REVIEW ARTICLE

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 antibodies (aPL). Unlike in the case of congenital thrombophilias, in which venous thromboses are more likely to occur as compared with arterial events, aPL may cause thrombosis in both types of vascular systems. Arterial thrombosis in APS is fairly common and often involve 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 patients with APS are summarized based on a comprehensive literature search of available case reports. Preventive and treatment strategies are discussed based on the 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 sex dominance, often normal coronaries without the sign of atherosclerosis, high risk of recurrent thrombotic events. Treatment of acute MI in patients with APS is often challenging and adverse events, including stent thrombosis, are more frequent as compared with 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 in the management of patients with APS with arterial thrombosis due to the high risk of recurrent events.

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Introduction Antiphospholipid syndrome (APS) is a systemic autoimmune disorder characterized by arterial and venous thrombosis and/or pregnancy morbidity associated with the presence of persistent antiphospholipid antibodies (aPL).[1-5] Antiphospholipid antibodies are a group of diverse antibodies that share the common feature of being directed against antiphospholipid-bound proteins. Traditionally, aPL, namely, lupus anticoagulant (LA), anticardiolipin antibodies (aCL), and anti–β_2-glycoprotein I (anti-β_2GPI) can be identified by clot-based assays (LA) or enzyme-linked immunosorbent assays (aCL and anti-β_2GPI). Laboratory criteria for a persistently positive test are a positive test result of any of the aPL on 2 or more occasions at least 12 weeks apart. A definitive diagnosis of APS is based on the presence of at least 1 clinical and 1 laboratory criteria.[6]

Antiphospholipid syndrome has been described relatively recently, in 1983, as a type of acquired thrombophilia.[7] It typically presents

in young or middle-aged adults and can be classified as a primary disease or as 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, for example, malignancies or infections. The presence of aPL can lead to a variety of clinical scenarios, from asymptomatic individuals positive for aPL, through classic APS fulfilling 1 clinical and 1 laboratory criterion, to catastrophic APS, a rare manifestation of the disease characterized by widespread microthrombosis and cytokine storm leading to a rapid development of multiorgan failure with high mortality rates.[7] Interestingly, the prevalence of aPL in the general population without any clinical manifestations can range between 1% to 10%, and only a fraction of these individuals will develop APS.[1]

In the past decade, important advances were made regarding the pathophysiology of aPL leading to thrombosis; however, the exact mechanism is still not understood completely. Unlike in the case of congenital thrombophilias, in which venous thromboses are more likely to occur as compared with arterial thromboses,[8,9] aPL may cause thrombosis in both types of vascular systems. Arterial thrombosis in APS is fairly common and often involve coronary or cerebral arteries leading to myocardial infarction (MI) or stroke. According to a large dataset of 1000 patients with APS from 13 European countries, the most common thrombotic manifestations included deep vein thrombosis (38.9%), but arterial thrombosis was also common (stroke, 19.8%; MI, 5.5%; peripheral arterial thrombosis, 7%).[10] However, APS was rarely diagnosed in relation 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 studies, aPL were found in 13.5% of patients with stroke and 11% of patients with MI of the general population (not diagnosed with APS previously).[11] This highlights the importance of identifying patients in whom APS manifests in the form of arterial thrombosis.

TABLE 1 **Probable mechanisms of thrombosis in antiphospholipid syndrome**

Endothelial cell dysfunction
aPL-mediated eNOS inhibition
Upregulation of adhesion molecule expression (ICAM-1, VCAM-1, E-selectin, etc)
Increased leukocyte-endothelial adhesion
Increased production of endothelin-1 and tissue factor
Reduced prostacyclin production
Platelet activation
Increased thromboxane A_2 production
Increased platelet activation leading to increased glycoprotein IIb / IIIa expression
Interference of VWF-mediated platelet adhesion
Increased platelet-derived microparticle formation
Complement system activation
Complement activation (C3, C5) and deposition
Inflammatory cell-mediated mechanisms
Increased monocyte (and monocyte derived microparticle) tissue factor expression
Increased IL-8 release by neutrophils
Release of neutrophil extracellular traps (NETosis)
Disturbances of anticoagulant mechanisms
aPL-mediated disruption of annexin A5 anticoagulant shield
Inhibition of the protein C pathway
Interference with the action of antithrombin
Inhibition of TFPI
Reduced fibrinolysis/abnormal clot structure
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

Pathomechanism of antiphospholipid antibodies leading to thrombosis and myocardial infarction Venous and arterial thrombotic diseases were traditionally viewed as separate pathophysiological entities, focusing on the role of platelets in arterial thrombosis and 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 a good example, although many aspects regarding the effects of aPL are still to be explored. Despite immense research to unravel the puzzling nature of these antibodies, their exact cause-and-effect relation with 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 in healthy individuals without clinical consequences has led to the conclusion that these antibodies alone are insufficient for the pathogenesis of thrombosis and APS. The main antigen targeted by aPL causing thrombosis is β_2-glycoprotein I (β_2GPI). There has been no definite biological function assigned to this protein.[1] In particular, immunoglobulin G (IgG) antibodies against domain I β_2GPI have been reported to have a stronger correlation with thrombosis. β_2GPI can exist in 2 conformations: domain I is cryptic in the

circular form, but once the protein is bound to anionic phospholipid membranes, it becomes open and domain I becomes exposed. In patients with genetic susceptibility for developing APS, the exposure of domain I as a neoepitope stimulates autoimmune response and the formation of aPL–β_2GPI complex.[13] Several other antigenic targets are also known for aPL, including prothrombin, protein C, protein S, annexin A5, annexin A2, etc.[1] The common link between venous and arterial thrombosis in APS might be the damage to endothelial cells, which seems necessary for the development of clinical symptoms.[2] Patients with APS have significantly impaired production of nitric oxide mediated by aPL-induced endothelial nitric oxide synthase inhibition that can lead to increased predisposition to atherosclerosis and thrombosis.[14] Endothelial cells can be activated by aPL with anti-β_2GPI specificity. Activated endothelial cells upregulate the expression of adhesion molecules and the production of tissue factor. It has been shown that in APS, aPL-induced endothelial cell dysfunction is associated with increased carotid intima-media thickness that leads to a greater risk of cardiovascular events, and multiple clinical studies have shown accelerated atherosclerosis mediated by circulating aPL.[2,15] An inflammatory insult has been demonstrated to play a key role in the triggering of thrombosis in patients with APS.[2] This can be linked to triggers associated with infections, trauma, surgery, or pregnancy. Traditional cardiovascular risk factors, such as smoking, might also have an important role. 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 disrupt the anticoagulant shield provided by annexin A5 on endothelial cells. This effect corresponds with antibody identification of the epitope domain I of β_2GPI, which has been shown to correlate with an increased risk of thrombosis.[16,17] In the presence of anti-β_2GPI directed against domain I, conformational change and dimerization of β_2GPI occurs, and anti-β_2GPI–β_2GPI 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 can interfere with the protein C pathway in many different ways and increase thrombotic risk.[1] In patients with APS, the regulation of thrombin generation is often derailed, which leads to an enhanced prothrombin conversion, particularly in those with a history of thrombosis.[18] Fibrinolysis is hindered by aPL via multiple mechanisms.[1] Tissue-plasminogen activator and plasminogen binding to annexin A2 endothelial surface receptor may be hindered in APS.[19] Not only plasminogen activation but also plasmin activity may be directly inhibited by aPL. Elevated plasminogen activator inhibitor-1 levels in APS can also contribute to reduced fibrinolysis.[20] It has been shown that in APS, the so-called prothrombotic fibrin clot phenotype contributes to thrombotic events, particularly to arterial thrombotic events.[21,22] Patients with prothrombotic fibrin clot phenotype have unfavorable fibrin clot properties composed of denser fibrin networks with thinner fibers, leading to less permeable clots that are less susceptible to lysis.[21,23] Moreover, recent proteomic studies demonstrated that the protein composition of fibrin clots generated in the plasma of thrombotic patients with APS differs significantly from those without APS who suffered thrombosis.[24] 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 of patients with antiphospholipid syndrome

Diagnostic tests The diagnosis of APS requires at least 1 clinical and 1 laboratory criteria. Clinical criteria are as follows: 1) venous thrombosis (deep vein thrombosis, pulmonary embolism), 2) arterial thrombosis (coronary artery disease, cerebral ischemia or stroke, peripheral arterial disease), 3) obstetric complications (spontaneous abortion, fetal death, premature birth).[1,6] Laboratory criteria are based on 2 antigen assays (anti-β_2GPI, aCL) and a third functional test (LA). The latter is not a single test, but a set of assays that are sufficient to declare this entity, based on recent guidelines.[25,27] Although this 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 2 occasions 12 weeks apart. The importance of the repeated testing lies in the fact that aPL 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 the diagnosis of APS, the anti-β_2GPI measurement is an indispensable test and is either measured by an enzyme-linked immunosorbent assay or a chemiluminescent immunoassay.[6,28,29] Depending on the test type, anti-β_2GPI 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 test. The term cardiolipin reflects archaic nomenclature as this lipid was first described in bovine heart. Similarly to the above test, also in the case of aCL, there is no evidence for the usefulness of the IgA isotype, thus IgG and IgM isotypes need to be determined.[6] Despite current guidelines, standardization of the assays used has not been achieved in many aspects and no reference material is available to date. Results of aCL and anti-β_2GPI tests are not expressed in international units (usually IgG phospholipid [GPL] or IgM phospholipid units [MPL] for aCL and arbitrary units, eg, U/l for anti-β_2GPI assays). The threshold for medium titer antibodies is generally defined as more than 40 GPL and more than 40 MPL 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 population.[28] Moderate to high titers of aCL or anti-β_2GPI correlate better with clinical events as compared with lower titers, and the strongest association with thrombosis was observed with antibodies of the IgG isotype.[5,31] High-risk and low-risk aPL profile for thrombosis and obstetric complications according to the European League Against Rheumatism recommendations are summarized in TABLE 2.[30]

Noncriteria antigen assays Although several other autoantibodies have been identified in patients with APS, these have not been included in the guidelines.[25,26,32] Nevertheless, autoantibodies to phosphatidylserine / prothrombin have been described in 50% to 90% of aPL-positive patients.[33] These autoantibodies may well have a pathogenic role as was shown in LA-positive patients[34] and more recently it has also been identified that patients with autoantibodies to phosphatidylserine / prothrombin have denser and poorly lysable fibrin clots and these antibodies may mediate prothrombotic clot properties.[35]

Lupus anticoagulant There is a single term used for the functional testing of aPL that is a well-known misnomer—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.[25] 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 a significant inter-laboratory variation in LA testing.[36] If the guidelines are appropriately followed, laboratories can exclude the presence of LA based on double negativity of an LA-sensitive activated partial thromboplastin time assay and the dilute Russel viper venom test. If these tests are not negative, there are 2 approaches to confirm the presence of LA. Either a mixing test is done first, followed by a confirmatory test using excess phospholipids to shorten prolonged clotting times, or the confirmatory tests are done first and the mixing study will only be secondary. Besides the above mentioned analytical aspects, one preanalytical consideration is of importance, that is, all samples stored for LA testing need to be centrifuged twice to eliminate phospholipid-containing exosomes that may interfere with the antibodies and lead to false results.[36] Although a lot of progress has been made in the past decades in standardizing LA testing, a recent comprehensive study highlights the need for a more widespread standardization.[37]

For the overall evaluation of patients with APS, 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 1 of the above assays were positive (double or triple aPL positivity).[38,39] Most importantly, the correct assessment of LA is crucial at 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-β_2GPI (TABLE 2).[5]

Despite paying attention to preanalytical variables and recognizing current guidelines, a lack of conformity remains in LA testing that calls for the the development of widely available reference materials, new assays that better identify

TABLE 2 Definitions of high-risk and low-risk antiphospholipid antibody profile for thrombosis and obstetric complications according to the recommendations of the European League Against Rheumatism

Profile	LA	aCL	Anti-β_2GPI
High risk	+		
	+	+	
	+		+
		+	+
	+	+	+
Low risk		+[a]	
			+[a]

For detailed information, see Tektonidou et al.[30]

a Low or medium titers. The presence of persistently high titers is considered high-risk profile.

Abbreviations: aCL, anticardiolipin antibody; anti-β_2GPI, anti-β_2 glycoprotein I antibody; LA, lupus anticoagulant

clinically important aPL, and a clear-cut interpretation to avoid pitfalls when diagnosing APS.

Interferences in laboratory testing of antiphospholipid syndrome In the presence of aPL, laboratory evaluation of the patients with APS may be challenging as these antibodies may interfere with several hemostasis tests as well as with some immunoassays. The interferences can be of 2 types. Either the LA antibody interferes with other laboratory assays or LA testing is influenced by the presence of laboratory interferences or drugs.

The latter is a frequent laboratory dilemma. Vitamin K antagonists (VKAs) interfere with LA tests and thus the guidelines recommend that LA tests should not be carried out if the international normalized ratio (INR) is over 1.5 in patients on VKAs. Other factors interfering 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 (DOACs) have become even more widely used than VKAs, resulting in an overwhelming number of hemostasis tests being 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.[40] For this reason, it has been suggested that LA testing should be performed 2 to 3 days after the last dose of DOACs.[41]

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

Prognostic tests in antiphospholipid syndrome In APS, some diagnostic tests may serve as prognostic predictors. The decrease in platelet count has been described[45] as well as platelets being the primary target of aPL.[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 pesentation, thus should be considered as a prognostic marker and a warning signal.[47]

Further assessment of aPL may also be useful as a prognostic marker. It was shown that antibodies to the domain I of the β_2GPI are strongly associated with thrombotic events.[16,48] As mentioned above, the presence of LA is also associated with future thrombotic risk. The need to increase assay specificity to domain I of anti-β_2GPI and to develop more specific tests for subtypes of LA that are most likely linked to thrombotic complications has been discussed, but the exact clinical value of those tests remains speculative.[44]

Although there may be a handful of tests potentially used for predicting thrombosis in APS, only 1 or 2 reflect the patomechanism of APS. Recently, by using the global hemostasis

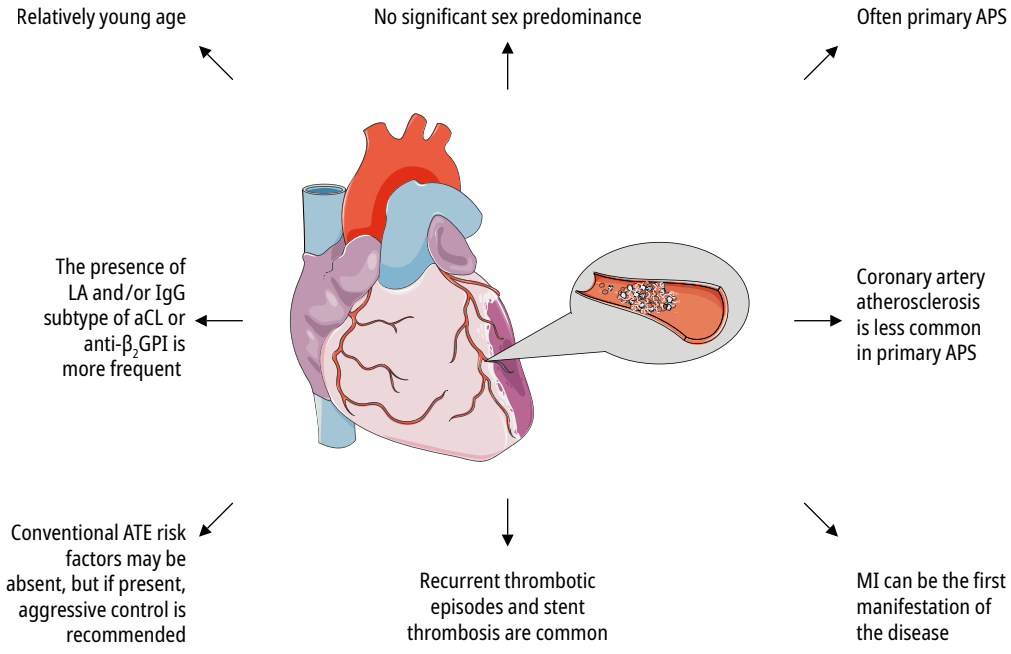

FIGURE 1 Common features of myocardial infarction associated with antiphospholipid syndrome

Abbreviations: APS, antiphospholipid syndrome; ATE, atherothrombotic event; IgG, immunoglobulin G; MI, myocardial infarction; others, see TABLE 2

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 conversion of prothrombin to thrombin, and this phenomenon was associated with patient history of thrombosis.[18] Still, the identification of patients who are at a higher risk for thrombosis remains an unmet clinical need. While specific laboratory tests are awaited, thrombotic risk stratification / prediction models are under development and await validation in the clinical setting.[5,49,50]

Specific features of myocardial infarction in antiphospholipid syndrome

Clinical features of acute myocardial infarction in antiphospholipid syndrome In order to identify the main clinical features of MI in patients with APS, a literature search was performed from January 2000 to September 2019. The PubMed database was searched, and the following terms were used: "antiphospholipid syndrome" or "antiphospholipid" or "lupus anticoagulant" and "myocardial infarction" or "cardiovascular disease." Few additional articles from the references 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 from 58 articles were identified where APS was presenting in the form of acute MI. All cases are listed in Supplementary material, *Table S1*. The following 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 aPL type. Main conclusions drawn from data extraction are summarized in FIGURE 1. Median (interquartile range) age at the presentation of MI was 36 (29–48) years. No significant sex predominance was observed (male sex, 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 (24%), 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%]), for example, the presence of aPL 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-β_2GPI 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, the measurements of aPL 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-β_2GPI antibodies, IgG isotype seems to be associated with a higher risk of MI. In a large multicenter population-based case-control study (RATIO [Risk of Arterial Thrombosis In Relation to Oral Contraceptives]), LA was the aPL laboratory parameter that correlated best with coronary occlusion.[51]

Of note, in many cases, coronary thrombosis without significant coronary atherosclerosis was found. The term myocardial infarction with nonobstructive coronary arteries (MINOCA) has been coined for this entity.[52-54] This finding is in line with the most recent publication where it was shown that patients with MINOCA have 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 disorder, 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 APS.[56] Recurrent coronary thrombosis and stent thrombosis were frequent complications in patients with MI after primary percutaneous coronary intervention (PCI). These findings are consistent with the results of a recent systematic review by Nazir et al[57] who analyzed 40 MI cases from 27 studies. As the authors concluded, MI associated with APS was typically present in relatively young patients regardless of sex, and coronary arteries were often described as normal. Similar conclusions were drawn in the case series by Davies et al[58] who highlighted that coronary artery atherosclerosis is less commonly the underlying etiology in the relatively younger age group, thus a more comprehensive assessment of the cause of thrombosis is required.

In 12% of the assessed case reports, MI occurred in patients with APS associated with SLE. In contrast to the relatively frequent scenario of thrombosis in normal coronaries in the case of patients with primary APS, 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 that in patients with primary APS. Although premature atherosclerosis might be a feature of primary APS, its prevalence in SLE-associated APS is estimated to be at least 2-fold higher.[59] Both APS and SLE are associated with a number of other

thrombotic or nonthrombotic cardiac manifestations, which may make the clinical presentation even more diverse. Of note, coexisting inherited or acquired risk factors for atherothrombosis are not exclusion criteria for APS. Particularly in patients with SLE, hypertension, hyperlipidemia, or other common atherothrombosis risk factors, for example, 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 might be induced upon tissue necrosis during MI and their transient presence may not be responsible for the thrombotic event.[58] Careful interpretation and repeated testing are crucial for the identification of APS in patients with acute MI. The diagnosis of APS is particularly critical as the recommended treatment is different once the diagnosis is made.

In 7 cases listed in the Supplementary material, *Table S1*, 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 positivity. Due to the severity and high mortality rates 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 ischemic cardiovascular events in antiphospholipid syndrome Primary prevention of MI in aPL-positive individuals or patients with APS is 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 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.[60,61] Risk stratification might be aided by prediction models providing a quantitative score, such as the adjusted Global Antiphospholipid Syndrome Score, that facilitates risk prediction in patients with APS younger than 50 years.[49] According to the current European League Against Rheumatism 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.[30] 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.[5,62] Additional studies are warranted in patients with primary APS to determine the risk reducing effect of this treatment.[5]

Optimal treatment of acute MI might be challenging in patients with APS. Those undergoing PCI are prone to thrombotic recurrences.[63] The results of a recent meta-analysis 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 with those without APS or SLE.[64] After PCI, dual antiplatelet therapy is recommended in addition to oral anticoagulation, but individual bleeding risk should be kept in focus.[63] Maintaining the right balance between bleeding and recurrent thrombosis is a challenging task in patients with APS after PCI.

The cornerstone of long-term treatment in patients with APS after MI is long-term anticoagulation with VKAs (target INR, 2–3).[5,30,63] However, in patients with APS with arterial thrombosis, the recurrence risk is higher as compared with those with venous thrombosis. In patients with APS experiencing recurrent arterial events despite adequate anticoagulation or in 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 the recommendations, but more evidence is needed regarding the efficacy and safety of intensified therapy.[5,30] In any case, artificial prolongation of prothrombin time and falsely elevated INR by aPL must be excluded when VKA therapy fails despite therapeutic INR. Based on the recommendations of an expert panel, besides increasing target INR to 3 to 4 or the addition of low-dose aspirin, switching to low-molecular-weight heparin may be considered in individual cases of recurrent arterial thrombosis despite VKA treatment.[30]

Based on the current body of evidence, the use of DOACs cannot be promoted in patients with APS and arterial events due to the high risk of recurrent thrombosis.[5,30,63] According to the results of the TRAPS (Trial of Rivaroxaban in AntiPhospholipid Syndrome) study, where high-risk (triple positive) patients were included, the use of rivaroxaban was associated with an increased rate of events as compared with warfarin, thus it showed no benefit and excess risk.[65] The trial was prematurely terminated after the enrollment of 120 patients due to increased events in patients with APS in the rivaroxaban arm. Both VTE and arterial events were more frequent, including MI (3 out of 59 patients [5%] vs none in the VKA group). In addition, an ongoing trial of apixaban in APS (ASTRO-APS [Apixaban for the Secondary Prevention of Thromboembolism among patients with the AntiphosPholipid Syndrome]) was modified after the initial evaluation of data to

exclude patients with arterial thrombosis due to the high risk of recurrent events.[30,66] In a recent meta-analysis where results from 47 studies corresponding to 447 patients with APS treated with DOACs (rivaroxaban, 290; dabigatran, 144; apixaban, 13) were analyzed, 73 out of 447 patients (16%) experienced recurrent thrombosis while on DOACs.[67] 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 the most recent cohort study of 176 patients with APS.[68] Patients with APS treated with DOACs had increased risk of recurrent thromboembolic events compared with those on VKAs (HR, 3.98; 95% CI, 1.54–10.28). Moreover, patients on DOACs had an increased risk of major bleeding or clinically relevant nonmajor 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 patients with APS with arterial events due to high risk of recurrent thrombotic events.[30,40,69] Further clinical trials are warranted to better define the potential role of DOACs in subgroups of patients with APS.[68,70]

Conclusions APS encompasses a wide spectrum of manifestations that may prevail in the form of venous or arterial thrombosis or lead to pregnancy complications in the presence of persisting aPL. aPL are highly heterogeneous, which makes the understanding of their pathomechanism and their laboratory diagnosis challenging. Nevertheless, important advances in the knowledge of particular steps of the thrombosis pathogenesis have been identified in the past years and risk stratification based on aPL profile has improved. Unlike in the case of congenital thrombophilias, in which venous thromboses are more likely to occur as compared with arterial events, aPL may cause thrombosis in both types of vascular systems. The risk of MI in patients with APS is relatively lower as compared with 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 sex dominance, often normal coronaries without the sign of atherosclerosis, high risk of recurrent thrombotic events. Treatment of acute MI in patients with APS is often challenging and adverse events including stent thrombosis are more frequent as compared with 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 patients with APS and arterial thrombotic events.

SUPPLEMENTARY MATERIAL

Supplementary material is available at www.mp.pl/kardiologiapolska.

ARTICLE INFORMATION

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