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Abstract

Persistence of serum antiphospholipid antibodies (aPL) is associated with a high thrombotic risk, both arterial and venous, and with pregnancy complications. Due to the potential morbidity and mortality associated with the presence of aPL, identifying and recognizing risk factors for the development of aPL and thrombosis in aPL carriers may help to prevent and reduce the burden of disease. Multiple elements are involved in the pathomechanism of aPL development and aPL-related thrombosis such as genetics, malignancy, and infections. This review will address the role of both well-known risk factors and their evolution, and of emerging risk factors, including COVID-19, in the development of aPL and thrombosis in aPL carriers.

Keywords
- antiphospholipid syndrome
- antiphospholipid antibody
- thrombosis
- risk factor

The antiphospholipid syndrome (APS) is a syndrome characterized by a prothrombotic state, with the potential to cause both venous and arterial thrombosis, as well as pregnancy morbidity, in patients with a persistent presence of antiphospholipid antibodies (aPL). Among an ever-growing list of potential aPL involved in clinical APS, so far three antibodies have been included in the updated 2006 Sydney classification criteria for APS: lupus anticoagulant (LAC) measured according to the International Society on Thrombosis and Haemostasis (ISTH) guidelines, anticardiolipin antibody (aCL) of immunoglobulin (Ig) G and IgM isotype and anti-beta-2 glycoprotein-I antibody (aβ2GPI) of IgG and IgM isotype (►**Table 1**).[1] In these classification criteria, an APS diagnosis can be made in a patient with serum positivity for at least one of the three defined antibodies measured twice at least 12 weeks apart with a history of arterial or venous thrombosis or pregnancy-related events.[1]

The current laboratory criteria comprise assays that detect LAC as influencers of coagulation, and immunoassays that detect both aCL and aβ2GPI. Unfortunately, no gold standard assays exist for aPL detection. LAC testing can be difficult to interpret in patients on anticoagulation, affecting both activated partial thromboplastin time and dilute Russell viper venom time, and anticoagulation is common in patients with previous thrombotic events. In addition, standardization of enzyme-linked immunoassays (ELISA) and other newer assays that detect aβ2GPI and aCL remains a concern to this day. Assay cutoff values are also a subject of discussion, since different authors may categorize a given aPL value as "low" or "high" depending on their laboratory-specific cutoff, leading to potential discrepancies among studies and laboratories. To minimize the discrepancies, the revised classification APS criteria proposed a cutoff value (> 99th percentile) for LAC and aβ2GPI in an attempt to standardize titers both in clinical practice and in scientific literature; yet, cutoff values still depend on parameters such as the type of assay used and the reference population.[1,2]

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Table 1 Revised 2006 Sydney APS criteria

Clinical criteria	Laboratory criteria (1 or more, on 2 or more occasions at least 12 wk apart)
Vascular thrombosis: 1 or more confirmed episodes of arterial, venous, or small vessel thrombosis in any organ	LAC detected according to the guidelines of the ISTH
	aCL antibody of IgG and/or IgM isotype present in medium or high titer (>40 IgG or IgM units or > 99th percentile) measured by a standardized ELISA
Pregnancy morbidity: 1 or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation; or 1 or more premature births of a morphologically normal neonate before the 34th week of gestation because of eclampsia, preeclampsia, or placental insufficiency; or 3 or more unexplained consecutive spontaneous abortions before the 10th week of gestation	aβ2GPI antibody of IgG and/or IgM isotype present in medium or high titer (>40 IgG or IgM units or > 99th percentile) measured by a standardized ELISA

Abbreviations: LAC, lupus anticoagulant; ISTH, International Society on Thrombosis and Haemostasis; aCL, anti-cardiolipin; aβ2GPI, anti-beta-2 glycoprotein; ELISA, enzyme-linked immunosorbent assay; APS, antiphospholipid syndrome.
Note: Definite APS is present if at least 1 clinical criterion and 1 laboratory criterion are met.
Source: Adapted from: Vandevelde A, Devreese KMJ. Laboratory diagnosis of antiphospholipid syndrome: insights and hindrances. J Clin Med 202213;11(8):2164.

The APS criteria are classification criteria, and hence developed for scientific research. For the clinical diagnosis, a wide range of other manifestations related to aPL positivity has been described,[3] including livedo reticularis, cytopenias, and neurological complications, adding complexity to APS diagnosis and management. APS can be found as an independent entity, known as primary antiphospholipid syndrome (PAPS) or coexist with other autoimmune diseases, mainly systemic lupus erythematous (SLE), also referred to as secondary antiphospholipid syndrome (SAPS).[4] A rare (<1%) and devastating form of APS is the catastrophic antiphospholipid syndrome (CAPS), characterized by a high mortality rate due to rapid multiorgan failure following extensive thrombosis throughout the body.[3]

Although different inflammatory and thrombotic factors are suggested as key elements in APS pathophysiology, its pathogenic mechanism is not yet fully understood.[5] Some theories about the development of APS have been postulated. Probably the most accepted is the "two-hit" theory: genetically susceptible individuals develop aPL in the context of an infection or in the setting of an autoimmune disease, creating a clotting-prone environment (or first hit). This hypercoagulable state is believed to be induced by both direct interaction of aPL with proteins regulating plasma coagulation pathways and activation of endothelial cells and platelets through aPL interaction with membrane proteins and receptors. An additional insult (or second hit) that damages vascular integrity, like other infections, cancer, other procoagulant conditions, or drugs such as chemotherapy, is needed to result in thrombus formation.[6,7]

Two topics regarding aPL are of special clinical relevance. First, the pathomechanisms of aPL development are not clearly established, and its understanding might be key to its prevention. Furthermore, assessing thrombosis risk in both aPL carriers and APS patients can help clinicians to take preventive measures in selected patients.

In this review, we therefore aim to define the known risk factors for developing aPL and to summarize the risk factors for developing thrombotic non–pregnancy-related events in aPL carriers (summarized in ►**Table 2**) and APS patients.

Asymptomatic aPL Carriers

Incidence and Prevalence

The prevalence of aPL positivity in asymptomatic aPL-positive individuals is difficult to estimate. Studies in asymptomatic individuals are generally old studies that provide data of aPL measured only once. This might overestimate the clinical relevance of aPL, as its positivity can be transient and bear limited clinical value in many scenarios, unlike sustained aPL positivity, which is linked to higher thrombosis risk.

aPL positivity ranges between 5 and 10% in healthy blood donors,[8–11] yet as mentioned previously studies in this group either usually measure titers only once or aPL positivity notably decreases in the second measurement. Studies on aPL positivity in general population remain scarce. Some have described differences between single, double, and triple positivity, with the last group being the least common.[12] aPL is well-studied in individuals with SLE, and in this population aPL positivity is estimated to be present in 30 to 40%.[8,9]

Risk Factor for Developing aPL

Genetic Susceptibility

Human leukocyte antigen (HLA) class II genes are associated with APS and aPL development, but studies show large heterogeneity due to small size samples, low statistical power, and overall complexity of the HLA region.[13] Some non-HLA genes have been proposed as contributors to disease susceptibility. For instance, a meta-analysis including 1,507 APS patients and 1,450 healthy individuals found a significant association between the polymorphism leading

Table 2 Summary of risk factors for thrombosis in aPL carriers

Risk factors for thrombosis in aPL carriers		Level of evidence
Contraceptives (COC)	Stroke OR = 201 in LAC + COC[100] Myocardial infarction OR = 21.6 in LAC + COC[100]	III
Previous thrombosis	OR = 2.89 for VTE in LAC patients with discontinued anticoagulation[108] 24.4% arterial recurrence 4[109] 15.4% venous recurrence[109]	II
Age	In <50 y, up to almost 6-fold CVD risk[57]	II
SLE	Baseline 2–10-fold risk of CVD[85] 2-fold risk for VTE if aPL + [88] More CV risk factors in aPL + [90]	II
Sex	OR = 3.77 myocardial infarction for men[26] RR = 1.3–1.6 recurrent VTE for men[54]	III
aPL profile	LAC most thrombogenic (6-fold CVD)[17] Triple positivity (OR = 5.2–33)[31,32]	II
Thrombocytopenia	Up to OR = 5.9 in aPL carriers[45]	III
Hypertension	Up to OR = 1.78 for arterial thrombosis in APS[56]	III
Hyperlipidemia	Up to OR = 2.00 for arterial thrombosis in APS[56]	III
Nephropathy	aPL carriers with kidney involvement have more arterial thrombosis than those without kidney involvement[53]	III
Smoking	More thrombosis than non-smokers in aPL carriers ($p = 0.006$)[69]	III
Diabetes mellitus	Up to OR = 2.02 in DM/APS patients[72]	III
Systemic sclerosis	More thrombotic events in aPL-positive patients ($p < 0.005$)[49]	II
Ethnicity	Asians have more arterial events than Europeans (cerebral infarction: 61 vs. 19.8%) in APS[59] Arabs more venous thrombosis than Asians and Ashkenazi Jews ($p < 0.001$)[60] Asians more mortality than Arabs or Ashkenazi Jews ($p = 0.05$)[60] African Americans HR = 5.94[62]	III
Malignancy	Contradictory[111,112]	III
COVID-19	Contradictory: most studies don't find association[116]	III
Sjogren's syndrome	No association[92]	III
Rheumatoid arthritis	No association[95]	III

Abbreviations: aPL, antiphospholipid antibodies; APS, antiphospholipid syndrome; COC, combined oral contraceptives; CVD, cardiovascular disease; DM, diabetes mellitus; HA, hazard ratio; LAC, lupus anticoagulant; SLE, systematic erythematous lupus; OR, odds ratio; VTE, venous thromboembolism disease. Levels of evidence, I: evidence from a systematic review or meta-analysis of all relevant RCTs (randomized controlled trial) or evidence-based clinical practice guidelines based on systematic reviews of RCTs or three or more RCTs of good quality that have similar results; II, evidence obtained from at least one well-designed RCT (e.g., large multisite RCT); III, evidence obtained from well-designed controlled trials without randomization (i.e., quasi-experimental); IV, evidence from well-designed case–control or cohort studies.

to an amino acid change (valine to leucine) at position 247, located in domain 5 of β2GPI (a potential epitope site for aβ2GPI), and both APS and aβ2GPI positivity.[14] Moreover, several loci (such as signal transducer and activator of transcription 4, or STAT4) associated with SLE might be related to aPL and APS, but evidence is scarce. Some theories point to mutations in the loci encoding rapamycin kinase (mammalian target of rapamycin [mTOR]) pathway, leading to a significantly higher activation of the mTOR pathway in PAPS.[15] In addition, a German study based on a cohort of almost 5,000 individuals described two loci (APOH and MACROD2) associated with the presence of aPL. Both were associated only with the presence of aβ2GPI IgG.[16]

In conclusion, while many genes have been proposed as being key to aPL development, precise association is still unknown.

Infections

Since its discovery, aPL have been linked to different infectious diseases, raising the question of its exact role and thrombotic risk in these patients compared to those with an autoimmune disorder.

Fleeting, low-titer aPL are seen during infections, such as HIV, parvovirus B19, or *Mycoplasma pneumoniae*, revealing no or little clinical relevance concerning thrombotic events.[17,18] In a major systematic review and meta-analysis of 60 studies and 4,952 patients, a significantly increased risk for developing aCL was found in patients with HIV, HCV, HBV, EBV, and HTLV-1 infections compared with controls. This association was found only between aβ2GPI and HCV and none was established for LAC.[19] In most recent studies, it is even suggested that gut microbiota can play a role in triggering APS autoimmunity acting as a source of cross-reactive antigens through molecular

mimicry.[20] The potential relationship between aPL and COVID-19 (coronavirus disease 2019) is detailed in a later section.

Age

Though studies are scarce, aPL positivity tends to increase with age. This is demonstrated in a study of 64 healthy elderly individuals with a mean age of 81 years. Here, 51.6% tested positive for aCL, yet its clinical significance is unclear.[21] This might be linked to age-related increased production of antibodies, but evidence is not robust since usually aPL are only measured once.

Malignancy

Both solid and hematological malignancies are linked to the presence of aPL. A 2020 meta-analysis of aPL and solid tumors described an increased positivity of aPL (especially aCL) in gastrointestinal, genitourinary, and lung cancers; yet, the association with thrombosis was found only in lung cancers.[7] Concerning hematological malignancies, some studies have pointed out that 24 to 60% patients with leukemia, Hodgkin lymphoma, and non-Hodgkin lymphoma are positive for at least one aPL.[22] Overall, exact prevalence and thrombotic risk seem difficult to determine because of the small number of patients enrolled in the studies and lack of consistency in the measurement of antibodies.

Thrombosis in aPL Carriers and APS Patients

Incidence and Prevalence

Estimating the exact frequency of APS is daunting. Different and changing APS classification criteria, non-standardized measures to detect aPL, and the need of a second aPL positivity at least 12 weeks after the first measurement add difficulty to this challenge. Nevertheless, new studies in the last decade have helped better understand APS epidemiology.

A population-based cohort from Olmsted County, Minnesota, has estimated an annual incidence of 2.1 and a prevalence of 50 per 100,000 inhabitants, respectively, for APS.[23] In other cohorts in Argentina and Korea, similar annual incidences were described (2.6 per 100,000 and almost 1 case per 100,000 inhabitants, respectively), while prevalence in the Asian cohort was remarkably lower (6.19 per 100,000 inhabitants).[24] Regarding its association with SLE, in a Spanish study, 13.9% of SLE patients had secondary APS.[25]

Concerning differences between sexes, the female-to-male ratio in APS has been defined around 3:1 to 5:1 in different populations. This is probably explained by the majority of SAPS that are linked to SLE, of which the majority is an autoimmune disease more commonly diagnosed in young women. However, when describing only PAPS, the female-to-male ratio decreases or is even inverted.[3,26]

Since thrombotic events are easier to assess and register than aPL positivity in the healthy population, more accurate data are available on APS.

Risk Factors for Thrombosis in Patients with aPL Positivity

aPL Profile

aPL persistence (at least twice, 12 weeks apart) is a necessary criterion to define APS diagnosis and is linked to higher risk of thrombosis.[11,17] Moreover, different thrombotic risk may be described depending on positivity for different aPL in an individual, in what is described as an aPL profile.

In general terms, an individual with more than one positive aPL has a higher risk of a thrombotic event compared to those with one single aPL positivity,[27] with LAC thought to be the most thrombogenic aPL of the triad.[17,28] While some studies question this statement when analyzing aPL carriers,[12] the Vienna Lupus Anticoagulant and Thrombosis Study (LATS) shows this association. In this study, both aPL carriers and APS patients were followed up during a mean time of 8.2 years, in which increased mortality rate, probability of thrombosis recurrence, and a 6-fold thrombogenic risk in LAC-positive patients were described compared to LAC-negative patients.[29] In APS patients, high aCL and aβ2GPI titers have also been linked to higher risk of thrombosis when combined positivity exists with other aPL, especially LAC.[27,30] High titers were defined as >40 IgG phospholipid units or IgM phospholipid units, or >99th percentile and in titer >99th percentile, respectively, measured by a standardized ELISA.[1] Triple positivity is also considered an independent risk factor for thrombosis, with reported odds ratio (OR) ranging from 5.2 to 33 in different studies, compared to single or double positivity.[31,32]

Following the new classification criteria to define APS,[1] a subclassification depending on the aPL profile is strongly advised. Using this subclassification can help in assessing both APS patients and aPL carriers, since different profiles translate into different thrombotic risk. The EULAR recommendations for the management of APS in adults define aPL profile as the combination of the presence of multiple (vs. single) aPL isotypes, their titer, and the persistence of aPL positivity in repeated measurements.[30] ►**Table 3** illustrates this classification. One of the advantages of classifying a patient within this score is that it can lead to intervention with thrombotic prevention in aPL carriers if necessary.

While secondary thrombotic prophylaxis in APS patients is well defined, primary prophylaxis in aPL carriers is still a controversial subject. Whether to use low-dose aspirin (LDA; 75–100 mg daily) or not in aPL carriers with a high-risk profile to prevent first thrombotic event has been discussed widely in literature. On the one hand, EULAR 2019 recommendations for the management of APS in adults are clear: LDA use in asymptomatic carriers with high-risk profile (as defined previously in this section) is recommended.[30] On the other hand, American studies are more conservative and do not recommend LDA for prophylaxis based on aPL profile.[33] Apart from the described classical aPL, other similar antibodies are linked to higher thrombotic risk. Seronegative APS (SN-APS) was coined to describe patients with clinical signs highly suggestive of APS (mainly thrombosis and miscarriage), but who are persistently negative for conventional aPL

Table 3 Definition of aPL medium-high titers and aPL risk profile

Definition of medium-high aPL titers
- aCL antibody of IgG and/or IgM isotype in serum or plasma present in titers > 40 IgG and/or IgM phospholipid units, or > 99th percentile, measured by a standardized ELISA. aβ2GPI antibody of IgG and/or IgM isotype in serum or plasma in titer > 99th percentile, measured by a standardized ELISA
Definition of risk concerning aPL profile
Low-risk profile - Isolated aCL antibody *or* aβ2GPI antibody at low titers, particularly if transiently positive
High-risk profile - The presence (in 2 or more occasions at least 12 wk apart) of LAC, or of double (any combination of LAC, aCL, or aβ2GPI) or triple positivity (all three subtypes), or the presence of persistently high aPL titers

Abbreviations: aCL, anti-cardiolipin; aβ2GPI, anti-beta2 glycoprotein; ELISA, enzyme-linked immunoassays; LAC, lupus anticoagulant.
Source: Adapted from: Tektonidou MG et al. EULAR recommendations for the management of antiphospholipid syndrome in adults. Ann Rheum Dis 2019;78(10):1296–1304.

or other hypercoagulant states.[34] However, some of these patients present positivity for "non-criteria" antibodies. These comprise a wide range of antibodies, also directed against different components of the cell membrane, with heterogeneity in terms of their thrombogenic effect. Anti-IgA aβ2GPI is perhaps the allegedly most thrombogenic "non-criteria" aPL. Not only these are being studied as potential biomarkers in SN-APS patients, but they also seem to increase thrombosis risk when associated with classical aPL or other prothrombotic risk factors.[35] Although some higher-quality studies are arising,[36,37] most of the data currently available comes from low-grade evidence[38] and its role in thrombogenesis is still a subject of reasonable debate and study.

As we have seen, scoring systems concerning aPL positivity can be a useful tool. Given the potential heterogeneity of presentation and clinical course of patients, different thrombosis risk score systems have been defined. One of the most used is aGAPSS (the adjusted Global Antiphospholipid Syndrome Score), proposed in 2013, taking both aPL profile and classical cardiovascular (CV) risks into account,[39,40] and will be further discussed.

Noncriteria APS Manifestations

Apart from the criteria described in the revised 2006 Sydney classification criteria for APS,[1] other clinical manifestations related to APS have also been proposed.[30] It is fundamental to remember that classification criteria are developed for research purposes. Nevertheless, these noncriteria APS manifestations are usually relevant for its diagnosis, and some of them seem to add thrombotic risk in aPL carriers.

Thrombocytopenia and Hemolytic Anemia

Considering one of the most common noncriteria manifestations, thrombocytopenia (platelet count <150,000/μL) is present in about 20 to 40% of APS patients.[3,41] According to a recent analysis of a large international cohort, thrombocytopenia ranges from 16% in primary APS to 28% in SAPS.[42] Although generally asymptomatic and mild,[43] thrombocytopenia has been linked to a higher risk of thrombosis in several studies. The first association between thrombocytopenia and aPL was described in 1986, when a study noted that high titers (>6 standard deviations above mean normal control level) of IgG aCL have 78 and 77% predictive values for thrombosis and thrombocytopenia, respectively.[44] This finding was confirmed in subsequent studies[45,46] and is considered independent of the presence of SLE.[47] In summary, thrombocytopenia is associated with higher thrombotic risk in patients with aPL positivity.

An acute and severe drop in platelet count (<30,000 μL) in APS patients or known aPL carriers is associated with the presence of CAPS, a devastating form of APS even when properly treated. Therefore, clinicians should search for signs for microangiopathy or organ damage in the presence of sudden thrombocytopenia.[48]

Another hematological manifestation associated with APS is autoimmune hemolytic anemia (AIHA). The pooled prevalence of AIHA ranges between 23 and 26% in SAPS and 4% in PAPS. Moreover, it has also been described that AIHA is more common in thrombotic SAPS than in SLE patients (26.8 vs. 10%).[49] Some studies have suggested that APS patients with AIHA are expected to develop a second clinical APS manifestation sooner than patients without AIHA.[50]

Skin Manifestations

It has been stated that the presence of skins lesions typically found in APS patients, such as livedo reticular and livedo racemosa, seem to be related to thrombotic events in these patients. In particular, livedo racemosa has been strongly linked to CV disease (CVD).[3,51]

Nephropathy

Some studies have pointed out that glomerular microthromboses in kidney biopsies were more likely to be found in aβ2GPI carriers,[52] especially in aPL carriers without APS criteria. In these aPL carriers with kidney involvement, APS-related manifestations (especially arterial thrombosis) were more common than in aPL carriers without kidney involvement.[53]

Sex, Age, and Ethnicity

Sex

In spite of females making up the majority of APS patients (mostly due to its association with SLE and obstetric events),

male patients have an increased risk of thrombosis and thrombosis recurrence compared to females in most studies.[26,54,55]

Age

Some studies, including a systematic review of 43 studies with stroke related to APS, showed that aPL may have a big role in strokes in younger patients. Individuals younger than 50 years and positive aPL have an increased risk for thrombotic cerebrovascular events by almost sixfold compared to those younger than 50 years and negative aPL.[56,57] The exact contribution of aPL to the thrombotic risk is less defined in patients older than 50 years, since its effect is diluted by traditional CV risk factors.[58]

Ethnicity

While ethnicity can be intricate to address, differences in thrombosis risk have been pointed out in relation to APS. A study showed that Japanese APS patients tend to have more arterial events than Europeans, while the latter group is more prone to suffer venous events (estimated prevalence: 23.4 vs. 38.9%, respectively).[59] In an Israeli study,[60] Arab patients, compared to the other ethnicities studied (Asians and Ashkenazi Jews), were younger and more prone to venous thrombosis recurrence (46 vs. 16%), though mortality was higher in the Asian group (8.8 vs. 1.1%). In a Spanish cohort,[61] a higher prevalence of APS was found in Roma SLE patients compared to Caucasians, highlighting a higher prevalence of abortions in the former group. Finally, a small study suggested that African American ethnicity can be a risk factor for thrombosis.[62]

As a whole, age (<50 years old) and sex (males) are well-defined risk factors for thrombosis in aPL carriers. Conversely, ethnicity plays a role of yet imprecise importance since exact knowledge concerning the weight of environmental versus genetic factors in ethnicity is lacking.

Classical Cardiovascular Risk Factors

Classic CV risk factors have been widely studied in APS patients, but information in aPL carriers remains scarce.

Hypertension

Hypertension is the most common CV risk factor encountered in APS patients, especially in arterial thrombosis. According to the Euro-phospholipid project (a 10-year prospective observational study of 1,000 APS patients from 13 different European countries), around 15 to 20% of all APS patients suffer from hypertension and/or hyperlipidemia.[3] The percentage increases to 33 and 45%, as shown in both Italian and Brazilian studies, when it comes to only hypertension.[63–65] A retrospective study of patients with arterial thrombosis and APS showed an approximate twofold increased odds for the development of thrombosis for hypertension and hypercholesterolemia, respectively.[56]

Hyperlipidemia

Hyperlipidemia is an independent risk factor for CV events, with a prevalence of up to 25% in several APS studies.[3,56,63,66] However, clinicians tend to sometimes disregard CV risks treatment. A 2022 French cross-sectional study assessed lipid profile in APS patients and demonstrated that two-thirds of patients with a history of CVD had not reached the cholesterol level target proposed by the 2019 European Society of Cardiology/European Atherosclerosis Society guidelines for the management of dyslipidemia.[67]

Smoking

The link between smoking and atherosclerosis has been described abundantly in the literature.[68] Its role in thrombosis, especially concerning arterial thrombosis in both APS and aPL carriers, has also been described. In a Finnish prospective nationwide cohort study,[69] aPL carriers who smoked were more prone to develop thrombosis than non-smoking aPL carriers. Moreover, smoking is linked to an almost threefold risk of thrombocytopenia (platelets $\leq$ 100,000/μL) in aPL carriers,[45] an additional risk for the development of thrombosis as described earlier. A history of tobacco use in APS patients use ranges from 15%[64] to almost 28%.[56] Smoking has also been related to seizures in patients in APS.[70] Overall, one common limitation when exploring smoking as a risk factor is that smoking is depicted as a qualitative item (yes/no or current/past history) rather than a quantitative measurement (cigarettes/year). However, evidence concerning tobacco and thrombosis risk is strong and should not be disregarded.

Diabetes

Diabetes mellitus (DM) type 2 is also a risk factor for thrombosis. The presence of DM in aPL carries appears not to further increase the risk of thrombosis,[71] whereas in APS patients a twofold increased risk has been described in the simultaneous presence of DM.[72] In addition, a different cohort study[73] described that type 2 diabetes was a risk factor for overall venous (but not arterial) thrombosis in APS patients.

Risk Stratification Scores

As mentioned earlier, aGAPSS is a useful tool to measure thrombotic risk in APS patients, since it assesses thrombotic risk in patients taking both aPL profile and CV risk into account. However, aGAPSS has several limitations; the subtypes of immunoglobulin and aPL titer are not addressed, and hypertension and dyslipidemia are the only CV risk factors included. Moreover, it includes APS/PT complex antibody measurement, a technique not yet widely available in hospitals.[38,39] In 2018, the aGAPSS score was revisited and updated in the aGAPSS for cardiovascular disease ($aGAPSS_{CVD}$), adding obesity, smoking habit, and diabetes as CV risk factors. An aGAPSS of >10 is described to be associated with almost a threefold higher CVD risk, while an $aGAPSS_{CVD}$ >11 exhibited almost a fivefold increased CVD risk. Although capable of detecting a higher rate of CVD, especially in patients < 50 years, and being validated in several cohorts, $aGAPSS_{CVD}$ also presents similar limitations to aGAPSS (like still disregarding aPL titers).[74] ►**Table 4** shows the $aGAPSS_{CVD}$/aGAPSS scale and its variables.

Table 4 Adjusted Global Antiphospholipid Syndrome Score (aGAPSS) and aGAPSS for Cardiovascular Disease ($aGAPSS_{CVD}$)

	aGAPSS	$aGAPSS_{CVD}$
aCL IgG/IgM	5	5
aβ2GPI IgG/IgM	4	4
aPS/aPT IgG/IgM	3	3
LAC	4	4
Hyperlipidemia	3	3
Arterial hypertension	1	1
Obesity	–	2
Diabetes type 2	–	2
Smoking habit	–	1
$aGAPSS > 10$ or $aGAPSS_{CVD} > 11$ = higher thrombotic risk		

Abbreviations: aCL, anti-cardiolipin; aβ2GPI, anti-beta-2 glycoprotein; aPS/aPT, anti-phosphatidylserine/prothrombin; LAC, lupus anticoagulant.
Source: Adapted from: Calcaterra I, Ambrosino P, Vitelli N, Lupoli R, Orsini RC, Chiurazzi M, Maniscalco M, di Minno MND. Risk assessment and antithrombotic strategies in antiphospholipid antibody carriers. Biomedicines 2021;9(2):1–11. MDPI AG.

Some other stratification scores have been proposed, like the antiphospholipid score (aPL-S) from Kato et al, validated in different cohorts[75] adding cutoff values for the different aPL titers, setting aPL-S of ≥ 30 as high risk for thrombosis.

Atherosclerosis and Heart Disease Association with aPL

Some studies have shown that the risk of plaque development is higher in SAPS patients compared to PAPS patients, while APS patients in general have a 3.3-fold risk of new atherosclerotic plaque compared to healthy controls.[76–78] Compared to healthy controls, APS patients showed an increased CV risk in different measurements: intimal media thickness, a commonly marker of preclinical atherosclerosis, and impaired flow-mediated dilatation, used to measure endothelial dysfunction.[79,80]

A recent study compared the odds of acute coronary syndrome (ACS) in both SLE and APS patients aged 18 to 40 years versus patients older than 40 years while monitoring traditional CV risk factors. In both groups, an independent association with classical CV risk factors was found, while the association between ACS and APS was described only in the younger group.[81] Concerning heart disease, according to the Euro-phospholipid project, 1.2% of PAPS patients developed myocardial infarction versus 3.1% of SAPS patients in a 10-year follow-up study.[3]

In summary, there is evidence for a major role of CV risk factors in APS morbidity, especially in SAPS, and data suggest that its management could be improved.[82]

Autoimmune Diseases

As previously stated, SAPS is mostly associated with SLE, but its link with other autoimmune diseases, such as Sjogren's syndrome (SS) or rheumatoid arthritis (RA), has been described as well.

SLE

The link between aPL and SLE is widely known and studied. SLE patients have a higher risk of thrombotic events than the general population, even when taking aPL positivity out of the equation.[83,84] Concerning CV risk, it is also estimated that SLE patients have a 2- to 10-fold increased risk of CVD compared to the general population, especially among younger patients, particularly when associated with aPL.[85]

In a 10-year multicenter prospective observational study of 1,000 SLE patients, 92 thrombotic events were recorded.[86] Furthermore, thrombosis was the cause of death in 18 patients, mainly due to cerebrovascular accidents, all of them associated with aPL presence. In the Euro-Lupus project,[87] aCL and LAC were both predictors for the development of all clinical manifestations of APS.[87] Various studies have corroborated this,[88,89] linking thrombosis (especially venous) in SLE patients with serum aPL positivity, estimating twofold and almost sixfold increased risk for aCL and LAC positivity, respectively, in a meta-analysis.

A large study comparing patients with SLE, SLE-APS, and SLE-aPL[90] demonstrated that SLE-APS patients had a higher rate of hypertension, dyslipidemia, DM, and more severe clinical manifestations (cardiac, renal, respiratory, and neuropsychiatric) than SLE-aPL patients. SLE-APS patients also had more irreversible organ damage, as indicated by the SLICC index. In general, SLE-APS patients usually pose more CV risk factors, which, as seen before, have been associated with a higher rate of thrombotic events.[42]

While in general it is accepted that aPL positivity in SLE patients increases thrombosis risk, about 20% of SLE patients with thrombosis are negative for aPL, which probably reflects alternative prothrombotic mechanisms.[91]

Overall, aPL positivity confers more thrombotic and CV risk to SLE patients, a group already prone to thrombosis and CV risk factors.

Sjogren's Syndrome

Concerning SS, a retrospective analysis of 74 patients[92] pointed out that 38% were aPL positive, mainly aCL (34%), not showing correlation with thrombotic events but with hypergammaglobulinemia. Interestingly, in this study organ-specific autoimmune diseases associated with SS (such as primary biliary cirrhosis) were more common among aPL patients, and aPL levels were catalogued as low.

Systemic Sclerosis

A 2016 meta-analysis addressed systemic sclerosis (SSc) and aPL positivity. The prevalence of participants positive for IgG aβ2GPI and IgG aCL was higher in SSc than in controls (6.1 vs. 0.58% and 2.8 vs. 1.6%, respectively). Concerning LAC, it was more prevalent in SSc patients, although without statistical significance. When focusing on thrombotic events, they were more prevalent in aPL-positive SSc patients than in the aPL-negative group. Moreover, the study pointed out that the prevalence of pulmonary arterial hypertension was higher in aCL-positive than in aCL-negative patients.[93]

Rheumatoid Arthritis

In literature, the estimated prevalence of aPL in RA patients varies from 4 to 49%, with the average prevalence of 28%.[94] Studies have suggested that aPL in RA do not correlate with thrombotic events, even though aPL prevalence is relatively high.[95] Some suggestions conclude that aPL in these patients may have a specificity similar to the ones found during infections rather than those found in other autoimmune diseases.[96]

Other

APL positivity and APS have also been described in other autoimmune diseases, like polymyositis/dermatomyositis, but evidence and clinical significance is scarce due to its low prevalence.[97]

Contraceptives and Hormone Therapy

Combined oral contraceptive (COC) pills that contain estrogens are a well-known risk factor for CV events. aPL carriers are usually excluded from safety studies regarding COC use in SLE patients, like in the Safety of Estrogens in Lupus Erythematosus—National Assessment (SELENA).[98] Nevertheless, there are several studies addressing the issue, such as case reports linking COC and thrombotic events in young women[99] and the RATIO study (Risk of Arterial Thrombosis In relation to Oral contraceptives).[100] The RATIO study described an OR for stroke of 43.1 in LAC carriers, that increased to 201 in LAC carriers + COC use, while in LAC carriers, myocardial infarction had an OR of 5.3, increasing to 21.6 in LAC + COC use. In female users of COC without LAC, the OR for ischemic stroke was 2.9.[100] In conclusion, COC use increases the risk of stroke and myocardial infarction substantially in LAC-positive patients.

Thrombosis in progesterone users is a rare complication[101]; so, progesterone-only contraceptives are usually regarded as the best option for aPL carriers and APS patients. Both oral and intrauterine device (IUD) presentations are widely recommended, with depot medroxyprogesterone acetate being an exception due to higher thrombotic risk.[102] Progesterone can also add a potential benefit in patients on anticoagulants, since it frequently decreases menstrual bleeding, especially IUDs.[103]

Based on previous studies, an article was published on contraceptive and exogenous hormone use in APS/aPL carriers, adapting ACR recommendations on reproductive health.[102] There are no data available in low-titer or non-criteria aPL carriers.

Although no data are available on APS and trans-female patients undergoing hormone therapy, these individuals have a threefold increase in CV death and higher venous thromboembolism (VTE) risk when using long-term oral ethinylestradiol. This CV mortality risk was not observed when changing to other estrogen formulations and lower dose of estradiol.[104] Moreover, other studies favor transdermal estrogens over oral administration concerning VTE risk in transgender individuals. Whether it is a dose or a delivery method effect is not clear.[105] With respect to testosterone, its use in trans-males is not typically considered thrombogenic,[106] though in this group there are some case reports linking exogenous testosterone use with thrombotic events in SLE patients and aPL positivity.[107]

History of Thrombosis

Recurrent thrombosis is common in APS patients. A 2014 systematic review established an OR of 2.8 for VTE recurrence in APS patients with LAC positivity when anticoagulation was discontinued.[108]

During the 2022 15-year follow-up retrospective analysis of 312 Israeli patients with PAPS, 143 (45.8%) had at least a second APS-related event (excluding obstetric causes).[109] During the follow-up, arterial thrombosis affected 24.4% of the patients. This clinical presentation was linked to heart valve disease, hypertension, aβ2GPI IgM positivity, and arterial thrombosis at presentation. Meanwhile, 15.4% were diagnosed with venous thrombosis, where heart valve disease, venous thrombosis at presentation, and higher aGAPSS score were identified as risk factors. Interestingly, 70% of the 143 patients with non–pregnancy-related thrombotic events were under proper guideline-based treatment. Within this cluster of patients, the associations found were mainly heart valve disease, leg ulcers, venous thrombosis at presentation, hypertension, and higher aGAPSS score. In concordance with this, a Greek study described that APS patients with arterial thrombosis were more prone to recurrence (and in the same arterial bed) than venous thrombosis in APS patients.[50] In summary, a history of thrombosis is a well-known risk factor for recurrent thrombosis in APS patients, even when treated with anticoagulants.

Malignancy

Cancer is a widely known risk factor for thrombosis through a complex interaction of tumoral and host cells.[110] Some studies state that patients with solid malignancies are more likely to have a thrombotic event, yet others point out a similar risk between solid and hematologic cancer. For instance, in an Italian study,[111] of 100 patients with lymphoma, 27 tested positive for LAC or aCL; yet, in an Asian study adenocarcinoma was the most common histology finding in patients with thrombosis, cancer, and aPL positivity.[112] Another study has described cases of aPL disappearance after effective cancer treatment, even in patients with thrombotic events.[113]

COVID-19

COVID-19 infection and aPL positivity is a subject still engulfed in controversy. While aPL positivity, especially LAC, and thrombotic events are a feature of COVID-19 infection, the prothrombotic nature of the disease and other several cofounders (prolonged immobilization, for instance) make it difficult to define exactly the role of aPL in this scenario.[114]

There are several considerations regarding COVID-19 and aPL positivity. First, aPL in COVID-19 infection seems to behave like in a regular viral infection (low-titer, transient). A systematic literature review studied the link between COVID-19 infection and autoimmune diseases[115]: in a total

of 3,288 COVID patients, 16.6% were positive for at least one aPL. In another study,[116] the association between LAC in mortality in 190 hospitalized COVID-19 patients was described. While LAC was a common finding (49%), it was not linked either to higher risk of mortality or need for mechanical ventilation. A recent review is consistent with previous literature: though aPL positivity may be indeed a feature of COVID-19 infection, it rarely translates into APS or CAPS.[117] One of the main sources of criticism concerning COVID-19 and aPL studies is the lack of assessment of aPL persistency over time and the erratic report of aPL levels. Double and triple positivity has been reported only in isolated cases.[118,119]

Other

Some other elements have been proposed as potential risk factors for developing thrombosis in different scenarios.

Extracellular Vesicles

Extracellular vesicles of endothelial origin, key to cell-to-cell communication, are being studied as potential risk assessment of recurrent thrombotic events in patients with defined APS, given that endothelial dysfunction is a hallmark of the disease.[120]

Vitamin D Deficiency

A controversial factor is vitamin D, since a significant deficiency has been demonstrated in APS patients compared to healthy individuals. A retrospective cohort study and meta-analysis of four case–control studies confirmed that the combined mean difference in serum vitamin D levels between APS and controls was −3.605 ng/mL and that APS patients had a threefold higher prevalence of vitamin D deficiency.[121] Studies regarding supplementation and antithrombotic effect of vitamin D, although theoretical,[122] are yet to be demonstrated in nonobstetric APS. Overall, vitamin D deficiency should be corrected in all aPL carriers based on the general population guidelines.[123]

Interferon Signature

Type 1 interferons are cytokines whose expression has been linked to the pathogenesis of several autoimmune diseases. An increased expression of type I interferon-regulated genes (interferon signature) has been identified mainly in SLE patients, leading to a better understanding and new therapy targets. Some studies have described a possible association between interferon signature and thrombotic PAPS and SAPS patients but not in aPL carriers. Nevertheless, evidence is scarce and its definitive role is yet to be determined.[124,125]

Conclusion

Antiphospholipid antibodies and thrombosis are the two key characteristics of APS. While there is still no definitive answer as to why some people develop aPL, it seems that a second hit (infection, malignancy) in a genetically susceptible individual is necessary for these antibodies to develop. The presence of aPL can help assessing thrombosis risk depending on its profile, persistence, and titer. Several other features, such as coexistence with other autoimmune diseases and traditional CV risk factors, play a role in thrombogenesis in aPL-positive patients, while other interesting concepts, such as interferon signature, are arising also as potential risk factors. Risk scores such as aGAPSS or aPL-S can help clinicians evaluate thrombosis risk in aPL carriers. The importance of detection techniques and cutoff values standardization should be emphasized in order to facilitate comparison among studies.

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Conflict of Interest

None declared.

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