An update on the management of antiphospholipid syndrome

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Abstract: Antiphospholipid syndrome (APS) is a systemic autoimmune disorder characterized by recurrent venous or arterial thrombosis with or without pregnancy morbidity in the presence of persistent antiphospholipid (aPL) autoantibodies. Anticoagulation has, until now, formed the cornerstone of treatment but a significant proportion of patients continue to experience thrombosis and pregnancy morbidity despite this treatment. Thrombosis is the most common cause of mortality and accounts for two fifths of deaths. Direct oral anticoagulant drugs represent an attractive alternative to conventional vitamin K antagonist drugs but emerging evidence suggests these may not be suitable for high-risk patients with thrombotic APS. Laboratory studies and case reports of the successful use of different classes of drugs in APS is increasing our understanding of the other pathophysiological mechanisms which may contribute to the high morbidity of APS. This review summarizes current accepted anticoagulant treatment for APS and examines other potential drugs such as immunomodulating agents, statins and novel agents such as sirolimus and defibrotide.

Keywords: antiphospholipid antibodies, antiphospholipid syndrome, treatment

Introduction
Antiphospholipid syndrome (APS) is a systemic autoimmune disorder characterized by recurrent venous or arterial thrombosis with or without pregnancy morbidity in the presence of persistent antiphospholipid (aPL) autoantibodies. These include the lupus anticoagulant (LA), anticardiolipin (aCL) and antibeta-2 glycoprotein (anti-β2GPI) autoantibodies, which should be present in moderate-to-high titre on two occasions at least 12 weeks apart. The condition was first described in association with systemic lupus erythematosus (SLE) but in 53% of patients, it exists alone as primary APS (PAPS).1 Classification criteria for definite APS were devised in Sapporo, Japan, in 19992 and were later updated in Sydney, Australia, in 20063 (Table 1). APS is also less commonly associated with other autoimmune rheumatic diseases such as rheumatoid arthritis, dermatomyositis, systemic sclerosis and Sjögren’s syndrome.

APS is a significant cause of morbidity and mortality. It is estimated to account for 6% of all pregnancy morbidity, 13.5% of stroke, 11% of myocardial infarction and 9.5% of deep vein thromboses.4 Other commonly reported but non-classification criteria manifestations include thrombocytopenia, autoimmune haemolytic anaemia, livedo reticularis, superficial thrombophlebitis, aPL-associated nephropathy, cognitive dysfunction, skin ulcers, epilepsy, cardiac valve dysfunction and vegetations. Obstetric manifestations include recurrent early and late pregnancy loss, pre-eclampsia, eclampsia and intrauterine growth restriction.

A striking feature of the disease is that thromboses can occur in any vascular bed. Catastrophic APS (CAPS) is a rare, life-threatening variant of APS. It is characterized by the acute development of widespread thrombosis resulting in the failure of three or more organs in less than 1 week. It can occur as the presenting event or in those with known APS. The mortality rate is high, 30–50% despite treatment.1,5 In patients with previous thrombosis attributable to APS, anticoagulation has formed the cornerstone of treatment to date. Active inflammation in any...
associated autoimmune disease such as SLE, and especially in the presence of aPL, is associated with an increased thrombotic risk, and medical management of such conditions is imperative. Anticoagulation appears to have improved the morbidity and mortality associated with thrombotic APS but significant challenges remain in preventing APS-related morbidity. Treatment of patients with obstetric APS has improved live birth rates from 40% to 85%, but 15% still fail to achieve a live birth. Data from the largest published cohort study of APS, the Euro-Phospholipid cohort, reported a reduction in mortality from 5.3% in the initial 5 years of follow up to 4.5% in the latter 5 years. In the same cohort, however, severe thrombotic events still accounted for the majority of deaths (37%), infection and major haemorrhage were the second and third most common causes of death and accounted for 27% and 11% of deaths, respectively. The increased risk of infection appears not only to be limited to SLE-associated APS (SLE-APS) individuals receiving immuno-suppressive drugs, but also to patients with PAPS.

Several nonanticoagulant drugs have demonstrated therapeutic potential in the treatment of the disease, and our increasing understanding of the pathophysiology may lead to a more multifaceted approach to treatment and further reduction of such complications. In this review, we aimed to summarize the current recommended and emerging treatment for thrombotic, obstetric and non-criteria manifestations of APS.

### Primary antithrombotic prophylaxis: antiplatelet agents

Low-dose aspirin (LDA) is used in the general population for the secondary prevention of arterial thrombosis. In patients with SLE and persistent aPL, but no prior thrombosis, there is evidence that aspirin reduces the incidence of first thrombosis (arterial or venous). The role of aspirin for primary prevention in asymptomatic patients with persistent aPL is less clear. Retrospective studies suggest that aspirin reduces the incidence of thrombosis in this population, but no prospective studies have demonstrated the same effect. Retrospective studies also suggest a stronger protective effect for arterial events. Recently published European League Against Rheumatism (EULAR) guidance recommends prophylactic

### Table 1. Revised classification criteria for APS 2006 (adapted from Myakis et al.3).

| Clinical criteria* |
|-------------------|
| (1) Vascular thrombosis: one or more clinical episodes of arterial, venous, or small vessel thrombosis, in any tissue or organ |
| (2) Pregnancy morbidity: |
| (a) one or more unexplained deaths of a morphologically normal foetus at or beyond the 10th week of gestation; or |
| (b) one or more premature births of a morphologically normal neonate before the 34th week of gestation because of: (i) eclampsia or severe pre-eclampsia; or (ii) recognized features of placental insufficiency; or |
| (c) three or more unexplained consecutive spontaneous abortions before the 10th week of gestation, with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded |

| Laboratory criteria*+ |
|----------------------|
| (1) Lupus anticoagulant present in plasma |
| (2) Anticardiolipin antibody of IgG or IgM isotype in serum, in medium or high titre (i.e. >40 GPL or MPL, or >99th percentile measured by a standardized ELISA) |
| (3) Anti-β2 glycoprotein-I antibody of IgG or IgM isotype in serum [in titre > 99th percentile] measured by a standardized ELISA |

*At least one clinical and one laboratory criterion are required for the diagnosis of definite APS.
†Include abnormal foetal surveillance tests, abnormal Doppler velocimetry waveform analysis, oligohydramnios or a postnatal birth weight less than the 10th percentile for the gestational age.
+Must be present on two occasions at least 12 weeks apart.
APS, antiphospholipid syndrome; ELISA, enzyme-linked immunosorbent assay; GPL, IgG antiphospholipid units/mL; IgG, immunoglobulin G; MPL, IgM antiphospholipid units/mL.
LDA in asymptomatic aPL carriers with a high-risk profile [persistently high aPL titres, ‘double’ or ‘triple positivity’ (a combination of LA and one of aCL or β2GPI, or all three)].

Secondary antithrombotic prophylaxis: anticoagulant treatment

Vitamin K antagonists
The gold standard treatment for APS patients who have suffered a thrombosis is treatment with an oral vitamin K antagonist (VKA) to achieve a target international normalized ratio (INR) of 2.0–3.0.9 Recurrence rates without anticoagulation are high and given this, it is generally accepted that anticoagulation should be continued lifelong. The Euro-Phospholipid cohort, a descriptive study of 1000 patients followed up over a 10-year period found 17.7% of patients had recurrent thromboses despite standard anticoagulant treatment.1 Retrospective studies have suggested that this risk is reduced with higher-intensity anticoagulation.12 Two randomized controlled trials (RCTs), however, concluded that a target INR of 3.0–4.0 does not confer any increased benefit compared with standard-intensity anticoagulation (target INR 2.0–3.0).13,14 These studies, however, did not consider the heterogeneity of clinical and laboratory features of individuals included in the study. It is well recognized that previous arterial thromboses, recurrent thromboses (venous or arterial) while on anticoagulation and autoantibody ‘triple positivity’ (the presence of LA, aCL and β2GPI) convey a high risk of recurrent thrombosis. Neither study tested for β2GPI and the rate of triple positivity was therefore not determined. The Warfarin in the AntiPhospholipid Syndrome (WAPS) study included less than 30% of patients with previous arterial thrombosis and the study by Crowther and colleagues excluded patients with previous recurrent thrombosis on anticoagulation. Crowther and colleagues found a higher rate of thrombotic recurrence in the group assigned high-intensity anticoagulation but this did not reach statistical significance (10.7% versus 3.4%). Actual INRs at the time of thrombosis were also <3.0 in four of the six individuals who developed thrombotic recurrences in the high-intensity group.14 Furthermore, the INR was below target in all individuals for a significant proportion of time in both the Crowther and colleagues’ and WAPS studies (43% and 19%, respectively). This supports clinical evidence that it is often difficult to consistently maintain INRs in the target range in APS, particularly in those with high-intensity target ranges. This is often due to difficulty in managing dosing by prescribers and the potentially lower acceptability to patients. A systematic review by Ruiz-Irastorza and coworkers included both prospective and retrospective studies, and found that 86% of recurrences occurred with actual INRs < 3.0. Recurrent arterial thromboses that occur at a target INR 2.0–3.0, appear to occur more commonly than venous events and are more likely to be fatal.15 A metanalysis by Finazzi and colleagues, the review by Ruiz-Irastorza and coworkers and a recent EULAR review all supported standard-intensity anticoagulation for APS patients with first venous events, but the latter two reviews recommended a target INR > 3.0 in those with recurrent venous or arterial events.8,13,15

Thrombosis is the major cause of death in APS and accounts for around three times as many deaths as haemorrhage1 but the correlation between high-intensity anticoagulation and bleeding risk has not been clearly elucidated. In the Euro-Phospholipid study, 33% of major bleeds occurred at INR > 3.0 but clinical studies have suggested no significant difference in bleeding between target INRs of 2.0–3.0 and 3.0–4.0.16 As noted above, however, actual time spent within target is frequently suboptimal. Further studies with larger numbers of high-risk APS patients are required but are difficult to conduct.

The 13th International Congress on Anti-phospholipid Antibodies task force, as well as current EULAR guidance recommend that patients with definite APS and a first venous event receive lifelong oral anticoagulation to a target INR of 2.0–3.0. EULAR also distinguishes those patients with unprovoked first venous thrombosis and recommends that anticoagulation in this group be continued for a duration for patients without APS, unless a high-risk aPL profile or other risk factors for recurrence are present.14 Lifelong high- or standard-intensity anticoagulation plus an antiplatelet drug (APD) are advised; however, for those with arterial thrombosis or recurrent venous thromboembolism (VTE) on standard intensity treatment.9,11

Direct oral anticoagulants
Direct oral anticoagulants (DOACs) such as rivaroxaban, apixaban and dabigatran are licensed
for use in the general population for the secondary prevention of VTE and the prevention of arterial thrombosis in nonvalvular atrial fibrillation. They are attractive alternative agents to VKAs because they do not require blood monitoring, have fewer dietary and drug interactions and have a rapid and predictable onset of action which precludes the need for heparinization in the acute setting. It should be noted that several commonly prescribed drugs can potentiate or inhibit DOAC activity and include diltiazem, ketoconazole and carbamazepine. Such interactions have recently been reviewed in detail elsewhere.\(^\text{17}\)

To date, two RCTs have been published comparing warfarin treatment with rivaroxaban for secondary thrombotic prophylaxis in APS. The Rivaroxaban in APS (RAPS) study used a laboratory surrogate: the percentage change in endogenous thrombin potential (ETP) time as its primary outcome measure. It was not powered to assess clinical outcomes and patients with previous arterial thromboses and recurrent venous thrombotic events were excluded. The authors concluded inferiority of rivaroxaban based on the ETP surrogate outcome measure but suggested that the drug may be a safe alternative to warfarin in uncomplicated APS patients with a single previous VTE, as no thromboses and no episodes of major bleeding occurred during the short follow-up period of 6 months.\(^\text{18}\)

Several observational cohort studies of DOACs for secondary thrombotic prophylaxis have been published. The patients included in these studies are heterogenous in terms of aPL profiles, history of previous venous/arterial events and length of follow up. Of note, in all studies, the majority of recurrent thrombotic events during treatment with a DOAC occurred in triple-positive patients.\(^\text{19}\)

The Trial on Rivaroxaban in Anti-Phospholipid Syndrome (TRAPS) study was a noninferiority trial, designed to compare rivaroxaban with standard-intensity anticoagulation with warfarin in triple-positive patients.\(^\text{20}\) It was prematurely terminated after the enrolment of 120 patients, due to an excess risk of thrombotic events in seven subjects treated with rivaroxaban (versus zero in the arm randomized to warfarin). DOACs may therefore not be suitable for triple-positive APS patients with arterial events/recurrent venous events until further data are available. They might be considered for the prevention of VTE in patients with low-risk aPL profiles who are intolerant of, or poorly compliant with, VKAs. When there are concerns regarding VKA compliance, it should also be considered that such individuals may also be nonadherent to DOACs where monitoring of the anticoagulant effect is not routinely measured. Moreover, the European Medicines Agency also recently issued a special warning that DOACs are not recommended for APS patients with a history of thrombosis, especially in those that are triple positive.\(^\text{21}\)

There have been no trials using DOACs for non-criteria APS manifestations but one case report has described the successful use of apixaban in the treatment of pyoderma gangrenosum which did not respond to VKA or rivaroxaban. The authors postulate that the twice-daily dosing of apixaban may have explained a poor response to rivaroxaban administered once daily.\(^\text{22}\) ASTRO-APS is a pragmatic phase II open label RCT comparing apixaban with standard-intensity warfarin (target INR 2.0–3.0) for secondary thrombosis prevention, and is currently ongoing.\(^\text{23}\)

**Pregnancy morbidity**

Prepregnancy counselling in patients with known APS is vital to ensure conventional cardiovascular and APS-specific risk factors can be identified and managed. Previous pregnancy outcomes and triple-antibody positivity are the best predictors of adverse pregnancy outcomes in APS, but other factors include SLE-APS and previous history of thrombosis. Of the three diagnostic aPLs, LA is most predictive of adverse pregnancy outcome.\(^\text{24}\)

VKAs are teratogenic; therefore, in APS patients with prior thrombosis or pregnancy morbidity, therapeutic dose low-molecular-weight heparin (LMWH) and LDA is accepted treatment. For those patients with purely obstetric APS and no prior thrombosis (OAPS), prophylactic dose LMWH and LDA until 6 weeks postpartum is recommended.\(^\text{7}\) In addition to routine foetal monitoring scans, monthly ultrasound scans with power Doppler imaging, are recommended during the third trimester of pregnancy to assess for signs of placental insufficiency.\(^\text{7}\) These measures have improved live birth rates from 40% to 85%.\(^\text{7}\)

aPL antibodies themselves bind and cause a direct cytotoxic effect to syncytiotrophoblasts.\(^\text{25}\) Prednisolone in the first trimester, intravenous immunoglobulin and plasmapheresis have all been suggested as treatment for refractory cases but well-conducted studies are lacking.
Interestingly, low-dose prednisolone was shown in a small RCT to improve pregnancy outcomes in women with unexplained recurrent pregnancy loss unrelated to APS. Low-dose prednisolone might therefore reasonably be trialled in refractory APS cases under specialist obstetric care.

A logical assumption is that pregnancy morbidity in APS is caused only by thrombosis, but studies examining placental histology have found that this is not invariable, and microvascular thrombosis is also found in miscarriage secondary to other aetiologies. A recent systematic review identified six histological obstetric APS hallmark features, including placental infarction, impaired spiral artery remodelling, decidual inflammation and complement deposition. The role of complement in the pathophysiology of OAPS, is supported by the finding that anticoagulant treatment with fondaparinux, a factor Xa inhibitor, and hirudin, a thrombin inhibitor, does not confer the same benefits as heparin. The therapeutic effect conferred by heparin appears therefore to be due to its effect on complement and not solely its anticoagulant effect.

OAPS and thrombosis

There is no real consensus on whether patients with OAPS should continue long-term antithrombotic or anticoagulant treatment. These patients are at increased risk of thrombotic manifestations compared with the general population. One longitudinal cohort study included 517 individuals with OAPS and reported annual rates of deep vein thrombosis of 1.46%, pulmonary embolism 0.43%, superficial vein thrombosis 0.44% and stroke 0.32% over a 10-year follow-up period. These rates were significantly higher than in women with a history of recurrent miscarriage with/without hereditary thrombophilia and despite treatment with low-dose aspirin. A more recent but smaller retrospective study included 47 OAPS patients and found a much higher thrombosis risk of 63%. These occurred a mean of 7.6 years after initial pregnancy morbidity and were associated with multiple aPL positivity, noncriteria APS manifestations and conventional cardiovascular risk factors. EULAR recommends that individuals with a history of OAPS be offered prophylactic-dose LDA and pending further studies, it seems appropriate to consider LDA ± anticoagulant treatment in patients with OAPS and other risk factors for thrombosis.

Immune-modulating therapies in thrombotic and pure obstetric APS

Hydroxychloroquine

In the 1970s, antimalarials were used as postoperative VTE prophylaxis following the observation that in vitro, hydroxychloroquine (HCQ) reduced erythrocyte aggregation and in rabbits reduced thrombus size. It is a low-cost drug that is generally well tolerated. The benefits associated with its long-term use in patients with SLE are well recognized and it is recommended treatment for all SLE patients (with and without APS) without contraindication to the drug. In SLE-APS, and also those without aPL, HCQ use is associated with a reduction in the rates of arterial and venous thromboses. It has been suggested to also have a similar effect in PAPS. HCQ administration in mouse models of APS limits aPL binding on target cells and causes a reduction in pro-inflammatory activity, and the size and duration of thrombus. The role of HCQ in primary prophylaxis in PAPS is yet to be determined. A small, nonrandomized study of HCQ use in the prevention of VTE in PAPS suggested a significant reduction in arterial recurrence when given alongside a VKA, compared with a VKA alone. A recent multicentre international RCT was designed to test these findings but was terminated early due to low recruitment and a low rate of clinical events. Another recent study, HIBISCUS, plans to examine the effect of HCQ on secondary thrombosis and APS-related pregnancy morbidity in PAPS. Pending these results and given the long-term relative safety of HCQ, it seems reasonable to consider the addition of HCQ to VKA in the treatment of PAPS patients with previous arterial or recurrent thrombosis especially in high-risk patients.

In vitro HCQ appears to partially reverse aPL-induced impaired trophoblast migration and in a murine APS model, HCQ inhibits complement and prevents placental insufficiency and cerebral foetal abnormalities. Retrospective studies in humans, have suggested that the addition of HCQ to conventional treatment may be associated with a reduction of first-trimester miscarriages and an increase in live births, but only one study has examined this in PAPS patients, specifically. The first RCT in this context, the HYPATIA trial, is a multicentre trial currently ongoing. It will examine the use of HCQ versus placebo in aPL-positive women planning to conceive.
results, it again seems reasonable to consider the addition of HCQ to those patients with obstetric PAPS refractory to conventional treatment and before any consideration of low-dose prednisolone given its more favourable safety profile in pregnancy.

Rituximab

*In vitro* studies have shown that B lymphocytes are involved in aPL production and rituximab is an anti-CD20 monoclonal antibody which deletes CD20-positive B cells. The RITAPS study, an open label phase II trial, examined the safety of rituximab in 19 patients with noncriteria APS manifestations. Thrombocytopenia and skin ulcers appeared to respond most favourably to rituximab treatment.46 There was no significant difference in aPL titres before and after treatment, which led authors to suggest that clinical benefits may occur through mechanisms independent of autoantibody production.

Two published cohort studies suggest that rituximab may be effective for preventing thromboses in patients with SLE-APS. Wang and coworkers described five patients treated with rituximab for recurrent thromboses despite anticoagulation with VKA and a target INR 2.0–3.0.47 Only one patient developed thrombosis, but this was CAPS, 36 months after treatment. aPL titres were noted to reduce in all patients. Emmi and colleagues reported seven patients given rituximab for active SLE and, similar to the study by Wang and coworkers, only one patient developed thrombosis (again, CAPS).48 There was, however, no significant difference in aPL titres before and after treatment. Of note, 5/7 had had previous arterial events and 4/7 were taking anticoagulants. Further study is needed to confirm these positive effects, but rituximab appears to be a promising treatment for SLE-APS patients with thrombotic disease refractory to conventional anticoagulant treatment, particularly if they have evidence of active SLE.

Belimumab

Belimumab has recently been reported in the treatment of two patients with PAPS. One achieved clinical remission after treatment for 6 months with belimumab for recurrent pulmonary necrotizing neutrophilic capillaritis. The other patient suffered recurrent skin ulcers and demonstrated an initially good healing response but treatment had to be stopped due to infection of the biopsy site.49 Despite these promising data, it is highly unlikely that B-cell-directed therapies will replace conventional anticoagulant therapies, particularly in PAPS patients, given the high cost of these drugs and the extensive data supporting VKAs.

Future treatment: the emerging role of vasculopathy

Thrombosis has been traditionally regarded as the hallmark of APS but there is increasing evidence that APS is a disease not only of thrombosis, but also of chronic vasculopathy, which can develop in patients despite anticoagulation. *In vitro*, complement activation by aPL of varying specificities induce the expression of tissue factor and adhesion molecules and the activation of platelets and polymorphonuclear cells.50 Through a number of different signalling pathways, pro-inflammatory cytokine expression results in several outcomes, including neointimal proliferation, fibrosis, neutrophil extracellular trap activation and release (NETosis), thrombosis with or without atherosclerosis. In APS patients with pregnancy morbidity, decidual vasculopathy is ubiquitous, and vascular lesions have also been implicated in cognitive impairment caused by APS (a noncriteria manifestation). aPL positivity in SLE patients also, somewhat paradoxically, confers an increased risk of haemorrhagic complications following renal biopsy, most likely due to renal vasculopathy.51

Eculizumab

Eculizumab is a humanized monoclonal antibody against the C5 complement component. It is licensed for the treatment of paroxysmal nocturnal haemoglobinuria and atypical haemolytic uraemic syndrome. It has also been used successfully to prevent thrombotic microangiopathy following renal transplantation for APS nephropathy in several case reports52,53 and a phase II trial of eculizumab for the prevention and treatment of kidney graft reperfusion injury is currently ongoing [ClinicalTrials.gov identifier: NCT01756508]. Eculizumab has also been used in patients with CAPS and one patient during pregnancy. In the latter patient, only small traces of the drug were found to cross the placenta,54 suggesting potential safety in pregnancy. Another phase II trial which aimed to examine the use of another C5a inhibitor in the treatment of noncriteria APS manifestations was unfortunately terminated prematurely due to
slow recruitment [ClinicalTrials.gov identifier: NCT02128269]. Given the high cost of C5 inhibitors, their role may be limited to off-label use in severe cases of CAPS in which mortality is high despite conventional treatment, and RCTs are near impossible to conduct.

**Sirolimus**

Sirolimus kinase also known rapamycin, inhibits neointimal proliferation after endovascular injury through inhibition of mammalian target of rapamycin complex (mTORC) signalling. It is used in coronary artery stents to prevent restenosis and thrombosis. Canaud and colleagues examined vascular specimens from patients with APS nephropathy and CAPS and found increased mTORC expression. In vitro it was shown that aPL activate the mTORC signalling pathway and thereby induce vascular intimal hyperplasia.55 Patients treated with sirolimus following renal transplantation for APS nephropathy had a higher graft survival and function. Biopsy specimens also showed a reduction of vascular proliferation on histology.55

**Defibrotide**

Defibrotide is a mixture of single (90%) and double-stranded (10%) phosphodiester oligonucleotides which has antithrombotic, anti-inflammatory and anti-ischaemic properties. It is currently approved for the treatment of hepatic veno-occlusive disease in patients following stem-cell transplant.56 Richardson and coworkers reported its successful use in the treatment of one patient with CAPS. In the same patient, markers of vascular endothelial cell stress, such as antitumour necrosis factor alpha, also were reduced.57

**Statins**

Statins are widely used for the treatment of hypercholesterolaemia and in secondary prevention of atherosclerotic disease. There is extensive in vitro evidence of the pleiotropic effects of these drugs including the inhibition of vascular adhesion molecules, interleukin 6 and tissue factor in endothelial cells.58 In humans, fluvastatin has been shown to significantly reduce pro-inflammatory and pro-thrombotic markers in APS patients. Follow up was limited to 3 months and one patient (1/41) with SLE-APS suffered a deep vein thrombosis; but the study was not designed to assess clinical outcomes.59 The reduction in pro-inflammatory markers was independent of whether the patient had primary or APS with an associated rheumatic disease, or was an asymptomatic aPL carrier. Another small study administered pravastatin to pregnant individuals with APS who had developed pre-eclampsia or intrauterine growth restriction despite treatment with LDA and LMWH. Pravastatin was associated with improved placental blood flow and a longer gestation compared with those who did not receive the drug.50

There is a clear need for clinical trials examining the effect of statins on thrombosis and pregnancy morbidity in APS. In the meantime, it seems appropriate to offer APS patients with hypercholesterolaemia, other cardiovascular risk factors or thrombotic disease resistant to conventional anticoagulation, treatment with a statin.

**Conclusion**

The Euro-Phospholipid study has demonstrated that conventional anticoagulant treatment has improved the life expectancy of APS patients. Thrombosis, however, remains the most common cause of death and further study is required to elucidate the optimal means of secondary prevention. VKAs are the drug of choice for most patients and the improved availability of point of care INR testing may offer patients more autonomy, better quality of life, and therefore, better compliance with VKA treatment. APS is a heterogeneous condition, and this must be carefully considered in the design of clinical trials. In particular, adequate numbers of patients who are at high risk of thrombosis must be included. Further work and continued international collaboration are required to guide evidence-based treatments for conventional and noncriteria APS manifestations. Our increasing recognition and understanding of the disease as a vasculopathy may lead to the development of new antiproliferative agents or increasing use of existing drugs such as sirolimus and defibrotide for which further study is required.

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