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Antiphospholipid syndrome and the risk of myocardial infarction: current evidence and uncertainties

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Abstract

Antiphospholipid syndrome (APS) encompasses a wide spectrum of disease manifestations that may prevail in the form of venous or arterial thrombosis or lead to pregnancy complications in the presence of persisting antiphospholipid (aPL) antibodies. Unlike in the case of congenital thrombophilias where venous thromboses are more likely to occur as compared to arterial events, aPL antibodies may cause thrombosis in both types of vascular system, often including the coronary or cerebral arteries leading to myocardial infarction (MI) or stroke. In this review we summarize the complex pathomechanisms leading to aPL-associated thrombosis and list challenges during the laboratory detection of these antibodies. Specific features of MI in APS patients are summarized based on a comprehensive literature search of available case reports. Preventive and treatment strategies are discussed based on current recommendations and most recent evidence.

We conclude that the risk of MI in patients with APS is considerable and MI may be the first manifestation of the disease. MI in APS shows specific clinical features including relatively young age at presentation, no gender dominance, often normal coronaries without the sign of atherosclerosis, high risk of recurrent thrombotic events. Treatment of acute MI in APS patients is often challenging and adverse events including stent thrombosis are more frequent as compared to patients without APS. Preventive strategies in APS should be personalized and include strict management of additional cardiovascular risk factors and long-term anticoagulation with vitamin K antagonists. Current evidence does not support the use of direct oral anticoagulants (DOACs) in the management of APS patients with arterial thrombosis due to the high risk of recurrent events.
Keywords

acute myocardial infarction, antiphospholipid syndrome, antiphospholipid antibodies, lupus anticoagulant, thrombosis
Introduction

Antiphospholipid syndrome (APS) is a systemic autoimmune disorder characterized by arterial, venous thrombosis and/or pregnancy morbidity associated with the presence of persistent antiphospholipid antibodies\textsuperscript{1-5}. Antiphospholipid (aPL) antibodies are a group of diverse antibodies that share the common feature of being directed against antiphospholipid-bound proteins. Traditionally, aPL antibodies, namely lupus anticoagulant (LA), anticardiolipin antibodies (aCL) and anti-β\textsubscript{2} glycoprotein I (anti-β\textsubscript{2}GPI) can be identified by clot-based assays (LA) or enzyme-linked immunosorbent assays (ELISAs) for aCL and anti-β\textsubscript{2}GPI. Laboratory criteria of persistently positive test requires a positive test result of any of the aPL antibodies on 2 or more occasions at least 12 weeks apart. A definitive diagnosis of APS is based on the presence of at least one clinical and one laboratory criterion\textsuperscript{6}.

APS is relatively “young” disease described in 1983 as a form of acquired thrombophilia\textsuperscript{7}. APS typically presents in young or middle-aged adults and can be classified as a primary disease or it may be associated with other diseases, most often with systemic lupus erythematosus (SLE), or occasionally with other autoimmune disorders, the use of certain medications, or underlying diseases e.g. malignancies or infections. The presence of aPL antibodies can lead to a variety of clinical scenarios ranging from asymptomatic individuals testing positive for aPL antibodies, to classic APS fulfilling one clinical and one laboratory criterion, and at the end of the spectrum catastrophic APS, a rare manifestation of the disease characterized by widespread microthrombosis and cytokine storm leading to rapid development of multiorgan failure with high mortality\textsuperscript{7}. Interestingly, the prevalence of aPL antibodies in the general population without any clinical manifestations can range between 1-10\%, and only a fraction of these individuals will later develop APS\textsuperscript{1}. 
In the past decade, important advances were made regarding the pathophysiology of aPL antibodies leading to thrombosis, however, the exact mechanism is still incompletely understood. Unlike in the case of congenital thrombophilias where venous thromboses are more likely to occur as compared to arterial events, aPL antibodies may cause thrombosis in both types of vascular system, often including the coronary or cerebral arteries leading to myocardial infarction (MI) or stroke. According to a large dataset of 1,000 APS patients from 13 European countries, the most common thrombotic manifestations in APS patients included deep vein thrombosis (38.9%), but arterial thrombosis was also significant (stroke: 19.8%, MI: 5.5%, peripheral arterial thrombosis: 7%)\(^9\). However, APS was rarely diagnosed linked to MI as the first manifestation of the disease, only in 2.8% of patients. On the other hand, in a critical review based on the analysis of 120 full-length papers, aPL antibodies were found to be positive in 13.5% of stroke and 11% of MI patients of the general population (not being diagnosed with APS previously)\(^1\), highlighting the importance to recognize and identify patients in whom APS manifests in the form of arterial thrombosis.

**Pathomechanism of antiphospholipid antibodies leading to thrombosis and myocardial infarction**

Venous and arterial thrombotic diseases have been traditionally viewed as separate pathophysiological entities, focusing on the role of platelets in arterial and on the role of the clotting system in venous thrombosis. Today, a growing body of evidence suggests that this dichotomy might be an oversimplification of a more complex mechanism of thrombus formation\(^12\). The pathogenesis of thrombosis in APS is an excellent example of this, although many aspects regarding the effects of aPL
antibodies are still to be explored. Despite immense research to unravel the puzzling nature of these antibodies, the exact cause-effect relation to thrombosis remains a complicated question to answer. Nevertheless, important advances in particular steps of the pathogenesis of thrombosis have been identified and the most relevant mechanisms are listed in Table 1. The detection of aPL antibodies in healthy individuals without clinical consequences has lead to the conclusion that these antibodies alone are insufficient for the pathogenesis of thrombosis and APS. It has been proposed that a “first-hit” injury leads to endothelial priming only and the “second-hit” injury triggers thrombus formation. The main antigen targeted by aPL antibodies causing thrombosis is β2-glycoprotein I (β2GPI). There has been no definite biological function assigned to this protein. In particular, IgG antibodies against domain I β2GPI have been reported to have a stronger correlation with thrombosis, since a binding site exposed after the opening of the circular protein once bound to phospholipids. Several other antigenic targets are also known for aPL antibodies, including prothrombin, protein C, protein S, annexin A5, annexin A2, etc. The common link between venous and arterial thrombosis in APS might be the damage to endothelial cells, which seems a necessity for the development of clinical symptoms. Patients with APS have significantly impaired NO production mediated by aPL-induced eNOS inhibition that can lead to increased predisposition to atherosclerosis and thrombosis. Endothelial cells can be activated by aPL antibodies with anti-β2GPI specificity. Activated endothelial cells upregulate the expression of adhesion molecules and the production of tissue factor. It has been shown that in APS, aPL antibody-induced endothelial cell dysfunction is associated with increased carotid intima-media thickness that leads to increased risk of cardiovascular events, and multiple clinical studies have shown accelerated atherosclerosis mediated by
circulating aPL antibodies\textsuperscript{2,15}. An inflammatory insult ("second-hit injury") has been demonstrated to play key role in triggering thrombosis in APS patients\textsuperscript{2}. This can be linked to triggers associated with infections, trauma, surgery or pregnancy. Traditional cardiovascular risk factors, such as smoking might have an important role at this point. The exact pathomechanism leading to thrombosis is a complex combination of events that include platelet activation and aggregation, complement activation and deposition and multiple prothrombotic and antifibrinolytic hemostasis changes. The latter include changes in anticoagulant actions, increased expression of tissue factor by endothelial cells and monocytes, reduced fibrinolysis and abnormal fibrin clot properties. Activation of the complement cascade is often an important final element in the chain of events provoking thrombosis. There is direct evidence that aPL antibodies disrupt the anticoagulant shield provided by annexin A5 on endothelial cells. This effect has been shown to correlate with antibody recognition of the epitope domain I of \( \beta_2 \)GPI, which has been correlated with increased risk of thrombosis\textsuperscript{16,17}. In the presence of anti-\( \beta_2 \)GPI directed against domain I, conformational change and dimerization of \( \beta_2 \)GPI occurs, and anti-\( \beta_2 \)GPI-\( \beta_2 \)GPI complexes displace annexin A5 on the phospholipid surface. This leads to a gap in the anticoagulant shield of annexin A5, resulting in distorted hemostasis balance and thrombosis. In APS, aPL antibodies can interfere with the protein C pathway in many different ways and increase thrombotic risk\textsuperscript{1}. In APS patients regulation of thrombin generation is often derailed leading to enhanced prothrombin conversion, particularly in those associated with a history of thrombosis\textsuperscript{18}. Fibrinolysis is hindered by aPL antibodies via multiple mechanisms\textsuperscript{1}. Tissue-plasminogen activator (t-PA) and plasminogen binding to annexin A2 endothelial surface receptor may be hindered in APS\textsuperscript{19}. Not only plasminogen activation but
plasmin activity may be also directly inhibited by aPL antibodies. Elevated plasminogen activator inhibitor-1 (PAI-1) levels in APS can also contribute to reduced fibrinolysis. It has been shown that in APS the so-called prothrombotic fibrin clot phenotype contributes to thrombotic events, particularly to arterial thrombotic events. Patients with prothrombotic fibrin clot phenotype have unfavourable fibrin clot properties composed of denser fibrin networks with thinner fibers, leading to less permeable clots that are less susceptible to lysis. Moreover, recent proteomic studies demonstrated that the protein composition of fibrin clots generated in the plasma of thrombotic APS significantly differs from patients without APS who suffered thrombosis. These results confirm a role of upregulated complement components and platelet proteins as well as downregulated antithrombotic proteins in the pathomechanism of thrombus formation in APS.

**Challenges in the evaluation of laboratory results in antiphospholipid syndrome**

*Diagnostic tests*

The diagnosis of APS implies that the patient displays at least one clinical and one laboratory criteria. Clinical criteria are as follows: (i) venous thrombosis (deep vein thrombosis, pulmonary embolism) (ii) arterial thrombosis (coronary artery disease, cerebral ischemia or stroke, peripheral arterial disease) (iii) obstetric complications (spontaneous abortion, fetal death, premature birth). Laboratory criteria are based on two antigen assays (anti-β2GPI, aCL) and a third functional test (LA). This latter is not a single test but a set of assays that are sufficient to declare this entity based on recent guidelines. Although it is not always followed, it must be emphasized that the diagnosis of APS requires that the diagnostic tests described below are measured at least on two occasions 12 weeks apart. The importance of the
repeated testing lies in the fact that aPL antibodies that occur transiently after infections have no clinical relevance and they are not associated with thrombotic complications 1,5.

Criteria antigen assays

In all guidelines for APS diagnosis, the anti-β2GPI antibody measurement is an indispensable test and is either measured by ELISA or a chemiluminescent immunoassay6,28,29. Depending on the test type, anti-β2GPI is fixed onto a solid surface or to magnetic beads. Evidence based data suggest that IgG and IgM, but not IgA isotypes should be measured simultaneously in all cases. The other antigen assay that is compulsory in APS is the aCL antibody test. The term cardiolipin reflects an archaic nomenclature as this lipid was first described in bovine heart. Here, again there is no evidence for the usefulness of the IgA isotype, thus IgG and IgM isotypes need to be determined similarly to the anti-β2GPI 6. Despite current guidelines, standardization of the assays used has not been achieved in many aspects and no reference material is available as yet. Results of aCL and anti-β2GPI antibody tests are not expressed in international units (usually GPL/MPL for aCL and arbitrary units, e.g. U/L for anti-β2GPI antibody assays). The threshold for medium titer antibodies is generally defined as >40 IgG phospholipid (GPL) units and >40 IgM phospholipid (MPL) units for aCL or greater than the 99th percentile of the reference population (for both assays) 6,29,30. Given the high variability among commercially available assays, it is advised that cut-off values should be checked in the local patient population28. Moderate to high titers of aCL or anti-β2GPI correlate better with clinical events as compared to lower titers, and the strongest association with thrombosis was observed with antibodies of the IgG isotype 5,31. High-risk and low-
risk aPL antibody profile for thrombosis and obstetric complications according to the EULAR (European League Against Rheumatism) recommendations are summarized in Table 2.  

**Non criteria antigen assays**

Although several other autoantibodies have been identified in APS patients these have not been included in the guidelines. Nevertheless, autoantibodies to phosphatidylserine/prothrombin (aPS/PT) have been described in 50-90% of aPL antibody positive patients. These autoantibodies may well have a pathogenic role as was shown in LA positive patients and more recently it has also been identified that patients with aPS/PT antibodies have denser and poorly lysable fibrin clot formation and these antibodies may mediate prothrombotic clot properties.

**Lupus anticoagulant**

There is one single term used for the functional testing of aPL antibodies, that is a well known misnomer: lupus anticoagulant (LA). The capacity of LA to prolong clotting times resulted in its designation as an anticoagulant entity. In recent guidelines a panel of tests is recommended to reliably identify LA. These prolongations are sometimes translated to numerical values as the index of circulating anticoagulant or the Rosner index, however in all recent external quality control surveys only a qualitative evaluation of LA (positive/negative) is required without the need for quantitation. It must be noted that external quality control surveys often show significant inter-laboratory variation of LA testing. If the guidelines are appropriately followed, laboratories can exclude the presence of LA based on double negativity of an LA sensitive APTT assay and the dilute Russel viper venom test.
(dRVVT). If these tests are not negative there are two approaches to confirm the presence of LA. Either a mixing test is done first followed by a confirmatory test using excess phospholipids to shorten to prolonged clotting times, or the confirmatory tests are done first and the mixing study will only be secondary. Further to the analytical aspects one important preanalytical consideration is important i.e. all samples stored for LA testing need to be centrifuged twice to eliminate the presence of phospholipid containing exosomes that may interfere with the antibodies and may lead to false results. Although a lot of progress has been made in the past decades in standardizing LA testing a recent comprehensive study highlights the need for widespread standardization.

For the overall evaluation of APS patients the antigen and the functional assays are equally important and it has been suggested that the risk of thrombosis may be higher when more than one of the above assays were positive (double or triple aPL antibody positivity). Most importantly, the correct assessment of LA is crucial from laboratories as the presence of LA has been shown to be strongly associated with a high-risk profile for thrombosis, with or without a moderate-high titer of aCL or anti-β2GPI (Table 2).

Despite paying attention to pre-analytical variables and recognizing current guidelines, a lack of conformity remains in LA testing that calls for the development of widely available reference materials, new assays that better identify clinically important aPL antibodies and clear definition of interpretation to avoid pitfalls when diagnosing APS.

Interferences in laboratory testing of antiphospholipid syndrome
In the presence of aPL antibodies, laboratory evaluation of the APS patients may be challenging as these antibodies may interfere with several hemostasis tests as well as with some immunoassays. The interferences can be of two types. Either the LA antibody interferes with other laboratory assays or LA testing is influenced by the presence of laboratory interferences or drugs.

The second option is a quite frequent laboratory dilemma. Vitamin K antagonists (VKA) interfere with LA tests and thus the guidelines recommend that LA tests should not be carried out if the INR is over 1.5 in patients on VKAs. Other interfering factors with LA measurements are the presence of heparin and an anti-factor antibody that in most cases is anti-factor VIII. Recently direct oral anticoagulants (DOAC) have become even more widely used than VKA resulting in an overwhelming number of hemostasis tests affected by the DOAC treatment. LA testing is no exception to this and clotting times in LA tests are falsely prolonged both in the presence of the direct thrombin or factor Xa inhibitors\textsuperscript{40}. For this reason, it has been suggested that LA testing should be performed 2-3 days after the last dose of DOAC\textsuperscript{41}.

High titers of LA causing a falsely elevated INR in warfarin-treated patients has generated some concern in the past\textsuperscript{42}. However, there appears to be little if any interference by LA on the prothrombin time and INR if insensitive thromboplastin is used with an instrument-specific international sensitivity index (ISI)\textsuperscript{43,44}.

**Prognostic tests in antiphospholipid syndrome**

In APS some diagnostic tests may serve as a prognostic indicator. The decrease in platelet count has been described\textsuperscript{45} as well as the platelet being the primary target of aPL antibodies\textsuperscript{46}. Nevertheless, thrombocytopenia is a relatively infrequent finding even in triple positive APS. However, it is observed in all patients
with catastrophic APS and precedes the full clinical picture, thus should be considered a prognostic marker and rather a warning signal. Further characterization of the aPL antibodies may also be useful as a prognostic marker. It has been shown that antibodies to the domain I of the β2GPI associate strongly with thrombotic events. As it has been mentioned, the presence of LA also strongly associates with future thrombotic risk. The need to focus on increasing assay specificity further to domain I of anti-β2GPI and to develop more specific tests for subtypes of LA that are most likely linked to thrombotic complications are raised but their exact clinical value remains speculative as yet.

Although there may be a handful of tests potentially used for predicting thrombosis in APS, only one or two reflects the patomechanism of APS. Recently, by using the global hemostasis test the thrombin generation assay, it has been shown that in APS the hemostatic balance is shifted towards a more prothrombotic phenotype that is not related to altered thrombin inactivation but is due to the accelerated prothrombin conversion to thrombin and this phenomenon was associated with a history of thrombosis in patients. Still, the identification of patients who are at higher risk for developing thrombosis is an unmet clinical need. While specific laboratory tests are awaited, thrombotic risk stratification/prediction models are under development and validation in the clinical setting.

**Specific features of myocardial infarction in antiphospholipid syndrome**

**Clinical features of acute myocardial infarction in antiphospholipid syndrome patients based on case reports**

In order to identify the main clinical features of MI in APS patients, a literature search was performed from January 2000 to September 2019. The PubMed
database was used with the terms “antiphospholipid syndrome” or “antiphospholipid” or “lupus anticoagulant” and “myocardial infarction” or “cardiovascular disease”.

Few additional articles from reference sections of selected manuscripts were also obtained. Besides one systematic review, only case reports or case series were found based on the search criteria. In total 66 cases of 58 articles were identified where APS was presenting in the form of acute MI. All cases are listed in Supplementary Table S1. In this Table the following list of information was extracted: demographic data, culprit vessel, history of atherothrombotic events (ATE) or venous thromboembolism (VTE), potential association with other autoimmune disorder, presence of other atherothrombotic risk factor, and the presence of aPL antibody type. Main conclusions drawn from data extraction of these cases are summarized in Figure 1.

Age at the presentation of MI was considerably young (median: 36 years, IQR: 29-48 years). No significant sex predominance was observed (male: 34/66, 51.5%). In the majority of cases MI was the first presentation of APS, only 10 cases with previous ATE and 19 cases with VTE in the history were described. APS was primary in 48/66 cases (73%), while it was associated with other autoimmune disorders in 16/66 cases, most frequently with SLE (8 cases, 12%). In 7 cases MI was part of the presentation of catastrophic APS. Among conventional risk factors, smoking (17/55, 30%) and hypertension (7/55, 13%) were most frequently mentioned, but it must be noted that often MI occurred in the absence of known ATE risk factors (18/55, 14.5%), e.g. the presence of aPL antibody was the only risk factor for thrombosis. Among aPL profiles, LA was the most frequent (44/50, 88%), followed by aCL IgG (23/51, 45%) or IgM (10/46, 22%) and anti-β2GPI IgG (10/27, 37%) or IgM (4/24, 17%). Double positivity was described in 28 cases while triple positivity was rarely described (6 cases). It must be noted, however, that in a number of case reports measurements of
aPL antibodies were incomplete or inadequately described, and repeated testing after 12 weeks was often not mentioned. Nevertheless, the above results suggest that similarly to what has been known from the literature regarding the association of aPL profiles and thrombosis risk in general, the presence of LA significantly contributes to the risk of MI and among aCL and anti-β2GPI antibodies, the presence of IgG isotype seem to be associated with higher risk of MI. In a large multicenter population-based case-control study (RATIO), LA was the aPL laboratory parameter that correlated best with coronary occlusion⁵¹.

Of note, in many cases, coronary thrombosis without significant coronary atherosclerosis was found. The term myocardial infarction with non-obstructive coronary arteries (MINOCA) has been coined for this entity⁵²-⁵⁴. This finding is in line with a most recent publication where it was shown that MINOCA patients exhibit high prevalence of thrombophilia, particularly APS (APS was found in 15.5% of 84 consecutive MINOCA patients)⁵⁵. Coronary thrombosis is an obvious cause of this entity but coronary spasm and spontaneous coronary dissection may be involved as well. Intraventricular thrombus formation has also been described as a cardiac manifestation associated with APS⁵⁶. Recurrent coronary thrombosis and stent thrombosis were frequent complications in MI patients after primary percutaneous coronary intervention (PCI). These findings are consistent with the results of a recent systematic review by Nazir et al in which 40 MI cases of 27 articles were identified and studied. As the authors concluded, MI associated with APS was typically present in relatively young patients without sex predominance and coronary arteries were often described as normal⁵⁷. Similar conclusions were drawn in the case series by Davies et al, where they highlight that coronary artery atherosclerosis is less
commonly underlying aetiology in the relatively younger age group thus more comprehensive investigation of the cause of thrombosis is required\textsuperscript{58}. 

In 12\% of the studied case reports, MI occurred in patients with APS associated with SLE. In contrast to the relatively frequent scenario of thrombosis in normal coronaries in case of primary APS patients, MI in patients with SLE is usually associated with a different etiology primarily due to accelerated atherosclerosis. Thus, in SLE associated APS, the appearance of MI can be substantially different from primary APS patients. Although premature atherosclerosis might be a feature of primary APS, its prevalence in SLE associated APS is estimated to be at least double\textsuperscript{59}. Both APS and SLE are associated with a number of other thrombotic or non-thrombotic cardiac manifestations, which may make the clinical picture even more diverse. Of note, coexisting inherited or acquired risk factors for atherothrombosis are not exclusion criteria for APS classification. Particularly in patients with SLE, hypertension, hyperlipidemia or other common atherothrombosis risk factors e.g. insulin resistance might be present due to the combination of disease pathomechanism and its treatment with corticosteroids. Therefore, it must not be forgotten that aPL antibodies might be induced upon tissue necrosis during MI and their transient presence may not be responsible for the thrombotic event\textsuperscript{58}. Careful interpretation and repeated testing is crucial for recognising APS in patients suffering acute MI. The right diagnosis of APS is particularly critical due to the fact that recommended treatment is different once the diagnosis is made.

In 7 cases listed in Supplementary Table 1, MI was a feature of catastrophic APS. Due to the variable manifestation of microthromboses involving multiple organs the diagnosis might be challenging, particularly if there is no history of aPL antibody positivity. Due to the severity and high mortality of the disease early treatment is
critical. In the listed case reports where MI was part of the manifestation of catastrophic APS, mortality was 28% (2/7).

Prevention and treatment of myocardial infarction and cardiovascular ischemic events in antiphospholipid syndrome

Primary prevention of MI in aPL positive individuals or in APS patients are essentially the same as in the general population. The first step is objective risk stratification based on age, concomitant autoimmune disorders (particularly SLE) and other traditional risk factors. It is of outmost importance that traditional risk factors, when present must be addressed and strictly managed. It has been demonstrated that traditional cardiovascular risk factors, particularly smoking and diabetes are major determinants of both arterial and venous thrombotic risk in patients with LA, thus their management may be crucial for future events. Risk stratification might be aided by prediction models providing a quantitative score, such as the adjusted Global Antiphospholipid Syndrome Score (aGAPSS), that facilitates risk prediction in APS patients younger than 50 years. According to current EULAR recommendations, in asymptomatic aPL carriers with high-risk aPL profile (presence of LA, or double or triple positivity, see Table 2), prophylactic treatment with low-dose aspirin is recommended. In patients with SLE and low-risk profile, without a history of thrombosis or pregnancy complications, prophylactic treatment with low-dose aspirin may be considered. In SLE, experimental and clinical evidence suggests that hydroxychloroquine reduces the risk of thrombosis. Additional studies are warranted in primary APS patients to see the risk reducing effect of this treatment.

Optimal treatment of acute MI might be challenging in APS patients. APS patients undergoing PCI are prone to thrombotic recurrences. Results of a recent
metaanalysis showed that in patients with APS and/or SLE, significantly higher rates of adverse events (including repeated revascularization and mortality) were found after PCI as compared to those without APS or SLE. Post PCI, dual antiplatelet therapy is recommended in addition to oral anticoagulation, but individual bleeding risk should be kept in focus. Maintaining the right balance between bleeding and re-thrombosis is a challenging task in post-PCI APS patients.

The cornerstone of long-term treatment in APS patients after MI is long-term anticoagulation with VKAs (target INR: 2-3). It must be noted, however, that in APS patients with arterial thrombosis the recurrence risk is higher as compared to those with venous thrombosis. In case of APS patients experiencing recurrent arterial events despite adequate anticoagulation or in case of those with clinically significant risk factors for cardiovascular disease most often aspirin is added to anticoagulant therapy, but long-term dual antiplatelet therapy is uncommon due to the risk of major hemorrhage. Higher intensity VKA therapy (target INR: 3-4) is a common practice at some centers and it is included in recommendations, but more evidence is needed regarding the efficacy and safety of intensified therapy. In any case, artificial prolongation of prothrombin time and falsely elevated INR by aPL antibodies must be excluded when VKA therapy fails despite therapeutic INR. Based on the recommendations of expert panel, besides increasing target INR to 3-4, or the addition of low-dose aspirin, switching to LMWH may be considered in individual cases of recurrent arterial thrombosis despite VKA treatment.

Based on current evidence, as for today, the use of DOACs cannot be promoted in APS patients with arterial events due to the high risk of recurrent thrombosis. According to the results of the TRAPS study, where high-risk (triple positive) patients were included, the use of rivaroxaban was associated with an
increased rate of events as compared to warfarin, therefore it showed no benefit and excess risk. The trial was prematurely terminated after the enrollment of 120 patients due to increased events in APS patients on the rivaroxaban arm. Both VTE and arterial events were more frequent, including MI (3/59 patients [5%] vs. none in the VKA group). In addition, an ongoing trial of apixaban in APS (Apixaban for the Secondary Prevention of Thromboembolism among patients with the Antiphospholipid Syndrome [ASTRO-APS]) was modified after the initial evaluation of data to exclude patients with arterial thrombosis due to the high risk of recurrent events. In a recent metaanalysis where results from 47 studies corresponding to 447 APS patients treated with DOACs (rivaroxaban=290, dabigatran n=144, apixaban n=13) were analyzed, 73/447 (16%) patients experienced recurrent thrombosis while on DOACs. Rates of recurrent thrombosis were similar in the anti-Xa or dabigatran group. Triple positivity and a higher number of clinical number for APS classification were associated with higher rates of recurrence. Similar results were obtained in a most recent cohort study of 176 APS patients. APS patients treated with DOACs had increased risk of recurrent thromboembolic events compared to those using VKAs (HR: 3.98, 95%CI: 1.54-10.28). Moreover, patients on DOACs had increased risk of major bleeding or clinically relevant non-major bleeding (HR: 3.63, 95%CI: 1.53-8.63). Based on the above data, as of today, the use of DOACs is not proposed in APS patients with arterial events due to high risk of recurrent thrombotic events. Further clinical trials are warranted to better define the potential role of DOACs in subgroups of APS patients.
Conclusions

APS encompasses a wide spectrum of disease manifestations that may prevail in the form of venous or arterial thrombosis or lead to pregnancy complications in the presence of persisting aPL antibodies. aPL antibodies are highly heterogeneous that makes the understanding of their pathomechanism and their laboratory diagnosis challenging. Nevertheless, important advances in particular steps of the pathogenesis of thrombosis have been identified in the past years and risk stratification based on aPL profile has improved. aPL antibodies may cause thrombosis in both type of vascular system, often including the coronary or cerebral arteries leading to MI or stroke. The risk of MI in APS patients is relatively less as compared to venous events and stroke, nevertheless it is considerable and it may be the first manifestation of the disease. MI in APS shows specific clinical features: relatively young age at presentation, no gender dominance, often normal coronaries without the sign of atherosclerosis, high risk of recurrent thrombotic events. Treatment of acute MI in APS patients is often challenging and adverse events including stent thrombosis are more frequent as compared to patients without APS. Preventive strategies in APS should be personalized and include strict management of additional cardiovascular risk factors and long-term anticoagulation with VKAs. As of today, the use of DOACs is not recommended for the long-term management of APS patients with arterial thrombotic events.

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## Table 1: Probable mechanisms of thrombosis in antiphospholipid syndrome

<table>
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<th>Mechanism</th>
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<tr>
<td><strong>Endothelial cell dysfunction</strong></td>
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<td>aPL-mediated eNOS inhibition</td>
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<tr>
<td>Upregulation of adhesion molecule expression (ICAM-1, VCAM-1, E-selectin, etc.)</td>
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<tr>
<td>Increased leukocyte-endothelial adhesion</td>
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<tr>
<td>Increased production of endothelin-1 and tissue factor</td>
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<tr>
<td>Reduced prostacyclin production</td>
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<tr>
<td><strong>Platelet activation</strong></td>
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<tr>
<td>Increased thromboxane A2 production</td>
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<tr>
<td>Increased platelet activation leading to increased glycoprotein IIbIIIa expression</td>
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<tr>
<td>Interference of VWF-mediated platelet adhesion</td>
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<tr>
<td>Increased platelet-derived microparticle formation</td>
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<tr>
<td><strong>Complement system activation</strong></td>
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<tr>
<td>Complement activation (C3, C5) and deposition</td>
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<tr>
<td><strong>Inflammatory cell mediated mechanisms</strong></td>
</tr>
<tr>
<td>Increased monocyte (and monocyte derived microparticle) tissue factor expression</td>
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<td>Increased IL-8 release by neutrophils</td>
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<td>Release of neutrophil extracellular traps (NETosis)</td>
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<td><strong>Disturbances of anticoagulant mechanisms</strong></td>
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<tr>
<td>aPL-mediated disruption of annexin A5 anticoagulant shield</td>
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<tr>
<td>Inhibition of the protein C pathway</td>
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<tr>
<td>Interference with the action of antithrombin</td>
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<tr>
<td>Inhibition of TFPI</td>
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<tr>
<td>Reduced fibrinolysis/abnormal clot structure</td>
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</tbody>
</table>
Inhibition of plasminogen binding, activation and plasmin activity

Elevated PAI-1 levels

Prothrombotic clot phenotype: dense fibrin fiber networks, low permeability and lysability

Abbreviations: aPL, antiphospholipid antibody; C3, complement component 3; C5, complement component 5; eNOS, endothelial nitric oxide synthase; ICAM-1, intercellular adhesion molecule 1; IL-8, interleukin-8; NET, neutrophil extracellular traps; PAI-1, plasminogen activator inhibitor-1; TFPI, tissue factor pathway inhibitor; VCAM-1, vascular cell adhesion molecule 1; VWF, von Willebrand factor

**TABLE 2** Definitions of high risk and low risk antiphospholipid antibody profile for thrombosis and obstetric complications according to EULAR recommendations

<table>
<thead>
<tr>
<th></th>
<th>LA</th>
<th>aCL</th>
<th>anti-β2GPI</th>
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<tbody>
<tr>
<td><strong>High risk profile</strong></td>
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<tr>
<td><strong>Low risk profile</strong></td>
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<td>+*</td>
<td>+*</td>
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</tbody>
</table>

*Low or medium titers. The presence of persistently high titers are considered high risk profile. aCL, anticardiolipin antibody; anti-β2GPI, anti-β2 glycoprotein I
Figure 1. Common features of myocardial infarction associated with antiphospholipid syndrome.

Common demographic, laboratory and clinical features of myocardial infarction in antiphospholipid syndrome are summarized based on available case reports (Suppl Table 1).

Abbreviations: aCL, anticardiolipin antibody; anti-β2GPI, anti-β2 glycoprotein I; APS, antiphospholipid syndrome; ATE, atherothrombotic event; LA, lupus anticoagulant; MI, myocardial infarction

Supplementary materials:

TABLE S1 Summary of case reports on the association of antiphospholipid syndrome with myocardial infarction