWH, low-molecular-weight heparin.

*High-risk APL profile: lupus anticoagulant positivity, triple positivity (lupus anticoagulant + anticardiolipin + aβ2GPI antibodies), isolated persistently positive anticardiolipin antibodies at medium-high titers.

†Low-risk aPL profile: isolated, intermittently positive anticardiolipin or anti-β2-glycoprotein I at low-medium titers.