EULAR recommendations for the management of antiphospholipid syndrome in adults

Maria G Tektonidou,1 Laura Andreoli,2 Marteen Limper,3 Zahir Amoura,4 Ricardo Cervera,5 Nathalie Costedoat-Chalumeau,6 Maria Jose Cuadrado,7 Thomas Dörner,8 Raquel Ferrer-Oliveras,9 Karen Hambly,10 Munther A Khamashta,11 Judith King,12 Francesca Marchiori,13 Pier Luigi Meroni,14 Marta Mosca,15 Vittorio Pengo,16 Luigi Raio,17 Guillermo Ruiz-Irastorza,18 Yehuda Shoenfeld,19 Ljudmila Stojanovich,20 Elisabet Svensson,21 Denis Wahl,22 Angela Tincani,2  Michael M Ward23

ABSTRACT
The objective was to develop evidence-based recommendations for the management of antiphospholipid syndrome (APS) in adults. Based on evidence from a systematic literature review and expert opinion, overarching principles and recommendations were formulated and voted. 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 counselling. 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 international normalised ratio (INR) of 2–3. In patients with APS 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 patients with APS 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 low molecular weight heparin 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. 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 (aPL) antibodies. Common APS clinical features include venous thromboembolism, stroke, recurrent early miscarriages and late pregnancy losses. According to current laboratory criteria for APS, aPL antibodies can be one of three types: lupus anticoagulant, anticardiolipin antibodies or antibeta2 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). Rarely, a life-threatening form of multorgan thrombosis, known as catastrophic APS (CAPS), can occur. The presence of aPL in asymptomatic individuals or patients with SLE who do not confirm the diagnosis of APS but can be associated with increased risk of thrombosis or pregnancy morbidity, depending on aPL characteristics and coexistence of other risk factors. The aPL type, the presence of multiple (double or triple) versus single aPL type, their titre (moderate-high titre vs low) and the persistence of aPL positivity in repeated measurements are 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.

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 difficult to know the best approach to apply in daily practice. In addition, there is a paucity of high-quality randomised controlled trials (RCTs) in APS because of the difficulties in conducting adequately sized trials in an uncommon disease and using randomised 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 European League Against Rheumatism (EULAR) standardised operating...
The guidelines for cardiovascular disease (CVD) prevention in the general population should be followed. Screening for and management of venous thrombosis risk factors are also recommended. Heparin at prophylactic dosage, preferably low molecular weight heparin (LMWH), should be used in high-risk situations such as surgery, prolonged immobilisation and the puerperium.

All patients treated with vitamin K antagonists (VKA) should receive counselling about treatment adherence, the need for
close international normalised ratio (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. Counselling should be provided on the use of contraceptives, pregnancy planning and postmenopausal hormone therapy for all women with APS. Patients should also receive dietary counseling for CVD prevention. Physical activity is encouraged in patients with APS including those on oral anticoagulants.

RECOMMENDATIONS

Table 1 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’ judgement 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 half in those who used LDA versus those who did not use LDA. 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. Neither meta-analyses 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 subanalysis of eight studies, mostly observational, in a meta-analysis. In this analysis, risk of first thrombosis was reduced by almost 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 (HQC), suggesting that LDA offers additional benefit in this patient group. 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. A recent meta-analysis including five observational studies 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 first venous thrombosis, making this evidence indirect.

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. The pooled OR for first thrombosis associated with use of LDA was 0.25 (95% CI 0.10 to 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. 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 of 2–3 is recommended. Data from an RCT reporting exclusively on patients with venous events and pooled data from five studies that included a majority with venous events showed no additional benefit of a target INR of 3–4 vs INR of 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 also have 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. Direct oral anticoagulants (DOACs) could be considered in patients not able to achieve a target INR despite good adherence to VKA or those with contraindications to VKA (eg, 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, and in one RCT of rivaroxaban versus warfarin in patients with venous thrombotic APS, there were no differences in outcomes between treatment with DOACs and VKA for venous thrombosis, but the evidence is limited by small samples, under-representation of high-risk patients with APS and short follow-up. A recent RCT of rivaroxaban versus warfarin in patients with APS with triple aPL positivity was prematurely terminated due to an excess of thromboembolic events (mostly arterial) in the rivaroxaban arm. 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 of 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 (one RCT, one retrospective cohort) 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.
## Table 1  EULAR recommendations for the prevention and management of APS in adults

### Overarching principles

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<tr>
<td>1. 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 titre), history of thrombotic and/or obstetric APS, coexistence of other systemic autoimmune diseases such as SLE, and the presence of traditional cardiovascular risk factors.</td>
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<tr>
<td>2. General measures for aPL-positive individuals should include screening for and strict control of cardiovascular risk factors (smoking cessation; management of hypertension, dyslipidaemia 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 LMWH in high-risk situations such as surgery, hospitalisation, prolonged immobilisation and the puerperium.</td>
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<tr>
<td>3. Patient education and counselling on treatment adherence, INR monitoring in patients treated with VKA, use of perioperative bridging therapy with LMWH 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.</td>
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### Recommendations

#### Statement, LoE*/GoR† LoA (0–10)‡

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<thead>
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<th>Primary thromboprophylaxis in aPL-positive subjects</th>
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<tbody>
<tr>
<td>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).</td>
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<tr>
<td>2. In patients with SLE and no history of thrombosis or pregnancy complications:</td>
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<tr>
<td>A. With high-risk aPL profile, prophylactic treatment with LDA is recommended (2a/B).</td>
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<td>B. With low-risk aPL profile, prophylactic treatment with LDA may be considered (2b/C).</td>
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<tr>
<td>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 (2b/B).</td>
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**Secondary thromboprophylaxis in APS**

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<tr>
<td>4. In patients with definite APS and first venous thrombosis:</td>
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<tr>
<td>A. Treatment with VKA with a target INR 2–3 is recommended (1b/B).</td>
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<tr>
<td>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 (eg, allergy or intolerance to VKA) (5/D).</td>
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<tr>
<td>C. In patients with unprovoked first venous thrombosis, anticoagulation should be continued long term (2b/B).</td>
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<tr>
<td>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).</td>
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<tr>
<td>5. In patients with definite APS and recurrent venous thrombosis despite treatment with VKA with target INR of 2–3:</td>
</tr>
<tr>
<td>A. Investigation of, and education on, adherence to VKA treatment, along with frequent INR testing, should be considered (5/D).</td>
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<tr>
<td>B. If the target INR of 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).</td>
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**In patients with definite APS and first arterial thrombosis:**

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<tr>
<td>A. Treatment with VKA is recommended over treatment with LDA only (2b/C).</td>
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<tr>
<td>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).</td>
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<tr>
<td>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 the high risk of recurrent thrombosis (5/D).</td>
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**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 (4–5/D).**

**Obstetric APS**

<table>
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<td>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).</td>
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<td>9. In women with a history of obstetric APS only (no prior thrombotic events), with or without SLE:</td>
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<tr>
<td>A. With a history of ≥3 recurrent spontaneous miscarriages &lt;10th week of gestation and in those with a history of fetal loss (&gt;10th week of gestation), combination treatment with LDA and heparin at prophylactic dosage during pregnancy is recommended (2b/B).</td>
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<tr>
<td>B. With a history of delivery &lt;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).</td>
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<tr>
<td>C. With clinical ‘non-criteria’ obstetric APS such as a the presence of two recurrent spontaneous miscarriages &lt;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 the individual’s risk profile (4/D).</td>
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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 expert 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 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 a target INR of 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 of 2–3 has 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 of 2–3. Evaluation of the intensity of anticoagulation and adherence to treatment, patient counseling, frequent INR monitoring or a self-monitoring programme are important in optimising anticoagulation management. For adherent patients who have a recurrent thrombotic event, the addition of LDA, increase of INR target to 3–4 or switch to LMWH can be considered based on the individual's 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 versus LDA alone.31 32 An early study in older patients with strokes reported no difference in event recurrences between LDA and warfarin, but aPL was tested only once and was mainly of low titre in this study. These issues make it difficult to apply the latter results to patients of any age who fulfil 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.

Patients with APS with arterial thrombosis have a higher risk of recurrence compared with those with venous thrombosis, and a tendency for recurrences in the same vascular (arterial) bed.33 An earlier SLR including mainly observational studies reported that recurrent events occurred more often in patients with APS treated with VKA with a target INR of 2–3 compared with an INR of 3–4, but outcomes among patients with first arterial thrombosis were not analysed specifically.33 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 RCTs34–35 showed that there was no statistically significant difference in thrombosis recurrences between treatment with VKA with a target INR of 3–4 and treatment with INR of 2–3 (relative risk (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 of 2–3 or INR of 3–4
but without statistical significance (HR 3.1 (0.3–30.0)), although
the sample was small and the achievement of a target INR of
3–4 was low.21 Because of these limitations, the higher intensity
INR approach is preferred by some centres. In decision-making,
physicians should take into account the individual’s risk of
recurrent thrombosis and major bleeding, as well as the patient’s
preferences after discussion. Alternatively, treatment with VKA
with a target INR of 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 the 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 (Apixaban for the Secondary
Prevention of Thromboembolism among patients with the Anti-
phospholipid Syndrome ((ASTRO-APS)) (ClinicalTrials.gov
identifier: NCT02295475) was recently modified after evaluation
of their initial data to exclude patients with arterial throm-
embosis. Based on these data and those from case series reporting
arterial thrombosis recurrences in patients with APS treated
with DOACs, use of DOACs is not currently recommended in
patients with definite APS and arterial events.36 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 (eg, traditional
vascular 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 19–41

Obstetric APS
8.In women with a high-risk aPL profile but no history of throm-
bosis or pregnancy complications (with or without SLE), treat-
ment with LDA (75–100 mg/day) during pregnancy should be
considered.
Data from one placebo-controlled RCT of LDA in six women
with SLE42 and data from three low-quality studies (two RCTs,
one retrospective cohort)41–45 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 the 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 throm-
botic events), with or without SLE:
A.With a history of ≥3 recurrent spontaneous miscarriages<10th
week of gestation and in those with a history of fetal loss (≥10th
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 losses46 and eight supporting observational
studies47–54 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 with 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 UFH) should be added as soon as pregnancy is confirmed.
LMWH is preferred for practical reasons.
B.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 individu-
al’s risk profile.
Data from two studies (one RCT, one retrospective cohort)48 55
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
the individual’s risk assessment including aPL profile and other
risk situations (eg, presence of other cardiovascular risk factors
or immobility).
C. With clinical ‘non-criteria’ obstetric APS, treatment with LDA
alone or in combination with heparin might be considered based
on the individual’s risk profile.
The ‘non-criteria’ obstetric APS manifestations included in our
search were the presence of two recurrent spontaneous miscar-
riages <10th week of gestation or delivery ≥34 weeks of gesta-
tion 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 an individual’s risk profile (aPL
profile, concomitant SLE, prior live births, and additional risk
factors for pregnancy loss or thrombosis).
D. 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 preg-
nancy, 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 preg-
nancy complications despite combination treatment with LDA
and heparin at prophylactic dosage, increasing heparin dose to
therapeutic dose or addition of HCQ or low-dose prednisolone in
the first trimester may be considered. Use of intravenous immu-
noglobulin (IVIG) 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. Use of IVIG was not associated with a higher proportion of live births compared with conventional treatment in three small observational studies 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. Because a history of thrombotic APS is associated with increased risk for future thrombotic or obstetric events, 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.

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. Early diagnosis and management of infections and minimisation of discontinuation or low-intensity anticoagulation, especially perioperatively, are recommended. 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. Concurrent treatment of precipitating factors is also recommended (eg, infections, gangrene or malignancy). For refractory CAPS, B cell depletion (eg, rituximab) or complement inhibition (eg, eculizumab) therapy may be considered based on data from case reports.

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 patient 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 also involved 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 low power, mostly due to the rarity of the syndrome, were also common in RCTs. Therefore, a significant number of recommendations necessarily relied more, or only, on low-quality evidence or expert opinion. An important consideration for future research would be well-designed observational studies and RCTs of homogeneous 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 (box 2).

The cost and availability of suggested treatments are not a barrier to implementation of these recommendations, with the exception of IVIG and plasmapheresis. However, both treatments were recommended as first-line treatment only in CAPS which occurs in less than 1% of patients, while B cell depletion

Box 2 Research agenda

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<td>► 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.</td>
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</table>

Primary thrombosis prevention.

► Impact on thrombosis risk of intensive management of traditional risk factors such as smoking cessation, control of hypertension, dyslipidaemia and sedentary behaviour.

► Evaluation of the role of HCQ for primary thrombosis prevention in subjects with high-risk aPL profile: (1) asymptomatic aPL carriers, (2) patients with a history of obstetric APS without SLE and (3) non-criteria APS manifestations (eg, thrombocytopenia, heart valve disease and 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 of 3–4 versus combination treatment of VKA with target INR of 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 versus VKA plus HCQ for patients with a history of first arterial thrombosis.

► Controlled studies of the efficacy and safety of targeted therapies (eg, B cell depletion therapy, complement inhibitors, or mammalian target of rapamycin (mTOR) inhibitors) in recurrent arterial thrombotic events despite treatment with VKA with a target INR of 3–4.

► Adjunctive treatment for recurrent arterial thrombosis: HCQ, statins or vitamin D. Evaluation of the role of platelet inhibitors (other than LDA), for example, 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.

aPL, antiphospholipid antibody; APS, antiphospholipid syndrome; HCQ, hydroxychloroquine; INR, international normalised ratio; LDA, low-dose aspirin; SLE, systemic lupus erythematosus; VKA, vitamin K antagonist.
and complement inhibitors may be considered in refractory cases of CAPS. Implementation into clinical practice can be facilitated by the dissemination of the recommendations using 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 the pathophysiological 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.

Author affiliations
1First Department of Propaedeutic Internal Medicine, Joint Rheumatology program, National and Kapodistrian University of Athens, Athens, Greece
2Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy
3Department of Rheumatology and Clinical Immunology, University Medical Center Utrecht, Utrecht, The Netherlands
4Sorbonne University, French National Center for SLE and APS, Service de Medecine Internes 2, InstitutE3M, Pitie Salpetriere, Paris, France
5Autoimmune Diseases, Hospital Clinic, IDIBAPS, University of Barcelona, Barcelona, Spain
6Centre de reference maladies auto-immunes et systemiques rares de l’île de France, Centre de reference maladies auto-immunes et systemiques rares de l’île de France, Paris, France
7Rheumatology Department, Clinica Universidad de Navarra, Madrid, Spain
8Department of MedRheumatology and Clinical Immunology, Charite University Hospital, Berlin, Germany
9Obstetrics and Gynecology Department and Systemic Diseases Research Unit, Vall d’Hebron Research Institute-VHIR, Barcelona, Spain
10School of Sport and Exercise Sciences, University of Kent, Chatham, UK
11Rheumatology Department, Dubai Hospital, Dubai, United Arab Emirates
12EULAR PARE Patient Research Partner, London, UK
13EULAR PARE Patient Research Partner, Rome, Italy
14MaACR, Immunohematoimmunology Research Laboratory, Istituto Auxologico Italiano, Milan, Italy
15Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy
16Department of Cardiac Thoracic and Vascular Sciences and Public Health, University of Padova, Padua, Italy
17Department of Obstetrics and Gynaecology, University Hospital of Bern, Inselspital, Bern, Switzerland
18Autoimmune Diseases Unit, Hospital Universitario Cruces, Barakaldo, Spain
19Zabłudowicz Center for Autoimmune Diseases, Sheba Medical Center, Tel-Aviv University, Israel
20Bezhaniska Kosa, Belgrade University, Belgrade, Serbia
21Department of Medicine, Solna, Rheumatology Unit, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden
22Vascular Medicine Division and Regional Competence Center for Rare Vascular and Systemic Autoimmune Diseases and Vascular Medicine Division, Nancy University Hospital, INSERM UMR-S 1116 University of Lorraine, Nancy, France
23Intramural Research Program, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, Maryland, USA

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Contributors Full-text review, data abstraction and risk of bias assessments were performed by LA and ML, and independently double-checked by MGT and MMW. MGT supervised the methodology of the SLR and prepared the evidence report. MGT and AT prepared the first draft of recommendations, and all authors participated in the discussion and formulation of recommendations. MGT supervised the project and drafted the manuscript. All authors reviewed the manuscript and approved its final version.

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REFERENCES
Recommendation


Managing antiphospholipid syndrome
This is the lay version of the EULAR recommendations for the management of antiphospholipid syndrome in adults. The original publication can be downloaded from the EULAR website: www.eular.org.


Introduction
EULAR recommendations give advice to doctors, nurses and patients about the best way to treat and manage diseases. For the first time, EULAR has developed recommendations on the management of adults with antiphospholipid syndrome.

Expert physicians, health professionals and patients worked together to develop these recommendations. Patients in the team ensured that the patient point of view was integrated in the recommendations. The authors performed a systematic literature review of the evidence for different treatments in adults with antiphospholipid syndrome.

What do we already know?
Antiphospholipid syndrome is a rare autoimmune disorder that causes inflammation and blood clots. The syndrome affects women more frequently than men. It is associated with the presence of at least one of three antiphospholipid antibodies in the blood. These three types of antibodies are called 1) lupus anticoagulant, 2) anticardiolipin antibodies and 3) antibeta2glycoprotein I antibodies. Antiphospholipid syndrome can be split into different risk categories. These are based on the levels of antibodies in your blood. Having high levels – or having two or three types of the different antiphospholipid antibodies – would put you in the high-risk category.

People with antiphospholipid syndrome are at higher risk of having a stroke or heart attack, or suffering from deep vein thrombosis (often shortened to DVT). Pregnant women with antiphospholipid syndrome have an increased risk of pregnancy complications. These complications include early miscarriage, loss of the baby in later stages of pregnancy, and preterm birth.

What do the recommendations say?
Overall, there are three general principles and 12 recommendations. The general principles say that it is important to identify factors that put people at high risk of having blood clots or pregnancy complications. They also suggest that people with antiphospholipid syndrome should follow general guidelines to prevent cardiovascular disease, and that everyone should receive education and counselling about the importance of taking their medicine as prescribed, as well as advice to help them stay fit and healthy.

Each recommendation is based on available scientific evidence or expert opinion. The more stars a recommendation has the stronger the evidence is.

One star (*) means it is a weak recommendation with limited scientific evidence.

Two stars (**) means it is a weak recommendation with some scientific evidence.

Three stars (***) means it is a strong recommendation with quite a lot of scientific evidence.

Four stars (****) means it is a strong recommendation supported with a lot of scientific evidence.
• People with a high-risk antiphospholipid antibody profile should take low-dose aspirin even if they do not have any symptoms.***
In people with a high-risk antiphospholipid antibody profile, the risk of having a first blood clot is halved by taking low-dose aspirin (75–100 mg daily).

• In people with Lupus and no history of blood clots or pregnancy complications, use of low-dose aspirin depends on their risk profile.**/***
  High-risk profile: Low-dose aspirin (75–100 mg daily) is recommended for people with Lupus and a high-risk antiphospholipid antibody profile.
  Low-risk profile: Low-dose aspirin (75–100 mg daily) can also be considered in people with Lupus and a low-risk antiphospholipid antibody profile.

• For women with a history of antiphospholipid syndrome during pregnancy, low-dose aspirin treatment is recommended once the pregnancy has come to an end.***
The use of low-dose aspirin (75–100 mg daily) will depend on your antiphospholipid antibody profile, and your general cardiovascular risk.

• In people with definite antiphospholipid syndrome and a first blood clot in a vein, treatment with an anticoagulant called a vitamin K antagonist is recommended.****
Vitamin K antagonists are recommended to treat blood clots in people with antiphospholipid syndrome. In people with clotting problems despite good adherence to a vitamin K antagonist, a class of drugs called direct oral anticoagulants can be considered instead. Direct oral anticoagulants can also be used in people with an allergy or intolerance to vitamin K antagonists. Triple aPL positivity: However, a type of direct oral anticoagulant called rivaroxaban should not be used in people who have all three kinds of antiphospholipid antibodies (often called triple aPL positivity).

• In people with definite antiphospholipid syndrome and repeated blood clots in veins despite treatment with a vitamin K antagonist, monitoring or changing treatment may be needed.*
Monitoring may be needed to make sure that the vitamin K antagonist is being taken properly, and that blood clotting targets are met. If targets are met, adding low-dose aspirin or changing treatment to a low molecular weight heparin (sometimes shortened to LMWH) could also be considered to help prevent blood clots.

• In people with definite antiphospholipid syndrome and a first blood clot in an artery, treatment with a vitamin K antagonist is recommended.**
Clots in an artery are more likely to come back. Vitamin K antagonists are recommended in people with a blood clot in an artery.
  Triple aPL positivity: Rivaroxaban should not be used in people with triple aPL positivity and arterial thrombosis.

• In people with blood clots in their arteries that have come back despite taking a vitamin K antagonist, adding low-dose aspirin or changing to LMWH may be considered.*
Other drugs such as anti-malarials or statins could also be considered.

• In women with a high-risk antiphospholipid antibody profile but no history of blood clots or pregnancy complications, low-dose aspirin during pregnancy should be considered.*
This recommendation applies to women with or without Lupus. Low-dose aspirin can help to prevent pregnancy complications and should be given at a dose of 75–100 mg per day.
• In women with a history of antiphospholipid syndrome during pregnancy only (no prior clots), low-dose aspirin on its own or in combination with heparin might be needed depending on previous pregnancy complications.***

  *Three or more miscarriages*: Women who have had three or more spontaneous miscarriages before the 10th week should receive low-dose aspirin and heparin at a prophylactic dose during pregnancy.
  *Fetal loss at or after the 10th week*: Low-dose aspirin and heparin at a prophylactic dose during pregnancy is recommended.
  *Preterm birth*: Low-dose aspirin on its own or in combination with heparin is recommended for women who have had a baby before the 34th week of pregnancy because of eclampsia or severe pre-eclampsia, or placental insufficiency.
  *Two miscarriages, or delivery after 34 weeks due to severe pre-eclampsia or eclampsia*: Low-dose aspirin either alone or in combination with heparin might be considered for women who have had two recurrent spontaneous miscarriages before the 10th week or delivered a baby after 34 weeks due to eclampsia or severe pre-eclampsia (based mainly on expert’s opinion).
  *After delivery*: Women who receive heparin during pregnancy should continue the dose for 6 weeks after the baby is born to reduce the risk of blood clots.

• Women who have repeated pregnancy complications despite treatment with low-dose aspirin and heparin can consider increasing the heparin dose or adding a different medicine.*

  An increased heparin dose, the addition of hydroxychloroquine during pregnancy, or addition of low-dose prednisolone in the first trimester might be considered for women who keep having pregnancy complications despite taking low-dose aspirin.

• Women with a history of blood clots due to antiphospholipid syndrome should receive higher dose (therapeutic dose) of heparin during pregnancy.**

  Women who are taking a vitamin K antagonist for their antiphospholipid syndrome should switch to heparin as soon as their pregnancy is confirmed, and ideally before week 6.

• In people with antiphospholipid antibodies, any infections should be treated quickly, and interruptions in anticoagulation medicine should be minimised.*

  This can help to prevent the development of catastrophic antiphospholipid syndrome (often shortened to CAPS). CAPS can happen when people stop taking their anticoagulation treatment, have infections, or after surgery.

Summary

Overall, the recommendations highlight the general management for people with antiphospholipid syndrome. If you have this condition, these recommendations will give you some guidance on what to expect from your doctor and what treatments you may be offered.

Recommendations with just one or two stars are based mainly on expert opinion and not backed up by appropriate clinical studies. They may be as important as those with three or four stars.

If you have any questions or concerns about your disease or your medication, you should speak to a health professional involved in your care.