

Cardiovascular disease and antiphospholipid syndrome: how to predict and how to treat?

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ABSTRACT

Antiphospholipid syndrome (APS) is an autoimmune systemic disease characterized by a hypercoagulable state secondary to the presence of antiphospholipid antibodies and associated with vascular thromboses and/or pregnancy complications. Although venous thrombosis represents approximately 60% of thrombotic manifestations, also cardiovascular events can occur in patients with APS, including coronary and/or noncoronary complications. Moreover, several studies consistently showed a more significant atherosclerosis in patients with APS than controls. Thus, a stratification of thrombotic and cardiovascular risk according to clinical and immunologic features is mandatory in order to prevent APS-related vascular events. The most appropriate antithrombotic treatment of patients with arterial APS still represents an open issue, mainly in primary prevention settings. After a thrombotic event, in the absence of an adequate antithrombotic treatment, a 50% recurrence rate is reported in APS patients over a 5-year follow-up. Vitamin K antagonists still remain the mainstay treatment to prevent a recurrent event in patients with APS. The use of non-vitamin K oral anticoagulants in those with APS is still controversial, and identification of patients who could benefit from this therapy is still an open issue. Low-dose aspirin should be considered in arterial APS in addition to vitamin K antagonists in a high-risk subset, or alone for primary prophylaxis in high-risk antiphospholipid antibodies carriers. Furthermore, statins and immunomodulation therapies have an emerging role in the treatment of APS. Overall, ad hoc designed high-quality studies are needed to definitely determine optimal therapeutic strategies for arterial APS.

Introduction Antiphospholipid syndrome (APS) is an autoimmune systemic disease characterized by a hypercoagulable state secondary to the presence of antiphospholipid antibodies (aPL), a cluster of autoantibodies directed against plasma proteins that bound membranes phospholipids.¹ In particular, the most frequently found types of aPL are lupus anticoagulant (LA), anticardiolipin antibodies (aCL, immunoglobulin G [IgG] and immunoglobulin M [IgM]), and anti- β 2-glycoprotein I antibodies (anti- β 2GPI, IgG and IgM).^{2,3} APS is clinically associated with vascular thromboses (venous, arterial, or small vessel) and/or pregnancy complications (recurrent embryonic or fetal loss, premature birth).²

The prevalence of APS is estimated at about 50/100 000 population,³ and can occur both

in patients with underlying autoimmune disease,⁴ infections, malignancies, drugs⁵ (secondary APS) and in those without any concomitant clinical condition (primary APS).⁶

Diagnostic criteria for APS were firstly published in 1999 after a workshop in Sapporo, Japan,⁷ and updated in 2006 during an international consensus in Sydney, Australia (TABLE 1).⁸

The diagnosis of APS is confirmed by the presence of at least 1 clinical criterion (thrombotic event or pregnancy complication) and at least 1 laboratory criterion (persistently medium/high titer IgG/IgM aCL, medium/high titer IgG/IgM anti- β 2GPI, and/or a positive LA test, confirmed at least 12 weeks apart). Medium-titer aCL is defined as an antibody titer of 40 U/l or greater,

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TABLE 1 Clinical and laboratory criteria for the diagnosis of antiphospholipid syndrome according to International Consensus Statement (Sidney 2006 update)⁸

Type	Description
Clinical criteria	
Vascular thrombosis	≥1 clinical episodes of venous, arterial or small vessel thrombosis, in any tissue or organ
Pregnancy morbidity	<ul style="list-style-type: none"> • ≥1 unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation • ≥1 premature births of a morphologically normal neonate before the 34th week of gestation because of eclampsia, severe preeclampsia, or recognized features of placental insufficiency • ≥3 unexplained consecutive spontaneous abortions before the 10th week of gestation, with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded
Laboratory criteria	
Lupus anticoagulant	Present in plasma, on 2 or more occasions at least 12 weeks apart, detected according to the guidelines of the International Society on Thrombosis and Hemostasis ⁹
Anticardiolipin antibody	IgG and/or IgM isotype in serum or plasma, present in medium or high titer (ie, 40 or more GPL or MPL, or greater than the 99th percentile), on 2 or more occasions, at least 12 weeks apart, measured by a standardized ELISA
Anti-β2-glycoprotein-I antibody	IgG and/or IgM isotype in serum or plasma (in titer greater than the 99th percentile) present on 2 or more occasions, at least 12 weeks apart, measured by a standardized ELISA

Abbreviations: ELISA, enzyme-linked immunosorbent assay; GPL, IgG phospholipid; Ig, immunoglobulin; MPL, IgM phospholipid

and high-titer aCL, as greater than the 99th percentile.^{9,10}

Epidemiological data clearly suggest that approximately 60% of thrombotic APS manifestations is represented by venous thrombosis. However, it is well established that also cardiovascular manifestations can occur in patients with APS, including acute coronary syndrome, stroke, transient ischemic attack (TIA), peripheral artery disease (PAD).¹¹ Interestingly, an increasing number of studies shows an association between APS and atherosclerosis development, suggesting other potential underlying mechanisms besides the prothrombotic status.^{12,13}

Furthermore, the aPL positivity found in asymptomatic “carriers” without clinical manifestations (thrombotic events or pregnancy complications) seems to predispose to thrombotic events as well as to subclinical and overt atherosclerosis development.^{12,13}

In the present review, we will summarize literature data on cardiovascular manifestation, cardiovascular risk stratification and therapeutic approach in patients with APS.

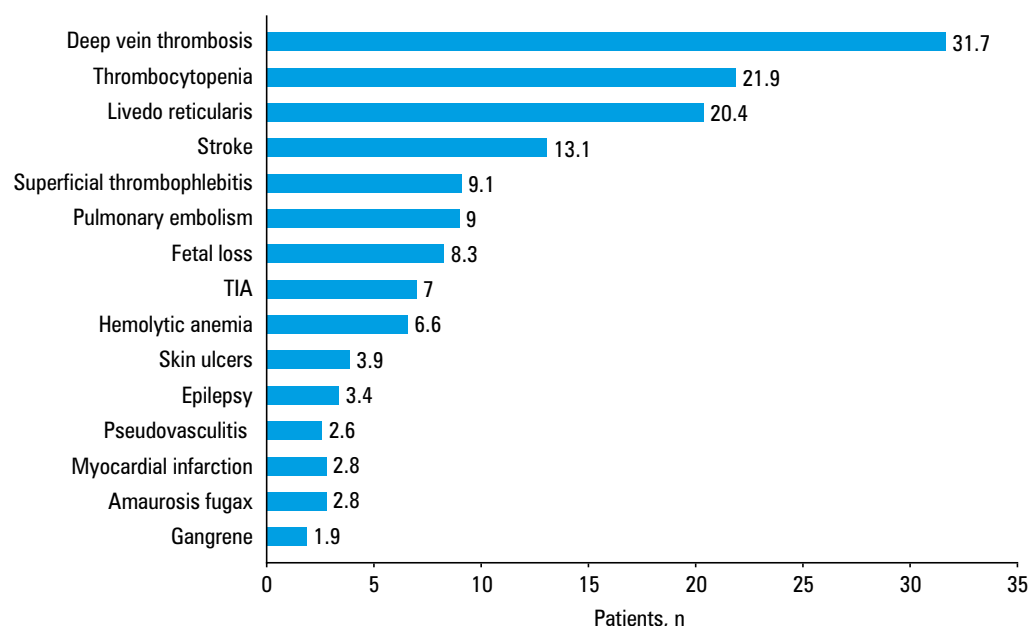
Clinical manifestation in antiphospholipid syndrome: a look into cardiovascular disease and events

Although venous thromboembolism is the most frequent clinical manifestation in patients with APS, a non-negligible percentage of patients report arterial thrombotic events (acute coronary syndrome, stroke, TIA). Arterial thrombosis represents the presenting manifestation in 27% of patients, with the cerebral district being the most commonly involved. Indeed, as showed by data from “Euro-Phospholipid cohort” (including 1000 patients with APS), stroke

has been reported by 13% of patients and TIA by 7% (FIGURE 1).^{11,12}

More precisely, APS is recognized as a major cause of stroke and it has been estimated that up to 20% of all juvenile stroke events (before 45 years of age) are associated with APS.^{14,15} The clinical spectrum of cerebrovascular manifestation in APS varies considerably and ranges from TIA and focal lesions (amaurosis fugax, towed spread cerebral infarction, ataxia, bladder and gait disturbance) to multi-infarct dementia (FIGURE 1).¹¹ Besides cerebrovascular manifestations, also cardiac events represent an important cause of morbidity and mortality in patients with APS. These comprise a wide spectrum of clinical manifestations and can include coronary and/or noncoronary complications. The most common presentation is represented by acute myocardial infarction (AMI), reported in 2.8% of APS patients (FIGURE 1).^{11,12} It is widely recognized that several autoimmune diseases, also including APS, are often associated with accelerated coronary atherosclerosis because of chronic inflammation.¹⁶ Interestingly, besides classical atherothrombotic mechanisms, also coronary embolism should be considered in AMI etiology in APS patients. Indeed, AMI often occurs in juvenile APS in the absence of significant epicardial coronary artery stenosis.¹⁷ Moreover, AMI in APS is often accompanied by a high percentage of postprocedural complications (coronary bypass rethrombosis and stent restenosis). This suggests that the follow-up of these patients should be very tight due to the persistence of a residual risk.¹² In the context of extracoronary manifestations, ventricular dysfunction is also reported in APS patients. Left ventricular (LV) diastolic

FIGURE 1 Clinical manifestations and patterns of disease expression in patients with antiphospholipid syndrome. Data from the Euro-Phospholipid Project, Cervera et al¹¹ Abbreviations: TIA, transient ischemic attack



dysfunction is more common in primary APS, while systolic dysfunction is more frequent in APS associated with systemic lupus erythematosus (SLE).^{12,18} The underlying mechanisms of ventricular dysfunction are still unclear but data from histological studies show the presence of microvascular thrombosis, intra-myocardial arteriolar immune deposits, disseminated thrombosis, with diffused micro-infarcts, and endomyocardial fibrosis. Furthermore, myocardial fibrosis seems to have a key role in LV diastolic dysfunction and could be related to the presence of concomitant cardiovascular risk factors.^{12,18} Overall, cardiac manifestations of APS are extremely variable and further examinations are needed to clarify their pathophysiological mechanisms.

The reasons for the different prevalence of cerebral and noncerebral APS manifestations are not fully understood and difficult to be identified. However, some potential pathophysiological mechanisms should be considered. First, coagulation homeostasis of the central nervous system differs from that of other organs. The brain endothelium expresses less thrombomodulin, known for binding thrombin in a 1:1 stoichiometric ratio and leading to subsequent activation of protein C (a natural anticoagulant). This implies an imbalance in the hemostatic homeostasis leading to a prothrombotic state. Moreover, some experimental data suggested that aPL may have specific antineuronal ties, determining a further potential damage.¹⁴

Overall, these data suggest that although venous thrombosis is the most frequently reported vascular manifestation in APS subjects, the burden of arterial thrombosis is not negligible and accurate primary and secondary cardiovascular prevention strategies are useful to avoid potentially disabling vascular events. Whereas indications for thrombophilia testing are better defined for venous thromboembolism, very limited evidence-based recommendations are available

for arterial thrombotic events.¹⁹ However, considering that aPL positivity would have an impact on therapeutic regimen choice, we should consider to perform aPL screening in: 1) patients with arterial events and rheumatic / autoimmune comorbidity²⁰; 2) young patients (<50 years) with arterial events in absence of documented risk factors^{21,22}; 3) patients with cryptogenic stroke and myocardial infarction with nonobstructive coronary arteries.²³

Atherosclerosis in patients with antiphospholipid syndrome The assessment of atherosclerosis development and progression could be useful to stratify cardiovascular risk in patients with APS and mainly in aPL carriers.²⁴⁻²⁶

Several studies consistently showed a greater intima-media thickness (IMT) with an increased prevalence of carotid plaques in APS patients than in non-APS controls¹³ also accompanied by a 7-fold higher prevalence of symptomatic peripheral artery disease (20.5% vs 4.4%; see FIGURE 2).¹³ More precisely, patients with arterial APS exhibited a more severe atherosclerosis than those with venous thrombosis or recurrent miscarriage.²⁷ In contrast, no difference in carotid atherosclerosis was documented in women with APS and recurrent miscarriage as compared with those without APS.²⁸

Besides the IMT impairment, patients with APS consistently exhibit lower flow-mediated dilation, nitrate-mediated dilation, and higher pulse-wave velocity and augmentation index, suggesting the presence of endothelial dysfunction and arterial stiffness in this clinical setting.^{13,25,29,30}

The next relevant manifestation of atherosclerosis in patients with APS is renal artery stenosis observed in about 26% of APS patients and frequently associated with hypertension, a well-known cardiovascular risk factor closely related with stroke and coronary events.³¹ Indeed, a recent study using ultrasonography

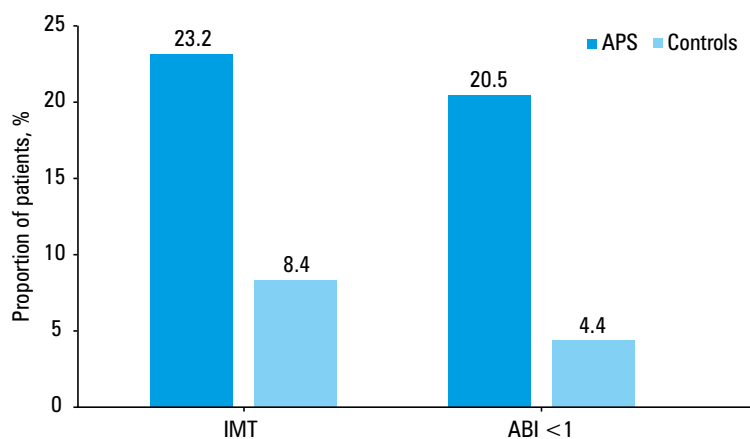


FIGURE 2 Prevalence of subclinical atherosclerosis in patients with antiphospholipid syndrome as compared with controls. Data from Ambrosino et al.¹³

Abbreviations: IMT, intima-media thickness; ABI, ankle-brachial index; others, see

TABLE 2

for the diagnosis of renal stenosis showed elevated intrarenal vascular resistance in 14% of APS patients as compared with none of the aPL carriers.^{32,33}

Extending these findings, a more recent case-control study showed that, besides APS patients, also aPL carriers without a history of thrombotic events have a greater common carotid artery IMT, bulb-IMT and prevalence of carotid plaques as compared with controls negative for aPL.³⁴ This information strongly suggests that the pro-atherogenic effect of aPL is independent from the presence of a concomitant thrombotic event.

In addition, more severe atherosclerosis is observed in patients with high-titer antibodies or with multiple antibodies positivity.³⁴ This is in line with the evidence of a higher thrombotic risk exhibited by patients with triple-aPL positivity and in those with high-titer aPL.^{35,36}

Overall, this evidence from the literature strongly supports the hypothesis of a close association between aPL positivity and systemic atherosclerosis, also suggesting different underlying pathophysiological mechanisms. Several studies suggested an important role of β 2GPI both in blood coagulation and in atherogenesis. Indeed, besides its role in primary and in secondary hemostasis,³⁷ this protein can bind lipoprotein fractions, in particular products of lipid peroxidation, oxidized low-density lipoprotein (LDL) and lipoprotein a and some aPLs can bind complexes of β 2GPI with either oxidated LDL or lipoprotein a.³⁸

This is the key point of a complex interaction between oxidative modification of native LDL and chronic inflammation (proinflammatory and chemotactic cytokines) that leads to modification of arterial wall resulting in early-onset and faster progression of atherosclerosis.¹⁶ Further supporting this evidence, some recent data suggested that patients with anti- β 2GPI antibodies show a greater IMT.²⁷ Furthermore, the presence of anti- β 2-GPI Ab specifically directed against domain I has

lupus anticoagulant activity and is strongly associated with thrombosis, suggesting that carriers of this antibody subgroup represent a high-risk clinical setting.³⁹ Thus, the identification of different antibody subclasses could be useful to better stratify thrombotic risk. Finally, recent data indicate that β 2-GPI drives the inflammatory response of the T helper 1 cell and T helper 17 cell in atherosclerotic plaques of patients with primary APS and SLE-related APS.^{40,41}

A longitudinal screening of atherosclerosis progression, accompanied by assessment of the presence of cardiometabolic risk factors, could represent an appropriate system to stratify cardiovascular risk in aPL carriers.

Thrombotic risk stratification in patients with antiphospholipid syndrome Considering the relevant burden of cardiovascular events, atherosclerosis development and progression in APS patients and aPL carriers, it is necessary to stratify cardiovascular risk in these clinical settings.

To address this issue, a recent study investigated the ability of the adjusted Global Antiphospholipid Syndrome Score (aGAPSS), designed for the estimation of overall thrombotic complications in aPL carriers,⁴² to specifically predict cardiovascular disease.

The study, enrolling 83 consecutive young APS patients (≤ 50 years old) with arterial or venous thromboembolic events, showed significantly higher aGAPSS values in APS patients with AMI when compared with those with a history of other thrombotic events. Applying a further stratification, patients with acute coronary syndrome showed significantly higher aGAPSS values as compared with those with a history of peripheral or cerebrovascular arterial thrombotic events. Overall, these data suggest that aGAPSS might be a useful tool for AMI risk stratification in young patients with APS.⁴³ Confirming and extending these results, a more recent study including 192 aPL carriers showed that an aGAPSS score greater than 10 was associated with an approximately 3-fold higher cardiovascular risk and predicted 63% of cardiovascular events. Moreover, when a modified scoring system was implemented, also including obesity, diabetes, and smoking habit (aGAPSS_{CVD}), the cardiovascular event prediction power reached 71.4%. Although a validation of this tool is still needed, these findings underline the importance of the concomitant assessment of aPL positivity/profile along with cardiovascular risk factors for a more accurate cardiovascular risk stratification in aPL carriers.⁴⁴ Such an approach could guide physicians to implement primary and secondary cardiovascular prevention strategies in aPL carriers including lifestyle changes (smoking cessation, physical activity), management of hypertension, dyslipidemia, and diabetes, particularly in high-risk aPL profile subjects.⁴⁵

Regarding risk stratification of patients with APS, a further factor to consider is the evaluation of antibody isotypes. IgG and IgM isotypes

TABLE 2 Antithrombotic treatment of arterial antiphospholipid syndrome according to literature evidence and guidelines

Drug	Therapy		Prophylaxis	
	Pros	Cons	Pros	Cons
VKA (INR target, 2–3)	Efficacy proved in RCTs	Residual risk of recurrence especially in high-risk patients Few data on arterial APS	No indication	
VKA (INR target, 3–4)	↑ protection from recurrence	↑ INR fluctuations Few data on arterial APS	No indication	
LDA (75–100 mg)	LDA alone is not indicated as therapeutic option; ↓ efficacy than VKA; preliminary data on aspirin 325 mg		Indicated in high-risk patients; valuable in low-risk + cardiovascular risk factors	More evidence needed
LDA + VKA (INR target, 2–3)	↑ efficacy than LDA; valuable in recurrent events despite adequate treatment	More evidence are needed Data available mainly on stroke	No indication; ↑ bleeding risk; efficacy = LDA alone	
DAPT	High efficacy	Only 1 study available	No indication	

Abbreviations: APS, antiphospholipid syndrome; DAPT, dual antiplatelet treatment; ↓, decreased; ↑, increased; INR, international normalized ratio; LDA, low-dose aspirin; RCT, randomized clinical trial; SLE, systemic lupus erythematosus; VKA, vitamin K antagonist

of aPL could be associated with different subsets of events. In particular, IgG are mainly prevalent in subjects with venous thrombosis, whereas IgM are primarily found among patients with arterial events.⁴⁶ However, this finding has been challenged by a recent study showing that 83% of patients with arterial events were positive for IgG aCL and 63% were positive for IgG anti-β2GPI antibodies.⁴⁷ It is therefore clear that further ad hoc designed studies are needed to address this issue. Furthermore, patients positive for multiple antibodies exhibit a higher event rate than patients with single positivity.⁴⁸

According to the recommendations of the 13th International Congress on Antiphospholipid Antibodies, patients should be classified as high risk and low risk. The high-risk group includes patients with multiple aPL positivity, or LAC positivity, or persistent aCL positivity with medium-high titer.²⁰ In addition, the concomitant presence of autoimmune disease (ie, SLE or rheumatoid arthritis) always defines a high-risk profile.²⁰ Besides confirming these criteria, the latest recommendations of the European League Against Rheumatism (EULAR) also included history of thrombotic events and the presence of traditional cardiovascular risk factors in the definition of high-risk profile.⁴⁵

Antithrombotic therapy in patients with antiphospholipid syndrome and arterial events

After a thrombotic event, in the absence of an adequate antithrombotic treatment, the recurrence risk in APS patients is reported to be approximately 50% over a 5-year follow-up. Vitamin K antagonists (VKAs) still remain the mainstay treatment to prevent recurrent event in patients with APS.^{49–51} However, whereas there is an overall agreement on the indication to long-term

moderate-intensity anticoagulation (international normalized ratio [INR] target, 2–3) for APS patients with venous thrombosis (1B recommendation),^{20,52} the therapeutic management of patients with a history of arterial events is more debated, still representing an open issue. Indeed, widely heterogeneous therapeutic options are suggested to manage APS patients with a history of arterial thrombosis: moderate or high-intensity anticoagulation, low-dose aspirin (LDA), other antiplatelet drug strategies, or combined treatments (TABLE 2).⁵³

The latest EULAR recommendations for the management of APS, elaborated by a multidisciplinary task force, suggested treatment with moderate-intensity VKAs (INR target, 2–3) over treatment with LDA in patients with APS experiencing the first arterial thrombosis.⁴⁵ However, the residual thrombotic recurrence risk seems to be not negligible, especially in high-risk settings.^{54,55} Thus, patients with recurrent thrombotic events despite adequate treatment, as well as those with a high-risk profile, could be treated with high-intensity VKA (INR target, 3–4) or with a moderate-intensity VKA+LDA combined therapy.^{20,45}

However, high-intensity anticoagulation did not show significant difference in the rate of thrombotic events (risk ratio, 2.22; 95% CI, 0.79–6.23) as compared with moderate/standard intensity anticoagulation in patients with APS, stroke, and other arterial thrombosis.⁵⁶ Furthermore, high-intensity anticoagulation regimen often leads to wider INR fluctuations, potentially leading to a higher bleeding risk.⁵³ This suggests that this therapeutic option should be used cautiously in highly selected settings.

As to the use of LDA in APS-related stroke, a RCT comparing LDA to LDA plus

moderate-intensity anticoagulation showed a higher rate of stroke recurrence in patients treated with LDA alone as compared with patients receiving the combination therapy. The incidence of hemorrhagic complications was similar in the 2 treatment arms, suggesting that the combination therapy might provide the best risk/benefit profile in the prevention of APS-related ischemic stroke recurrence.⁵⁷

Although providing a good protection from thrombotic recurrence, the combination therapy should be limited to patients with clinically significant cardiovascular risk factors or to those reporting a failure of a single antithrombotic agent in preventing recurrence.⁵⁸

A further attempt was made using high-dose aspirin in APS-related stroke in the Antiphospholipid Antibodies and Stroke Study (APASS). In this randomized clinical trial (RCT), aspirin in a dose of 325 mg was as effective as anticoagulation in the secondary prevention of APS-related stroke.⁵⁹ However, since the patients included in the study had a low thrombotic risk profile, results of this trial should be interpreted with great caution and are only partly generalizable.

Data from a retrospective cohort study on 90 APS patients evaluating the efficacy of different therapeutic regimens for the prevention of recurrent arterial thrombosis showed that patients receiving anticoagulation alone experienced a thrombotic recurrence in 11.6% of cases. Interestingly, recurrence rate was 5.5% in LDA, 3.7% in LDA plus anticoagulation, and 1.8% among subjects receiving dual antiplatelet therapy. These results suggest that also dual antiplatelet therapy may be an effective approach for prevention of recurrent arterial thrombosis in high-risk patients with arterial APS.⁶⁰

Overall, although other studies are needed to evaluate safety and efficacy of different antithrombotic therapies, currently available evidence suggests that standard-intensity anticoagulation alone could be considered a therapeutic option for long-term treatment of arterial thrombosis in low/moderate-risk patients with APS, whereas LDA plus moderate-intensity anticoagulation or dual antiplatelet therapy could be taken into account in high-risk patients or in those reporting failure of standard-intensity treatment.

Primary prevention strategies in carriers of antiphospholipid antibodies Prophylactic therapies in aPL carriers without previous thrombotic events represent a clinical challenge because of the absence of strong evidence-based data. Thus, recommendations are mainly based on low-quality studies and expert opinions.^{45,61}

Efficacy of antiplatelet drugs in primary prevention of aPL carriers is not consistently confirmed by available evidence. In the APLASA study, a randomized, double-blind, placebo-controlled trial evaluating 98 aPL carriers treated in primary prevention with LDA or placebo, no significant difference in the rate of thrombotic

events was found between the 2 groups.⁶² In contrast, a meta-analysis of 11 studies (1208 aPL carriers) suggested that the risk of the first thrombotic event was significantly decreased by LDA. However, these results were no longer significant when only prospective studies or high-quality ones were considered.⁶³

To clarify contrasting results, a patient-level meta-analysis including 5 clinical trials on a total of 497 patients was performed and showed 2 important findings: 1) no significant benefit of LDA as prevention strategy on the first thrombotic event in the overall aPL carriers population; 2) significant protective effect of LDA in aPL carriers with concomitant SLE.⁶⁴

To investigate a potential role for combined therapy, the ALIWAPAS trial, a prospective, multicenter, randomized, open, controlled study compared LDA and LDA with a low-intensity VKA (INR target, 1.5) for primary prevention in aPL carriers and showed no difference in the number of thrombotic events between the 2 treatment arms. In contrast, a higher number of bleeding episodes was reported in the LDA with a low-intensity VKA group, suggesting that this treatment option was significantly less safe, without any efficacy advantage over LDA alone in primary prevention settings.⁶⁵ Similar results were also confirmed by a recent Cochrane review, showing that LDA was associated with a similar thrombosis risk as compared with VKA with or without LDA. However, minor bleeding risk (nasal bleeding, menorrhagia) was higher in subjects receiving VKA + LDA.⁶⁶

Accordingly, the recommendation from the 13th International Congress on Antiphospholipid Antibodies, in line with the latest EULAR recommendations, suggested prophylaxis with LDA (75–100 mg daily) in asymptomatic aPL carriers with a high-risk profile and in aPL subjects with concomitant SLE, regardless the presence of traditional cardiovascular risk factors (grade 2B recommendation).^{20,45}

In addition, EULAR recommendations suggested that prophylaxis with LDA can be considered in aPL carriers without cardiovascular symptoms with low-risk profile, especially in the presence of traditional cardiovascular risk factors (grade 2C recommendation).⁴⁵

Potential therapeutic approaches in antiphospholipid syndrome treatment **Non-vitamin K oral antagonists** The introduction of non-vitamin K oral antagonists (NOACs) in clinical practice changed therapeutic management of several thrombotic diseases. The use of NOACs to treat patients with APS is still controversial. Post hoc analyses from RCTs comparing dabigatran and VKA in patients with thrombophilia or APS showed similar rates of recurrent thrombosis and major bleeding.^{67,68} On the other hand, 3 RCTs failed to demonstrate the noninferiority of rivaroxaban as compared with VKA in prevention of thrombotic events recurrence.⁶⁹⁻⁷¹ A relevant

TABLE 3 Randomized clinical trials comparing efficacy of non–vitamin K oral anticoagulants with vitamin K antagonists

Study	Year	Study design	Events	Conclusions
Ordi-Ros et al ⁶⁹	2019	Rivaroxaban 20 mg vs VKA (INR, 2–3); noninferiority	Rivaroxaban, 11.6%; VKA, 6%	Rivaroxaban did not reach noninferiority criteria to dose-adjusted VKAs for thrombotic APS
Pengo et al ⁷⁰	2018	Rivaroxaban 20 mg vs VKA in high-risk APS (TRAPS)	Rivaroxaban, 7% (IS), 5% (MI); VKA, 0	The trial was stopped due to an excessive number of arterial events in the rivaroxaban arm
Cohen et al ⁷¹	2017	Rivaroxaban 20 mg vs VKA (INR 2–3) to treat patients with APS, with or without SLE (RAPS)	Rivaroxaban, 0; VKA, 0; ETP was higher in the rivaroxaban than in the VKA group	ETP for rivaroxaban did not reach the noninferiority threshold. No increase in thrombotic risk compared with a standard-intensity VKA
Goldhaber et al ⁶⁸	2016	Dabigatran 150 mg twice daily vs VKA (INR, 2–3); post hoc analyses of RE-COVER I, RE-COVER II, and RE-MEDY	Dabigatran, 4.2%; VKA, 5%	Efficacy and safety of dabigatran were not significantly affected by the presence of thrombophilia or APS

Abbreviations: ETP, endogenous thrombin potential; IS, ischemic stroke; MI, myocardial infarction; VTE, venous thromboembolism; others, see TABLES 1 and 2

clinical message can be derived from the TRAPS trial comparing rivaroxaban with VKA in high-risk triple-positive patients with APS.⁷⁰ Although no episode of venous thromboembolism was recorded in rivaroxaban and VKA arms, the trial was prematurely stopped due to an excessive number of arterial events in the rivaroxaban arm. Indeed, ischemic stroke occurred in 7% and myocardial infarction in 5% of subjects receiving rivaroxaban, whereas no arterial thrombotic events were reported in the VKA arm (TABLE 3).⁷⁰

In line with these data, a patient-level meta-analysis including 47 studies with a total of 447 APS patients treated with NOACs (apixaban, rivaroxaban, dabigatran) showed that patients treated with anti-Xa inhibitors (apixaban and rivaroxaban), a history of arterial thrombosis, and triple aPL positivity were associated with an increased risk of recurrent thrombosis.⁷²

However, further data specifically focused on the use of NOACs in arterial APS subjects, considering that different risk profiles could be useful to identify a specific APS patient subset who could potentially benefit from this therapeutic option.

Based on these data, in May 2019, the European Medicines Agency recommended that NOACs should not be used for secondary prevention in patients with APS.⁷³ Consistent recommendations are provided by the EULAR guidelines suggesting that NOACs should not be used in patients with APS and arterial events.⁴⁵ However, NOACs could be considered in patients not able to achieve an adequate INR target despite good adherence to VKAs or in those with contraindications to VKAs (eg, allergy or intolerance to VKAs).⁴⁵ In these cases, a cautious selection of patients, a stratification of thrombotic risk profile, and a strict clinical follow-up should be planned.

Statins Since oxidated LDL is involved in the pathophysiological mechanism of atherosclerosis and hyperlipidemia is one of the factors considered for cardiovascular risk stratification, a potential role for statins in the primary prevention

of arterial events in patient with APS should be considered. Apart from the lipid lowering effect of statins, other potential pleiotropic effects, with particular regard to the anti-inflammatory and antithrombotic ones, are supported by in vitro and ex vivo studies.^{15,53}

Data from in vitro studies showed that statins inhibit the synthesis of tissue factor in endothelial cells (ECs), suppress endothelial adhesiveness induced by anti-β2GPI antibodies, reduce the adhesion of monocytes to the vascular endothelium and prevent aPL-induced vascular cell adhesion molecule up-regulation. Moreover, the use of fluvastatin in patients with APS seems to block IgG-mediated reactivation of factor Xa involved in the calcium flux in endothelial cells and related signaling pathways.⁷⁴

In line with these pathophysiological data, a trial on 42 patients with APS showed that a 30-day therapy with fluvastatin decreased monocyte expression of several thrombogenic and inflammatory mediators.⁷⁵ Moreover, a significant reduction of proinflammatory and procoagulant parameters was reported after a 3-month treatment with fluvastatin in 41 aPL asymptomatic carriers.⁷⁵

Hydroxychloroquine and other immunomodulatory treatments

Hydroxychloroquine is a disease-modifying antirheumatic drug with not only anti-inflammatory but also cardioprotective features.⁷⁶ A retrospective, propensity score-matched cohort study, showed a significant reduction in aPL titer associated with a reduction in the incidence of arterial thrombotic events in patients with APS.⁷⁷ Moreover, a recent prospective study confirmed the ability of hydroxychloroquine in reducing aPL levels and showed a significant effect on thrombosis prevention.⁷⁸

While there are conflicting data on the effect of the anti-CD20 rituximab in terms of aPL reduction and thrombosis prevention,^{79,80} a potential role of the B-lymphocyte stimulator, belimumab, in APS has recently been proposed.⁸¹ Indeed, data on small case series^{82,83} and a post

hoc analysis of a large RCT⁸⁴ suggested that belimumab reduces aPL levels in patients with SLE. However, prospective ad hoc studies are needed to confirm these preliminary data.

More recently, the involvement of the mammalian target of rapamycin pathway in APS-related vascular lesions has been suggested by in vitro and in vivo studies.^{85,86} This could represent a further molecular target to prevent thrombotic events in patients with APS.

Conclusions and take-home messages Cardiovascular disease and atherosclerosis are important clinical manifestation in APS. Although cerebrovascular events are the most commonly reported arterial manifestation in patients with APS, cardiac manifestations are reported in a non-negligible percentage of cases. Patients with APS and aPL carriers have an enhanced atherosclerosis burden and it is crucial to stratify cardiovascular risk as high-risk or low-risk profile, considering both immunological features and traditional cardiovascular risk factors. The lack of consensus on treatment strategies still represents an open issue, mainly in primary prevention settings.

Primary and secondary cardiovascular prevention strategies should include lifestyle changes and specific treatment of cardiovascular risk factors. In addition, primary prophylaxis with LDA is indicated in asymptomatic aPL carriers with a high-risk profile or with concomitant SLE. LDA could be also considered case-by-case in low-risk profile aPL carriers with concomitant traditional cardiovascular risk factors.

The secondary prevention approach in APS patients experiencing the first arterial thrombotic event is based on VKA treatment (INR target, 2–3). In case of recurrent events despite adequate treatment, high-intensity VKA (INR target, 3–4) or combined VKA + LDA therapy should be considered. The use of NOACs is not recommended in patients with arterial APS due to the high risk of recurrent thrombosis.

Some promising results are derived by studies on hydroxychloroquine, rituximab, belimumab, inhibitors of the mammalian target of rapamycin pathway, and statins in recurrent arterial thrombotic events prevention in aPL carriers and APS patients.

Overall, high quality clinical trials are needed to identify and validate therapeutic options effective and safe in reducing arterial thrombotic events in aPL carriers and APS subjects.

ARTICLE INFORMATION

CONFLICT OF INTEREST None declared.

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