We are IntechOpen,
the world's leading publisher of
Open Access books
Built by scientists, for scientists

5,800
Open access books available

142,000
International authors and editors

180M
Downloads

154
Countries delivered to

Our authors are among the

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities

CLARIVATE ANALYTICS
BOOK CITATION INDEX
INDEXED

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Antiphospholipid Syndrome and Stroke

Kathryn Grimes, Adam P. Klein, Rakhee Lalla, Adeolu Morawo, Sana Somani, Mathew J. Woodward and John W. Cole

Abstract

Thromboses of the cerebral arterial and venous systems are a common manifestation of antiphospholipid syndrome (APS) often leading to ischemic and hemorrhagic stroke. APS increases stroke risk via many mechanisms, including hypercoagulability and inflammation. These mechanisms, among others, must be considered by physicians when evaluating and treating such patients to achieve optimal short- and long-term outcomes. In this chapter, we will discuss the epidemiology of APS as it relates to neurological disease focusing on stroke, APS stroke mechanisms, suggested clinical evaluations, acute treatment strategies, and long-term secondary stroke prevention strategies. Current consensus statements and the most recent literature will be summarized.

Keywords: antiphospholipid syndrome, stroke, epidemiology, etiology, treatment

1. Introduction

Antiphospholipid syndrome (APS) was first described in 1983 with steadily improving clinical and scientific refinements since that time. It was initially recognized with the discovery of lupus anticoagulant immunoglobulin that binds to phospholipids and proteins associated with the cell membrane and its association with other autoimmune conditions. Over the years, the clinical manifestations of APS were further delineated, followed by the discovery of other antiphospholipid antibodies. Currently, APS is defined as an autoimmune condition characterized by the presence of venous or arterial thrombosis and/or pregnancy-related complications in patients with antiphospholipid antibodies [1]. Notably, APS can occur as a *primary* disease process or *secondary* to another condition, primarily autoimmune conditions, including systemic lupus erythematous (SLE), rheumatoid arthritis, sjogren's disease, or systemic sclerosis. It can more rarely be secondary to malignancy [2] and infections, including syphilis and HIV [3].

Clinically, APS can manifest in a variety of ways and affect multiple organ systems. Presenting symptoms can range from relatively benign to severe. One subtype (to be discussed in Section 2) termed catastrophic APS (CAPS) is defined as APS that affects >3 organs in a short period of time (<7 days) with pathologic evidence of small-vessel occlusion. The most common venous manifestation of APS

is deep vein thrombosis, while stroke is the most common arterial manifestation of this disease [4]. Obstetric complications include placental insufficiency and recurrent pregnancy loss, typically after 10 weeks of gestation. There are, however, a multitude of other manifestations including cardiac valvular disease, coronary artery disease, livedo reticularis, renal small artery vasculopathy, and thrombocytopenia, which are *not* included in the formal classification criteria [1]. Neurologically, antiphospholipid antibodies have also been found to be more rarely related to migraine, seizures, movement disorders, and cognitive impairment [5]. Given this broad range of clinical manifestations, it is important that clinicians have a clear understanding of when to suspect this condition and its appropriate management.

Antiphospholipid antibodies (aPL) are a serological marker for APS and their presence is key to the definition and classification for APS. Phospholipids are molecules found in the blood that aid in clot formation. They form complexes with other plasma proteins and are the target of aPL antibodies; thus, one may expect to clinically see a bleeding disorder when phospholipids are disrupted. However, these autoantibodies primarily cause endothelial dysfunction and disruption of coagulation factors as they compete with coagulation factors for available phospholipids, thereby leading to a procoagulant state and clot formation [6]. The pathophysiology of aPL antibodies is not fully elucidated, but the current thought is that of a "two-hit" hypothesis. The first hit being a patient-specific susceptibility, and the second hit being a trigger or inciting event. This theory is based on the idea that about 1–5% of the population may have positive aPL antibodies without any clinical manifestations, indicating the need for a trigger that leads to the pathologic state [2, 4]. In a patient carrying aPL antibodies, endothelial cell activation occurs in the setting of oxidative stress in conditions such as infection, surgery, and pregnancy. This is thought to subsequently lead to a series of events including complement activation, cytokine release, increased expression of tissue factor on endothelial cells, increased platelet adhesiveness, and impairment of thrombolysis [2, 4]. Overall, this creates a procoagulant state leading to the range of clinical manifestations as described.

aPL antibodies are a heterogeneous group of autoantibodies that primarily include *lupus anticoagulant (LA), anti-cardiolipin IgG/IgM (aCL), and anti-beta-2 glycoprotein-I (aB2GPI) IgG/IgM,* with these three specific antibodies included in the formal classification criteria for APS [1]. As shown in **Figure 1** there is some overlap between these antibodies, but overall, they are distinct leading to a variety of clinical manifestations [5]. In addition to the three antibodies in the classification criteria, there are a number of other proposed antibodies of yet unclear clinical significance and diagnostic value. These include anti-prothrombin and anti-phosphatidylserine-prothrombin complex, aCL IgA and anti-B2GPI IgA. These antibodies are sometimes used to aid in diagnosis if there is a very high clinical suspicion for APS without the presence of the typical autoantibodies in the classification criteria [7]. It is important to note that while B2GPI is considered a primary APS antigen, subgroups of protein domains can be targeted by specific antibodies. For example, antibodies targeting B2GPI Domain I, in particular, have been correlated with a high risk of thrombosis [8].

The presence of LA alone is thought to hold the highest risk for thrombosis among all antiphospholipid antibodies. Thrombotic risk is much lower in patients who have only a positive aCL or anti-B2GPI antibody [1, 3]. The risk is thought to be much higher however in patients with multiple positive antibodies, especially those found to be "triple positive" [3]. Thrombotic risk is also much higher in patients who have secondary APS is associated with SLE and in patients with primary APS with concurrent vascular comorbidities including hypertension, hypercholesterolemia, tobacco, and oral contraceptive use [7].
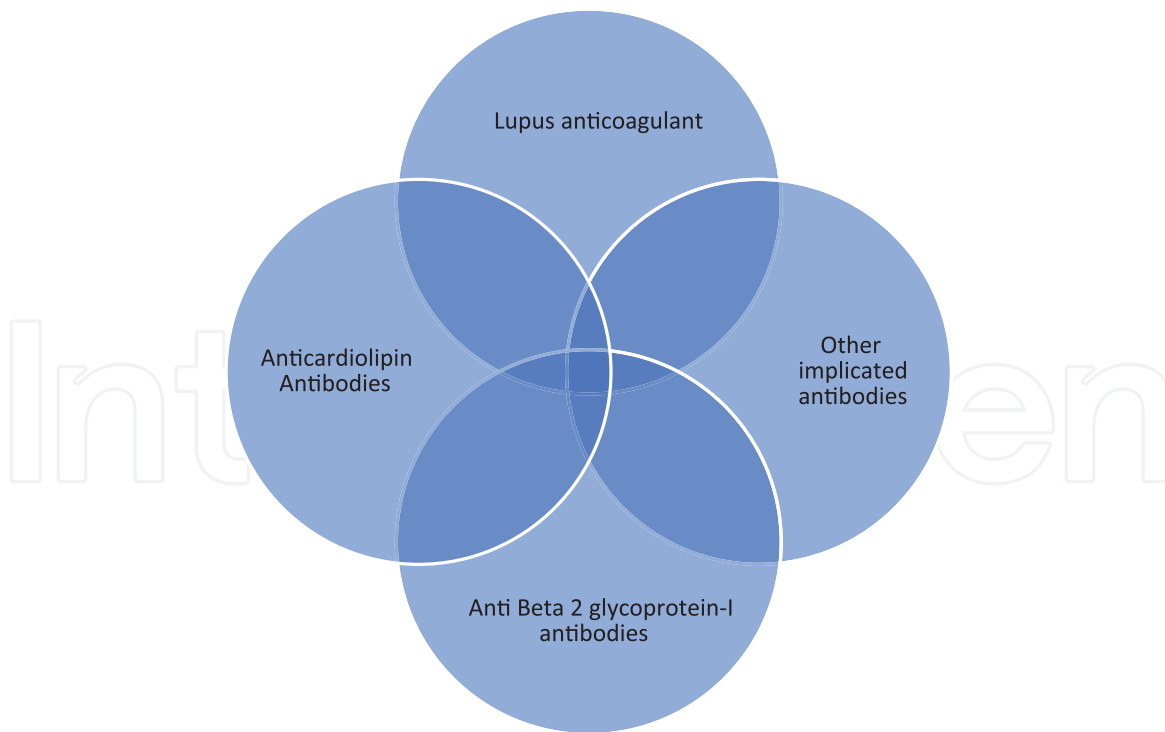
Figure 1.
There are a variety of antiphospholipid antibodies associated with APS, as detected with different methods, some are overlapping, but each has distinct properties. Image adapted from Misita et al. [6].

The initial classification criteria for APS, called the Sapporo criteria, was first developed in 1999 and most recently updated in 2006 [1]. As shown in **Table 1**, the criteria currently require one clinical manifestation of thrombosis or pregnancy complication, and one laboratory criteria present on two occasions at least 12 weeks apart.

As mentioned, there are other autoantibodies implicated in APS that are not yet included in the classification criteria. The remainder of this chapter will discuss the clinical manifestations, epidemiology, pathophysiology, diagnosis, and treatment in more detail.

2. Clinical presentation

APS can present as a wide range of clinical manifestations with the major clinical features consisting of arterial and venous thromboses, and obstetrical complications. The most common obstetrical manifestations of APS are recurrent early miscarriage, placental insufficiency, early pre-eclampsia, and fetal death, all of which should prompt evaluation for the presence of aPL [12].

Thrombotic events in APS may occur in virtually any vascular bed, with the cerebral circulation being the arterial territory most commonly affected, usually in the form of stroke or transient ischemic attack [13]. APS has also been associated with many other clinical features including livedo reticularis, epilepsy, thrombocytopenia, and cognitive dysfunction, however, the strength of association is not sufficiently high to include them in the syndrome definition. The clinical characteristics of a cohort of 1000 patients with APS (Euro-Phospholipid Project) are displayed in **Table 2** [14].

2.1 Classification criteria: additional considerations

As described in Section 1, the first set of criteria for APS was established in Sapporo, Japan in 1999 after an expert workshop [9]. This was modified, including

Antiphospholipid antibody syndrome (APS) is present if at least one of the clinical criteria and one of the laboratory criteria that follow arc met[*] clinical criteria

1. Vascular thrombosis[†]
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 (i.e. unequivocal findings of appropriate imaging studies or histopathology). For histopathologic confirmation, thrombosis should be present without significant evidence of inflammation in the vessel wall.

2. Pregnancy morbidity
 a. 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
 b. One or more premature births of a morphologically normal neonate before the 34th week of gestation because of (i) eclampsia or severe pre-eclampsia defined according to standard definitions [9], or (ii) recognized features of placental insufficiency[¶], or
 c. 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, investigators arc strongly encouraged to stratify groups of subjects according to a, b, or c above.

Laboratory criteria[**]
1. Lupus anticoagulant (LA) present in plasma, on two or more occasions at least 12 weeks apart, detected according to the guidelines of the International Society on Thrombosis and Hemostasis (Scientific Subcommittee on LAs/phospholipid-dependent antibodies) [10, 11].

2. Anticardiolipin (aCL) antibody of IgG and/or IgM isotype in scrum or plasma, present in medium or high titer (i.e. >40 GPL or MPL, or >the 99th percentile), on two or more occasions, at least 12 weeks apart, measured by a standardized ELISA.

3. Anti-β_2 glycoprotein-I antibody of IgG and/or IgM isotype in scrum or plasma (in titer > the 99th percentile), present on two or more occasions, at least 12 weeks apart, measured by a standardized ELISA, according to recommended procedures.

[*]*Classification of APS should be avoided if less than 12 weeks or more than 5 years separate the positive aPL test and the clinical manifestation.*
[†]*Coexisting inherited or acquired factors for thrombosis arc, not reasons for excluding patients from APS trials. However, two subgroups of APS patients should be recognized, according to (a) the presence, and (b) the absence of additional risk factors for thrombosis. Indicative (but not exhaustive) such eases include: age (>55 in men, and >65 in women), and the presence of any of the established risk factors for cardiovascular disease (hypertension, diabetes mellitus, elevated LDL or low HDL cholesterol, cigarette smoking, family history of premature cardiovascular disease, body mass index $\geq$30 kg m^{-2}, microalbuminuria, estimated GFR < 60 ml min^{-1}), inherited thrombophilias, oral contraceptives, nephrotic syndrome, malignancy, immobilization, and surgery. Thus, patients who fulfill criteria should be stratified according to contributing causes of thrombosis.*
[‡]*A thrombotic episode in the past could be considered as a clinical criterion, provided that thrombosis is proved by appropriate diagnostic means and that no alternative diagnosis or cause of thrombosis is found.*
[§]*Superficial venous thrombosis is not included in the clinical criteria.*
[¶]*Generally accepted features of placental insufficiency include: (i) abnormal or non-reassuring fetal surveillance test (s), e.g. a non-reactive non-stress test, suggestive of fetal hypoxemia, (ii) abnormal Doppler flow velocimetry waveform analysis suggestive of fetal hypoxemia, e.g. absent end-diastolic flow in the umbilical artery, (iii) oligohydramnios, e.g. an amniotic fluid index of 5 cm or less, or (iv) a postnatal birth weight less than the 10th percentile for the gestational age.*
[**]*Investigators arc strongly advised classifying APS patients in studies into one of the following categories: I, more than one laboratory criteria present (any combination): IIa, LA present alone; IIb, aCL antibody present alone; IIc, anti-β_2 glycoprotein-I antibody present alone.*

Table 1.
The classification criteria for APS [1].

the addition of anti-β2GPI antibodies in Sydney, Australia in 2006. The revised APS classification criteria strongly recommend investigating coexisting inherited and acquired thrombosis risk factors in patients with APS [1]. A recent assessment of the 2006 revised APS classification criteria has shown that only 59% of the patients meeting the 1999 APS Sapporo classification criteria met the revised criteria [15]. In addition, many of the older studies evaluated for only a few of the specific aPL

Manifestation	No. (%) of patients
Peripheral thrombosis	
Deep vein thrombosis	389 (38.9%)
Other peripheral thrombi	248 (24.8%)
Neurologic manifestations	
Migraine	202 (20.2%)
Stroke	198 (19.8%)
Transient ischemic attack	111 (11.1%)
Epilepsy	70 (7.0%)
Multi-infarct dementia	25 (2.5%)
Chorea	13 (1.3%)
Acute encephalopathy	11 (1.1%)
Transient amnesia	7 (0.7%)
Cerebral venous thrombosis	7 (0.7%)
Cerebellar ataxia	7 (0.7%)
Transverse myelopathy	4 (0.4%)
Hemiballismus	3 (0.3%)
Pulmonary manifestation	
Pulmonary embolism	141 (14.1%)
Other pulmonary manifestations	56 (5.6%)
Cardiac manifestations	
Valve thickening/dysfunction	116 (11.6%)
Other cardiac manifestations	153 (15.3%)
Intraabdominal manifestations	
Renal manifestations	27 (2.7%)
Gastrointestinal manifestations	42 (4.2%)
Cutaneous manifestations	
Livedo reticularis	241 (24.1%)
Other cutaneous manifestations	155 (15.5%)
Osteoarticular manifestations	
Arthralgia	387 (38.7%)
Other osteoarticular manifestations	295 (29.5%)
Ophthalmological manifestations	
Amaurosis fugax	54 (5.4%)
Other ophthalmological manifestations	34 (3.4%)
Ear, nose, throat manifestations	8 (0.8%)
Hematologic manifestations	
Thrombocytopenia	296 (29.6%)
Hemolytic anemia	97 (9.7%)
Obstetric manifestations (n = 590 pregnant women)	
Preeclampsia	56 (9.5%)

Manifestation	No. (%) of patients
Other obstetric manifestations	41 (7.1%)
Fetal manifestations (n = 1580 pregnancies)	
Live birth	753 (47.7%)
Other fetal manifestations (fetal loss, premature births)	827 (52.3%)

Table 2.
Cumulative clinical features during the evolution of the disease in 1000 patients with APS (adapted [14]).

Criteria
1. Evidence of involvement of three or more organs, systems, and/or tissues.
2. Development of manifestations simultaneously or in less than a week.
3. Confirmation by histopathology of small vessel occlusion in at least one organ or tissue.
4. Laboratory confirmation of the presence of antiphospholipid antibodies (lupus anticoagulant, anticardiolipin antibodies, and/or anti-beta2-glycoprotein I antibodies).
Classification
Definite catastrophic APS
Requires all four criteria
Probable catastrophic APS
All four criteria, except for only two organs, systems, and/or sites of tissue involvement **or**
All four criteria, except for the laboratory confirmation at least six weeks apart due to the early death of a patient never tested for aPL before the catastrophic APS **or**
Criteria 1, 2, and 4 above **or**
1, 3, and 4 and the development of the third event in more than a week but less than a month, despite anticoagulation.

Table 3.
Preliminary criteria for the classification of catastrophic antiphospholipid syndrome (CAPS) [18, 19].

antibodies now thought to be important in stroke risk, accepted low positive titers and many looked at only one-time point, hence it is difficult to apply the results of those studies [16]. While the purpose of the criteria was to help choose patients for clinical trials, it is the best available tool to avoid over-diagnosis of APS in clinical practice [17].

CAPS is a rare and potentially fatal complication of APS. As described in **Table 3**, the clinical presentation is characterized by acute multi-organ failure due to thromboses of three or more organs within 1 week, associated with the presence of aPL and thrombocytopenia [16]. CAPS can be seen as the first presentation of APS or can be triggered by infection, surgery, or trauma in patients with known APS [19].

In the setting of pregnancy, Obstetric APS (OAPS) is diagnosed if at least one of the clinical criteria and one of the laboratory criteria are met as outlined in **Table 4** [1, 20].

2.2 Ischemic stroke

Although up to 5% of the population might be positive for aPL antibodies, only a small fraction is diagnosed with APS as per the mentioned criteria [21]. Based on the analysis of 120 full-text papers, the overall estimated aPL frequency in stroke

Clinical criteria	Laboratory criteria

1. One or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation.
2. One or more preterm births of a morphologically normal neonate before the 34th week of gestation because of:
   i. eclampsia or severe pre-eclampsia or
   ii. recognized features of placental insufficiency.
3. Three or more unexplained consecutive spontaneous miscarriages before the 10th week of gestation, with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded.
	1. LA present in plasma, on two or more occasions at least 12 weeks apart.
	2. aCL of immunoglobulin (Ig)G and/or IgM isotype in serum or plasma, present in medium or high titer (i.e. >40 GPL units or MPL units, or > the 99th percentile), on two or more occasions, at least 12 weeks apart.
	3. Anti-β2GPI of IgG and/or IgM isotype in serum or plasma (in titer > the 99th percentile), present on two or more occasions at least 12 weeks apart.

Table 4.
Obstetric APS (OAPS) is diagnosed if at least one of the clinical criteria and one of the laboratory criteria are met [1, 20].

patients of all ages is 13.5% [22]. Sciascia et al. [7], in a systematic review of data from 5217 patients concluded that the overall aPL frequency was estimated as 17.2% for stroke and 11.7% for the transient ischemic attack, and the presence of aPL seems to confer a five-fold higher risk for stroke or TIA when compared with controls. The cumulative prevalence in the Euro-Phospholipid Project Study was 19.8% for stroke and 11.1% for TIA [14], making it the most common and severe arterial complication of APS.

Notably, it has been suggested that more than 20% of strokes in patients younger than 45 years are associated with APS [23], although this estimate may be inflated by referral bias [24]. The presence and magnitude of the ischemic stroke risk associated with aPL in the older population are more evenly split between finding an increased risk and no increased risk. This suggests that aPL may be a more important stroke mechanism in young people whereas, in older populations, other stroke risk factors take on a greater importance.

aPL associated strokes pose a higher risk for women. The Framingham cohort and offspring study found an increased risk of strokes and TIAs for women with high anticardiolipin but not in men [25]. In another study of 34 women under 45 years of age with ischemic strokes and no traditional vascular risk factors, 35% were found to have anticardiolipin antibodies [26].

Another study demonstrated that high serum concentrations of aPL, regardless of other cardiovascular risk factors, were an important predictor of the risk of future stroke and TIA in only females [27]. The presence of anti-β2GP1 antibodies in young women may increase the stroke risk 2.3-fold according to the RATIO study [28].

In terms of traditional vascular risk factors in APS patients, it is debated whether these or the circulating aPL antibodies are responsible for the accelerated atherosclerosis seen in APS. Hypertension is more prevalent in SLE and APS than in the general population. A study showed that hypertension was the only independent risk factor for arterial manifestations, mainly stroke, in APS [29]. The risk of stroke for LA-positive patients was two-fold in smokers and six-fold in smokers receiving oral contraceptives [25]. The Italian Project on Stroke in Young Adults, a prospective study of 1867 patients showed that family history of strokes, migraines with auras, aPL, discontinuation of antiplatelet or antihypertensive medications and increase in at least one traditional vascular risk factor were independent predictors for thromboembolic events [30]. Overall, this emphasizes the importance of aggressively treating all modifiable stroke risk factors like hypertension, diabetes,

Patient age < 50 years of age
Female gender
Lack of traditional vascular risk factors
Positive family history for arterial or venous thromboses
Recurrent strokes
Thrombocytopenia, obstetric complications, venous thromboses, or other arterial thromboses
SLE or presence of other connective tissue diseases

Table 5.
Key factors warranting evaluation of antiphospholipid syndrome.

hypercholesterolemia, obesity, OCP use, and tobacco use to reduce additional thrombotic risks.

A summary of factors that warrant an evaluation of APS in stroke patients is listed in **Table 5**.

Stroke subtypes in APS may be either thrombotic or cardioembolic depending on the location and size of the occluded vessel [31]. Intracranial stem or branch arterial occlusions and stenosis were reported in 50% of APS patients with stroke [32]. Narrowing of multiple intracranial arteries may occur in APS and indicates vasculopathy rather than vasculitis. Occasionally, there is involvement of the extra-cranial carotid artery. In a small case series of 17 patients, 32% had extracranial arterial abnormalities [33]. Cardioembolic strokes in APS are associated with left cardiac valvular abnormalities, including irregular thickening of leaflets, non-bacterial vegetations, and valve dysfunction [32]. Stroke subtypes in APS can also vary according to the types of antibodies [34]. Saidi et al. [35], in an analysis of 208 patients with their first stroke, reported that antiphosphatidylserine IgG was asso-ciated with cardioembolic strokes, lupus anticoagulant with lacunar strokes, and anticardiolipin IgG and IgM with lacunar, atherosclerotic and cardioembolic strokes. The severity of the thromboembolic event does not relate to the aPL antibody titer.

The type of antibodies present also appears to have an association with increased thrombotic risk. The presence of antiphosphatidylserine antibodies had the highest risk for clinical manifestations of APS, and IgG antiphosphatidylserine antibodies correlated strongly with the presence of lupus anticoagulant. The presence of antiphosphatidylserine antibodies (IgG or IgM) or anti-b2GP-1 (IgG, IgM, or IgA) antibodies improved the specificity for APS over anticardiolipin antibodies alone [36]. In another study, the positive predictive value for antiphosphatidylserine and anti-b2GP-1 antibodies was stronger for arterial thromboses than for venous thromboses [37]. Another study of pregnant women with APS reported that patients with triple aPL positivity (LA, aCL, and anti-B2GPI) and/or previous thromboembolism had an increased likelihood of poor neonatal outcomes than patients with double or single aPL positivity and no thrombosis history [38].

The recurrent risk of stroke in APS patients has been less widely studied as compared to other types of thromboses. Pezzini et al. calculated a cumulative risk of 14% for brain ischemia at 10 years [30]. Recurrent strokes and other thromboem-bolic events in patients with aPL antibodies have been reported both early (within the first year of an index stroke event) and late (5–10 years) [39]. The initial type of thromboembolic event (i.e. arterial, venous, miscarriage) appears to be the most likely type of event to recur in a given patient according to some studies [40]. The Euro-Phospholipid Project Group reported thrombotic events in 16.6% of patients in the first 5 years of follow-up and in 14.4% in the second 5-year follow-up period.

Factor	Point value
Anticardiolipin Antibody IgG/IgM	5
Anti-B2-glycoprotein I IgG/IGM	4
Lupus anticoagulant	4
Hyperlipidemia	3
Arterial hypertension	1

Table 6.
Adjusted global antiphospholipid syndrome score. Adapted [41, 42].

The most common events during follow-up were strokes, TIAs, DVTs, and pulmonary emboli with survival probability at 10 years being 90.7% [14].

The first model to develop a predictive model for aPL associated thrombosis risk in SLE patients was modified in 2013 by Sciascia et al. to include data on clinical manifestations, and risk factors forming a quantitative score called the Global Antiphospholipid Syndrome Score (GAPSS) [41]. This was further modified in 2019 to form the aGAPSS (Adjusted Global Antiphospholipid Syndrome Score) as outlined in **Table 6** [42]. The goal of the aGAPSS is to risk-stratify patients based on the likelihood of developing recurrent thrombosis in the setting of APS.

Taken together, screening for APS is indicated in stroke patients who meet even some of the clinical and laboratory criteria and those with recurrent strokes despite maximal medical management and no clear etiology. The goal of these scoring systems is to further refine the risk of recurrent thromboses associated with APS.

2.3 Venous sinus thrombosis

Cerebral venous sinus thrombosis (CVST) usually presents with headaches, nausea, vomiting, often associated with seizures, and focal neurological deficits. Papilledema, coma, and death also occasionally contribute to the clinical manifestation of CVST. In patients with CVST, reported frequency of aCL positivity ranges from 7 to 22% [43], and predisposes to CVST at a relatively younger age and to a more extensive cerebral venous involvement [44]. In addition, a higher rate of post-cerebral venous sinus thrombosis headache and more infarctions on brain imaging studies are seen in patients with aPL antibodies than in those without them [45].

2.4 Other neurologic manifestations

While intracranial hemorrhage (ICH) is not a common manifestation of APS, there have been reports of reversible vasoconstriction syndrome (RCVS) [46] which is characterized by thunderclap headaches (severe pain peaking in seconds), and focal neurologic deficits.

Moyamoya disease, a progressive narrowing of cerebral vasculature with collateralization, has also been reported to have associations with APS. Of the 16 cases reported in a small series of moyamoya and aPL, 21% fulfilled APS criteria [47].

Sneddon syndrome is a rare entity that may be considered during workup for APS. It is a chronic disorder, usually non-inflammatory, notable for generalized livedo racemosa (which may be confused with livedo reticularis seen in APS), and recurrent strokes [48]. Livedo racemosa is characterized by a violaceous netlike patterning of the skin similar to the familiar livedo reticularis, although it differs by

its location (more generalized and widespread, found not only on the limbs but also on the trunk and/or buttocks). Approximately 40–50% of patients with Sneddon's syndrome present aPL antibodies, suggesting that some patients should be classified as APS [49].

Cognitive dysfunction has been reported 19–40% in aPL-positive patients [50]. While many believe that the cognitive decline is due to multiple subcortical infarcts, there have been theories that it is multifactorial, with genetic predisposition, antibody specificity, and direct antibody effects as potential contributors [51].

Migraines are the most prevalent neurologic manifestation in APS, estimated prevalence of around 20% [52].

Other rare clinical manifestations of APS include seizures, acute ischemic encephalopathy, transverse myelitis, amaurosis fugax, optic neuropathy, and other neuropsychiatric disorders.

3. Epidemiology of stroke in the setting of APS

3.1 How many strokes can be attributed to antiphospholipid antibodies?

APS has been a recognized cause of cerebrovascular events (CVE) especially in those without classic cardiovascular risk factors. Traditionally, it has been estimated that one in five strokes in patients younger than 45 could be associated with APS, but there have been concerns that this is an over-estimate due to referral bias [53]. Systematic reviews have provided much of our current knowledge on the prevalence of aPL in patients with vascular events, however broad population studies are lacking. One large study evaluating stroke, pregnancy morbidity, myocardial infarction, and deep vein thrombosis estimated that aPL antibodies were present in ~14% of stroke patients [22].

APS, either primary or secondary, garners consideration especially in young patients with CVE. To address events in the young, the previous study [21] was repeated for those less than 50 years of age and positive aPL was found in 17.4% of cases [54]. Regardless of diagnosis, the presence of any aPL increased the risk of CVE by 5.48-fold for those under the age of 50, and the risk of thrombosis progressively increases with the increasing number of positive antibodies [54]. It has also been reported that patients with stroke and aPL positivity are younger and more likely to be female than patients with strokes who are aPL negative [51]. A similar risk for CVE has been recently reported in another study, where persistently positive aPL increased the risk of CVE by 4.62-fold and where the positive criteria and non-criteria aPL was found in 20/89 (22%) CVE patients [55].

3.2 How common are cerebrovascular events among patients with APS?

The Euro-Phospholipid Project cataloged the largest group of patients with APS. At the initiation of this study, prevalence data were obtained with 13.1% of patients having a stroke as their presenting manifestation [52]. Stroke was the fourth most common presenting symptom behind deep vein thrombosis, thrombocytopenia, and livedo reticularis. Of the 1000 patients, 204 (about 20%) experienced a stroke at some point during their disease course [52]. Cervera et al. [52] made a delineation regarding age-of-onset, defining "older-onset" APS as diagnosis after the age of 50. Comparatively, the over-50 patients were more likely to have strokes (30%) and were more likely to be male (34%), and were more likely to experience angina pectoris (9%) [52]. These patients were followed over a 10-year time period, and over that time period, 5.3% of the patients experienced a stroke. Stroke was the

most prevalent thrombotic event. It was also the 4th leading cause of death in these patients following bacterial infection, myocardial infarction, and malignancy [14].

Patients with APS hospitalized with a stroke also have increased mortality compared to patients without APS [55]. APS has also been identified as an independent risk factor for hemorrhagic transformation of ischemic stroke (OR 2.57, 95%CI 1.14–5.81, p = 0.0228) and extended hospital length of stay [56].

3.3 What types of cerebrovascular events occur in patients with APS?

One of the unique aspects of APS is the diversity of types of vasculature involved—arteries and veins, small vessels, and large vessels. Multiple mechanisms of the prothrombotic state have been theorized and will be discussed in Section 4 of this chapter. APS has been implicated in multiple stroke etiologic subtypes including large-artery atherosclerosis, cardio-embolism, and small-vessel occlusion. However, the percentage breakdown between these etiologies has not been consistently reported.

As previously stated, APS is responsible for venous events as well as arterial events. In the cerebrovascular system, these include CVST. APS has been implicated in 6–17% of all cases of CVST and tends to predispose to CVST at a relatively younger age [44].

Vasculopathies, described in detail in Section 2, including Moyamoya and Sneddon's syndrome, overlap with APS at a rate of 21% and 50% respectively. Reversible cerebral vasoconstriction syndrome (RCVS) has also been described in patients with APS [46].

Other neurologic manifestations of the antiphospholipid syndrome include headache (20%), seizures (8%), and chorea (1.3–4.5%), with less frequent neurological manifestations including parkinsonism (especially progressive supranuclear palsy), dystonia, ballismus, myoclonus, cerebella ataxia, transverse myelitis, cognitive impairments, psychiatric symptoms, and peripheral neuropathy [4, 57].

3.4 Does the pattern of antibody positivity influence the likelihood of stroke?

As outlined in **Table 7**, some aPL are associated with a higher risk of ischemic stroke than others. Isolated LA positivity induces the greatest individual antibody risk for ischemic stroke [58]. Anti- β2-GPI were also associated with increased risk but to a lesser degree [58]. aCL and antiprothrombin antibodies have been reported variably with some studies showing no increased risk as an independent risk factor [27] while others reported to be independent risk when considering young patients exclusively [58]. As mentioned, triple positivity with positive LA, β2-GPI antibodies and aCL antibodies confers the highest risk [58].

High risk	Moderate risk	Low risk
Triple positivity (LA + aCL + anti-β2-GPI)	Isolated aCL when persistently positive in patients with SLE	Isolated anti-β2-GPI positivity
Isolated LA positivity		Inconsistent and low titer isolated aCL positivity

Table 7.
Risk for cerebrovascular event based on serologic profile. Adapted [58].

3.5 Does the presence of other risk factors for cerebrovascular events increase the risk in patients with APS?

Traditional cardiovascular risk factors also play a role in outcomes for patients with APS. Studies reveal that hypertension and smoking are the risk factors most associated with repeat thrombotic arterial events [59]. Combinations of risk factors have also been shown to increase the risk of repeat events [60]. Prospective studies evaluating the results of risk factor control have yet to be reported.

The RATIO study (Risk of Arterial Thrombosis In relation to Oral contraceptives) identified that the use of oral contraceptives (OCPs) and smoking carried an extremely high risk for women with APS in terms of risk for myocardial infarction and ischemic stroke [28]. The data revealed that the relative risk for ischemic stroke was higher in those who were smoking and in women with OCPs. The odds ratio for ischemic stroke was 43.1 (95%CI 12.2–152.0), which increased to 201.0 (95%CI 22.1–1828.0) in women who used oral contraceptives and 87.0 (14.5–523.0) in those who smoked. In women who had anti- β2-GPI, the risk of ischemic stroke was 2.3 (95%CI 1.4–3.7), but the risk of myocardial infarction was not increased (OR 0.9, 95%CI 0.5–1.6). Neither aCL nor anti-prothrombin antibodies affected the risk of myocardial infarction or ischemic stroke [28].

4. Etiology and mechanisms of stroke in APS

4.1 Pathophysiology of stroke in APS

Vascular thrombosis in APS can affect a wide variety of organ systems, but cerebrovascular thrombosis leading to stroke and transient ischemic attack is the most prevalent and perhaps the most consequential arterial event [61]. In a retrospective study of 135 APS patients, the highest morbidity was linked to neurologic involvement especially due to arterial thrombosis [62]. APS is also an important cause of stroke in the young, but as described can also affect older individuals [60]. The mechanisms of stroke in APS are diverse and include thrombosis in arteries, veins, and the microvasculature, as well as cardioembolism from non-bacterial thrombotic endocarditis.

The pathophysiology of vascular thrombosis in APS is not completely understood, but several studies suggest multiple converging pathways involving not only antibodies but also endothelial cells, platelets, monocytes, coagulation cascade proteins, and complements [63] producing a systemic thrombo-inflammatory state. The presence of aPL is not the sole cause for the significant clinical manifestations of APS as there can be asymptomatic "carriers" [17, 60]. Therefore, as previously mentioned, a "two-hit" hypothesis has been theorized, where the first-hit involves the presence of circulating aPL and associated endothelial dysfunction, and the second-hit presents an inflammatory insult such as trauma, surgery, or infection, leading to upregulation of β2GPI receptors on endothelial cells, as schematically demonstrated in **Figure 2**.

Even though aPL can be detected either by clotting tests, such as LA, or by an ELISA, such as aCL and anti-β2GPI, they are predominantly directed against β2GPI [17] and prothrombin [64]. Other important antigens recognized by aPL are annexin V, phosphatidylethanolamine, and phosphatidylserine [65]. Mechanistically these autoantibodies target phospholipid-binding plasma proteins bound to the surface of vascular endothelial cells and thrombocytes [60]. Plasma proteins predominantly bind to phosphatidylserine [17]. Normally located in the inner surface of cell membranes, phosphatidylserine becomes externalized when endothelial cells, platelets, and monocytes are activated. The avidity with which β2GPI binds to
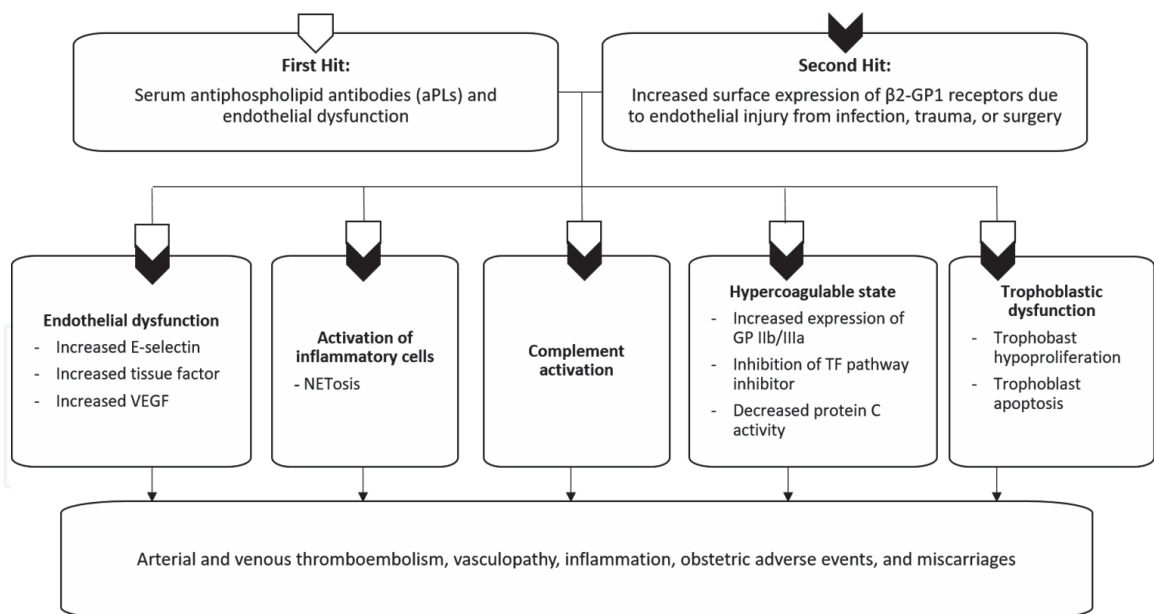
Figure 2.
The pathophysiology of vascular thrombosis in APS is not completely understood, but a 2-hit hypothesis is widely proposed. The first hit involves the presence of circulating aPL and endothelial injury, while the second hit requires an inflammatory insult such as trauma, surgery, or infection, leading to upregulation of beta-2 glycoprotein 1 (β2-GP1) receptors on endothelial cells. The aPLs-β2-GP1 receptor interaction unleashes multiple converging downstream pathways culminating in a thrombo-inflammatory state. VEGF: vascular endothelial growth factor; neutrophil extracellular traps (NETosis); GP: glycoprotein; TF: tissue factor (adapted [64, 66, 67]).

phosphatidylserine is further enhanced by the 'β2GPI'- 'β2GPI antibody dimerization' [66]. The downstream effect of β2GPI antibodies on endothelial cells and monocytes includes increased expression of tissue factor and thromboxane A2 which trigger the extrinsic coagulation pathway [64, 67]. Furthermore, the antibody binding inhibits the tissue factor pathway inhibitor and protein C activity [64, 67]. Taken together, the net effect is the synergistic production of a prothrombotic state. Endothelial cells, upon stimulation with aPL, also downregulate their nitric oxide production and increase the surface expression of adhesion molecules such as E-selectin leading to pro-inflammatory and pro-coagulation endothelial phenotype [17, 57, 67, 68]. This antibody-induced endothelial injury can lead to intimal hyperplasia, micro-vasculopathy, and accelerated atherosclerosis [69]. Activated platelets increase their surface expression of GPIIb-IIIa, synthesis of thromboxane A2 and platelet factor-4a, all acting to facilitate thrombosis [67]. Activation of neutrophils with accompanying release of Neutrophil Extracellular Traps (NETosis) and IL-8 may also play a role [67]. Annexin V, a natural anticoagulant, binds to phosphatidylserine (a procoagulant) forming an anticoagulant shield in the physiologic state in APS, this shield is disrupted tipping the system in favor of coagulation [70]. Upregulation in the mTOR (mechanistic target of rapamycin) pathway on endothelial cells may partly explain the microvascular thrombosis seen in APS.

In addition to vascular thrombosis, up to one-third of patients with APS develop non-bacterial thrombotic endocarditis (NBTE) in which there is a deposition of sterile platelet thrombi on heart valves, particularly the mitral and aortic valves, which can be a source of cardioembolic strokes [66].

4.2 Genetic considerations

Population and family studies, as well as animal studies, have suggested genetic disposition may be relevant to the development of APS. Like many autoimmune

disorders, predisposition to APS has been mapped to genes in the major histocompatibility complex (MHC), among others. Also, epigenetic phenomena such as altered microRNA biogenesis in neutrophils, leading to accelerated atherosclerosis, have been implicated in APS [63].

5. Diagnostic workup for APS

The initial workup for stroke in the setting of APS is consistent with that of other stroke etiologies. Specifically, a multisystem approach evaluating from *"heart to head"* should be performed. However, in the setting of APS, a *"head to toe"* examination may be more aptly described. Prior to initiating an APS workup, there need to be history and examination findings that begin to clue the diagnostician towards an underlying process related to APS. Such findings, as previously mentioned in Section 2 and to be discussed, are important to consider before initiating an extensive and potentially costly workup. Although, among appropriate patients, APS should be considered in numerous stroke/cerebrovascular settings including acute ischemic infarct, hemorrhagic infarct, cerebral venous sinus thrombosis, and TIA.

5.1 When to test?

What raises the suspicion for APS in stroke? When should it be considered that more information and studies are needed besides the typical workup usually undertaken? The most pertinent situation would be when a younger patient (<50 years) presented with a thrombotic stroke without identified classic risk factors for ischemic/embolic stroke [71]. Initial workup may reveal exam and laboratory findings that may raise the concern for APS as listed in **Table 8**. Notably, subtle renal, cardiac, hematologic, and dermatologic system alterations can be indicative. Further, a family history of early-onset stroke, clotting, or other systemic features should be queried. Absence of typical risk factors including hypertension, diabetes, atrial fibrillation, or known history of coagulopathy (e.g. protein

---

1. Hematologic
    a. Thrombocytopenia
       i. Mild/common: platelets 50,000–100,000 cells per mm [3]
      ii. Severe/uncommon: platelets <20,000 cells per mm [3]
    b. Hemolytic Anemia
       i. Autoimmune hemolytic anemia (no schistocytes)
      ii. Thrombotic microangiopathy (with schistocytes)

---

2. Neurologic
    a. Cognitive impairment (with no evidence of stroke)
    b. Subcortical white matter change

---

3. Dermatologic
    a. Livedo reticularis or racemosa (consider Sneddon syndrome)
    b. Livedo vasculitis (painful, recurrent ulcerations of bilateral lower extremities

---

4. Cardiac
    a. Thickening (>3 mm) of the cardiac valves (proximal/middle part of valve leaflet, nodules with irregularity on atrial side of mitral valve or vascular side of aortic valve)
    b. Valve vegetations

---

5. Renal
    a. Acute kidney injury due to/or evidence of acute microangiopathic thrombosis

---

Table 8.
Other important clinical signs of APS not noted in Sapporo criteria, by body system. Adapted [63].

C deficiency, protein S deficiency, antithrombin III), among others, further increases the consideration for APS. Notably, as many as 17% of cardiovascular events in those under 50 reveal aPL antibodies and up to 22% including anticardiolipin antibodies [54].

Of note, without suggestion of underlying coagulopathy or clinical findings (see **Table 8**) a young patient without classic risk factors, testing for many coagulopathies is not routinely performed. When performed, there is also the question of whether this workup needs to occur in the inpatient setting, during the patient's admission for stroke, or if it can be done post-discharge. When considering this, the most important question is: Will any findings acutely change management? It should also be noted that for a positive diagnosis APS testing needs to occur multiple times over a 3 month or longer time period. If considering the APS diagnosis, formal hematology and/or rheumatology consult is recommended. In general, the recommendation for inpatient vs. outpatient is that some workup may be deferred if necessary, to the outpatient setting, either under the care of the patient's primary physician/provider, neurologist, hematologist, or rheumatologist.

5.2 What to test?

Consistent with all stroke patients, every patient should receive standard stroke workup testing including brain imaging (CT brain, MRI brain), vessel imaging of the head, neck, and great vessels of the chest (CTA, MRA), cardiac imaging including a transthoracic echocardiogram (TTE) and laboratory testing (CMP, CBC, PT/INR, aPTT, TSH, HgbA1C, lipid profile). A bubble study with the TTE should be considered if a paradoxical embolus from a DVT is on the differential. It is also recommended to obtain basic inflammatory markers such as sedimentation rate (ESR) and C-reactive protein (CRP) to evaluate for suggestion of diffuse inflammatory disease [24].

Transesophageal echocardiogram (TEE) should also be considered if the etiology remains uncertain, this is due to the increased frequency of valvular abnormalities in the setting of APS that may include irregular nodules/vegetations most commonly on the atrial side of the mitral valve or vascular side of the aortic valve, or if thickening of the valves is noted on TTE. Most commonly, the left side of the heart is the affected side with the mitral valve more commonly affected compared to the aortic valve. These cardiac changes are postulated to be due to immune complex damage and fibrosis [72].

If APS is being considered, it is recommended that while inpatient with the acute stroke the patient should have all antiphospholipid antibodies checked, according to the revised Sapporo laboratory criteria (see **Table 1**). Notably, this includes ELISA IgM/IgG for anticardiolipin (aCL) with a positive test showing medium to high titers (>40 GPL/MPL units or >99th percentile), which will need to be confirmed on at least two or more occasions, 12-weeks apart. Lupus anti-coagulant (LA) should also be checked by two tests including dilute Russell viper venom time (dRVVT) and LA-sensitive PTT (PTT-LA)), again conformed on at least two occasions, 12-weeks apart. Lastly, an ELISA IgM/IgG for anti-beta2-glycoprotein I (β2GPI) should also be tested, with a positive value determined by titer in the 99th percentile, and again, should be tested on at least two occasions 12-weeks apart.

At least one clinical criterion (in the context of this chapter, most likely stroke) and one laboratory criterion should be met to diagnosis APS. As described, these tests are done 12-weeks apart, so the first set of lab tests will be performed inpatient and then the second 12-weeks later, typically performed in the outpatient setting.

As outlined in **Table 8**, if the patient does not meet revised Sapporo criteria, APS may still be diagnosed if clinical suspicion remains high based on multi-system abnormalities and if further etiologies are not identified [64].

If a patient inconsistently tests positive for APS, it may be warranted to also check for other autoimmune diseases, namely systemic lupus erythematosus (SLE), as up to 36% of those with APS will be positive for SLE. Having both APS and SLE increases the risk for stroke beyond having only one or the other [31].

5.3 Understanding the tests

As described above, there are 3 primary antibody tests for APS including aCL, LA, and β2GPI. Anticardiolipin (aCL) testing was first developed as a test for syphilis in the 1900s [71]. The aCL antibody was found not to be specific to just syphilis, thus its utility as a test for APS was also found after many false-positive syphilis tests showed an increased risk for thrombotic events. The tests presently use tissue derived from bovine tissue. Both IgG and IgM are evaluated by ELISA for the presence of aCL antibodies. Notably, due to cross-reactivity as discussed with syphilis, the presence of aCL does not alone confirm APS.

Lupus anticoagulant (LA) is a test for immunoglobulins that while associated with thrombosis, are associated with preventing coagulation in vivo. The process for testing LA is three tests including screening (usually with aPTT or dRVVT, clotting of phospholipid factors), mixing (correct with normal plasma), and confirmation (shortening prolongation with added phospholipid) [67]. Once again, LA by itself cannot confirm APS due to cross-reactivity. LA testing is outlined in **Figure 3**.

Anti-β2 glycoprotein I (β2GPI) enzyme-linked immunosorbent assay (ELISA) testing is the last of the trio of tests for APS. There are 5 main domains of the β2GPI,
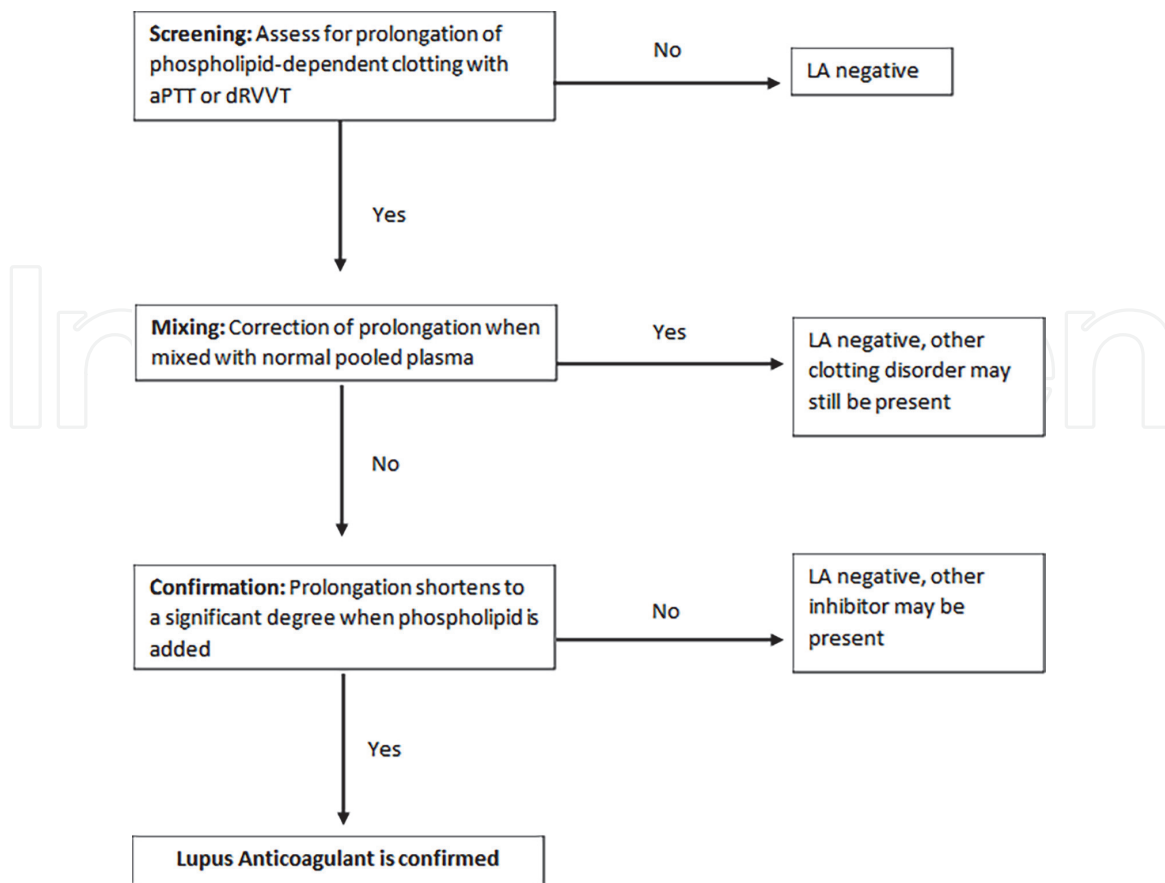
Figure 3.
Testing for lupus anticoagulant (Adapted [67]).

labeled DI through DV. Anti-β2GPI largely targets domain I (DI). When this domain is targeted, it has been shown an association with thrombosis. The other domains DII through DV being targeted have not been shown to have as strong a connection for promoting thrombosis. Of note, there are some more rare entities that may also raise anti-β2GPI levels, such as leishmaniasis, leptospirosis, or leprosy. For APS, the associated antibodies are against the IgG form, whereas other elevates of anti-β2GPI may be directed towards the IgM variety [73].

5.4 Implications of acute diagnosis

Unless the patient presents with a prior history of APS, the diagnosis of APS will likely be in question during the acute and subacute stroke window. This is because APS by laboratory criteria needs to be performed 12-weeks apart with two positive tests to confirm. That said, a patient that presents with a stroke and has one or more laboratory results that are concerning for APS (positive LA, aCL, anti-β2GPI), there is a question if confirming APS would change acute management. Oftentimes, the answer is yes; this even in the setting of likely APS, because thrombosis can be multifactorial and can progress between confirmatory APS testing [67]. As such, management should focus on appropriate treatment for the source of the stroke. For example, if the source is cardioembolic, the timing of initiation of anticoagulation should be considered, weighing the risk of a second embolic event while not on indicated therapy versus the risk of hemorrhagic conversion of the primary infarct.

6. Treatment: primary and secondary prevention

Once the workup for APS is complete, and if positive, the next logical step is to address treatment. However, prior to addressing treatment, let us first consider if APS is a primary risk factor for stroke risk. Numerous studies have been performed to address this question, culminating with a meta-analysis evaluating 15 different studies in aggregate [54]. In this evaluation, 13 of the 15 studies reported a significant association between a CVE and aPL antibodies with a cumulative odds ratio of 5.48 [54]. While this study provides insight into primary event risk, a follow-up question relates to the risk of APS with recurrent stroke. A second meta-analysis was completed looking at 8 studies to answer this question, demonstrating no statistically significant risk of recurrent ischemic stroke among APS patients [74]. Understanding why one meta-analysis demonstrated a link between aPL antibodies and single ischemic events, while another did not show a link with recurrent events remains challenging to understand. One hypothesis used to explain these incongruent findings is that clinical events do not occur frequently occur despite the presence of the antibodies, suggesting that treatment and/or lifestyle modifications after a first stroke affect the chance of a second event [74, 75]. Therefore, an understanding that APS is associated with the single cerebral vascular event, and that treatment affects the chance of a second event, indicates that secondary prevention is highly warranted.
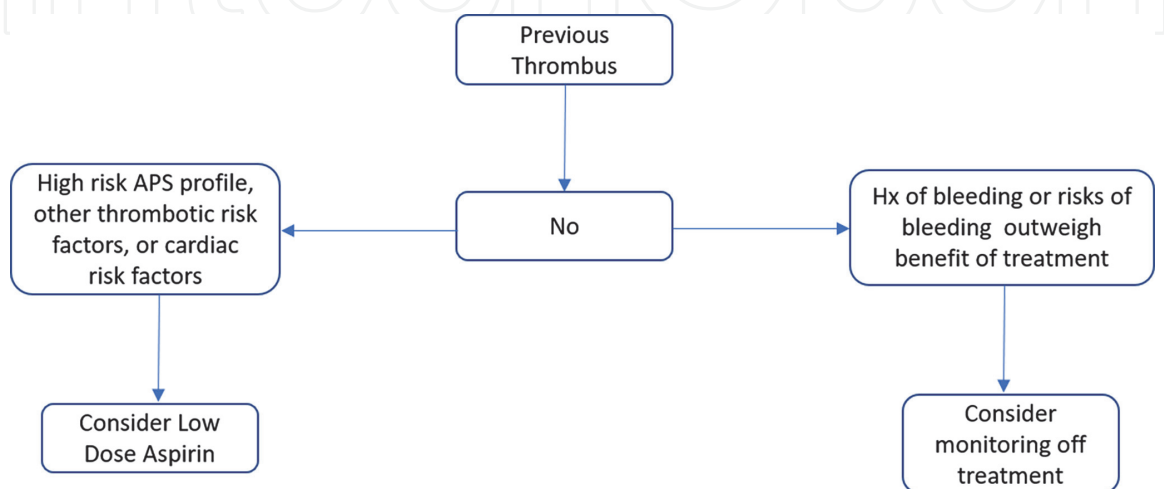
6.1 Primary prevention

Knowing that therapy is indicated, we can now evaluate various treatments on the risk of thrombosis in the setting of APS. In those individuals without any other risk factors, the risk of thrombosis is less than 1% per year [76, 77]. In this group, when they do present with a thrombus, it is normally in the setting of another thrombotic risk factor, such as cancer, surgery, pregnancy, estrogen use, acute

infection, smoking, and hypertension. On the other hand, the risk of thrombosis can be as high as 5% per year in individuals with a persistent moderate high-risk profile including aPL antibodies and a systemic autoimmune disease [78]. Therefore, with the risk of thrombosis being so variable, sometimes as low as 1% or other times as high as 5%, the question of optimal prevention strategies can be challenging.

Regarding primary prevention (before a stroke or vascular event) the answer remains controversial with only scant data based on prospective trials [79]. Some of these trials have demonstrated a decrease in thrombosis with the use of aspirin. For example, a meta-analysis of 11 mostly observational studies demonstrated a 2-fold risk reduction in the first thrombotic event with a more significant effect in those with arterial thrombosis [79]. Post subgroup analysis of only prospective trials demonstrated there was no significant difference between aspirin and those not treated [79]. Therefore, with conflicting data on aspirin, one may ask could there be a benefit with the use of anticoagulation as well as aspirin for primary prevention. While the data was limited, one primary prevention study evaluated the use of aspirin alone vs. aspirin plus anticoagulation in 166 patients, demonstrating no significant difference in terms of the amount of thrombotic events between groups, with an increased risk of bleeding in the aspirin plus warfarin arm [80]. Therefore, given the increased bleeding risk, the use of aspirin and warfarin in combination is not recommended for primary prevention, with the question of aspirin use in isolation remaining. Many agencies have weighed in on this subject including the 13th International Congress on Antiphospholipid Antibodies as well as the European League Against Rheumatism making recommendations suggesting the use of aspirin in high-risk antiphospholipid profiles, those with other thrombotic risk factors, as well as those with SLE [58, 81]. Even with these recommendations, one must also consider the risk of bleeding with the use of aspirin. One meta-analysis looking at six randomized control trials showed an association of increased annual risk of major bleeding in those patients using aspirin with hypertension, age > 65, diabetes, and male sex being the most significant associated risk factors [82].

In summary, the decision to use primary prevention remains an individualized choice based on a patient-centric decision. Overall, though one should consider the use of primary prevention with aspirin in those with cardiac risk factors, high risk antiphospholipid antibody profile, presence of other thrombotic risk factors and in the presence of other autoimmune disease always ensuring a thorough risk benefit analysis is done with concern for bleeding. See **Figure 4** for breakdown of treatment option algorithm.

Figure 4.
Treatment options algorithm (adapted [10]).

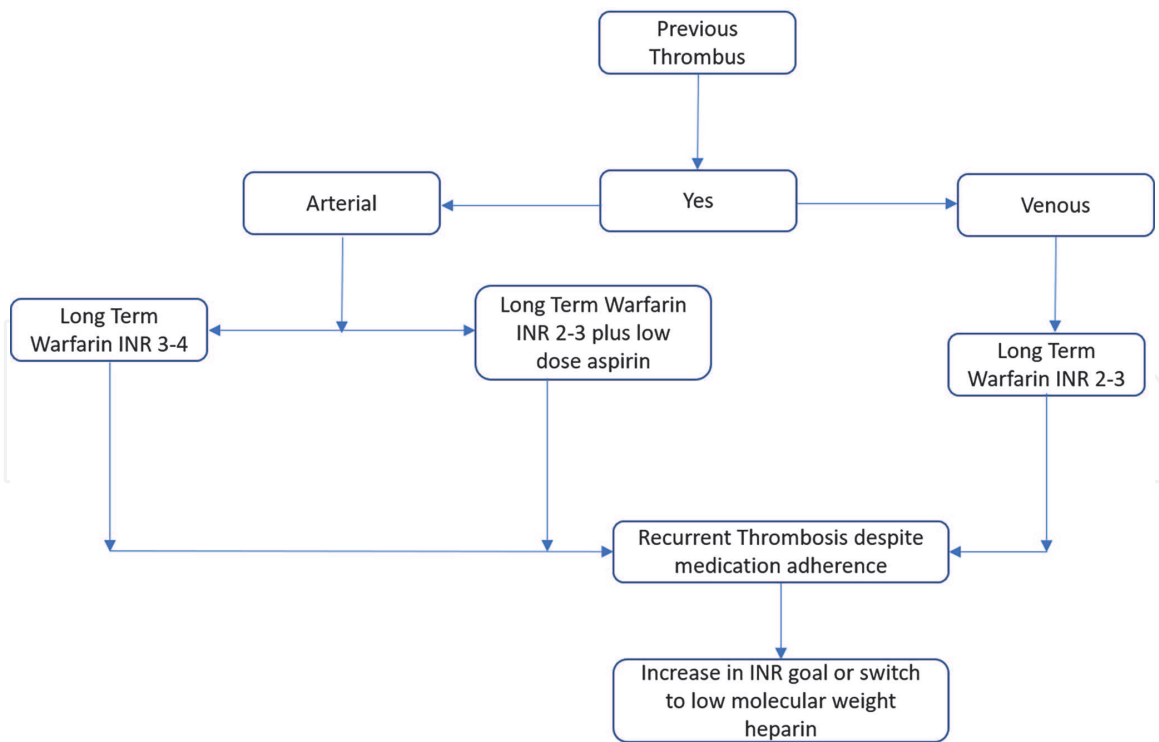## 6.2 Secondary prevention: arterial primary event

Knowing the indications for the use of primary prophylaxis we now consider secondary prophylaxis. Data regarding the need for secondary prophylaxis specifically in previous arterial thrombi remains scant without any consensus. For example, one study demonstrated the use of warfarin with a goal INR of 1.4–2.8 was not superior to full dose aspirin 325 mg alone for stroke prevention, with concerns that this study was flawed due to transient positivity of aPL antibodies [27]. Another study evaluating 20 patients with ischemic stroke demonstrated that the use of low-dose aspirin and warfarin with a goal INR of 2–3 was superior to low-dose aspirin alone in the prevention of further arterial thrombi [11]. While two other studies demonstrated that for older patients with stroke, and a single test showing low titers of anticardiolipin antibodies, that aspirin may be as effective as warfarin [27, 83]. With this conflicting data, there remains no consensus statement on secondary prophylaxis with many agencies weighing in on this subject. For example, the 13th International Congress on Antiphospholipid Antibodies as well as the European League Against Rheumatism both recommended secondary prophylaxis with high-intensity warfarin with an INR > 3 or low dose aspirin combined with moderate-intensity warfarin with an INR from 2 to 3 [58, 81]. Both agencies decided on using a goal INR of >3 for warfarin because in previous studies evaluating different doses of warfarin in treating thrombi, relatively few patients with arterial thrombi were enrolled [84, 85]. Overall, data remains scarce and guidelines are based upon a consensus of expert opinion. In those with recurrent arterial events, some recommend increasing target INR level and or switching to low molecular weight heparin with the addition of other adjective therapies to include statins [86].

In summary, the decision on which patient to treat and which agent to use for secondary prophylaxis with arterial thrombi remains a patient-centric decision. Those with high-risk aPL profiles, presence of other systemic autoimmune diseases, and or other risk factors for thrombus would likely benefit from treatment with either aspirin and warfarin with a goal 2–3 or warfarin alone with a goal INR 3–4. Those with recurrent events would likely benefit from increasing the INR goal or if not feasible switching to low molecular weight heparin. Moving forward it would be beneficial to validate a risk stratification model to identify those with arterial thrombosis who would benefit from more aggressive treatment [67]. See **Figure 5** demonstrates a treatment options algorithm.

6.3 Secondary prevention: venous primary event

Now knowing the indications and treatment options for the use in secondary arterial prophylaxis we now move on to secondary venous prophylaxis, which in the case of stroke would be beneficial in treating paradoxical emboli. Much different from that in arterial secondary prophylaxis, there is more of a consensus regarding the treatment of secondary venous prophylaxis using warfarin with a goal INR of 2–3 showing a decrease in recurrent venous events of 80–90% [57, 87]. Some studies have evaluated the use of higher intensity anticoagulation with a goal INR of 3.1–4.5 showing no reduced risk in thrombosis, but a significant excess of minor bleeding [84, 85].

Therefore, with the above data, we can safely say in summary for secondary prevention for venous thrombi in those with a chance of paradoxical emboli treatment with warfarin with a goal INR of 2–3 is indicated. See **Figure 5** for a treatment options algorithm.

Figure 5.
Arterial versus venous thrombus treatment options algorithm (adapted [13]).

6.4 Other treatment considerations

6.4.1 Direct oral anticoagulants

Following the basics of both primary and secondary prevention, one may question other anticoagulation options as adjuvant therapies. Regarding the use of direct oral anticoagulants (DOACs) there remains insufficient evidence with data suggesting an increased risk of thrombosis [88]. For example, two studies demonstrated no difference in the rate of venous thromboembolism and an increased risk of arterial thrombotic with the use of rivaroxaban over warfarin [89, 90]. Looking at this data more closely, a meta-analysis of these two studies did not find an increased risk of thrombosis in patients treated with rivaroxaban over warfarin at a 6 month follow up, however for unclear reasons, almost 3/4 of the thrombi occurred post the 6 months follow up [39]. Given the lack of prospective data, the utility of DOACs in the treatment of thrombus formation remains uncertain.

6.4.2 Other therapies

Beyond DOACs, other adjuvant therapies have been studied including statins and hydroxychloroquine. With statins being a mainstay of treatment post-stroke, it would not be unreasonable to think that they may be beneficial in APS, potentially exhibiting pleiotropic effects including anti-inflammatory, antithrombotic, and as well as the expected lipid-lowering potential [13]. To date, there have been no randomized controlled trials looking at the efficacy in this group of patients. One study however did look at the levels of pro-inflammatory and prothrombotic markers post use of Fluvastatin, which were significantly decreased suggesting their benefit in APS [91]. At this time without a randomized control trial, the 15th International Congress on Antiphospholipid Antibodies has recommended the use of statins in those with high cardiovascular risks and or recurrent thrombosis

despite adequate AC [88]. Regarding the use of hydroxychloroquine, similar to statins in addition to its immunomodulatory effect, it also has antithrombotic properties making it a good candidate as adjunctive therapy [88]. Two studies have been performed demonstrating differing results regarding treatment with hydroxychloroquine plus aspirin vs. aspirin alone. The first demonstrated no difference between rates of thrombosis between both groups [92]. The other demonstrated a significantly lower thrombotic rate compared to standard of care alone, in addition to down-trending antibody titers [93]. These data suggest that both statins and hydroxychloroquine could be beneficial as adjunctive therapies in specific situations, although more data is needed for consensus.

6.4.3 Stopping therapy

Throughout this section, we have addressed the need for primary and secondary prevention, but one question left unanswered is safety as associated with therapy cessation. Unfortunately, there remains a multitude of answers to this question, hence each case should be considered independently. In those with a history of arterial thrombotic events, the risk of repeat thrombus formation off anticoagulation is too high and therefore indefinite anticoagulation is warranted [94]. In those with a history of transient positivity of antiphospholipid antibodies who eventually become negative based on two separate studies, one can consider stopping anticoagulation [95, 96]. Specifically, this would be associated with those who only have primary APS with persistently negative antibodies where if there was a thrombotic event it occurred in association with a transient risk factor including pregnancy or immobilization as examples [96]. In these cases, it is thought that the antibodies do not play a pathogenic role, but rather are a "phenomenon". Therefore, some have recommended a 3–6-month course of anticoagulation with consideration to look for residual thrombus, which has been shown to increase the rate of recurrence by 50% [94]. Notably, the data and recommendations regarding stopping anticoagulation are based upon two small case series. Therefore, with such insufficient data, unless the risk of anticoagulation outweighs the benefit it would not be recommended to stop anticoagulation in those that become persistently negative.

6.4.4 Final thoughts on therapy

Throughout this section we have addressed both preventions of stroke in APS, but what if someone should fail prevention and come in with an acute stroke. The answer to this question unlike many of the other is simple. Acute management is no different than those with or without APS [97]. Lastly, as described, APS often requires treatment with anticoagulant medications such as heparin to reduce the risk of further episodes of thrombosis and improve the prognosis of pregnancy. Warfarin (brand name Coumadin) should not be used during pregnancy because it crosses the placenta and is teratogenic. Unfractionated heparin (UFH) and low molecular weight heparin do not cross the placenta and are safe for the fetus, but long-term treatment with UFH is problematic because of its inconvenient administration, the need to monitor anticoagulant activity, and because of its potential side effects, such as heparin-induced thrombocytopenia and osteoporosis [98].

7. Conclusion

Thromboses of the cerebral arterial and venous systems are a common manifestation of APS leading to ischemic and/or hemorrhagic stroke. APS has been a

recognized cause of CVE especially in those without classic cardiovascular risk factors. It has been estimated that one in five strokes and patients younger than 45 could be associated with APS and some newer studies show that APL antibodies are present in approximately 14% of stroke patients. Persistently elevated APL seems to increase the risk for CV by at least fourfold. Stroke is the fourth most common presenting symptom behind deep venous thrombosis, thrombocytopenia, and livedo reticularis. The recurrent risk of stroke in APS patients has been less widely studied as compared to other types of thromboses, however, cumulative risk of 14% for brain ischemia at 10 years has been reported. APS increases stroke risk via many mechanisms including hypercoagulability, inflammation, accelerated atherosclerosis, and cardiac manifestations, among others. Mechanistically these lead to in-situ clot formation and/or embolic phenomena. Physicians must carefully consider all these potential mechanisms when evaluating and treating stroke patients to achieve both optimal short- and long-term outcomes. While the exact underlying pathophysiology of APS remains uncertain, underlying genetics in the setting of a triggering event (e.g., surgery, trauma, infection) is believed to play a key role in the development of the disease. While primary and secondary prevention recommendations continue to evolve, each case should be considered independently to achieve optimal results. Results from more randomized control trials are needed to further infer upon the ever-evolving consensus guidelines. For the time being, the decision to use primary and/or secondary prevention therapies, and of which type, will continue to be an individualized patient-centric decision requiring careful interpretation of test results with multispecialty (neurology, hematology, rheumatology) input.

Author details

Kathryn Grimes[1,2], Adam P. Klein[1,2], Rakhee Lalla[1,2], Adeolu Morawo[1,2], Sana Somani[1,2], Mathew J. Woodward[1,2] and John W. Cole[1,2*]

1 University of Maryland School of Medicine, Baltimore, MD, USA

2 Baltimore Veterans Affairs Medical Center, Baltimore, MD, USA

*Address all correspondence to: jcole@som.umaryland.edu

IntechOpen

References

[1] Miyakis S, Lockshin MD, Atsumi T, Branch DW, Brey RL, Cervera R, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). Journal of Thrombosis and Haemostasis. 2006;**4**:295-306. DOI: 10.1111/j.1538-7836.2006.01753.x

[2] Žigon P. Do antiphospholipid antibodies enhance thromboembolic risk in patients with cancer? Polish Archives of Internal Medicine. 2020; **130**(12):1026-1028. DOI: 10.20452/ pamw.15724. Epub 2020 Dec 22

[3] Khangura RK, Cooper S, Luo GY. Antiphospholipid antibody syndrome: Pathogenesis, diagnosis, and management in pregnancy. Maternal-Fetal Medicine. 2019;**1**:38-42. DOI: 10.1097/FM9.0000000000000007

[4] Lim W. Antiphospholipid syndrome. Hematology. American Society of Hematology. Education Program. 2013; **1**:675-680. DOI: 10.1182/asheducation-2013.1.675

[5] Fleetwood T, Cantello R, Comi C. Antiphospholipid syndrome and the neurologist: From pathogenesis to therapy. Frontiers in Neurology. 2018;**9**: 1001. DOI: 10.3389/fneur.2018.01001

[6] Misita CP, Moll S. Antiphospholipid antibodies. Circulation. 2005;**112**:39-44. DOI: 10.1161/CIRCULATIONAHA. 105.548495

[7] Sciascia S, Radin M, Cecchi I, Rubini E, Scotta A, Rolla R, et al. Reliability of lupus anticoagulant and anti-phosphatidylserine/prothrombin autoantibodies in antiphospholipid syndrome: A multicenter study. Frontiers in Immunology. 2019;**10**:376. DOI: 10.3389/fimmu.2019.00376

[8] De Laat B, Pengo V, Pabinger I, Musial J, Voskuyl AE, Bultink IE, et al. The association between circulating antibodies against domain I of beta2-glycoprotein I and thrombosis: an international multicenter study. Journal of Thrombosis and Haemostasis. Nov 2009;**7**(11):1767-1773

[9] Wilson WA, Gharavi AE, Koike T, et al. International consensus statement on preliminary classification criteria for definite antiphospholipid syndrome: Report of an international workshop. Arthritis and Rheumatism. 1999;**42**(7): 1309-1311. DOI: 10.1002/1529-0131 (199907)42:7<1309::AID-ANR1>3.0. CO;2-F

[10] Ghembaza A, Saadoun D. Management of antiphospholipid syndrome. Biomedicines. 2020;**8**(11):508

[11] Okuma H, Kitagawa Y, Yasuda T, Tokuoka K, Takagi S. Comparison between single antiplatelet therapy and combination of antiplatelet and anticoagulation therapy for secondary prevention in ischemic stroke patients with antiphospholipid syndrome. International Journal of Medical Sciences. 2010;**7**(1):15

[12] Uthman I, Noureldine MHA, Ruiz-Irastorza G, Khamashta M. Management of antiphospholipid syndrome. Annals of the Rheumatic Diseases. 2019;**78**(2): 155-161. DOI: 10.1136/annrheumdis-2018-213846. Epub 2018 Oct 3

[13] Khamashta M, Taraborelli S, Sciascia A, Tincani. Antiphospholipid Syndrome. Best Practice & Research Clinical Rheumatology. 2016;**30**: 133-148. DOI: 10.1016/j. berh.2016.04.002

[14] Cervera R, Serrano R, Pons-Estel GJ, Ceberio-Hualde L, Shoenfeld Y, de Ramón E, et al. Morbidity and mortality in the antiphospholipid syndrome during a 10-year period: A multicentre prospective study of 1000 patients.

Annals of the Rheumatic Diseases. 2015;**74**(6):1011-1018. DOI: 10.1136/ annrheumdis-2013-2048

[15] Kaul M, Erkan D, Sammaritano L, Lockshin MD. Assessment of the 2006 revised antiphospholipid syndrome classification criteria. Annals of the Rheumatic Diseases. 1 Jul 2007;**66**(7): 927-930

[16] Caplan L, Biller J. Uncommon Causes of Stroke. 3rd ed. Cambridge, United Kingdom: Cambridge University Press; 2018. pp. 305-316

[17] Cervera R. Antiphospholipid syndrome. Thrombosis Research. 2017; **151**(Suppl 1):S43-s47

[18] Aguiar CL, Erkan D. Catastrophic antiphospholipid syndrome: How to diagnose a rare but highly fatal disease. Therapeutic Advances in Musculoskeletal Disease. 2013;**5**(6):305-314. DOI: 10.1177/ 1759720X13502919

[19] Chinnery PF, Shaw PJ, Ince PG, et al. Fulminant encephalopathy due to the catastrophic primary antiphospholipid syndrome. Journal of Neurology, Neurosurgery, and Psychiatry. 1997;**62**(3):300-301. DOI: 10.1136/jnnp.62.3.300

[20] Arachchillage DRJ, Laffan M. Pathogenesis and management of antiphospholipid syndrome. British Journal of Haematology. 2017;**178**(2): 181-195. DOI: 10.1111/bjh.14632. Epub 2017 Mar 24

[21] Gómez-Puerta JA, Cervera R. Diagnosis and classification of the antiphospholipid syndrome. Journal of Autoimmunity. 2014;**48-49**:20-25. DOI: 10.1016/j.jaut.2014.01.006. Epub 2014 Jan 24

[22] Andreoli L, Chighizola CB, Banzato A, et al. Estimated frequency of antiphospholipid antibodies in patients with pregnancy morbidity, stroke, myocardial infarction, and deep vein thrombosis: A critical review of the literature. Arthritis Care & Research. 2013;**65**(11):1869-1873. DOI: 10.1002/ acr.22066

[23] Hughes G. Migraine, memory loss, and "multiple sclerosis"; Neurological features of the antiphospholipid (Hughes') syndrome. Postgraduate Medical Journal. 2003;**79**(928):81-83

[24] Panichpisal K, Rozner E, Levine SR. The management of stroke in antiphospholipid syndrome. Current Rheumatology Reports. 2012;**14**:99-106

[25] Janardhan V, Wolf PA, Kase CS, et al. Anticardiolipin antibodies and risk of ischemic stroke and transient ischemic attack: The Framingham cohort and offspring study. Stroke. 2004;**35**(3):736-741. DOI: 10.1161/01. STR.0000117575.48205.2D. Epub 2004 Feb 5

[26] Cojocaru IM, Cojocaru M, Burcin C, et al. Evaluation of antiphospholipid antibodies in young women with ischemic stroke. Romanian Journal of Internal Medicine. 2007;**45**(2):201-204

[27] Levine SR, Brey RL, Tilley BC, et al. Antiphospholipid antibodies and subsequent thrombo-occlusive events in patients with ischemic stroke. Journal of the American Medical Association. 2004;**291**(5):576-584. DOI: 10.1001/ jama.291.5.576

[28] Urbanus RT, Siegerink B, Roest M, Rosendaal FR, de Groot PG, Algra A. Antiphospholipid antibodies and risk of myocardial infarction and ischaemic stroke in young women in the RATIO study: A case-control study. The Lancet Neurology. 2009;**8**(11):998-1005. DOI: 10.1016/S1474-4422(09)70239-X

[29] de Souza AW, Silva NP, de Carvalho JF, et al. Impact of hypertension and hyperhomocystenemia on arterial thrombosis in primary antiphospholipid syndrome. Lupus. 2007;**16**:782-787

[30] Pezzini A, Grassi M, Lodigiani C, et al. Predictors of long-term recurrent vascular events after ischemic stroke at young age: The Italian Project on Stroke in Young Adults. Circulation. 2014;**129**(16):1668-1676. DOI: 10.1161/CIRCULATIONAHA. 113.005663. Epub

[31] de Amorim LC, Maia FM, Rodrigues CE. Stroke in systemic lupus erythematosus and antiphospholipid syndrome: Risk factors, clinical manifestations, neuroimaging, and treatment. Lupus. 2017;**26**(5):529-536. DOI: 10.1177/0961203316688784

[32] Babikian VL. Clinical and laboratory findings in patients with antiphospholipid antibodies and cerebral ischemia. The Antiphospholipid Antibodies in Stroke Study Group. Stroke. 1990;**21**(9):1268-1273

[33] Provenzale JM, Barboriak DP, Allen NB, Ortel TL. Antiphospholipid antibodies: Findings at arteriography. American Journal of Neuroradiology. 1998;**19**:611-616

[34] Kitagawa Y. Antiphospholipid syndrome and stroke. Rinshō Shinkeigaku. 2005;**45**(11):852-855

[35] Saidi S, Mahjoub T, Almawi WY. Lupus anticoagulants and anti-phospholipid antibodies as risk factors for a first episode of ischemic stroke. Journal of Thrombosis and Haemostasis. 2009;**7**(7):1075-1080. DOI: 10.1111/ j.1538-7836.2009.03446.x. Epub 2009 Apr 27

[36] Atsumi T, Ieko M, Bertolaccini ML, et al. Association of autoantibodies against the phosphatidylserine-prothrombin complex with manifestations of the antiphospholipid syndrome and with the presence of lupus anticoagulant. Arthritis and Rheumatism. 2000;**43**(9):1982-1993. DOI: 10.1002/1529-0131(200009)43:9 <1982::AID-ANR9>3.0.CO;2-2

[37] Lopez LR, Dier KJ, Lopez D, et al. Anti-beta 2-glycoprotein I and antiphosphatidylserine antibodies are predictors of arterial thrombosis in patients with antiphospholipid syndrome. American Journal of Clinical Pathology. 2004;**121**(1):142-149. DOI: 10.1309/YVQ6-PX76-XMYM-3J29

[38] Ruffatti A, Calligaro A, Hoxha A, et al. Laboratory and clinical features of pregnant women with antiphospholipid syndrome and neonatal outcome. Arthritis Care & Research. 2010;**62**: 302-307

[39] Sanchez-Redondo J, Espinosa G, Delgado DV, Cervera R. Recurrent thrombosis with direct oral anticoagulants in antiphospholipid syndrome: A systematic literature review and meta-analysis. Clinical Therapeutics. 2019;**41**(9):1839-1862

[40] Rosove MH, Brewer PM. Antiphospholipid thrombosis: Clinical course after the first thrombotic event in 70 patients. Annals of Internal Medicine. 1992;**117**(4):303-308. DOI: 10.7326/0003-4819-117-4-303

[41] Sciascia S, Sanna G, Murru V, et al. GAPSS: The global anti-phospholipid syndrome score. Rheumatology (Oxford, England). 2013;**52**(8): 1397-1403. DOI: 10.1093/rheumatology/ kes388. Epub 2013 Jan 12

[42] Radin M, Sciascia S, Erkan D, et al. The adjusted global antiphospholipid syndrome score (aGAPSS) and the risk of recurrent thrombosis: Results from the APS ACTION cohort. Seminars in Arthritis and Rheumatism. 2019;**49**(3): 464-468. DOI: 10.1016/j. semarthrit.2019.04.009

[43] Martinelli I, Battaglioli T, Pedotti P, Cattaneo M, Mannucci PM. Hyperhomocysteinemia in cerebral vein thrombosis. Blood. 2003;**102**(4): 1363-1366

[44] Silvis SM, Sousa DA, De FJM, Coutinho JM. Cerebral venous thrombosis. Nature Reviews. Neurology. 2017;**13**(9):555-565

[45] Carhuapoma JR, Mitsias P, Levine SR. Cerebral venous thrombosis and anticardiolipin antibodies. Stroke. 1997;**28**(12):2363-2369. DOI: 10.1161/01.str.28.12.2363

[46] Gupta S, Zivadinov R, Ramasamy D, et al. Reversible cerebral vasoconstriction syndrome (RCVS) in antiphospholipid antibody syndrome (APLA): The role of centrally acting vasodilators. Case series and review of literature. Clinical Rheumatology. 2014;**33**(12):1829-1833

[47] Wang Z, Fu Z, Wang J, et al. Moyamoya syndrome with antiphospholipid antibodies: A case report and literature review. Lupus. 2014;**23**(11):1204-1206. DOI: 10.1177/0961203314540761. Epub 2014 Jun 17

[48] Samanta D, Cobb S, Arya K. Sneddon syndrome: A comprehensive overview. Journal of Stroke and Cerebrovascular Diseases. 2019;**28**(8):2098-2108. DOI: 10.1016/j.jstrokecerebrovasdis.2019.05.013. Epub 2019 May 31

[49] Wu S, Xu Z, Liang H. Sneddon's syndrome: A comprehensive review of the literature. Orphanet Journal of Rare Diseases. 2014;**9**(1):768

[50] Yelnik CM, Kozora E, Appenzeller S. Non-stroke central neurologic manifestations in antiphospholipid syndrome. Current Rheumatology Reports. 2016;**18**(2):11

[51] Appenzeller S, Lapa AT, Guirau CR, et al. Cognitive impairment in antiphospholipid syndrome: Evidence from animal models. Clinical Rheumatology. 2012;**31**(3):403-406

[52] Cervera R, Piette J-C, Font J, Khamashta MA, Shoenfeld Y, Camps MT, et al. Antiphospholipid syndrome: Clinical and immunologic manifestations and patterns of disease expression in a cohort of 1,000 patients. Arthritis and Rheumatism. 2002;**46**(4):1019-1027

[53] Ricarte IF, Dutra LA, Abrantes FF, Toso FF, Barsottini OGP, Silva GS, et al. Neurologic manifestations of antiphospholipid syndrome. Lupus. 2018;**27**(9):1404-1414. DOI: 10.1177/0961203318776110

[54] Sciascia S, Sanna G, Khamashta MA, Cuadrado MJ, Erkan D, Andreoli L, et al. The estimated frequency of antiphospholipid antibodies in young adults with cerebrovascular events: A systematic review. Annals of the Rheumatic Diseases. 2015;**74**(11):2028-2033. DOI: 10.1136/annrheumdis-2014-205663

[55] Gašperšič N, Zaletel M, Kobal J, Žigon P, Čučnik S, Šemrl SS, et al. Stroke and antiphospholipid syndrome-antiphospholipid antibodies are a risk factor for an ischemic cerebrovascular event. Clinical Rheumatology. 2019;**38**(2):379-384. DOI: 10.1007/s10067-018-4247-3. Epub 2018 Aug 7

[56] Mehta T, Hussain M, Sheth K, Ding Y, McCullough LD. Risk of hemorrhagic transformation after ischemic stroke in patients with antiphospholipid antibody syndrome. Neurological Research. 2017;**39**(6):477-483. DOI: 10.1080/01616412.2017.1323382

[57] Leal Rato M, Bandeira M, Romão VC, Aguiar de Sousa D. Neurologic manifestations of the antiphospholipid syndrome—An update. Current Neurology and Neuroscience Reports. 2021;**21**(8):41. DOI: 10.1007/s11910-021-01124-z

[58] Ruiz-Irastorza G, Cuadrado M, Ruiz-Arruza I, Brey R, Crowther M,

Derksen R, et al. Evidence-based recommendations for the prevention and long-term management of thrombosis in antiphospholipid antibody-positive patients: Report of a Task Force at the 13th International Congress on Antiphospholipid Antibodies. Lupus. 2011;**20**(2):206-218. DOI: 10.1177/0961203310395803

[59] da Silva FF, Levy RA, de Carvalho JF. Cardiovascular risk factors in the antiphospholipid syndrome. Journal of Immunology Research. 2014;**2014**:621270. DOI: 10.1155/2014/621270

[60] Erkan D. A cross-sectional study of clinical thrombotic risk factors and preventive treatments in antiphospholipid syndrome. Rheumatology. 2002;**41**(8):924-929. DOI: 10.1093/rheumatology/41.8.924

[61] Ruiz-Irastorza G et al. Antiphospholipid syndrome. Lancet. 2010;**376**(9751):1498-1509

[62] Grika EP et al. Morbidity, mortality, and organ damage in patients with antiphospholipid syndrome. The Journal of Rheumatology. 2012;**39**(3):516-523

[63] Negrini S et al. The antiphospholipid syndrome: From pathophysiology to treatment. Clinical and Experimental Medicine. 2017;**17**(3):257-267

[64] Sciascia S, Sanna G, Murru V, Roccatello D, Khamashta MA, Bertolaccini ML. Anti-prothrombin (aPT) and anti-phosphatidylserine/prothrombin (aPS/PT) antibodies and the risk of thrombosis in the antiphospholipid syndrome. A systematic review. Thrombosis and Haemostasis. 2014;**111**(2):354-364. DOI: 10.1160/TH13-06-0509. Epub 2013 Oct 31

[65] Iuliano A, Galeazzi M, Sebastiani GD. Antiphospholipid syndrome's genetic and epigenetic aspects.

Autoimmunity Reviews. 2019;**18**(9):102352

[66] Schreiber K et al. Antiphospholipid syndrome. Nature Reviews Disease Primers. 2018;**4**:17103

[67] Garcia D, Erkan D. Diagnosis and management of the antiphospholipid syndrome. The New England Journal of Medicine. 2018;**378**(21):2010-2021. DOI: 10.1056/NEJMra1705454

[68] de Groot PG, de Laat B. Mechanisms of thrombosis in systemic lupus erythematosus and antiphospholipid syndrome. Best Practice & Research. Clinical Rheumatology. 2017;**31**(3):334-341

[69] Corban MT et al. Antiphospholipid syndrome: Role of vascular endothelial cells and implications for risk stratification and targeted therapeutics. Journal of the American College of Cardiology. 2017;**69**(18):2317-2330

[70] Irman Š, Škarabot M, Muševič I, Rozman B, Božič B. Thrombomodulatory effect of anti-B2-glycoprotein I antibodies on crystalline annexin A5 on phospholipid bilayers, as observed by atomic force microscopy. EJIFCC. 2011;**21**(4):81-93

[71] Pengo V, Tripodi A, Reber G, Rand JH, Ortel TL, Galli M, et al. Update of the guidelines for lupus anticoagulant detection. Subcommittee on Lupus Anticoagulant/Antiphospholipid Antibody of the Scientific and Standardisation Committee of the International Society on Thrombosis and Haemostasis. Journal of Thrombosis and Haemostasis. 2009;**7**(10):1737-1740. DOI: 10.1111/j.1538-7836.2009.03555.x. Epub 2009 Jul 17

[72] Levine JS, Branch DW, Rauch J. The antiphospholipid syndrome. The New England Journal of Medicine. 2002;**346**(10):752-763. DOI: 10.1056/NEJMra002974

[73] Giannakopoulos B, Passam F, Ioannou Y, Krilis SA. How we diagnose the antiphospholipid syndrome. Blood. 2009;**113**(5):985-994. DOI: 10.1182/blood-2007-12-129627. Epub 2008 Aug 28

[74] Kim Y, Kim SY. Antiphospholipid antibody and recurrent ischemic stroke: A systematic review and meta-analysis. Stroke. 2020;**51**(12):3728-3732

[75] Cohen D, Berger SP, Steup-Beekman GM, Bloemenkamp KW, Bajema IM. Diagnosis and management of the antiphospholipid syndrome. BMJ. 2010;**340**:c2541

[76] Giron-Gonzales JA, Garcia del Rio E, Rodriguez C, Rodriguez-Martorell J, Serrano A. Antiphospholipid syndrome and asymptomatic carriers of antiphospholipid antibody: Prospective analysis of 404 individuals. The Journal of Rheumatology. 2004;**31**: 1560-1567

[77] Pengo V, Testa S, Martinelli I, Ghirarduzzi A, Legnani C, Gresele P, et al. Incidence of a first thromboembolic event in carriers of isolated lupus anticoagulant. Thrombosis Research. 2015;**135**(1):46-49

[78] Pengo V, Ruffatti A, Legnani C, Testa S, Fierro T, Marongiu F, et al. Incidence of a first thromboembolic event in asymptomatic carriers of high-risk antiphospholipid antibody profile: A multicenter prospective study. Blood. 2011;**118**(17):4714-4718

[79] Arnaud L, Mathian A, Ruffatti A, Erkan D, Tektonidou M, Cervera R, et al. Efficacy of aspirin for the primary prevention of thrombosis in patients with antiphospholipid antibodies: An international and collaborative meta-analysis. Autoimmunity Reviews. 2014; **13**(3):281-291

[80] Cuadrado MJ, Bertolaccini ML, Seed PT, Tektonidou MG, Aguirre A, Mico L, et al. Low-dose aspirin vs low-dose aspirin plus low-intensity warfarin in thromboprophylaxis: A prospective, multicentre, randomized, open, controlled trial in patients positive for antiphospholipid antibodies (ALIWAPAS). Rheumatology. 2014; **53**(2):275-284

[81] Tektonidou MG, Andreoli L, Limper M, Amoura Z, Cervera R, Costedoat-Chalumeau N, et al. EULAR recommendations for the management of antiphospholipid syndrome in adults. Annals of the Rheumatic Diseases. 2019; **78**(10):1296-1304

[82] Baigent C, Blackwell L, Collins R, Emberson J, Godwin J, Peto R, et al. Aspirin in the primary and secondary prevention of vascular disease: Collaborative meta-analysis of individual participant data from randomised trials. Lancet. 2009; **373**(9678):1849-1860

[83] Amory CF, Levine SR, Brey RL, Gebregziabher M, Tuhrim S, Tilley BC, et al. Antiphospholipid antibodies and recurrent thrombotic events: Persistence and portfolio. Cerebrovascular Diseases. 2015;**40**(5–6):293-300

[84] Crowther MA, Ginsberg JS, Julian J, Denburg J, Hirsh J, Douketis J, et al. A comparison of two intensities of warfarin for the prevention of recurrent thrombosis in patients with the antiphospholipid antibody syndrome. New England Journal of Medicine. 2003; **349**(12):1133-1138

[85] Finazzi G, Marchioli R, Brancaccio V, Schinco P, Wisloff F, Musial J, et al. A randomized clinical trial of high-intensity warfarin vs. conventional antithrombotic therapy for the prevention of recurrent thrombosis in patients with the antiphospholipid syndrome (WAPS) 1. Journal of Thrombosis and Haemostasis. 2005; **3**(5):848-853

[86] Cohen H, Isenberg DA. How I treat anticoagulant-refractory thrombotic antiphospholipid syndrome. Blood. 2021;**137**(3):299-309

[87] Lim W, Crowther MA, Eikelboom JW. Management of antiphospholipid antibody syndrome: A systematic review. Journal of the American Medical Association. 2006;**295**(9):1050-1057

[88] Andrade D, Cervera R, Cohen H, Crowther M, Cuadrado MJ, Canaud G, et al. 15th international congress on antiphospholipid antibodies task force on antiphospholipid syndrome treatment trends report. In: Antiphospholipid Syndrome. Champions: Springer; 2017. pp. 317-338

[89] Cohen H, Hunt BJ, Efthymiou M, Arachchillage DR, Mackie IJ, Clawson S, et al. Rivaroxaban versus warfarin to treat patients with thrombotic antiphospholipid syndrome, with or without systemic lupus erythematosus (RAPS): A randomised, controlled, open-label, phase 2/3, non-inferiority trial. The Lancet Haematology. 2016;**3**(9):e426-e436

[90] Pengo V, Denas G, Zoppellaro G, Jose SP, Hoxha A, Ruffatti A, et al. Rivaroxaban vs warfarin in high-risk patients with antiphospholipid syndrome. Blood. 2018;**132**(13):1365-1371

[91] Erkan D, Willis R, Murthy VL, Basra G, Vega J, Ruiz-Limón P, et al. A prospective open-label pilot study of fluvastatin on proinflammatory and prothrombotic biomarkers in antiphospholipid antibody positive patients. Annals of the Rheumatic Diseases. 2014;**73**(6):1176-1180

[92] Wallace DJ, Linker-Israeli M, Metzger AL, Stecher VJ. The relevance of antimalarial therapy with regard to thrombosis, hypercholesterolemia and cytokines in SLE. Lupus. 1993;**2**(Suppl 1):S13-S15

[93] Kravvariti E, Koutsogianni A, Samoli E, Sfikakis PP, Tektonidou MG. The effect of hydroxychloroquine on thrombosis prevention and antiphospholipid antibody levels in primary antiphospholipid syndrome: A pilot open label randomized prospective study. Autoimmunity Reviews. 2020;**19**(4):102491

[94] Chighizola CB, Ubiali T, Meroni PL. Treatment of thrombotic antiphospholipid syndrome: The rationale of current management—An insight into future approaches. Journal of Immunology. Research. 2015;**2015**:951424

[95] Bazán EC, López CD, Lozano PM, Cervera R, Espinosa G. Discontinuation of anticoagulation or antiaggregation treatment may be safe in patients with primary antiphospholipid syndrome when antiphospholipid antibodies became persistently negative. Immunologic Research. 2013;**56**(2–3):358-361

[96] Criado-García J, Fernández-Puebla RA, Jiménez LL, Velasco F, Santamaría M, Blanco-Molina A. Anticoagulation treatment withdrawal in primary antiphospholipid syndrome when anticardiolipin antibodies become negative. Revista Clinica Espanola. 2008;**208**(3):135-137

[97] Bertsias GK, Ioannidis JP, Aringer M, Bollen E, Bombardieri S, Bruce IN, et al. EULAR recommendations for the management of systemic lupus erythematosus with neuropsychiatric manifestations: Report of a task force of the EULAR standing committee for clinical affairs. Annals of the Rheumatic Diseases. 2010;**69**(12):2074-2082

[98] Ageno W, Crotti S, Turpie AG. The safety of antithrombotic therapy during pregnancy. Expert Opinion on Drug Safety. 2004;**3**(2):113-118. DOI: 10.1517/eods.3.2.113.27343