EJR European Journal of Rheumatology

DOI: 10.5152/eurjrheum.2020.20058

Invited Review

New insights into the pathogenic mechanisms and treatment of arterial thrombosis in antiphospholipid syndrome

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Abstract

Antiphospholipid syndrome (APS) is a systemic disorder clinically characterized by widespread thrombosis and obstetric complications associated with the persistent presence of antiphospholipid antibodies (aPLs). The persistent presence of aPLs represents a thrombotic risk in APS, which can be stratified according to the aPL profile. Thrombosis occurs in both arteries and veins. Notably, arterial thromboses have a higher recurrence compared with venous thromboses and a tendency for recurrence in the same vascular (arterial) site. Secondary prevention of arterial thrombosis requires more intensive treatment than prevention of venous thrombosis. Data from randomized clinical trials indicated that factor Xa inhibitors should not be recommended for APS. Recurrent thromboses in patients with APS treated with factor Xa inhibitors were mainly arterial, with a high rate of stroke. Dual antiplatelet therapy may have some benefit for preventing the recurrence of arterial thrombosis in patients with APS. This review article describes pathogenic mechanisms, clinical features, risk assessment, and management of arterial thrombosis in patients with APS. Particularly, we discuss how secondary prophylaxis may be a useful approach to reduce the occurrence of arterial thrombosis.

Keywords: Antiphospholipid syndrome, antiphospholipid antibodies, arterial thrombosis, risk stratification

Introduction

Antiphospholipid syndrome (APS) is a systemic disorder clinically characterized by widespread thrombosis and obstetric complications associated with the persistent presence of antiphospholipid antibodies (aPLs) (1). The laboratory criteria used to diagnose APS include the presence of anticardiolipin antibodies (aCL), anti- b2-glycoprotein I antibodies (a b2GPI), and/or lupus anticoagulant (LA) (2). Furthermore, highly specific antibodies against the phosphatidylserine/prothrombin complex (aPS/PT) (3) and a cryptic epitope on the domain I of b2GPI (a b2GPI-DI) (4) are widely recognized as non-criteria antiphopholipid antibodies. The combination of aPS/PT and a b2GPI-DI tests shows a high predictive value for the diagnosis of APS (5). The presence of aPLs is a tool for risk stratification of thrombosis as well as the serological hallmark of APS (6). Thrombosis occurs in both arteries and veins, which is different from other thrombophilia that predominantly affect only veins, such as deficiency of protein S, protein C, antithrombin III, and factor V Leiden mutation. The prevalence of arterial and venous thrombotic events in patients with APS may vary in different ethnic populations due to genetic and environmental factors. For example, a lower incidence of deep vein thrombosis (DVT) and a higher incidence of arterial thrombosis were found in Japanese compared with European cohorts (7). The higher incidence of arterial thrombosis in APS is consistent with the general population in Japan (8) and associated with a high blood pressure compared with individuals in other countries (9, 10).

Primary and secondary thromboprophylaxes based on risk stratification are required in patients with persistent aPLs. The European League Against Rheumatism (EULAR) proposed that general recommendations for aPL-positive individuals should include screening for cardiovascular risk factors, such as smoking, hypertension, dyslipidemia, and diabetes. High-risk patients with APS have a high rate of thrombosis recurrence regardless of antithrombotic therapy (11). Hence, patients with a high-risk aPL profile should maintain strict control of these factors (6). This review provides a comprehensive overview of the pathogenesis, clinical features, risk stratification, and management of APS with a focus on arterial thrombosis.

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Cite this article as: Fujieda Y, Amengual O. New insights into the pathogenic mechanisms and treatment of arterial thrombosis in antiphospholipid syndrome. Eur J Rheumatol 2021; 8(2): 93-9.

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Submitted: April 07, 2020
Accepted: July 04, 2020
Available Online Date: November 19, 2020

Pathogenic mechanisms of thrombosis in APS

The aPLs are pathogenic antibodies that target activated or damaged endothelial cells, monocytes, and platelets (Figure 1). These antibodies bind to cellular membranes with phospholipid-binding plasma proteins, such as b2GPI or prothrombin (1). Subsequently, aPLs induce the phosphorylation of p38 mitogen-activated protein kinase, leading to the production of procoagulant substances and adhesion molecules that drive thrombus formation. There are a number of "cofactors" and specific antigens of aPLs, such as annexin V, protein S, protein C, and high-/low-molecular weight kininogens (1). Several candidate receptors that bind to aPLs have been identified, including apolipoprotein E receptor 2, glycoprotein Ib/IX/V, platelet factor 4, annexin A2, low-density lipoprotein receptor-related protein, megalin, very low-density lipoprotein receptor, P-selectin, and members of the Toll-like receptor (TLR) family, particularly TLR-2 and TLR-4 (12). Beyond the concept of engaging aPLs with cell surfaces, Wu et al. (13) reported that aβ2GPI triggered the release of "extracellular vesicles" from endothelial cells. The extracellular vesicles contained both interleukin-1 and microRNAs and activated endothelial cells through a mechanism that was dependent on the single-stranded RNA and TLR-7 signaling pathway.

The role of complement in APS is well discussed due to the close relationship between the complement and coagulation pathways. Hypocomplementemia was observed in patients with APS reflecting complement activation (14). Tissue injury mediated by aPLs induced complement activation leading to thrombosis or fetal loss (15). Animal models of APS also provide a role for complement (C3, C5, C6, or C5a receptors) in aPL-mediated thrombosis (16, 17). Meroni et al. showed that complement proteins colocalized with b2GPI and immunoglobulin (Ig) G in the arterial wall of a patient with APS, and complement inhibition with anti-C5 monoclonal antibody (eculizumab) successfully prevented recurrent thrombosis (18). In addition, Chaturvedi et al. (19) showed that a b2GPI activated complement and complement activation correlated with thrombotic events in patients with APS.

There is an increasing evidence that a b2GPI induces neutrophil extracellular traps (NETs) and enhances thrombosis. NETs are used as a defense mechanism by the host to trap and kill invading microbes by releasing chromatin fibers and antimicrobial intracytoplasmic proteins (20). NETs in the bloodstream exert strong effects on cardiovascular events by forming a prothrombotic scaffolding surface (21). NETs mediate pathology in both systemic lupus erythematosus (SLE) and APS by various mechanisms, such as exposure to autoantigens, priming of T cells, and activation of autoreactive B cells. Neutrophils from patients with APS demonstrated an enhanced propensity to spontaneously release NETs that was dependent upon both TLR4 activation and formation of reactive oxygen species (21). Furthermore, the prothrombotic potential of aPL-mediated NETs was demonstrated in a thrombin generation assay and an *in vivo* model (22).

Atherosclerosis and T cell responses mediated by aPLs have been considered as causes of arterial thrombosis. The primary trigger for arterial thrombosis is the rupture of an atherosclerotic plaque, which develops in the arterial wall through the accumulation of lipid deposits and lipid-laden macrophages (foam cells) (23). Activated platelets release the contents of granules that lead to platelet recruitment, adhesion, aggregation, and activation. The link between atherosclerosis and antigen-specific immunoreaction in patients with APS was clarified by focusing on the role of aPLs in plaque formation and abnormal arterial wall thickness (24). $CD4^+$ T cells derived from plaques recognized b2GPI in atherothrombotic lesions. In addition, b2GPI induced T cell proliferation and interferon (IFN)γ expression in plaque-derived T cell clones, suggesting that b2GPI-specific T cells exist in plaques of patients with APS. There are several findings regarding the function of b2GPI-specific T cells. b2GPI-specific T cells promote the production of monocyte matrix metalloproteinase-9 and tissue factor and perforin- or Fas/Fas ligand-mediated cytotoxicity, and could potentially assist autoantigen-specific B cells that have taken up and processed apoptotic cells (25). In a plaque, T cell responses against b2GPI, especially domain I, are associated with plaque instability that favors atherothrombosis. In addition, b2GPI binds to oxidized low-density lipoproteins (oxLDL) and likely promotes the proinflammatory and proatherogenic effects of the oxLDL molecule. The resulting oxLDL/β2GPI complex becomes an immunogenic trigger for an autoimmune response (26). Patients with APS have increased serum levels of the oxLDL and β2GPI complex (27) that lead to the activation of monocytes and tissue factor expression (28).

Main Points

- The antiphospholipid syndrome (APS) is a systemic disorder clinically characterized by widespread thrombosis and obstetric complications associated with the persistent presence of antiphospholipid antibodies (aPLs).
- The aPLs are pathogenic antibodies that target activated or damaged endothelial cells, monocytes, and platelets.
- In patients with APS, arterial thrombosis has a higher recurrence rate compared with venous thrombosis and a tendency to recur in the same vascular (arterial) territory.
- "Risk stratification" for the assessment of thrombotic risk is required when evaluating patients with the persistent presence of aPLs.
- Secondary prevention of arterial thrombosis requires a more intensive treatment compared with secondary prevention of venous thrombosis.

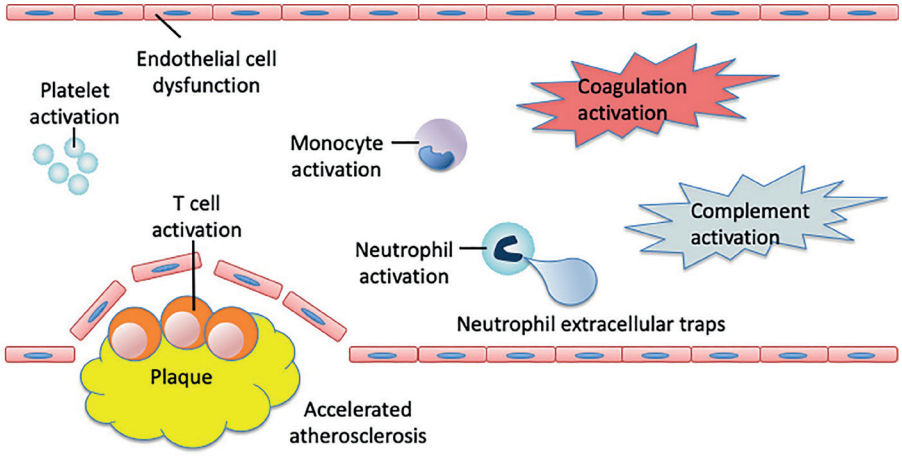

Figure 1. Pathogenic mechanisms of thrombosis in antiphospholipid syndrome. The antiphospholipid antibodies (aPLs) are pathogenic antibodies that target activated or damaged endothelial cells, monocytes, platelets, and neutrophils with coagulation activation and complement activation. Atherosclerosis and T cell responses mediated by aPLs have been considered causes of arterial thrombosis.

A new antigen presentation mechanism has recently been proposed that asserts misfolded proteins are transported to the cell surface in a complex with major histocompatibility complex (MHC) class II molecules and become "neo-self-antigens" (29). Specific human leukocyte antigen (HLA) class II alleles are associated with susceptibility to APS (30). Over 80% of patients with APS have antibodies against the complex of whole b2GPI and APS-associated HLA class II. APS is a representative disease for this concept, suggesting that the b2GPI/MHC class II complex is a major target antigen for autoantibodies in patients with APS (30, 31).

Antigen presentation links the innate and adaptive immune responses. We revealed the relationship between genetic background and lymphocyte subsets in patients with APS (32). An increase in plasmablasts and a decrease in memory B cells were observed in patients with APS compared with healthy subjects, and these changes were associated with a TLR-7 single nucleotide polymorphism (SNP). The SNP was associated with the upregulation of type I IFN-regulated genes. Furthermore, we demonstrated that CD20-negative B cells, which are composed mostly of plasmablasts, were a major source of aPLs.

Clinical features of arterial thrombosis

Arterial thrombosis in APS often involves coronary or cerebral arteries leading to myocardial infarction or stroke. The prevalence of arterial and venous thrombotic events in patients with APS varies in different ethnic populations (Table 1). According to a large dataset of 1,000 patients with APS from 13 European countries, the most common thrombotic manifestation included DVT (38.9%); however, arterial thrombosis was also common (stroke, 19.8%; myocardial infarction, 5.5%) (33). The Piedmont cohort from Italy reported characteristics of patients with APS, which comprised 217 patients with venous (45.6%) and arterial (35%) thrombosis (34). A single-center registration in Japan consisted of 141 patients with APS who presented the first thrombotic event in venous (32.6%) or arterial (66%) vascular territories (7). In the latter study, the most common thrombosis was cerebral infarction (61%) followed by DVT (23.4%). Recently, two population-based studies were reported from the United States (Olmsted County study) (35) and South Korea (HIRA study) (36). A total of 33 cases of APS in the Olmsted County study and 3,088 cases in the HIRA study were identified. In the Olmsted County study, DVT was the most frequent manifestation that occurred in 42% of the cases, while stroke was the most common arterial event (33%). Conversely, in the HIRA study, stroke and transient ischemic attack were identified as the most frequent manifestation in 28% of patients and DVT was present in 20% of patients. Given this information, it is likely that the genetic and/or environmental backgrounds affect the prevalence of thrombotic events in patients with APS. Hypertension was reported as a risk factor for arterial thrombosis in patients with APS, despite the lack of correlation with the aPL profile (7, 37). Blood pressure values are known to be relatively higher in the Japanese population compared with other populations (9), and that may explain why Japanese patients with APS are at higher risk for stroke than European patients with APS. A single-center prospective study from Slovenia focused on patients with cerebrovascular events, including stroke and transient ischemic attack, and revealed that aPLs represent an independent risk factor for cerebrovascular events as well as hyperlipidemia and arterial hypertension (38). Among 89 patients with cerebrovascular events, 22% were diagnosed with APS. There was a significant association between the persistently positive aPL and the cerebrovascular events (odds ratio, 4.62). In contrast, ischemic heart disease occurred less often compared with cerebrovascular events in patients with APS. Myocardial infarction, in relation to APS, occurred in less than 5% of patients (Table 1). However, a critical review of the literature based on the analysis of 120 studies showed that aPLs were found in 11% of patients from the general population who presented with myocardial infarction (39). Myocardial infarction in patients with APS shows specific clinical features: relatively young age at presentation, no gender dominance, often normal coronary arteries without signs of atherosclerosis, and high risk of recurrence (40).

Table 1. Comparison of clinical manifestations between APS cohorts that comprise different ethnic groups.

Cohort (reference no.)	Japanese cohort (7)	Euro-phospholipid project (33)	Piedmont cohort (34)	Olmsted county cohort (35)	HIRA study (36)
Country	Japan	Europe	Italy	USA	Korea
Number of patients with APS	141	1,000	217	33	3,088
Female, N (%)	119 (84.4)	820 (82)	162 (74.7)	18 (55)	1,873 (60.7)
Primary APS, N (%)	70 (49.6)	531 (53.1)	115 (52.9)	-	1,766 (57)
Thrombosis					
Stroke, N (%)	86 (61.0)	131 (13.1)	53 (24.4)	11 (33)	862 (27.9)
TIA, N (%)	6 (4.3)	70 (7.0)	-	4 (12)	
MI, N (%)	6 (4.3)	28 (2.8)	10 (4.6)	0 (0)	-
DVT, N (%)	33 (23.4)	317 (31.7)	81 (31.3)	14 (42)	619 (20.0)
PE, N (%)	14 (9.9)	90 (9.0)	26 (12.0)	13 (39)	540 (17.5)

APS: antiphospholipid syndrome; N: number; TIA: transient ischemic attack; MI: myocardial infarction; DVT: deep vein thrombosis; PE: pulmonary embolism.

Risk assessment and stratification

An individual thrombotic risk assessment and "risk stratification" are essential for good management of APS. Pengo et al. (41) identified the high-risk patients with aPLs on the number of positive aPL tests, including LA, aCL, and aβ2GPI. They showed that triple positivity was a strong independent risk factor for arterial or venous thrombotic events with an odds ratio of 33.3 (41). Two longitudinal follow-up studies confirmed the strong association between triple aPL positivity and an increased risk of thrombosis (42, 43).

The antiphospholipid score (aPL-S) was proposed by our group as a quantitative marker considering the heterogeneity of aPLs (44). This score is calculated according to the relative risk for vascular thrombosis that was approximated by odds ratio for each aPL, including LA, aCL (IgG and IgM), aβ2GPI (IgG and IgM), and aPS/PT (IgG and IgM). The IgG isotype of aCL, aβ2GPI, and aPS/PT are further divided into high titers and medium to low titers. The diagnostic value of the aPL-S for APS was found to be greater than that of the revised Sapporo criteria. An aPL-S of ≥30 was revealed to be an independent risk factor for future thrombotic events. In addition, our group has focused on thrombocytopenia, one of the non-criteria manifestations of APS, to further stratify patients with low to moderate risk profiles. A total of 290 aPL-positive patients were divided into two groups, according to the aPL-S (45). Among 242 patients with low to moder-

ate aPL-S (0<aPL-S<30), those with a platelet count of <150,000 per mm^3 developed arterial or venous thrombosis more frequently than those with a platelet count of ≥150,000 per mm^3. In contrast, 48 patients with a high aPL-S (aPL-S≥30) developed thromboses, regardless of the platelet count. These findings indicated that non-criteria manifestations of APS might be useful for risk assessment in patients with a low to moderate risk range (45).

The Global APS score (GAPSS) was developed, and a total of >16 points was considered an independent risk factor for future thrombotic events (46). There are two major differences between the aPL-S and the GAPSS. First, hyperlipidemia and arterial hypertension are included as scoring components in the GAPSS based on data for vascular thrombosis or pregnancy morbidity in patients with SLE. Second, scoring by aPL profiles was simplified in the GAPSS without taking into account the Ig isotypes (IgG and/or IgM) and the titers of the aPLs. Adjusted GAPSS (aGAPSS) that excludes aPS/PT was developed and further validated by the AntiPhospholipid Syndrome Alliance For Clinical Trials and InternatiOnal Networking (APS ACTION) (47). The analysis consisted of 379 patients with APS who presented with arterial and/or venous thrombosis. A significantly higher aGAPSS was observed in patients with recurrent thrombosis compared with those without recurrence (7.8±3.3 versus 6.0±3.9, p<0.05). Patients with recurrent arterial, but not venous, thrombosis had a higher aGAPSS (8.1±2.9 versus 6.0±3.9; p<0.05).

Management of arterial thrombosis

The pathophysiology of arterial thrombosis differs from that of venous thrombosis, as reflected in the different treatment methods. In general, arterial thrombosis is treated with antiplatelet agents, and venous thrombosis with anticoagulant agents. However, vitamin K antagonists (VKAs) for prophylaxis of thrombotic APS have been the gold standard regardless of arterial or venous thrombosis.

The EULAR recommendations for the treatment of APS in adult patients, published in 2019, mentioned the recommendations for the prevention of primary and secondary thromboses separately (6). The risk stratification is a principal strategy for improving the management of APS-mediated thrombosis. In the EULAR recommendations, a high-risk aPL profile was defined as the presence of LA, double positivity (any combination of LA, aCL, or a b2GPI), triple positivity (all three subtypes), or the presence of persistently high aPL titers.

For the prevention of primary thrombosis in both artery and vein, low-dose aspirin (LDA, 75-100 mg daily) is recommended for patients with a high-risk aPL profile with or without cardiovascular risk factors, such as smoking, hypertension, dyslipidemia, and diabetes (6). Meta-analyses regarding the use of LDA for primary prophylaxis showed a 50% reduction in the risk for the first thrombosis in asymptomatic, high-risk aPL carriers with low cardiovascular risk factors (48). Given the likelihood of benefit and low risk of adverse events, the use of LDA is recommended for asymptomatic individuals with high-risk aPL profiles. In addition, the use of LDA is recommended for patients with SLE with a high-risk aPL profile and for non-pregnant women with a history of obstetric APS according to their thrombosis/bleeding risk (6). SLE and pregnancy should be considered risk factors for thrombosis. There are two cohort studies that indicated an association between the use of LDA and a lower risk of thrombosis in this group (49, 50). A meta-analysis that included five observational studies also supported the evidence for the protective effect of LDA for primary thrombosis in women with a history of obstetric APS without SLE (48).

For secondary prevention of arterial thrombosis, more intensive treatment is required compared with the treatment of venous thrombosis. Arterial thrombosis has a high risk of recurrence and a tendency to recur in the same vascular (arterial) bed. In a Japanese APS cohort, 77.4% of the thrombotic events recurred in the same vascular territory (i.e., 86% of arterial events recurred in the same arterial area, and 55% of venous events occurred in the same venous vessel) (7). According to the EULAR recommendations, for secondary prophylaxis of arterial thrombosis, the use of VKAs is indicated, rather than LDA alone, with a target prothrombin time-international normalized ratio (PT-INR) of 2 to 3 (6). Evidence from observational studies showed a lower likelihood of recurrent thrombosis among patients with APS and prior arterial thrombosis (mainly stroke) treated with VKAs versus LDA alone (51, 52). Furthermore, it was recommended that patients with recurrent arterial thrombosis should be treated with either VKAs with a PT-INR of 3 to 4 or VKAs with a PT-INR of 2 to 3 plus LDA. The recommendations were based on one retrospective study (53) and two prospective randomized trials (54, 55). A previous study by Khamashta et al. (53) showed that high-intensity anticoagulation therapy (PT-INR>3) was necessary to prevent arterial thrombosis in patients with APS although standard anticoagulation treatment (PT-INR of 2-3) was sufficient for preventing venous thrombotic events. The two randomized trials mentioned above included patients with APS with mainly venous thrombotic events. One study consisted of treatment with two intensities of VKAs (54), and the other study included high-intensity VKA treatment versus conventional antithrombotic therapy (55). Therefore, the appropriate dose of VKA for the prevention of arterial thrombosis could not be established. Physicians should consider the risk of recurrent thrombosis and major bleeding for each patient, as well as the patient's preferences.

Factor Xa inhibitors are effective and safe options to venous thromboembolism (VTE) in patients with atrial fibrillation and venous thromboembolism. In non-APS patients with venous thromboembolism, factor Xa inhibitors demonstrated an efficacy equivalent to VKAs for inhibiting thrombin generation. To clarify whether factor Xa inhibitors would be an effective and safe alternative to VKAs in APS, three randomized controlled trials (RCTs) have been conducted. In the Rivaroxaban in APS (RAPS) trial (56), the primary endpoint was the change in thrombin generation between day 0 and day 42, and the secondary endpoints were the occurrence of thromboembolism and/or bleeding events up to day 210. Provided that no thrombotic events were documented during the study period, the authors concluded that there was no increase in thrombotic risk for patients treated with rivaroxaban compared with VKAs. However, the patients treated with rivaroxaban had a significant increase in thrombin generation, which was the thrombotic surrogate marker using endogenous thrombin potential (ETP). In contrast, the Trial on Rivaroxaban in Antiphospholipid Syndrome (TRAPS) showed that thrombotic or bleeding events occurred more frequently in the rivaroxaban group than in the VKA group (57). Thromboembolic events occurred in seven patients (12%) randomized to rivaroxaban, with no events in the warfarin group; all thrombotic events were arterial. The trial was terminated prematurely due to an excess of events among patients in the rivaroxaban group. Two issues of the TRAPS were discussed: (i) no thromboembolic events were observed in the warfarin group and (ii) only high-risk APS patients with triple positive aPLs were included. The frequency of thromboembolic recurrence in the warfarin group as a control was quite low and the prevalence of the triple positive aPLs did not cover all APS. In Spain, Ordi-Ros et al. (58) conducted a 3-year RCT to determine whether rivaroxaban was noninferior to VKA. The Spanish RCT covered the limitation of TRAPS. Of 190 thrombotic patients with APS, 60% had triple positive aPLs, and non-criteria aPLs, such as

aPS/PT, were tested. In addition, the frequency of thrombosis recurrence in the VKA group (6.3%) was close to the real-world data. The RCT concluded that rivaroxaban did not show non-inferiority to VKA for thrombotic APS. Post hoc analysis suggested that there was an increased risk for recurrent thrombosis in patients with previous arterial thrombosis, livedo racemosa, or APS-related cardiac valvular disease after treatment with rivaroxaban. We reconfirmed the inferiority of factor Xa inhibitors compared with warfarin in terms of efficacy and safety for the secondary prevention of thrombosis in Japanese patients with APS (59). Our study provided additional information as follows: (i) longitudinal efficacy and safety up to 5 years, (ii) data for heterogeneous APS patients, and (iii) the use of rivaroxaban and edoxaban. In a multivariate analysis using the Cox proportional hazard model, event-free survival for patients with anti-Xa therapy was significantly shorter compared with controls (hazard ratio: 11.9, 95% confidence interval: 2.93-56.0, p=0.0005).

Recurrent events in the factor Xa inhibitors groups were mainly arterial, with a high rate of stroke in our study (59), TRAPS (57), and Spanish RCT (58). Factor Xa inhibitors that only target factor Xa are different from VKAs, which target factors II, VII, IX, and X. Inhibition of only one factor rather than several might explain the difference in the recurrences. Another explanation may be the requirement for higher anti-Xa activity to prevent arterial events, as described in experimental models (60). The efficacy of a combination of antiplatelet agents and factor Xa inhibitors remains unknown for arterial thrombosis in patients with APS.

Dual antiplatelet therapy (DAPT) is commonly used in daily clinical practice for the secondary prevention of arterial thrombotic events in patients at high risk for recurrence. Accordingly, we hypothesized that DAPT might have some benefit for preventing the recurrence of arterial thrombosis in patients with APS. Using a longitudinal follow-up cohort of patients with APS, we explored the benefits of DAPT in patients with APS with a history of arterial thrombosis (61). This retrospective, longitudinal, and observational study involved 90 Japanese patients with APS who had a median follow-up period of 8 years (range: 5-13 years). The secondary prophylactic effects of warfarin monotherapy (Wf), antiplatelet monotherapy (AP), warfarin and antiplatelet combination therapy (Wf+AP), and DAPT were assessed. Thrombotic recurrence and serious adverse events were found in 40 (44%) and 20 (22%) patients, respectively. The incidence rates of recurrence per 100 patient-years were as follows: Wf, 11.6; AP, 5.5; Wf+AP, 3.7; DAPT 1.8. These data indicated that DAPT was effective for the prevention of thrombosis in patients with APS. Furthermore, we showed that DAPT did not increase bleeding risk. Some important limitations were indicated for the above study (62). First, the target INR of 1.5 to 2.5 was lower compared with the INR that was more broadly recommended. Second, the sample size was small. Third, the results may have been influenced by a more general benefit of DAPT in preventing cerebral ischemic events in a high-risk population, rather than being disease specific. However, our results introduced a new potential therapeutic approach that may have a positive impact on everyday clinical practice.

The efficacy of hydroxychloroquine and statins was not well described in the EULAR recommendations. Hydroxychloroquine was classically used as an antithrombotic agent. It has recently been suggested that hydroxychloroquine plays a role in preventing thrombotic recurrences as well as in lowering the titer of aPLs in patients with APS (63). Hydroxychroroquine treatment reduces the type I IFN signature in monocytes of patients with primary APS (64), which indicates its immunomodulatory effect on APS. Statins are lipid-lowering medications with pleiotropic anti-inflammatory and antithrombotic effects. Statins are considered as a potential prophylactic therapy for thrombosis in both the general population and APS. Our recent single-center retrospective study found a statistically significant protective effect of statins against vascular thrombosis in aPL-positive patients but not in aPL-negative patients (65). Furthermore, statin treatment has also been shown to decrease type I IFN signature in patients with primary APS (64).

Conclusion

There is no specific treatment for APS. Because antithrombotic medications are still the only established therapy, clinicians need to prevent thrombosis according to the risk stratification. In addition, the management of arterial thrombosis is still challenging in APS. Although factor Xa inhibitors should not be recommended for APS, DAPT may have some benefit for preventing the recurrence of arterial thrombosis in patients with APS. Further studies, particularly prospective RCTs, may validate effective and tolerable treatment regimens for high-risk aPL carriers. A better understanding of the pathophysiological mechanisms of APS has significantly expanded our knowledge of this disorder. Immunomodulatory treatment options may be a future strategy as new therapeutic targets. The best use of anticoagulation and immunomodulatory drugs will be established in accordance with pathological conditions in the future.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - Y.F., O.A.; Design - Y.F., O.A.; Supervision - O.A.; Literature Search - Y.F.; Writing Manuscript - Y.F., O.A.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

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