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EULAR Recommendations for the management of Antiphospholipid Syndrome in adults

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Abstract

Objective: To develop evidence-based recommendations for the management of antiphospholipid syndrome (APS) in adults.

Methods: Based on evidence from a systematic literature review and expert opinion, overarching principles and recommendations were formulated and voted.

Results: High-risk antiphospholipid antibody (aPL) profile is associated with greater risk for thrombotic and obstetric APS. Risk modification includes screening for and management of cardiovascular and venous thrombosis risk factors, patient education about treatment adherence, and lifestyle counseling. Low dose aspirin (LDA) is recommended for asymptomatic aPL carriers, patients with systemic lupus erythematosus without prior thrombotic or obstetric APS, and non-pregnant women with a history of obstetric APS only, all with high-risk aPL profiles. Patients with APS and first unprovoked venous thrombosis should receive long-term treatment with vitamin K antagonists (VKA) with a target INR 2-3. In APS patients with first arterial thrombosis, treatment with VKA with INR 2-3 or INR 3-4 is recommended, considering the individual's bleeding/thrombosis risk. Rivaroxaban should not be used in APS patients with triple aPL positivity. For patients with recurrent arterial or venous thrombosis despite adequate treatment, addition of LDA, increase of INR target to 3-4, or switch to LMWH, may be considered. In women with prior obstetric APS, combination treatment with LDA and prophylactic dosage heparin during pregnancy is recommended. In patients with recurrent pregnancy complications, increase of heparin to therapeutic dose, addition of hydroxychloroquine, or addition of low-dose prednisolone in the first trimester, may be considered.

Conclusion: These recommendations aim to guide treatment in adults with APS. High quality evidence is limited, indicating a need for more research.

Introduction

Antiphospholipid syndrome (APS) is a systemic autoimmune disorder with a wide range of vascular and obstetric manifestations associated with thrombotic and inflammatory mechanisms orchestrated by antiphospholipid antibodies (aPL). Common APS clinical features include venous thromboembolism, stroke, recurrent early miscarriages, and late pregnancy losses (1). According to current laboratory criteria for APS, aPL antibodies can be one of three types: lupus anticoagulant, anticardiolipin antibodies, or anti-beta2 glycoprotein I antibodies. Definite APS, fulfilling at least one clinical and one laboratory criteria of the updated Sapporo classification criteria, can occur in association with other autoimmune diseases, mainly systemic lupus erythematosus (SLE), or in its primary form (primary APS) (1, 2). Rarely, a life-threatening form of multi-organ thrombosis, known as catastrophic APS (CAPS), can occur. The presence of aPL in asymptomatic individuals or patients with SLE does not confirm the diagnosis of APS but can be associated with increased risk of thrombosis or pregnancy morbidity, depending on aPL characteristics and co-existence of other risk factors (3, 4). The aPL type, the presence of multiple (double or triple) versus single aPL type, their titer (moderate-high titer vs low), and the persistence of aPL positivity in repeated measurements, is defined as the 'aPL profile'. The aPL profile is an important factor determining the risk of thrombotic and obstetric events, and consequently the intensity of treatment (3, 4).

Clinical practice in APS is highly variable, in part because it is a rare disorder, and because knowledge about its diagnosis/classification, clinical spectrum, and management is continuously advancing. There is a great heterogeneity among studies on the laboratory and clinical criteria used to define APS and the treatment approaches used over the past four decades. These factors make it often difficult to know the best approach to apply in daily practice. In addition, there is a

paucity of high-quality randomized controlled trials (RCTs) in APS because of the difficulties conducting adequately sized trials in an uncommon disease and using randomized designs among patients with often devastating clinical presentations. The objective of this project was to develop evidence-based recommendations for the prevention and management of adult APS that will help guide practice and improve quality of care and patient outcomes.

Methods

We followed the updated EULAR Standardised Operating Procedure (5) and used the Appraisal of Guidelines for Research & Evaluation II (AGREE II) tool (6). The steering committee included the convenor (MGT), co-convenor (AT), methodologist (MMW), and two physicians responsible for the systematic literature reviews (both were EMEUNET members) (LA, ML).

The task force included members from 11 European countries: 12 specialists in rheumatology or internal medicine, 2 obstetricians (RF, LR), 2 physicians from vascular medicine/thrombosis centers (VP, DW), 1 healthcare professional (KH), and 2 patient representatives (FM, JK).

The convenor prepared the first task force meeting and the first set of research questions on four major topics: risk stratification and risk modification in asymptomatic aPL positive patients, primary and secondary thromboprophylaxis in APS, management of obstetric APS, and management of catastrophic APS. The research questions were discussed among the task force members, and a set of 31 research questions was formulated using the PICO format (P=population; I=intervention; C=comparator; O=outcomes) and voted according to the Delphi method at a meeting in December 2017.

The data sources for the systematic literature review (SLR) were PubMed, Embase, and the Cochrane Library, which were searched for relevant English-language published articles from

their inceptions through January 31, 2018. We included one RCT published after this date because of the importance of its reported safety results (TRAPS trial) (7). Search terms were developed with the aid of an experienced librarian, who performed the searches. All titles and abstracts of retrieved articles were first reviewed independently by the two literature reviewers. The full-text articles were then reviewed independently by three persons: one literature reviewer, convenor, and methodologist. The data abstraction was performed by the two literature reviewers according to a written protocol and supervised by the methodologist. Data abstraction was then independently double-checked by the convenor and methodologist. Each included article was graded for its methodological quality and assigned to the relevant PICO question by the convenor and methodologist. Data were tabulated and summarized by the methodologist in an evidence report that included summary of findings tables with pooled estimates of effect sizes for studies that directly addressed the population, intervention and comparator of PICO questions. Based on this evidence, a first draft of recommendations on 12 topics was prepared by the convenor and co-convenor. The draft recommendations and evidence report were sent to all task force members for review prior to the second task force meeting.

The second task force meeting, held September 3, 2018, included the presentation of SLR results, discussions of the first draft of recommendations in four working groups, working group presentations of the edited draft for each topic, and discussion and voting of the text.

Incorporating additional discussions on wording changes, the final set of overarching principles and recommendations, including the level of evidence (LoE) and grade of recommendations (GoR) according to Oxford Centre for Evidence-Based Medicine standards (8) prepared by the methodologist in collaboration with convenors, was sent by the convenor to all task force members who voted anonymously on the level of agreement (LoA). A rating scale of 0–10 (0: do

not agree, 10: fully agree) was used for each recommendation. The manuscript was reviewed and approved by all task force members and EULAR Executive Committee before submission.

Results

The SLR yielded 7534 articles and 15 hand search articles. After the titles and abstracts review, 670 articles were selected for full-text review. The full-text review yielded 249 articles for data abstraction; 61 were excluded and 188 articles were finally considered to be relevant. A detailed presentation of the results of the SLRs that informed the task force recommendations is published separately and should be reviewed together with this report (9). Based on the SLR results and expert's opinion, 3 overarching principles and 12 recommendations were developed.

Overarching principles

A. Risk stratification: Identifying the presence of factors associated with high risk for thrombotic and obstetric events is critical in patient management. A major risk factor is the high-risk aPL profile, including any of the following: the presence of lupus anticoagulant as the aPL subtype most closely related to thrombosis, the presence of double (any combination of lupus anticoagulant, anticardiolipin antibodies or anti-beta2glycoprotein I antibodies) or triple (all three subtypes) aPL positivity, or the presence of persistently high aPL titers (4, 10), as also shown by aPL-score (11) and GAPSS (12). Definitions of medium-high aPL titers, and of high-risk and low-risk aPL profiles are included in Table 1. Additional risk factors for clinical events are co-existence of other systemic autoimmune diseases, especially SLE, a previous history of thrombotic and/or obstetric APS, and the presence of traditional cardiovascular risk factors (3, 4, 10).

- B. General measures:** The guidelines for cardiovascular disease (CVD) prevention in the general population should be followed. Screening for and management of venous thrombosis risk factors is also recommended. Heparin at prophylactic dosage, preferably low molecular weight heparin (LMWH), should be used in high-risk situations such as surgery, prolonged immobilization, and the puerperium.
- C. Patient education:** All patients treated with vitamin K oral anticoagulants (VKA) should receive counseling about treatment adherence, the need for close INR monitoring especially in the setting of newly initiated treatment or bridging with heparin, the protocol of perioperative bridging therapy with heparin, and drug and food interactions. Counseling should be provided on the use of contraceptives, pregnancy planning and postmenopausal hormone therapy for all women with APS (13). Patients should also receive dietary counseling for CVD prevention. Physical activity is encouraged in patients with APS including those on oral anticoagulants.

Recommendations

Table 2 presents the LoE, GoR and LoA for each recommendation. For recommendations with B GoR, we used the statement “is recommended”. For C and D grades, we mostly used the terms “may be considered” or “could be considered”, with some exceptions according to experts’ judgment about the importance of the intervention. Recommendations that are phrased as “is recommended” are those that the task force meant, based on the evidence and their experience, should be followed in almost all cases.

Primary thromboprophylaxis in aPL positive subjects

1. In asymptomatic aPL carriers (not fulfilling any vascular or obstetric APS classification criteria) with a high-risk aPL profile with or without traditional risk factors, prophylactic treatment with low dose aspirin (LDA) (75-100 mg daily) is recommended.

Use of LDA for primary prophylaxis is supported by results of a meta-analysis of seven observational studies of 460 asymptomatic aPL carriers that found the risk of first thrombosis to be reduced by one-half in those who used LDA versus those not used LDA (14). Most patients had high-risk aPL profiles, but few had traditional CVD risk factors. An association of similar magnitude was present in a smaller individual-patient meta-analysis derived from these studies (15). Neither meta-analysis display worrisome variations as the directions were clear. Although evidence was largely from observational studies, the panel recommended the use of LDA for primary prophylaxis in asymptomatic aPL individuals with high risk profile given the likelihood of benefit and low risk of adverse events of this intervention.

2. In patients with SLE and no history of thrombosis or pregnancy complications: a. with high-risk aPL profile, prophylactic treatment with LDA is recommended; b. with low-risk aPL profile, prophylactic treatment with LDA may be considered.

Treatment with LDA for patients with SLE and high-risk aPL profile is supported by a sub-analysis of eight studies, mostly observational, in a meta-analysis (14). In this analysis, risk of first thrombosis was reduced by almost one-half among patients treated with LDA versus patients not treated, without major bleeding events. In an individual-patient analysis, this association was independent of the use of hydroxychloroquine (HCQ), suggesting that LDA offers additional benefit in this patient group (15). Patients with high-risk aPL profile comprised the majority (but not all) of patients in these studies. Although there was heterogeneity between the studies, the direction of effect was clear. Less evidence is available on the use of LDA in

patients with SLE and low-risk aPL profile, but pooled data from two cohort studies indicate that the use of LDA was also associated with a lower risk of thrombosis in this group (16, 17).

3. In non-pregnant women with a history of obstetric APS only (with or without SLE), prophylactic treatment with LDA after adequate risk/benefit evaluation is recommended.

The primary prevention of thrombosis with LDA in women with a history of obstetric APS without SLE was addressed in a meta-analysis including five observational studies (14). The pooled odds ratio for first thrombosis associated with use of LDA was 0.25 (95% CI 0.10, 0.62). Studies of women with SLE and prior obstetric APS are scarce, but the protective effect of LDA was supported by three retrospective studies that included a minority of patients with SLE (18-20). The panel recommended the use of LDA in women with a history of obstetric APS only, according to their thrombosis/bleeding risk (aPL profile, coexistent traditional cardiovascular risk factors, intolerance/contraindication to aspirin).

Secondary thromboprophylaxis in APS

4. In patients with definite APS and first venous thrombosis:

a. Treatment with VKA with a target INR 2-3 is recommended.

In patients with APS and first venous thrombosis, after an initial therapy with unfractionated heparin (UFH) or LMWH and bridging therapy of heparin plus VKA, treatment with VKA with a target INR 2-3 is recommended. Data from an RCT (21) reporting exclusively in patients with venous events, and pooled data from five studies that included a majority with venous events (21-25), showed no additional benefit of target INR 3-4 vs INR 2-3. However, evidence is limited by the frequent failure to achieve the target INR in the high-intensity groups in the RCTs. Data on bleeding were not reported for patients with venous thrombosis specifically. However,

although not based on data from these studies, higher level of anticoagulation would be anticipated to have also a higher risk of bleeding.

b. Rivaroxaban should not be used in patients with triple aPL positivity due to the high risk of recurrent events. DOACs could be considered in patients not able to achieve a target INR despite good adherence to VKA or those with contraindications to VKA (e.g. allergy or intolerance to VKA).

Despite the broadening use of DOACs in secondary thrombosis prevention in the general population, there is limited evidence about their effectiveness and safety in APS. In a post-hoc analysis of patients with APS included in three RCTs of dabigatran versus warfarin (26), and in one RCT of rivaroxaban vs warfarin in patients with venous thrombotic APS (27), there were no differences in outcomes between treatment with DOACs and VKA for venous thrombosis, but the evidence is limited by small samples, underrepresentation of high-risk APS patients and short follow-up. A recent RCT of rivaroxaban vs warfarin in APS patients with triple aPL positivity was prematurely terminated due to an excess of thromboembolic events (mostly arterial) in the rivaroxaban arm (7). Accordingly, rivaroxaban should not be used in patients with triple aPL positivity. The panel agreed that DOACs may be considered in patients with difficulty achieving a target INR 2-3 despite compliance with VKA or who have contraindications to VKA. Switching from treatment with VKA to DOACs due to low adherence to VKA or INR monitoring should be avoided.

c. In patients with unprovoked first venous thrombosis, anticoagulation should be continued long-term.

Use of long-term anticoagulation in patients with APS is supported by two small direct comparison studies (1 RCT, 1 retrospective cohort) (28, 29) that showed a lower risk of recurrent venous thrombosis among patients with APS on long-term vs 3-6 months of oral anticoagulation. However, studies did not specify the proportion of patients with unprovoked thrombosis, making this evidence indirect.

d. In patients with provoked first venous thrombosis, therapy should be continued for a duration recommended for patients without APS according to international guidelines. Longer anticoagulation could be considered in patients with high-risk aPL profile in repeated measurements or other risk factors for recurrence.

This recommendation was based on experts' opinion because we did not identify any studies that directly addressed the question of treatment duration after the initial provoked venous thrombosis. The panel recommended a duration of anticoagulation according to international guidelines for patients without APS (30), because the benefit of long-term anticoagulation in this population is unclear. In patients with repeatedly high-risk aPL profile or those with additional risk factors for thrombosis recurrence, longer anticoagulation may be considered. 5. *In patients with definite APS and recurrent venous thrombosis despite treatment with VKA with target INR 2-3: a. Investigation of, and education on, adherence to VKA treatment, along with frequent INR testing should be considered. b. If the target INR 2-3 had been achieved, addition of LDA, increase of INR target to 3-4, or change to LMWH may be considered.*

There is limited evidence, mainly from case series, about therapeutic strategies for patients who have recurrent venous thrombosis despite a target INR 2-3. Evaluation of the intensity of anticoagulation and adherence to treatment, patient counseling, frequent INR monitoring or a self-monitoring program, are important in optimizing anticoagulation management. For adherent

patients who have a recurrent thrombotic event, the addition of LDA, or increase of INR target to 3-4, or switch to LMWH, can be considered based on the individuals' characteristics and preferences (aspirin intolerance/contraindication, cost and side effects of continuous LMWH use). There is insufficient evidence to determine the relative efficacy and safety of these options in this patient group.

6. In patients with definite APS and first arterial thrombosis:

a. Treatment with VKA is recommended over treatment with LDA only.

The use of VKA over LDA is supported by data from observational studies that showed a lower likelihood of recurrent thrombosis among patients with APS and prior arterial thrombosis (mainly stroke) treated with VKA vs LDA alone (31, 32). An early study in older patients with strokes reported no difference in event recurrences between LDA and warfarin, but aPL were tested only once and were mainly of low titer in this study (33). These issues make it difficult to apply the latter results to patients of any age who fulfill the laboratory criteria for APS.

b. Treatment with VKA with INR 2-3 or INR 3-4 is recommended, considering the individual's risk of bleeding and recurrent thrombosis. Treatment with VKA with INR 2-3 plus LDA may also be considered.

APS patients with arterial thrombosis have a higher risk of recurrence compared to those with venous thrombosis, and a tendency for recurrences in the same vascular (arterial) bed (34). An earlier SLR including mainly observational studies reported that recurrent events occurred more often in APS patients treated with VKA with a target INR 2-3 compared to INR 3-4, but outcomes among patients with first arterial thrombosis were not analyzed specifically (35). This review did not compare the target INR 2-3 and INR 3-4 arms within the same study, but

disaggregated the arms. Pooled data from two retrospective studies and two RCTs (21-24), showed that there was no statistically significant difference in thrombosis recurrences between treatment with VKA with a target INR 3-4 and treatment with INR 2-3 (RR 0.46 (0.06 – 3.52). However, these studies included a mixture of patients with either venous or arterial thrombosis, and a minority had arterial events. In one trial that provided data specifically on patients with arterial thrombosis, there was no difference in recurrences between those treated to a target INR 2-3 or INR 3-4 but without statistical significance (HR 3.1 (0.3 - 30.0), although the sample was small and the achievement of target INR 3-4 was low (21). Because of these limitations, the higher intensity INR approach is preferred by some centers. In decision-making, physicians should take into account the individual's risk of recurrent thrombosis and major bleeding, as well as patients' preferences after discussion. Alternatively, treatment with VKA with target INR 2-3 plus LDA is used by some experts, supported by limited data from one retrospective cohort study and one small RCT (36-37).

c. Rivaroxaban should not be used in patients with triple aPL positivity and arterial events.

Based on the current evidence, we do not recommend use of DOACs in patients with definite APS and arterial events, due to high risk of recurrent thrombosis.

According to the results of the TRAPS trial (7), rivaroxaban should not be used in triple aPL positive patients with APS. In addition, an ongoing trial of apixaban in APS (ASTRO-APS) (ClinicalTrials.gov Identifier: NCT02295475) was recently modified after evaluation of their initial data to exclude patients with arterial thrombosis. Based on these data and those from case series reporting arterial thrombosis recurrences in APS patients treated with DOACs, use of DOACs is not currently recommended in patients with definite APS and arterial events (38). Ongoing clinical trials will help to better define the role of DOACs in APS.

7. In patients with recurrent arterial thrombosis despite adequate treatment with VKA, after evaluating for other potential causes, an increase of INR target to 3-4, addition of LDA, or switch to LMWH can be considered.

Evidence on the management of recurrent arterial thrombosis despite VKA treatment is limited.

The panel agreed that after evaluating other risk factors for thrombosis (e.g. traditional cardiovascular risk factors, cancer, other thrombophilic states) and investigating the adherence to VKA treatment, increase of target INR to 3-4, or INR 2-3 with the addition of LDA, or switching to LMWH, may be considered. Adjunctive therapy with antimalarials or statins could also be considered (4, 10, 39-41).

Obstetric APS

8. In women with a high-risk aPL profile but no history of thrombosis or pregnancy complications (with or without SLE), treatment with LDA (75-100 mg/day) during pregnancy should be considered.

Data from one placebo-controlled RCT of LDA in six women with SLE (42), and data from three low-quality studies (2 RCTs, 1 retrospective cohort) (43-45) of women without SLE found no difference in the prevalence of live births with use of LDA. However, these studies did not specifically include women with a high-risk aPL profile. The panel agreed that use of LDA should be considered in pregnant women with high-risk aPL profile due to risk of obstetric and thrombotic complications during pregnancy associated with high-risk aPL profile.

9. In women with a history of obstetric APS only (no prior thrombotic events), with or without SLE:

a. In women with a history of ≥ 3 recurrent spontaneous miscarriages <10th week of gestation, and in those with a history of fetal loss (≥ 10 th week of gestation), combination treatment with LDA and heparin at prophylactic dosage during pregnancy is recommended.

Pooled data from one RCT including only patients with a history of first trimester losses (46) and eight supporting observational studies (47-54) that did not exclusively study women with early pregnancy losses indicated a higher likelihood of live births with combination treatment with LDA and heparin at prophylactic dosage versus LDA alone. Some experts believe that LDA alone can be also effective. For women with a history of fetal loss, combination treatment with LDA and heparin was associated with a higher likelihood of live birth compared to treatment with LDA alone. However, these studies included women with histories of both early and mid-pregnancy losses (48-52). LDA should be preferably started prior to conception, and heparin (LMWH or unfractionated heparin) should be added as soon as pregnancy is confirmed. LMWH is preferred for practical reasons.

b. In women with a history of delivery <34th week of gestation due to eclampsia or severe pre-eclampsia or due to recognised features of placental insufficiency, treatment with LDA or LDA and heparin at prophylactic dosage is recommended considering the individual's risk profile.

Data from two studies (1 RCT, 1 retrospective cohort) (55, 48) showed that the likelihood of live births did not differ between women treated with LDA plus heparin and those treated with LDA alone. Physicians should tailor their treatment approach to individual's risk assessment including aPL profile and other risk situations (e.g. presence of other cardiovascular risk factors or immobility).

c. In women with clinical 'non-criteria' obstetric APS, treatment with LDA alone or in combination with heparin might be considered based on individual's risk profile.

The 'non-criteria' obstetric APS manifestations included in our search were the presence of two recurrent spontaneous miscarriages <10th week of gestation, or delivery \geq 34 weeks of gestation due to severe pre-eclampsia or eclampsia. Because studies combined several types of pregnancy losses without specifying on the proportion of 'non-criteria' APS and due to very limited evidence this recommendation is mainly based on expert opinion. Because of a potential higher risk for obstetric and/or thrombotic complications during pregnancy in women with a history of clinical 'non-criteria' obstetric APS, the panel agreed that treatment with LDA alone or in combination with heparin might be considered, based on individual's risk profile (aPL profile, concomitant SLE, prior live births history, and additional risk factors for pregnancy loss or thrombosis).

d. In women with obstetric APS treated with prophylactic dose heparin during pregnancy, continuation of heparin at prophylactic dose for 6 weeks after delivery should be considered to reduce the risk of maternal thrombosis.

No studies directly tested the efficacy of extending treatment with prophylactic heparin after delivery. The panel suggested that in women receiving prophylactic dose heparin during pregnancy, the same dosage of heparin should be continued for 6 weeks after delivery, due to an increased risk of thrombosis at puerperium.

10. In women with 'criteria' obstetric APS with recurrent pregnancy complications despite combination treatment with LDA and heparin at prophylactic dosage, increase heparin dose to

therapeutic dose, or addition of HCQ, or low dose prednisolone in the 1st trimester may be considered. Use of intravenous immunoglobulin might be considered in highly selected cases.

The most common practice if the combination of LDA and prophylactic dose heparin fails is to increase the dose of heparin to therapeutic dose, although no supporting evidence exists. Other treatment strategies may include the addition of HCQ or low prednisolone doses in the first trimester. Evidence directly supporting these treatment options is based on two small observational studies with limited representativeness (56, 57). Use of intravenous immunoglobulin (IVIG) was not associated with a higher proportion of live births compared to conventional treatment in three small observational studies (58-60) that directly addressed this question, although confounding by indication may have occurred. Although the expectation of benefit is small, the panel agreed that IVIG might be considered in highly selected cases when other treatments have failed.

11. In women with a history of thrombotic APS, combination treatment of LDA and heparin at therapeutic dosage during pregnancy is recommended.

In observational studies, treatment with LDA and therapeutic dose heparin was associated with live births in 79% of pregnancies on average (52, 61-64). Because a prior history of thrombotic APS is associated with increased risk for future thrombotic or obstetric events (65), treatment with LDA and heparin at therapeutic dosage during pregnancy is recommended. Switching treatment from VKA to therapeutic-dose LMWH or UFH is recommended as soon as pregnancy is confirmed, ideally before the sixth week of gestation, due to the teratogenic effects of warfarin (66).

Catastrophic APS

12. The most common precipitating factors for the development of CAPS are anticoagulation discontinuation among patients with prior diagnosis of APS, infections, and surgical procedures (67). Early diagnosis and management of infections and minimization of discontinuation or low-intensity anticoagulation, especially perioperatively, is recommended (68). Based on the recently published clinical practice guidelines for CAPS management, combination therapy with glucocorticoids, heparin and plasma exchange or IVIG is recommended over single agents as first-line treatment of patients with CAPS (69). Concurrent treatment of precipitating factors is also recommended (e.g. infections, gangrene or malignancy). For refractory CAPS, B-cell depletion (e.g. rituximab) or complement inhibition (e.g. eculizumab) therapies may be considered based on data from case reports (69).

Discussion

APS is a complex disorder and its management often involves collaboration among several medical specialties. The aim of these recommendations is to provide guidance to all health professionals involved in patients' care, inform patients and support their engagement in shared decision-making, and provide evidence to researchers, funders and policy makers. The task force included members from several professional groups covering different perspectives and involved also two patients who participated actively in both meetings.

The main challenge in developing recommendations for the management of adult APS was the low certainty of evidence. Many studies included patients with a mix of different clinical features and did not provide stratified data for arterial or venous thrombosis separately or for each of various types of obstetric APS. This resulted in only indirect evidence for many of the treatment decisions that were examined. Several meta-analyses also pooled studies of heterogeneous patient groups. A high risk of bias and of low power, mostly due to the rarity of the syndrome,

was also common in RCTs. Therefore, a significant number of recommendations necessarily relied more, or only, on low-quality evidence or expert's opinion. An important consideration for future research would be well-designed observational studies and RCTs of homogenous patient populations. These studies will hopefully increase the quality of evidence for the currently used treatments and answer questions about controversial issues and new potential therapies (Research agenda, table 3).

The cost and availability of suggested treatments is not a barrier to implementation of these recommendations, with the exception of IVIG. However, both treatments were recommended as first line treatment only in catastrophic APS that occurs in less than 1% of patients, while B-cell depletion and complement inhibitors may be considered in refractory cases of catastrophic APS. Implementation into clinical practice can be facilitated by the dissemination of the recommendations using the online media, by presentations in national and international congresses, development of workshops in meetings of different specialties involved in APS management, or educational lectures for health care providers in referral hospitals.

Better understanding of pathophysiologic mechanisms of APS will help to identify new therapeutic targets, and a balance between anticoagulation and immunomodulatory drugs for different APS manifestations. In addition, studies that examine homogeneous patient groups can better evaluate the efficacy and safety of the currently available and new treatments. When sufficient new information will be available, an update of the current recommendations will take place. The task force members believe that these recommendations will help to improve the quality of care in patients with APS and foster future research by highlighting evidence gaps.

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Table 1. Definitions of medium-high aPL titers and of high-risk and low-risk aPL profile

Medium-high aPL titers. Anticardiolipin (aCL) antibody of IgG and/or IgM isotype in serum or plasma present in titer >40 GPL or MPL, or > the 99th percentile, measured by a standardized ELISA. Anti-beta2glycoprotein-I antibody of IgG and/or IgM isotype in serum or plasma in titer >the 99th percentile, measured by a standardized ELISA (1).

High-risk aPL profile. The presence of lupus anticoagulant, or the presence of double (any combination of lupus anticoagulant, anticardiolipin antibodies or anti-beta2glycoprotein I antibodies) or triple (all three subtypes) aPL positivity, or the presence of persistently high aPL titers.

Low-risk aPL profile. Isolated anticardiolipin or anti-beta2glycoprotein I antibodies at low-medium titers, particularly if transiently positive (3).

Table 2. EULAR Recommendations for the prevention and management of Antiphospholipid Syndrome in adults

Overarching principles

A. Risk stratification in aPL positive individuals should include determination of the presence of a high-risk aPL profile (defined as any of the following: multiple aPL positivity, lupus anticoagulant or persistently high aPL titers), prior history of thrombotic and/or obstetric APS, co-existence of other systemic autoimmune diseases such as SLE, and the presence of traditional cardiovascular risk factors.

B. General measures for aPL positive individuals should include screening for and strict control of cardiovascular risk factors (smoking cessation; management of hypertension, dyslipidemia and diabetes, and regular physical activity) in all individuals and particularly those with a high-risk aPL profile, screening for and management of venous thrombosis risk factors, and use of low molecular weight heparin in high-risk situations such as surgery, hospitalization, prolonged immobilization and the puerperium.

C. Patient education and counseling on treatment adherence, INR monitoring in patients treated with vitamin K antagonists, use of perioperative bridging therapy with low molecular weight heparin for patients on oral anticoagulants, oral contraceptive use, pregnancy and postpartum period, postmenopausal hormone therapy, and lifestyle recommendations (diet, exercise) are important in the management of APS.

Recommendations

Statement, LoE* /GoR#	LoA (0-10) ¶
<i>Primary thromboprophylaxis in aPL positive subjects</i>	
1. In asymptomatic aPL carriers (not fulfilling any vascular or obstetric APS classification criteria) with a high-risk aPL profile with or without traditional risk factors, prophylactic treatment with LDA (75-100 mg daily) is recommended (2a/B).	9.1 (1.5)
2. In patients with SLE and no history of thrombosis or pregnancy complications:	9.5 (0.7)
a. with high-risk aPL profile, prophylactic treatment with LDA is recommended (2a/B).	
b. with low-risk aPL profile, prophylactic treatment with LDA may be considered (2b/C).	8.9 (1.7)
3. In non-pregnant women with a history of obstetric APS only (with or without SLE), prophylactic treatment with LDA after adequate	9.0 (1.3)

risk/benefit evaluation is recommended (2b/B).	
<i>Secondary thromboprophylaxis in APS</i>	
4. In patients with definite APS and first venous thrombosis: a. treatment with VKA with a target INR 2-3 is recommended (1b/B).	9.9 (0.3)
b. Rivaroxaban should not be used in patients with triple aPL positivity due to the high risk of recurrent events (1b/B). DOACs could be considered in patients not able to achieve a target INR despite good adherence to VKA or those with contraindications to VKA (e.g. allergy or intolerance to VKA) (5/D).	9.1 (1.3)
c. In patients with unprovoked first venous thrombosis, anticoagulation should be continued long-term (2b/B).	9.9 (0.3)
d. In patients with provoked first venous thrombosis, therapy should be continued for a duration recommended for patients without APS according to international guidelines (5/D). Longer anticoagulation could be considered in patients with high-risk aPL profile in repeated measurements or other risk factors for recurrence (5/D).	8.9 (1.4)
5. In patients with definite APS and recurrent venous thrombosis despite treatment with vitamin K antagonists with target INR 2-3: a. investigation of, and education on, adherence to VKA treatment, along with frequent INR testing should be considered (5/D).	9.6 (0.8)
b. if the target INR 2-3 had been achieved, addition of LDA, increase of INR target to 3-4, or change to LMWH may be considered (4-5/D).	9.4 (0.7)
6. In patients with definite APS and first arterial thrombosis: a. Treatment with VKA is recommended over treatment with LDA only (2b/C).	9.4 (0.8)
b. Treatment with VKA with INR 2-3 or INR 3-4 is recommended, considering the individual's risk of bleeding and recurrent thrombosis (1b/B). Treatment with VKA with INR 2-3 plus LDA may also be considered (4/C).	9.0 (1.3)
c. Rivaroxaban should not be used in patients with triple aPL positivity and arterial events (1b/B). Based on the current evidence, we do not recommend use of DOACs in patients with definite APS and arterial events, due to high risk of recurrent thrombosis (5/D).	9.4 (0.9)
7. In patients with recurrent arterial thrombosis despite adequate treatment with VKA, after evaluating for other potential causes, an	9.3 (1.1)

increase of INR target to 3-4, addition of LDA, or switch to LMWH can be considered (4-5/D).	
Obstetric APS	
8. In women with a high-risk aPL profile but no history of thrombosis or pregnancy complications (with or without SLE), treatment with LDA (75-100 mg daily) during pregnancy should be considered (5/D).	9.3 (1.5)
9. In women with a history of obstetric APS only (no prior thrombotic events), with or without SLE: a. In women with a history of ≥ 3 recurrent spontaneous miscarriages <10th week of gestation, and in those with a history of fetal loss (≥ 10 th week of gestation), combination treatment with LDA and heparin at prophylactic dosage during pregnancy is recommended (2b/B).	9.6 (0.9)
b. In women with a history of delivery <34 weeks of gestation due to eclampsia or severe pre-eclampsia or due to recognised features of placental insufficiency, treatment with LDA or LDA and heparin at prophylactic dosage is recommended considering the individual's risk profile (2b/B).	9.5 (0.8)
c. In women with clinical 'non-criteria' obstetric APS such as a the presence of two recurrent spontaneous miscarriages <10th week of gestation, or delivery ≥ 34 weeks of gestation due to severe pre-eclampsia or eclampsia, treatment with LDA alone or in combination with heparin might be considered based on individual's risk profile (4/D).	8.9 (1.7)
d. In women with obstetric APS treated with prophylactic dose heparin during pregnancy, continuation of heparin at prophylactic dose for 6 weeks after delivery should be considered to reduce the risk of maternal thrombosis (4/C).	9.5 (0.9)
10. In women with 'criteria' obstetric APS with recurrent pregnancy complications despite combination treatment with LDA and heparin at prophylactic dosage: increase heparin dose to therapeutic dose (5/D), or addition of HCQ (4/D), or low dose prednisolone in the 1st trimester (4/D), may be considered. Use of intravenous immunoglobulin might be considered in highly selected cases (5/D).	8.7 (1.7)
11. In women with a history of thrombotic APS, combination treatment of LDA and heparin at therapeutic dosage during pregnancy is	9.8 (0.5)

recommended (4/C).	
<i>Catastrophic APS (CAPS)</i>	
12. a. Prompt treatment of infections by early use of anti-infective medications in all aPL positive individuals, and minimization of interruptions in anticoagulation or low INR level in patients with thrombotic APS, is recommended to help prevent the development of CAPS (4/D).	9.6 (0.7)
b. For first-line treatment of patients with CAPS, combination therapy with glucocorticoids, heparin and plasma exchange or intravenous immunoglobulins is recommended over single agents or other combinations of therapies. Additionally, any triggering factor (e.g. infections, gangrene or malignancy) should be treated accordingly (5/D).	9.7 (0.6)
c. In patients with refractory CAPS, B-cell depletion (e.g. rituximab) or complement inhibition (e.g. eculizumab) therapies may be considered (4/D).	9.2 (1.0)

* Level of Evidence (LoE): 1a: systematic review of RCTs; 1b: individual RCT; 2a: systematic review of cohort studies; 2b: individual cohort study (and low-quality RCT); 3a: systematic review of case-control studies; 3b: individual case-control study; 4: case-series and poor quality cohort and case-control studies; 5: expert opinion without explicit critical appraisal, or based on physiology, bench research or ‘first principles’

Grade of Recommendation (GoR): A: consistent level 1 studies; B: consistent level 2 or 3 studies or extrapolations from level 1 studies; C: level 4 studies or extrapolations from level 2 or 3 studies; D: level 5 evidence or troublingly inconsistent or inconclusive studies of any level.

When there are multiple ratings, these follow the order of corresponding subpart of the recommendation.

¶ Numbers in column ‘LoA’ indicate the mean and SD (in parenthesis) of the level of agreement among task force members

EULAR, European League Against Rheumatism; LoE, level of evidence RCT; GoR, grade of recommendation; LoA, level of agreement; aPL, antiphospholipid antibodies; APS, antiphospholipid syndrome; SLE, systemic lupus erythematosus; INR, international normalized ratio; VKA, vitamin K antagonists; LDA, low dose aspirin; DOACs, direct oral anticoagulants; LMWH, low molecular weight heparin; IVIG, Intravenous immunoglobulin; CAPS, catastrophic APS; RCT, randomized controlled trial.

Table 3. Research agenda

Risk stratification

- Better definition of high-risk and low-risk aPL profile. Better delineation of the risk associated with different aPL profiles to allow improved classification of patients in research studies

Primary thrombosis prevention

- Impact on thrombosis risk of intensive management of traditional risk factors such as smoking cessation, control of hypertension, dyslipidemia, and sedentary behavior
- Evaluation of the role of HCQ for primary thrombosis prevention in subjects with high-risk aPL profile a. asymptomatic aPL carriers and b. patients with a history of obstetric APS without SLE c. non-criteria APS manifestations (e.g. thrombocytopenia, heart valve disease, aPL associated nephropathy)
- Evaluation of the role of statins or coenzyme Q10 for primary thrombosis prevention

Secondary thrombosis prevention

- Controlled studies of the efficacy and safety of treatment with VKA with target INR 3-4 vs combination treatment of VKA with target INR 2-3 and LDA for patients with a history of first arterial thrombosis
- Duration of VKA in provoked first venous thrombosis
- Controlled studies of the efficacy of therapy of VKA alone vs VKA plus HCQ for patients with a history of first arterial thrombosis
- Controlled studies of the efficacy and safety of targeted therapies (e.g. B cell depletion therapy, complement inhibitors, mTOR inhibitors) in recurrent arterial thrombotic events despite treatment with VKA with target INR 3-4
- Adjunctive treatment for recurrent arterial thrombosis: HCQ, statins or vitamin D. Evaluation of the role of platelet inhibitors (other than LDA) e.g. ADP receptor inhibitors, adenosine reuptake inhibitors and others.
- Discontinuation of VKA treatment in patients who became negative for aPL in repeated measurements

Obstetric APS

- Controlled studies of the efficacy and safety of treatment with LDA and heparin versus treatment with LDA, heparin, and HCQ in women with a history of recurrent obstetric complications
- Efficacy of 150 mg daily versus 100 mg daily of aspirin
- Safety and efficacy of statins in pregnant women with APS who develop pre-eclampsia despite treatment with LDA and heparin