Antiphospholipid syndrome

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Abstract | Antiphospholipid syndrome (APS) is an autoimmune disease characterized by the presence of antiphospholipid antibodies, such as lupus anticoagulant, anticardiolipin antibodies and anti-β2-glycoprotein 1 antibodies. APS can present with a variety of clinical phenotypes, including thrombosis in the veins, arteries and microvasculature as well as obstetrical complications. The pathophysiological hallmark is thrombosis, but other factors such as complement activation might be important. Prevention of thrombotic manifestations associated with APS includes lifestyle changes and, in individuals at high risk, low-dose aspirin. Prevention and treatment of thrombotic events are dependent mainly on the use of vitamin K antagonists. Immunosuppression and anticomplement therapy have been used anecdotally but have not been adequately tested. Pregnancy morbidity includes unexplained recurrent early miscarriage, fetal death and late obstetrical manifestation such as pre-eclampsia, premature birth or fetal growth restriction associated with placental insufficiency. Current treatment to prevent obstetrical morbidity is based on low-dose aspirin and/or low-molecular-weight heparin and has improved pregnancy outcomes to achieve successful live birth in >70% of pregnancies. Although hydroxychloroquine and pravastatin might further improve pregnancy outcomes, prospective clinical trials are required to confirm these findings.

Almost 35 years after the original description of antiphospholipid syndrome (APS), our understanding of this disorder is still evolving. Although APS was initially described as an acquired, autoimmune thrombophilia, we know today that mechanisms other than coagulation-mediated thrombosis contribute to some clinical manifestations; for instance, complement activation might mediate placental injury, which can cause fetal loss[1]. APS is an autoimmune disease associated with the presence of autoantibodies. These autoantibodies include anticardiolipin antibodies, anti-β2-glycoprotein 1 antibodies and lupus anticoagulant. Anticardiolipin antibodies are directed against cardiolipin, which is a phospholipid contained in cell membranes. Anti-β2-glycoprotein 1 antibodies are directed against β2-glycoprotein 1 — a cardiolipin-binding factor. Lastly, lupus anticoagulant is a mixture of various autoantibodies, which are detected by the prolongation of phospholipid-dependent coagulation tests.

The diagnosis of APS is based on the combination of clinical features (for example, thrombosis in the arteries, veins and/or small vessels or obstetrical complications such as recurrent miscarriage and placental insufficiency) and the detection of circulating antiphospholipid antibodies. The classification criteria presented in BOX 1 are often used as diagnostic tools[2]. However, other features such as thrombocytopenia and cardiac valve lesions also occur within the spectrum of APS.

The management of APS has been subject to controversy in recent years. Anticoagulation therapy is considered the cornerstone of therapy; however, the optimal agents and the intensity of treatment remain a matter of debate[3]. The final treatment decision is dependent on the clinical manifestations, the antiphospholipid antibody profile and the concurrent cardiovascular risk factors. In fact, despite the dearth of studies focused on the influence of treating hypertension, dyslipidaemia and diabetes mellitus as well as cessation of tobacco smoking in those with APS, such measures are considered by experts to be vital to reduce the risk of future thrombosis[3].

As APS is a fairly new and rare disease, good-quality data to guide treatment are scarce; treatment decisions have relied on expert opinion in many cases. This Primer provides an update on the pathogenesis, diagnosis and therapeutic aspects of APS from an academic and practical point of view and offers an outlook on future research topics, with the acknowledgement that many established concepts of today may change in ensuing years.

Epidemiology

Antiphospholipid antibodies are not specific to APS but can be detected in different clinical settings, including

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in healthy individuals, in individuals with a history of thrombosis and/or pregnancy morbidity and in individuals with other autoimmune conditions (including systemic lupus erythematosus (SLE)) (TABLE 1).

General population

The overall prevalence of antiphospholipid antibodies and APS in the general population remains to be determined, as no robust epidemiological population-based studies have been performed[4]. Moreover, despite considerable efforts over the past three decades geared towards the standardization of immunoassays that measure antiphospholipid antibodies, profound inter-assay and interlaboratory variation are still reported[5]. Consequently, the availability of solid epidemiological data on the prevalence of antiphospholipid antibody positivity and APS in the general population is limited.

Durcan and Petri estimated that the incidence of APS is ~5 new cases per 100,000 individuals per year and that the prevalence is ~40–50 cases per 100,000 individuals[6]. The prevalence of catastrophic APS, a rare, life-threatening form of APS, has been estimated to be <1% of all cases of APS[7]. Studies have estimated that the prevalence of antiphospholipid antibodies in the general population ranges between 1% and 5%, but the antibody titre in most of these studies was low[8]. An increased prevalence of antiphospholipid antibodies has been reported with ageing, with the highest values reported in healthy centenarians but without an association with clinical manifestations of APS[9].

Thrombosis

The presence of antiphospholipid antibodies is a risk factor for thrombosis; consequently, the prevalence of antiphospholipid antibodies is higher in individuals with thrombotic or cardiovascular events than in the general population. The APS ACTION group reported a literature review focused on the prevalence of antiphospholipid antibodies in the general population with pregnancy morbidity, stroke, myocardial infarction and deep vein thrombosis. The authors estimated that ~13% of individuals with stroke, ~11% of individuals with myocardial infarction and ~9.5% of individuals with deep vein thrombosis are positive for antiphospholipid antibodies[10]. Another study in women <50 years of age who had had a stroke showed that 17% were positive for lupus anticoagulant compared with 0.7% in the control group (OR of 43.1)[11]. Positivity for lupus anticoagulant combined with oestrogen-containing oral contraceptive use or smoking increased the risk further (to an OR of 201.0 and 87.0, respectively[11].

Individuals who have had obstetrical complications associated with APS are also at increased risk of developing thrombosis. A case–control study showed that the 12-year cumulative thrombotic incidence rate was significantly increased in women with APS and recurrent miscarriages (incidence of 19.3%, $n = 57$) compared with women with recurrent miscarriage of unknown aetiology (incidence of 4.8%, $n = 86$), women with recurrent miscarriage and thrombophilic genetic defects as the only aetiological factor for recurrent miscarriage (incidence of 0%, $n = 42$) and women who are antiphospholipid antibody-positive but otherwise healthy (incidence of 0%, $n = 30$)[12]. These results are in line with a 10-year observational cohort study of 1,592 women, which showed that women who were positive for antiphospholipid antibodies and who had experienced three consecutive spontaneous miscarriages at <10 weeks of gestation or one fetal death at ≥10 weeks of gestation had annual rates of deep vein thrombosis of 1.46% (range 1.15–1.82%), pulmonary embolism of 0.43% (range 0.26–0.66%), superficial vein thrombosis of 0.44% (range 0.28–0.68%) and cerebrovascular events of 0.32% (range 0.18–0.53%); these numbers were significantly higher than in women with mutations predisposing to thrombosis, such as factor V Leiden (rs6025) mutations and prothrombin 20210A (rs1799963) mutations, or in women who were negative for thrombophilia[13]. This finding was in contrast to a retrospective case–control study showing that the thrombosis rate in women with previous recurrent miscarriages associated with antiphospholipid antibodies is similar to the rate in those with idiopathic recurrent miscarriage[14].

Pregnancy complications

The APS ACTION group showed that 6% of patients with relevant pregnancy morbidity were positive for antiphospholipid antibodies[10]. Recurrent miscarriage is the most frequent complication and is observed in the majority (~54%) of women with obstetrical APS included in the European Registry on Obstetric Antiphospholipid Syndrome[15]. Fetal death is considered to be the consequence of placental dysfunction and is strongly associated with antiphospholipid antibodies[16,17]. In an analysis of 512 stillbirths enrolled in the Stillbirth Collaborative Research Network from 2006 to 2008, 11% (95% CI 8.4–14.4) of the women were positive for antiphospholipid antibodies[18].

Autoimmune diseases

Antiphospholipid antibodies can be detected in association with other systemic autoimmune diseases, most frequently SLE (TABLE 1). The prevalence of antiphospholipid antibodies among patients with SLE ranges from

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15% to 34% for lupus anticoagulant, from 12% to 44% for anticardiolipin and from 10% to 19% for anti-β2-glycoprotein 1 antibodies[6]. Of individuals with SLE who are positive for antiphospholipid antibodies, 20–50% develop thrombotic events[19].

Some reports have described considerable heterogeneity in the prevalence of immunoglobulin G (IgG) isotype anticardiolipin antibodies in SLE, ranging from 2% in individuals of Afro-Caribbean descent to 51% in individuals of Indian descent; the variation is partly explained by differences in the assays used[20,21]. When investigating the prevalence of antiphospholipid antibodies in Chinese individuals with SLE, a prevalence of 22.4% was found for lupus anticoagulant, 29% for anticardiolipin antibodies and 7.7% for anti-β2-glycoprotein 1 antibodies; these numbers are lower than in white individuals with SLE[22]. However, the 10-year thrombosis rate and rate of recurrent thrombosis in Chinese individuals with antiphospholipid antibodies was similar to that reported in a European prospective cohort of 1,000 patients with APS[22]. Thus, the observation of lower antiphospholipid antibody levels in Chinese individuals might represent differences in the assays used.

Mechanisms/pathophysiology

Antiphospholipid antibody formation

Infectious agents are the main triggers for the formation of antiphospholipid antibodies, a process that is best understood for anti-β2-glycoprotein 1 antibodies. Molecular mimicry between structures of bacteria or viruses and β2-glycoprotein-1-derived amino acid sequences are thought to contribute to the formation of autoantibodies[23]. In addition, misfolding of β2-glycoprotein 1 can also induce autoantibody formation[24]. Binding of β2-glycoprotein 1 to the surface protein H of *Streptococcus pyogenes* induces a conformational change in β2-glycoprotein 1, thereby exposing a cryptic epitope in domain 1 of β2-glycoprotein 1. Mice injected with the mouse protein H–β2-glycoprotein 1 complex developed antibodies against this epitope[25]. Healthy individuals seem to have the potential to produce antibodies against β2-glycoprotein 1; however, only with the appropriate genetic background or following secondary triggers do these antibodies become pathogenetic.

Two-hit model

Although antiphospholipid antibodies are persistently present, thrombotic events occur only occasionally, suggesting that the development of antiphospholipid antibodies is a necessary but insufficient step in the development of APS and that other factors play a part. Such 'second hits' or 'triggers' probably push the haemostatic balance in favour of thrombosis and might include environmental factors (such as infection), inflammatory factors (such as concomitant connective tissue diseases) or other nonimmunological procoagulant factors (such as oestrogen-containing contraceptives, surgery and immobility)[26]. The patient's genetic constitution, in relation to genes encoding inflammatory mediators, might also be a critical variable in the development of clinical APS manifestations. Familial studies suggest a genetic predisposition to APS, in part accounted for by the human leukocyte antigen (HLA) system, with the most consistent associations being those with *HLA-DR4* and *HLA-DRw53* (REFS 27–29). Furthermore, the presence of both lupus anticoagulant and anticardiolipin antibodies seems to be associated with these HLA genotypes[30]. Other genes outside the HLA system might also predispose to the development of APS, including *IRF5* (encoding interferon regulatory factor 5) and *STAT4* (encoding signal transducer and activator of transcription 4)[30].

Thrombosis

A striking observation is that patients with antiphospholipid antibodies can experience thrombotic complications in every blood vessel, although deep vein thrombosis (usually in the legs) and ischaemic stroke account for 90% of all complications[31]. The risk factors for thrombotic complications associated with arterial thrombosis are different from those for venous thromboembolism (including deep vein thrombosis and pulmonary embolism)[32], suggesting that the interference of antiphospholipid antibodies with homeostasis in each blood vessel type is unique. Alternatively, it is also possible that the autoantibodies interfere with metabolic pathways, which are differently involved in venous, arterial and microvascular thrombosis. Several mechanisms to explain the prothrombotic effects of antiphospholipid antibodies have been proposed, although none of these suggestions has been proven[33] (FIG. 1).

Antiphospholipid antibodies and thrombosis. Administration of antiphospholipid antibodies to mice, rats or hamsters does not result in spontaneous thrombotic

Box 1 | **The classification criteria for definite APS**

The revised classification criteria for antiphospholipid syndrome (APS) are referred to as the Miyakis criteria[2]. A patient has to fulfil at least one clinical criteria and at least one laboratory criteria.

Clinical criteria

Vascular thrombosis

≥1 clinical episode of arterial, venous or small-vessel thrombosis. Thrombosis must be objectively confirmed. If histopathological confirmation is used, thrombosis must be present without inflammation of the vessel wall.

Pregnancy morbidity

- ≥1 unexplained death of a morphologically normal fetus ≥10 weeks of gestation
- ≥1 premature delivery of a morphologically normal fetus <34 weeks gestation because of severe pre-eclampsia or eclampsia (defined according to standard definitions) or recognized features of placental insufficiency
- ≥3 unexplained consecutive miscarriages at <10 weeks of gestation, with maternal and paternal factors (such as anatomical, hormonal or chromosomal abnormalities) excluded

Laboratory criteria

The presence of antiphospholipid antibodies on ≥2 occasions at least 12 weeks apart and <5 years before clinical manifestations, as demonstrated by ≥1 of the following:

- Presence of lupus anticoagulant in plasma
- Medium titre to high titre of anticardiolipin antibodies (>40 GPL* or MPL*, or >99th percentile‡) of immunoglobulin G (IgG) or IgM isotypes
- Anti-β2-glycoprotein 1 antibodies of IgG or IgM isotypes present in plasma

*GPL and MPL are arbitrary units; 1 GPL or MPL refers to 1 μg of IgG or IgM antibody, respectively. ‡Exact value depends on the assay.

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complications. However, in keeping with a 'multihit' hypothesis of thrombosis, the thrombotic response after a priming event, such as a minor vascular injury, is much stronger in the presence of antiphospholipid antibodies than after infusion of a control antibody[34–36]. This observation in animal models fits with the finding that antiphospholipid antibodies are risk factors for thrombosis in humans. Indeed, individuals with antiphospholipid antibodies will respond more profoundly to thrombotic challenges than those without antiphospholipid antibodies.

Animal models have clearly shown that antibodies against β2-glycoprotein 1, especially those against domain 1, can induce a strong prothrombotic phenotype[37,38]. The epitopes to which the antibodies against β2-glycoprotein 1 are directed have been identified and were shown to be completely conserved in mice, making the injection of human anti-β2-glycoprotein 1 antibodies in mice a good model for the human situation[39].

A few papers have shown that anti-prothrombin antibodies can also induce a prothrombotic phenotype[40,41]. These experiments are less convincing than the results obtained with anti-β2-glycoprotein 1 antibodies because we do not know whether the epitope on prothrombin to which these autoantibodies are directed is present in mice.

One publication shows that anticardiolipin antibodies can also increase the thrombotic risk in mice, independently of β2-glycoprotein 1 and prothrombin[42]. However, to prove that anticardiolipin antibodies bind to anionic phospholipids independently of any cofactor is difficult. Moreover, cofactor-independent antibodies are common in infectious diseases that are not associated with an obvious increase in thrombotic risk[43].

Activation of endothelial cells, platelets and immune cells. Binding of anti-β2-glycoprotein 1 antibodies to β2-glycoprotein 1 at the cell surface results in the activation of cultured endothelial cells, platelets, monocytes, neutrophils, fibroblasts and trophoblasts as well as expression and release of cell type-dependent activation markers[33]. Animal models have confirmed that infusion of anti-β2-glycoprotein 1 antibodies increases the protein expression of tissue factor, which is responsible for the activation of the coagulation cascade, in monocytes and vascular homogenates[44].

Two important questions remain unanswered: which cell type is the major target for the antibodies, and how is this cell type activated? Different studies have identified different cells, but the major candidates seem to be platelets, endothelial cells and monocytes. It is possible that all are involved — directly or indirectly — through the shedding of prothrombotic microparticles[45]. How the cells are activated is a more challenging question. Activation of the cells likely involves binding of the β2-glycoprotein-1–antibody complex to Toll-like receptor 2 (TLR2), TLR4, annexin A2 or low-density lipoprotein receptor-related protein 8 (LRP8; also known as apolipoprotein E receptor 2) and activation of their intracellular signal transduction pathway, resulting in a more prothrombotic cellular phenotype (FIG. 1). Of note, LRP8 associates with β2-glycoprotein 1 at the cell membrane[46]. Studies with knockout mice have confirmed an important role for LRP8, annexin A2 and TLR4 in inducing a prothrombotic or thrombotic phenotype that is dependent on antiphospholipid antibodies[44]. Other receptors or a combination of the proposed receptors might be necessary to activate cells, but the exact mechanism is not yet completely understood[47].

Complement activation. Antiphospholipid antibodies also interfere with complement activation. Indeed, mice deficient in complement factors C3, C5 and C6 showed a reduced thrombotic response following antiphospholipid antibody administration combined with a vascular challenge compared with control mice[48]. Clearly, both haemostasis and complement activation play a part in the induction of thrombosis by antiphospholipid antibodies. However, because these enzyme cascades are intrinsically connected, activation of coagulation could be the cause and subsequent activation of complement could be the consequence.

Activated protein C resistance. An interesting aspect of antiphospholipid antibodies is that they induce activated protein C resistance *in vitro*; the autoantibodies compete with activated protein C for the binding to the catalytic phospholipids, thereby limiting the access of protein C to its substrates[49]. Activated protein C resistance strongly predisposes to venous thromboembolism[50]. Whether the activated protein C resistance observed *in vitro* also occurs *in vivo* is unknown. Indeed, antiphospholipid antibodies also induce prolongation of clotting *in vitro*[51], an observation not observed in patients as they do not bleed[52]. Animal models should answer the role of antibody-induced activated protein C resistance in the risk of venous thromboembolism in individuals with APS.

Table 1 | **Prevalence of antiphospholipid antibodies in different clinical conditions**

Condition	Prevalence of lupus anticoagulant (%)	Prevalence of anticardiolipin antibodies (%)	Prevalence of anti-β2-glycoprotein 1 antibodies (%)	Refs
Healthy individuals	1–5	0.1–5	3	6,20,220
Venous thrombosis	1–16	4–24	5–10	6,7,10,20,220–224
Arterial thrombosis	4–18	0.1–24	3–18	6,10,20,222,225–227
Pregnancy losses	7–12	3–16	2–8	6,20,228–230
Systemic lupus erythematosus	15–34	12–44	10–19	6

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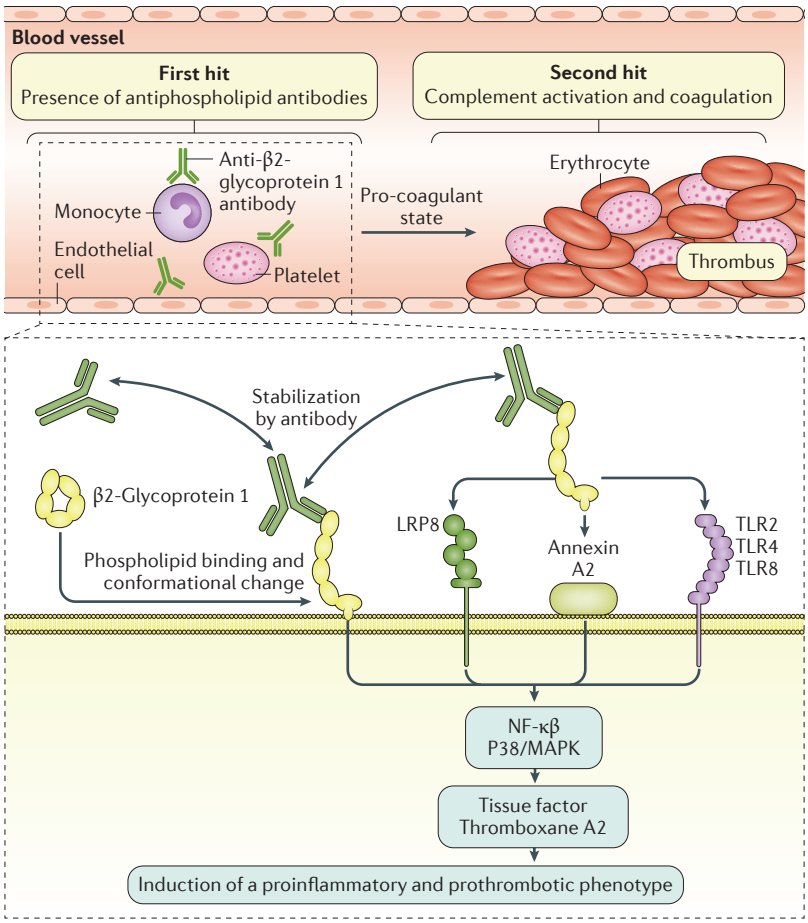

Figure 1 | **Pathophysiology of antiphospholipid antibody-associated thrombosis.** Thrombus formation associated with the presence of antiphospholipid antibodies involves a multihit model in which the thrombotic response is much stronger after a second hit (for example, a minor vascular injury) owing to the priming of immune cells, platelets and endothelial cells by anti-β2-glycoprotein 1 antibodies (the first hit). Which cells or activation pathways are involved remains under investigation (inset). Complement is activated, which strongly accelerates the formation of a thrombus. LRP8, low-density lipoprotein receptor-related protein 8; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor-κB; TLR, Toll-like receptor.

Pregnancy complications

The pathogenesis of recurrent first-trimester pregnancy loss associated with antiphospholipid antibodies is different from the pathogenesis of morbidity occurring in late pregnancy[53]. First-trimester pregnancy loss has been attributed to a direct inhibitory effect on proliferation[54] of trophoblast cells[54,55].

The late obstetrical manifestations of APS, including pre-eclampsia, intrauterine growth restriction and stillbirths, are the consequence of placental dysfunction. Potential causes of these outcomes are: failure of extravillous trophoblasts to adequately remodel the spiral arteries, resulting in reduced maternal blood flow to the placenta and hypoxic injury; inadequate delivery of nutrients to the fetus; and high-velocity and high-pressure blood flow that can damage the placenta[56]. Antiphospholipid antibodies play a part by reducing proliferation and invasion of extravillous trophoblasts and triggering inflammation at the maternal–fetal interface, which together drive impaired placentation (FIG. 2).

Proliferation and migration of trophoblasts. β2-Glycoprotein 1 is constitutively expressed at the cell surface by all placental trophoblast subpopulations and on maternal decidual endothelial cells[57]. Anti-β2-glycoprotein 1 antibodies can bind to human trophoblasts and the endothelium through the phospholipid binding site in domain 5 of β2-glycoprotein 1 and in various cell surface receptors. Antiphospholipid antibodies in *in vitro* studies have been shown to inhibit spontaneous trophoblast migration, increase trophoblast antiangiogenic soluble endoglin secretion and disrupt trophoblast–endothelial interactions in a model of spiral artery transformation[58–61]. These effects are mediated by LRP8, which, when activated by β2-glycoprotein 1 crosslinked by anti-β2-glycoprotein 1 antibodies, suppresses migration by reducing IL-6 levels and STAT3 activity[59,62]. The role of LRP8 in antiphospholipid antibody-mediated fetal loss and intrauterine growth restriction has also been confirmed *in vivo*[62] (FIG. 2a).

Inflammation. Mouse models have been instrumental in defining the role of local inflammation in the pathogenesis of pregnancy complications associated with antiphospholipid antibodies. Administration of polyclonal IgG antibodies from individuals who have APS with high titres of antiphospholipid antibodies or monoclonal human antiphospholipid antibodies to pregnant mice results in fetal resorption and growth restriction[63]. Antiphospholipid antibodies localize to the placenta, and associated inflammatory responses, particularly complement activation and recruitment and stimulation of neutrophils, are an essential cause of placental insufficiency, fetal loss and growth restriction[64]. In addition, *in vitro* studies with human first-trimester extravillous trophoblasts have shown that anti-β2-glycoprotein 1 antibodies trigger production of pro-inflammatory cytokines and chemokines (such as IL-1, IL-7 and IL-8) via TLR4 (REF. 58) (FIG. 2b).

Complement activation stimulates release of tumour necrosis factor (TNF) and the antiangiogenic factor soluble vascular endothelial growth factor receptor 1 (sVEGFR1; also known as sFLT1) by infiltrating leukocytes, both of which are associated with impaired placentation and the development of pre-eclampsia[65–67] (FIG. 2c). Mice deficient in components of the alternative and classical complement pathways and mice treated with various inhibitors of complement activation are resistant to fetal injury induced by antiphospholipid antibodies[64], indicating that both complement pathways contribute to damage. Indeed, the effectiveness of heparin in reducing pregnancy loss in humans may be, in part, because of its capacity to inhibit complement activation. Anticoagulation therapy with hirudin or fondaparinux, which do not affect complement activation, does not prevent pregnancy complications in antiphospholipid antibody-treated mice[68]. Complement fragment C4d, a marker of classical complement pathway activation, is present in the placentae of women with SLE and/or APS and women with pre-eclampsia, whereas it is absent in healthy controls[69–71]. Inherited hypofunctional variants of complement regulators increase the risk of pre-eclampsia in women with SLE who are positive or negative for

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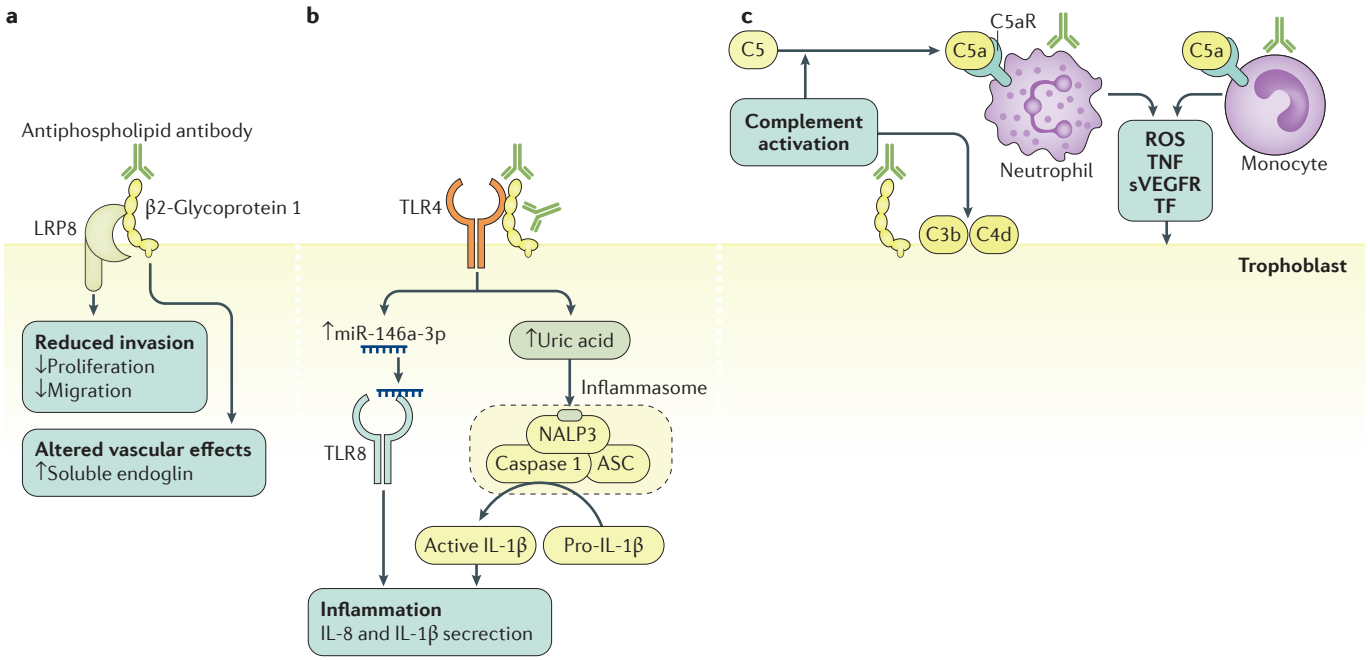

Figure 2 | **Effect of antiphospholipid antibodies on trophoblasts.** Antiphospholipid antibodies recognizing β2-glycoprotein 1 expressed by trophoblasts promote an anti-angiogenic profile and reduce cell proliferation and migration through low-density lipoprotein receptor-related protein 8 (LRP8) (part **a**), trigger secretion of inflammatory cytokines and chemokines by activating Toll-like receptor (TLR) and inflammasome pathways (part **b**) and activate complement on the cell surface, leading to neutrophil and monocyte activation with release of reactive oxygen species (ROS), tumour necrosis factor (TNF), antiangiogenic factors (soluble vascular growth factor receptor (sVEGFR)) and tissue factor (TF) (part **c**). ASC, apoptosis-associated speck-like protein containing a CARD (also known as PYCARD); c5aR, C5a anaphylatoxin chemotactic receptor; miRNA, microRNA; NALP3, NACHT, LRR and PYD domains-containing protein 3 (also known as NLRP3). Adapted with permission from REF. 219, John Wiley & Sons.

antiphospholipid antibodies[72]. Finally, two studies have shown mild hypocomplementaemia in patients with APS, suggesting ongoing activation and consumption of complement components[73,74].

Complement C5a–C5aR interactions drive effectors of placental injury, including tissue factor expression in neutrophils and monocytes, oxidative burst[75], release of antiangiogenic factors (sVEGFR1)[66] and release of TNF (FIG. 2c). That TNF is itself pathogenetic is suggested by studies showing that miscarriage induced by antiphospholipid antibodies is less frequent in mice deficient in TNF or treated with TNF blockers[65]. Evidence that TNF contributes to the pathogenesis of adverse pregnancy outcomes in humans includes increased TNF levels in the maternal blood and amniotic fluid of individuals with pre-eclampsia[76,77] and increased TNF levels at the fetal–maternal interface in intrauterine growth restriction[78].

Complement activation also recruits and activates neutrophils (FIG. 2c). Pregnant mice treated with antiphospholipid antibodies show neutrophil infiltration in the placenta, and the deleterious effects of antiphospholipid antibodies on fetal survival and growth are abolished by neutrophil depletion[64]. Similarly, in antiphospholipid antibody-independent mouse models of pre-eclampsia, neutrophils infiltrate the placenta and their depletion improves placental morphology, recovers spiral artery remodelling and improves pregnancy outcomes[67]. In both antiphospholipid antibody-dependent and antiphospholipid antibody-independent models, recruitment of neutrophils is triggered by complement activation at the maternal–fetal interface and leads to an increase of local TNF levels, reduction of VEGF levels and, ultimately, abnormal placentation and fetal death.

Neutrophils may also be directly activated by anti-β2-glycoprotein 1 antibodies that recognize β2-glycoprotein bound to their cell surface and stimulate neutrophil extracellular trap (NET) formation through mechanisms dependent on reactive oxygen species and TLR4[79]. Patients with APS show increased NET formation, impaired NET clearance and higher numbers of circulating low-density granulocytes, which have an increased capacity to produce cytokines and type 1 interferons[79]. Increased numbers of NETs are found infiltrating placental intervillous spaces, in association with inflammatory and vascular changes, in individuals with SLE and with pre-eclampsia[80].

Diagnosis, screening and prevention

Antiphospholipid antibody assays

In the current classification criteria for APS (BOX 1), testing for lupus anticoagulant, anticardiolipin antibodies and anti-β2-glycoprotein 1 antibodies is included[2]. Because clinical manifestations associated with APS are common and often determined by other underlying causes, the laboratory detection of circulating

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antiphospholipid antibodies defines the disease. The assays for the detection of antiphospholipid antibodies must be sufficiently sensitive and specific to correctly classify patients as having APS because overdiagnosis and misdiagnosis have severe implications for optimal treatment[81]. Thus, the performance and choice of assays used for detecting antiphospholipid antibodies should be well considered and follow the guidelines[82–84]. All assays routinely used to detect antiphospholipid antibodies show methodological shortcomings and lack of standardization[52,53,63]. Recommendations for the detection of lupus anticoagulant published in 2009 by the Scientific and Standardization Subcommittee on Antiphospholipid Antibodies of the International Society of Thrombosis and Haemostasis (SSC-ISTH) have been useful in the standardization of this assay[82]. Recommendations for the detection of anticardiolipin and anti-β2-glycoprotein 1 antibodies using immunoassays were published to provide additional details and specifications[83] (TABLE 2).

Testing for antiphospholipid antibodies should be limited to patients who have a considerable probability of having APS. A generalized search for antiphospholipid antibodies in the absence of any relevant condition is strongly discouraged to prevent incidental findings. Antiphospholipid antibodies should be tested in younger patients (<50 years of age) with unprovoked thrombotic events or thrombosis at unusual sites or in those who have thrombotic or pregnancy complications associated with autoimmune disease[82,83]. As antiphospholipid antibodies are a heterogeneous group of autoantibodies with overlapping, but not identical, characteristics, it is recommended to perform all assays at the same time with an integrated interpretation of all tests[82,83] (TABLE 2).

Lupus anticoagulant. The lupus anticoagulant assay detects all antiphospholipid antibodies. Detection involves two functional coagulation assays that measure the ability of antiphospholipid antibodies to prolong the phospholipid-dependent clotting time: diluted Russell viper venom time (dRVVT) and the activated partial thromboplastin time (aPTT). An individual is considered positive for lupus anticoagulant if at least one of these tests is positive. Lupus anticoagulant is traditionally detected by a three-step procedure involving a screening, mixing and confirmation step[82]. A test is defined as lupus anticoagulant-positive if it has an extended coagulation time during the screening step, which is not reversed in the mixing step (where patient plasma is mixed with normal plasma) but is reversed in the confirmation step by the addition of excess phospholipids, which confirms that anticoagulants present in the plasma are specific for phospholipids (that is, antiphospholipid antibodies).

Two tests with distinct performance principles are needed as no coagulation test is 100% sensitive; no other tests but dRVVT and aPTT are recommended to increase the harmonization in lupus anticoagulant testing using robust, reproducible, sensitive, commercially available and quality controlled assays. The mixing step is mandatory to avoid false-positive results. However, some discussion has been raised as coagulation might be corrected if antibody titres are low and because the step is time-consuming and reagent-consuming[82,85–88]. One of the major drawbacks of the lupus anticoagulant coagulation assays is their sensitivity to anticoagulant therapy[82,89]. Elevated factor VIII or C-reactive protein may lead to false-negative or false-positive test results, respectively[88]. The Taipan snake venom test is useful in those

Table 2 | **SSC-ISTH guidelines for antiphospholipid antibody detection**

	Lupus anticoagulant	Anticardiolipin antibodies and anti-β2-glycoprotein 1 antibodies
Patient selection	Testing should focus on patients <50 years of age with unprovoked venous or arterial thromboembolism, thrombosis at unusual sites or thrombotic or pregnancy complications associated with autoimmune disease; general screening is discouraged	
Autoantibodies	Lupus anticoagulant assay detects all antiphospholipid antibodies	• Anti-β2-glycoprotein 1 antibody assay: anti-β2-glycoprotein 1 antibodies • Anticardiolipin antibody assay: β2-glycoprotein-1-dependent anticardiolipin antibodies
Assay	Procedure involves two coagulation tests (dRVVT and aPTT) following a three-step procedure involving screening, mixing and confirmation	Solid-phase immunoassays to detect anticardiolipin antibodies and anti-β2-glycoprotein 1 antibodies, both isotype IgG and IgM. To detect anticardiolipin antibodies, human β2-glycoprotein 1 should be added to the assay
Assay interference	Anticoagulant therapy (heparin, anti-vitamin-K therapy and the direct oral anticoagulants), high factor VIII levels and increased C-reactive protein	Rheumatic factor, sample collection (icteric, haemolytic or lipaemic samples) and presence of high levels of heterophile antibodies, human anti-animal antibodies and (monoclonal) immunoglobulins
Cut-off values	Value in >99th percentile of a normal population	Value in >99th percentile of a normal population
Results	Present or absent or positive or negative	Analytical result according to the calibration of the assay; no international units available. All results above the assay and laboratory-specific cut-off value are regarded as positive

Recommendations by the Scientific and Standardization Subcommittee of the International Society of Thrombosis and Haemostasis (SSC-ISTH)[78,82,83]. aPTT, activated partial thromboplastin time; dRVVT, diluted Russell viper venom time; Ig, immunoglobulin.

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on warfarin treatment as it produces reliable lupus anticoagulant results, although it still labels some lupus anticoagulant-positive samples as negative[90].

Anticardiolipin antibodies and anti-β2-glycoprotein 1 antibodies. Anticardiolipin antibodies and anti-β2-glycoprotein 1 antibodies are measured by solid-phase immunoassays; the presence of either IgG or IgM isotypes is considered diagnostic[2,83]. With lupus anticoagulant tests, all antiphospholipid antibodies are detected independent of the cofactor protein of the antibodies. Immunoassays measure different groups of antiphospholipid antibodies, that is, antibodies towards cardiolipin (anticardiolipin antibody assay) or towards β2-glycoprotein 1 (anti-β2-glycoprotein 1 antibodies assay)[91,92], the principal cofactor protein for antiphospholipid antibodies[91,92]. Methodologically correct anticardiolipin antibody assays with anti-β2-glycoprotein 1 in the reagents have diagnostic value with similar sensitivities and specificities to anti-β2-glycoprotein 1 assays[93,94]. Detection of the same isotype for both antibodies reinforces the probability of APS[82], which is an argument to keep both IgG and IgM isotypes in the classification criteria[2,83]. A recent review of the literature revealed that thrombosis is more strongly associated with IgG-type antibodies than with the IgM isotype, but the review did not provide an answer on how many cases of APS would be missed if IgM is omitted[95]. The importance of IgA-type anticardiolipin antibodies and anti-β2-glycoprotein 1 antibodies remains controversial; measurement of this isotype is not recommended yet[2,83]. IgA testing probably has less value in screening but might be useful for confirmation of APS or restricted to patients with a strong suspicion of APS but negative for criteria antiphospholipid antibodies (see below)[96,97]. The anticardiolipin antibodies and anti-β2-glycoprotein 1 antibodies assays show interassay variation owing to differences in calibration and differences in assay characteristics[91,98]. Coating of the solid phase differs among assays, resulting in different antigen exposure[99]. Harmonization of working conditions using automated systems may contribute to a reduction in interlaboratory variation[100].

Antibody profile. Lupus anticoagulant positivity is regarded as the most important risk factor for APS-related thrombotic events[101]. However, tests for all three antibodies must be performed to define a patient's full antibody profile, as patients may be positive for only one of the antibodies. The concept of antiphospholipid antibody profiles was recommended initially in the 2006 Sydney APS classification criteria, with a categorization of patients according to their positivity for single or multiple antiphospholipid antibodies, which supports the concept that the antiphospholipid antibody profile defines the risk of developing APS-related events[2,102,103]. A modification has been proposed that takes into account the type and the number of positive tests[26,104]. Indeed, evidence has shown that patients with more than one positive test, and particularly those who are triple-positive for lupus anticoagulant, anticardiolipin antibodies (either IgG or IgM) and anti-β2-glycoprotein 1 antibodies (either IgG or IgM), show the strongest association with thrombotic APS[105,106]. Moreover, triple positivity in individuals with APS is associated with recurrence of thrombosis, whereas triple positivity in asymptomatic individuals is associated with first thrombosis[26,107]. In individuals with APS, those who are triple-positive usually maintain this profile and show similar results 3 months after the initial test[108]. However, the guidelines recommend retesting after 3 months to avoid overdiagnosis by classification of transient positivity of antibodies as APS, for example, as in those with a transient increase in antiphospholipid antibodies provoked by infection[2,82]. In addition, confirming test results ensure the reliability of the positive test, which is important in the context of poor standardization and interferences that affect the test results[91,109].

Noncriteria antiphospholipid antibodies. Other antiphospholipid antibodies are not included in a standard test panel owing to the lack of standardization and the absence of evidence on the utility in patients with APS[83,97,110,111]. The anti-domain 1 β2-glycoprotein 1 antibodies (anti-D1 antibodies), a subgroup of IgG anti-β2-glycoprotein 1 antibodies, were not included in the SSC-ISTH recommendations because adequate clinical studies and a commercial assay were not available at the time of writing[83]. A strong association of anti-D1 antibodies and thrombosis has been observed using research assays[112,113]. A commercial chemiluminescence immunoassay assay has now been developed to detect anti-D1 antibodies, and several studies using this assay have confirmed a high odds ratio for thrombosis and the role of anti-D1 antibodies in risk stratification of individuals with APS[114–119]. Anti-D1 antibodies (IgG isotype) are mainly detected and present at high titres in triple-positive individuals[115,116]. However, anti-D1 antibodies are not considered independent risk factors, as illustrated in a limited number of studies[115,120]. Thus, detection of anti-D1 antibodies is considered a confirmation of the higher thrombotic risk, rather than a candidate for replacement of the anti-β2-glycoprotein 1 antibodies. Addition of antibodies to phosphatidylserine–prothrombin to the current antibody panel shows promising diagnostic value[121] but requires further investigation.

Clinical manifestations

The main clinical manifestations of APS are the occurrence of thrombosis (arterial and/or venous) and/or pregnancy morbidity, including recurrent miscarriages, fetal deaths and late pregnancy complications such as pre-eclampsia and intrauterine growth restriction. In addition, APS can be associated with a wide variety of other clinical symptoms (FIG. 3).

In the past, the terms 'primary APS' and 'secondary APS' have been used. 'Secondary' indicated that APS was associated with another systemic autoimmune disease, usually SLE. However, we have refrained from using these terms, as follow-up of individuals with APS showed that most patients acquired other autoimmune diseases. Furthermore, APS is not 'secondary' to SLE in its effect.

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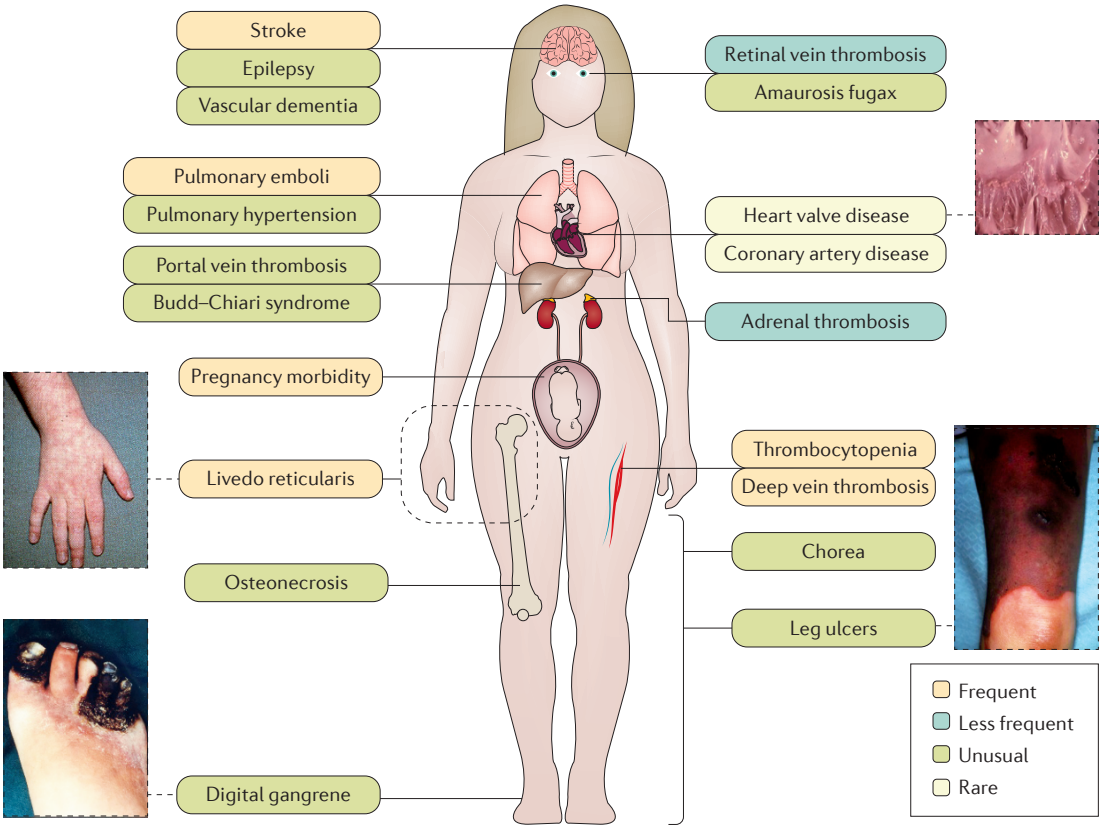

Figure 3 | **Clinical manifestation of antiphospholipid syndrome.** Antiphospholipid antibodies are associated with a variety of symptoms; in particular, deep vein thrombosis, pregnancy morbidity and stroke are frequent (occurring >20% of individuals with antiphospholipid antibodies). Other manifestations vary in frequency, ranging from less frequent (10–20% of individuals with antiphospholipid antibodies), unusual (<10%) and rare (<1%). For example, an unusual manifestation is thrombotic microangiopathy (not shown), which manifests in the skin, kidneys and/or heart. Livedo reticularis most commonly occurs on the upper arms and thighs. Images courtesy of Y. Shoenfeld.

Thrombosis. Single or multiple thrombi in veins, arteries and the microvasculature and the time interval between these manifestations may vary from days to years. This variability in location of the thrombi results in the wide spectrum of clinical presentations that may involve many organ systems[52,122] (FIG. 3).

Venous thromboembolism, particularly deep vein thrombosis of the lower limbs, is the most frequent manifestation of APS, with a prevalence of ~39% in the Euro-Phospholipid Project[122]. Although arterial thrombosis is less common than venous thromboembolism, it is usually more severe and life-threatening. Indeed, 20% of individuals with APS developed a stroke and 11% developed a transient ischaemic attack. The recurrence rate of thrombotic events in the untreated individuals after unprovoked first events is high and ranges from 19% to 29% per year[123]. Positivity for lupus anticoagulant, triple positivity and isolated, persistent positivity for anticardiolipin antibodies at medium-high titres are associated with an increased risk of developing thrombosis[124].

According to the APS classification criteria, thrombosis must be confirmed by objective validated criteria, such as unequivocal findings of appropriate imaging studies or histopathology. For histopathological confirmation, thrombosis should be present without considerable evidence of inflammation in the vessel wall[2].

Obstetrical morbidity. Obstetrical APS can be associated with various pregnancy complications, of which recurrent miscarriage at <10 weeks of gestation is the most frequent[15]. The maternal pregnancy morbidity of APS consists of pre-eclampsia, eclampsia and placental abruptions. Despite the transplacental transfer of maternal antiphospholipid antibodies, babies born to mothers with APS do not seem to have thrombosis or SLE[125]. Several risk factors predict poor pregnancy outcome, including an associated systemic autoimmune disease, in particular SLE, a history of previous thrombotic events, reduced complement levels[126] and lupus anticoagulant positivity or triple positivity[15,127].

Reduced blood flow in the uterine arteries measured by Doppler velocimetry is an indirect indicator for the development of placental insufficiency and/or pre-eclampsia[128]. Thus, pregnant women with APS should be offered obstetrical ultrasonography to assess fetal growth and amniotic fluid volume and second-trimester Doppler ultrasonography to assess end-diastolic blood flow in the umbilical artery. Normal end-diastolic blood flow in the uterine artery results at 20–24 weeks of gestation is a strong predictor for good fetal outcome[129]. In a study of 33 women with APS, the positive predictive value of abnormal uterine artery Doppler ultrasonography for later intrauterine growth restriction or

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pre-eclampsia was 67% with a negative predictive value of 93%[130]. Another prospective study of 100 pregnancies confirmed that Doppler ultrasonography in the second trimester is the best predictor for late pregnancy outcome in SLE and/or APS[129]. The European League Against Rheumatism (EULAR) has now included recommendations on the use of uterine artery Doppler ultrasonography in their guideline[131].

Neurological manifestations. Stroke is the most common and severe neurological manifestation of APS. However, many other neurological manifestations that are not included in the criteria have been associated with antiphospholipid antibodies, including cognitive dysfunction (owing to several cerebral small vessel thromboses), untreatable headaches and migraine, epilepsy and chorea[132]. Epilepsy is strongly associated with previous strokes and transient ischaemic attack, SLE, valvulopathy and livedo reticularis (a red or bluish alteration of the skin with a net-like pattern attributed to blood stasis and, occasionally, fibrin deposition in distal venules)[133].

Cardiac manifestations. Cardiac features associated with APS vary from valve lesions to accelerated atherosclerosis, myocardial infarction, intracardiac thrombi, pulmonary hypertension, cardiomyopathy and diastolic dysfunction[134]. Cardiac valve abnormalities are observed in 30–50% of individuals with APS and mainly include valve thickening and regurgitations, but valve vegetations (for example, Libman–Sacks endocarditis) and valve stenosis also occur[135,136]. The mitral valve is most commonly involved, followed by the aortic valve. Valve damage is most frequent in individuals with APS who also have another autoimmune disease[137]. Myocardial ischaemic events can result from coronary thrombosis without underlying atherosclerosis, accelerated atherosclerosis of the coronary arteries or microvascular injury. Myocardial infarction is observed in ~5.5% of patients in APS registries[52,138].

Thrombocytopenia. Thrombocytopenia occurs in at least 30% of individuals with APS and is most marked at times of thrombosis formation[52]. However, thrombocytopenia might also be associated with other systemic manifestations of APS, such as obstetrical morbidity, venous and/or arterial thrombosis, myocardial infarction and valve vegetations[139]. The prevalence of thrombocytopenia was found to be higher in individuals with APS who also have SLE than in those with APS alone[52,139]. However, platelet counts usually remain $>50 \times 10^9$ per litre; consequently, thrombocytopenia rarely results in major bleeding and does not require intervention. A positive Coombs test (confirming anti-erythrocyte antibodies) occurs in 10% of individuals with APS but is rarely associated with autoimmune haemolysis[140].

Pulmonary manifestations. Pulmonary emboli and infarction are the most frequent pulmonary manifestations, affecting ~14% of individuals with APS[52]. Other manifestations are pulmonary hypertension, acute respiratory distress syndrome and intra-alveolar haemorrhage[141].

Dermatological manifestations. Dermatological features may be the first clinical presentations of APS. The most frequent is livedo reticularis, which occurs in 16–25% of patients[142]. Livedo reticularis may be a prognostic marker of more-severe disease associated with the arterial and microangiopathic subtypes of APS[143,144]. Other manifestations include digital gangrene, skin ulcerations, superficial skin necrosis, pseudovasculitis lesions and pyoderma gangrenosum-like lesions, characterized by deep, necrotic ulcers[142].

Renal manifestations. Thrombosis might also result in renal manifestations. A thrombotic microangiopathy associated with antiphospholipid antibodies might manifest with a slow, occult onset of haematuria, proteinuria (ranging from mild to nephrotic) and renal insufficiency, or it may develop acutely and present with acute renal failure and hypertension[145]. Ideally, the diagnosis of antiphospholipid antibody-associated nephropathy should be supported by a kidney biopsy[146], particularly in those with SLE in whom nephropathy may be isolated or concomitant with lupus nephritis.

Catastrophic APS. Catastrophic APS — a rare, life-threatening form of APS occurring in <1% of patients — is defined as intravascular thrombosis affecting three or more organs, systems and/or tissues either simultaneously or within 1 week with histological confirmation of small vessel occlusion[147]. Although catastrophic APS usually involves small vessel thrombosis, large vessels are often occluded as well. Of all individuals who develop catastrophic APS, 60% only have APS, whereas 40% have APS associated with another systemic autoimmune disease[7]. Infections are the most common precipitating factor of catastrophic APS; 49% of individuals who develop catastrophic APS have had a previous infection[147]. The most common systems involved in catastrophic APS are the kidneys (in 73% of individuals with catastrophic APS), pulmonary system (in 60%), brain (in 56%), cardiac system (in 50%) and skin (in 47%). Among laboratory findings, thrombocytopenia is most frequently observed in individuals with catastrophic APS (in 67%), followed by schistocytes (fragmented red blood cells; in 22%). The 12-year mortality was 37% in the CAPS Registry (an international registry of patients with catastrophic APS)[147].

Management

Thrombosis

Primary thromboprophylaxis is used to describe the prevention of thrombosis in those without previous clots, whereas secondary thromboprophylaxis describes prevention of clot recurrence following a first thrombotic event. Thromboprophylaxis remains one of the major challenges in APS. Conventional management of cardiovascular risk factors by lifestyle changes is key in primary thromboprophylaxis. The use of antiplatelet

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agents such as low-dose aspirin (LDA) should be limited to individuals at very high risk[3]. Secondary thromboprophylaxis is based on anticoagulation, mainly with vitamin K antagonists (such as warfarin or heparin), although direct oral anticoagulants (DOACs; such as rivaroxaban) might have a role as well[3].

Primary thromboprophylaxis. The presence of antiphospholipid antibodies in asymptomatic individuals is a risk factor for thrombosis. To date, no randomized controlled trials (RCTs) have eliminated the antiphospholipid antibodies or their activity; thus, lifestyle modifications to address conventional cardiovascular risk factors in individuals with APS, regardless of thrombosis history, concomitant SLE or other features of APS, seem logical despite the lack of clinical trials to support this recommendation[148,149]. Modifications include cessation of tobacco smoking and addressing hypertension, obesity and hyperlipidaemia.

Management of asymptomatic individuals with persistent antiphospholipid antibodies is assessed on an individual basis, taking the presence of additional cardiovascular risk factors into account[3]. Individuals with a high-risk profile (that is, those with high antiphospholipid antibody titres, triple positivity or additional cardiovascular risk factors) may be considered for primary prevention with LDA or hydroxychloroquine[3]. In high-risk situations, such as surgery and long-term immobilization and in postpartum women, all individuals with persistent antiphospholipid antibody positivity should receive thromboprophylaxis with low-molecular-weight heparin (LMWH).

In an RCT of LDA versus placebo[150] in those with antiphospholipid antibodies without clinical symptoms, the incidence rate of acute thrombosis in the placebo arm was 0 per 100 patient-years; the trial was underpowered to detect any effect of LDA[150]. A meta-analysis including 11 (mainly observational) studies of LDA versus placebo involving 1,208 antiphospholipid antibody-positive individuals with 139 thrombotic events suggested that treatment with LDA in those with isolated antiphospholipid antibodies and those with APS is associated with a 50% risk reduction of thrombosis occurrence[151]. However, LDA treatment is associated with an increased bleeding risk. In a meta-analysis including >95,000 individuals from six RCTs, LDA intake increased the annual risk of developing a major bleed from 0.007% to 0.10%[152]. Older age (>65 years), male sex, diabetes mellitus and hypertension were risk factors for bleeding in those taking LDA[152].

Hydroxychloroquine has been suggested as an alternative to LDA in the setting of primary prevention. Hydroxychloroquine is used in the clinical setting on the basis of empiric evidence and *in vitro* data[153,154], but no rigorous RCTs have been performed[155].

Patients with previous obstetrical complications associated with antiphospholipid antibodies have a higher risk of future thrombosis than the general population. No specific treatment recommendation for the prevention of thrombosis in patients with a previous history of antiphospholipid antibody-related pregnancy complications currently exists. However, a retrospective cohort showed that those with obstetrical APS developed a thrombotic event later at a rate of 7.4 per 100 patient-years in the nontreated group and 1.3 per 100 patient-years in the group that received LDA[156].

Those with SLE and antiphospholipid antibodies may develop thrombotic events at a rate of 4% per year. The current EULAR guidelines recommend LDA for primary thrombosis prevention for antiphospholipid antibody-positive patients with SLE[3,157]. Primary thromboprophylaxis with hydroxychloroquine with or without LDA can be considered for individuals with SLE who are positive for lupus anticoagulant or who have persistent anticardiolipin antibodies at medium to high titres[157].

Secondary thromboprophylaxis. Venous thromboembolic events can be separated into provoked or unprovoked events; provoking factors include recent hospital admission, the use of oestrogen-containing medication or pregnancy. In provoked events, many physicians give only a short course of anticoagulation (3–6 months), irrespective of the presence of antiphospholipid antibodies, and then provide thromboprophylaxis at the time of haemostatic stress as one would do in anyone with a previous thrombotic event. Unprovoked venous thrombosis and arterial thrombosis are of concern and should be treated with indefinite anticoagulation therapy with a vitamin K antagonist (for example, warfarin) or, occasionally, LMWH[3]. More recently, the use of DOACs has been considered[158]. BOX 2 outlines the current recommendations of the 13th European Task Force on Antiphospholipid antibodies[3] for secondary thromboprophylaxis in APS in the setting of thrombosis[3].

Two systematic reviews on vitamin K antagonists have been published[123,159]. Lim *et al.*[159] included three RCTs involving individuals with APS with a history of arterial and venous thromboembolism. Two of these RCTs focused on the intensity of warfarin used[160,161], and both showed comparable rates of thrombosis and bleeding in patients treated with vitamin K antagonists targeted to achieve an international normalized ratio (INR; a parameter used to standardize prothrombin time) of 2–3 compared with high-intensity treatment (that is, a target INR of 3–4). However, the time in range in one of the studies for the INR 3–4 arm was only 14%[161], and no benefit of high-intensity treatment was found in the second study[160]. The systemic review by Lim *et al.*[159] concluded that patients with venous and arterial thrombosis without cerebral events should be treated indefinitely with oral anticoagulants targeted at INR 2–3, whereas a target INR of 1.4–2.8 is recommended for those patients with a previous stroke. However, it is important to note that this systemic review excluded high-risk patients with recurrent vascular events despite anticoagulation, and these patients may require high-intensity treatment with vitamin K antagonists according to current guidelines. By contrast, Ruiz-Irastorza *et al.*[123] conducted a systematic review based on 12 cohort studies and 4 RCTs, including a total of 1,740 patients. Most included studies

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were of evidence level II or III. In general, recurrent thrombotic events in these studies occurred in patients on vitamin K antagonists with an INR of <3. Patients with previous arterial events were at an increased risk of recurrences when treated with oral anticoagulation to a target INR of 2–3. Notably, recurrences were infrequent among those patients treated with vitamin K antagonists targeting an INR of 3–4 (REF. 123). In conclusion, the recommendations from this systematic review were to treat patients with a first-time venous thrombosis and definitive APS with warfarin at a target INR of 2–3 and with a target INR >3 in the case of recurrent venous or arterial thrombosis[123].

The DOAC rivaroxaban was compared to warfarin (INR target of 2–3) for secondary thromboprophylaxis in APS with previous venous thromboembolism in an open-label, multicentre, noninferiority RCT including 116 patients (the RAPS trial)[162]. The trial did not reach its primary end point, defined as the change in endogenous thrombin potential at day 42 (that is, it did not reach the noninferiority threshold), but the peak thrombin generation was lower in the rivaroxaban group than in the warfarin groups; thus, rivaroxaban might be an alternative to vitamin K antagonist treatment[162]. Furthermore, complement activation products of the classical pathway (C3a and C5a) and terminal pathway (SC5b-9) were significantly reduced in patients assigned to rivaroxaban compared with patients assigned to warfarin, highlighting that rivaroxaban may have effects in addition to anticoagulation[163]. Further studies assessing the role of DOACs in thrombosis associated with APS are currently ongoing and results are eagerly awaited[164–166]. Of concern are a handful of case reports with severe adverse events — usually recurrent thrombosis, especially arterial thrombosis — in patients treated with DOACs[167–169].

The Antiphospholipid Antibodies and Stroke Study (APASS), a prospective nested cohort, included 1,770 patients with antiphospholipid antibody-related ischaemic stroke and compared the efficacy of LDA ($n = 889$) with warfarin ($n = 881$) on a composite outcome of death, stroke, transient ischaemic attack, myocardial infarction, deep vein thrombosis, pulmonary embolism and other systemic thrombotic events[170]. No significant difference in event rate between LDA and warfarin was found. However, a major drawback was that patients included in the APASS did not fulfil the APS classification criteria as antiphospholipid antibodies were measured only once (instead of twice with a 12-week period)[2]. Thus, it is difficult to conclude that the studied cohort consisted of patients with APS[170].

The efficacy of hydroxychloroquine in reducing thrombotic rates was first reported in patients with SLE[171,172]. In patients with thrombotic APS ($n = 40$), hydroxychloroquine combined with vitamin K antagonists (target INR of 2–3) was not associated with recurrent thromboembolic events, whereas 30% of the control group who were treated with vitamin K antagonists alone experienced a recurrent event ($P = 0.0086$)[173]. How hydroxychloroquine exerts its antithrombotic effects in APS remains uncertain. Recent *in vivo* data suggest that hydroxychloroquine might alter tissue factor expression[174]. In summary, these studies suggest a role for hydroxychloroquine in the prevention of thrombosis in APS.

Acute management of patients with catastrophic APS is based on anticoagulation, corticosteroids, plasma exchange and/or intravenous immunoglobulin administration according to expert opinion based on data from the CAPS Registry[175]. No prospective trials have been conducted.

Antiphospholipid antibody-associated clinical manifestations suggesting underlying thrombotic microangiopathic processes (such as skin necrosis or renal disease) require close follow-up[176], but no RCTs can inform the most efficacious treatment choices. However, anecdotal evidence supports the use of warfarin with a target INR of 3–4 in those with microvascular thrombosis.

An observational, multicentre study involving 177 patients with thrombotic APS and a median follow-up of 5 years (range 1–26) showed that the thrombotic recurrence rate in APS was 7.5 per 100 patient-years in the first 5 years after the first event despite anticoagulation. Diabetes mellitus, inherited thrombophilia and oral anticoagulation withdrawal were independent risk factors for recurrence[177]. As such, many clinical APS experts feel that patients with previous arterial thrombosis or recurrent thrombotic events require a more aggressive approach towards secondary prophylaxis

Box 2 | **Secondary thromboprophylaxis in APS**

Treatment groups

- Individuals who are positive for antiphospholipid antibodies and who have had an arterial or venous thrombosis but do not meet criteria for antiphospholipid syndrome (APS)* should be managed in the same way as antiphospholipid antibody-negative patients with thrombotic events.
- Patients with definite APS* and a first venous thrombosis should receive oral anticoagulant therapy to a target international normalized ratio (INR) of 2–3.
- Patients with definite APS* and arterial thrombosis should receive vitamin K antagonists with a target INR of >3 or vitamin K antagonists with a target INR of 2–3 in combination with low-dose aspirin.
- Bleeding risk should always be assessed before starting high-intensity anticoagulant therapy or combined antiplatelet and anticoagulant therapy.
- For patients without systemic lupus erythematosus with a first noncardioembolic cerebral arterial event who have a low-risk antiphospholipid antibody profile‡ and reversible triggers, antiplatelet agents should be considered on an individual basis.

Duration of treatment

- Duration of therapy in patients with definite APS* and thrombosis is indefinite[3].
- Anticoagulation could be limited to 3–6 months in patients with a first venous event with a low-risk antiphospholipid antibody profile‡ and a known transient precipitating factor.

Refractory and difficult cases

Potential alternative therapies for patients who have recurrent thrombosis, fluctuating INR levels or major bleeding, or, for those who are at high risk of major bleeding, include long-term low-molecular-weight heparin, hydroxychloroquine or statins.

Treatment recommendations of the 13th European Task Force on Antiphospholipid antibodies[3] adapted from the evidence-based recommendations for the prevention and long-term management of thrombosis in individuals who are positive for antiphospholipid antibodies or in those with APS. *BOX 1 shows the classification criteria for definite APS[2]. ‡Low-risk antiphospholipid antibody profile: isolated, intermittently positive anticardiolipin antibodies or anti-β2-glycoprotein 1 antibodies at low titres to medium titres.

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Table 3 | **Management of pregnant women with antiphospholipid antibodies or APS**

Clinical manifestation	Treatment	Evidence
Persistent presence of antiphospholipid antibodies during first pregnancy or before the first pregnancy without previous adverse pregnancy outcomes	Close monitoring of fetus and mother during pregnancy with or without LDA treatment	Data support the use of LDA to prevent pre-eclampsia in high-risk pregnancies[231], but no studies have been performed in APS; treatment decision should be made on an individual basis
Persistent positivity for antiphospholipid antibodies and history of recurrent first-trimester pregnancy loss (without previous thrombosis)	LDA with or without prophylactic LMWH or unfractionated heparin	Low-quality randomized controlled trials[183–186]
History of miscarriage or previous history of ischaemic placental-mediated complications (second-trimester complications)	LDA with prophylactic LMWH or unfractionated heparin	Low-quality randomized controlled trials[232]
Patients with thrombotic APS (venous or arterial)	LDA and intermediate-dose or high-dose LMWH	Based on one prospective observational study[180]
Postpartum presence of antiphospholipid antibodies	LMWH thromboprophylaxis for 1–6 weeks postpartum on an individual basis depending on the presence of additional risk factors for thrombosis. Women with thrombotic APS can restart anticoagulation once haemostasis is achieved. Vitamin K antagonists are safe while breastfeeding; no safety data on DOACs are available[233,234].	Based on case–control studies and cohort studies[235]

APS, antiphospholipid syndrome; DOACs, direct oral anticoagulants; LDA, low-dose aspirin; LMWH, low-molecular-weight heparin.

than the recommended warfarin treatment targeted at INR 2–3, despite little high-quality evidence[1,3]. Options are either high-intensity vitamin K antagonist treatment (INR 3–4) or vitamin K antagonists (INR 2–3) combined with other agents such as antiplatelet agents.

Obstetrical complications

With current consensus management (TABLE 3), the overall live birth rate in women with obstetrical APS is around 70%[178]. Women with antiphospholipid antibodies and APS should receive counselling before pregnancy and close surveillance during pregnancy[131]. The specific objective of antenatal care in pregnant women with APS is close observation for maternal thrombosis, antiphospholipid antibody-related renal manifestations and features of pre-eclampsia and monitoring of fetal growth.

Risk stratification. A complete history and antiphospholipid antibody profile should be available before conception to aid risk stratification. Risk factors include a high-risk antiphospholipid antibody profile (BOX 2), coexisting SLE, previous thrombotic APS and adverse pregnancy outcomes[131], of which previous pregnancy outcomes is the best predictor[179]. Moreover, individuals with obstetrical APS can be separated into three different clinical phenotypes (that is, those with recurrent early pregnancy loss, those with previous ischaemic placental complications and those with previous maternal thromboses); each of these phenotypes is associated with different pregnancy outcomes. In a series of 83 pregnancies in 67 women, women with a previous history of thrombosis had less favourable neonatal outcomes with higher rates of preterm delivery (26.8% versus 4.7%, $P = 0.05$) and babies of small gestational size (9.5% versus 4.8%, $P = 0.003$) compared with those with a previous history of recurrent pregnancy loss at <10 weeks of gestation[179]. Limited data are available assessing pregnancy performance in women with a history of stroke. In one prospectively study including 23 pregnancies in 20 women with APS and previous stroke and/or transient ischaemic attack, 8 women developed pre-eclampsia and 3 women had a recurrent stroke despite treatment with LDA and LMWH[180]. All women with pulmonary hypertension, including those with APS as a cause, should be discouraged from pregnancy as maternal mortality is as high as 43%[1,181].

Obstetrical APS. Despite limited evidence, the standard of care for individuals with obstetrical APS is LDA, intermediate-dose LMWH or unfractionated heparin to prevent antiphospholipid antibody-related obstetrical complications[131,182]. Mothers with a previous history of thrombosis require intermediate or full-dose anticoagulation (usually LMWH) throughout pregnancy to prevent further thrombotic events. The prevention of early recurrent miscarriages as opposed to placental-mediated complications in the second and third trimesters is the field in obstetrical APS in which most clinical trials have been published. TABLE 3 summarizes the current recommendations for the treatment of pregnant women with antiphospholipid antibodies or APS.

The current recommendations are based on two RCTs in which women with antiphospholipid antibody-related recurrent first-trimester pregnancy losses were randomly assigned to either LDA or a combination of LDA and unfractionated heparin[183,184]. The combination of LDA and unfractionated heparin showed a significantly higher

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rate of live births versus LDA alone (71% versus 42%)[183]. The other RCT of 50 women alternately assigned either to the combination of LDA and heparin (unfractionated heparin or LMWH) or to LDA alone showed a significantly higher live birth rate associated with LDA and heparin (80% versus 44%)[184]. However, no differences in outcome with combination therapy versus LDA were found in two other RCTs. Indeed, an RCT of 98 women with recurrent miscarriages found no difference in live birth rate compared with women who were randomized to LDA alone (78% versus 72%)[185]. In the HepASA trial of 859 women with recurrent pregnancy loss, LDA and LMWH did not result in a significantly better live birth rate than LDA alone (79.1% versus 77.8%)[186]. The conflicting results of these four trials might be caused by the variation in live birth rates in those women randomized to LDA arms. Two other RCTs on unfractionated heparin compared with LMWH in women with recurrent pregnancy loss and antiphospholipid antibodies did not find a significant difference[187,188]. A 2015 Cochrane review concluded that treatment with unfractionated heparin in combination with LDA may reduce pregnancy loss by 54%[189].

Good clinical evidence is available for the use of LDA in women to reduce the risk of hypertensive disorders in pregnancy (such as pre-eclampsia and eclampsia). As the presence of antiphospholipid antibodies increases the risk of hypertensive disorders in pregnancy, LDA is offered to all individuals who have antiphospholipid antibodies[190–192].

Refractory obstetrical APS. Treatment options to improve pregnancy outcomes refractory to LDA and heparin include low-dose prednisolone in recurrent first-trimester pregnancy loss, which, when combined with conventional treatment with LDA and LMWH administered from positive pregnancy test until week 14, improved the rate of live births in refractory antiphospholipid antibody-related pregnancy loss or losses to 61% in a retrospective cohort of 18 patients[193]. The use of intravenous immunoglobulins has been assessed in two RCTs. The first trial, in which 40 women with antiphospholipid antibody-related recurrent first-trimester pregnancy loss were randomized to either intravenous immunoglobulins or the combination of LDA and LMWH, failed to show any benefit of intravenous immunoglobulins[194]. Furthermore, in a second trial, in which 16 women were randomized to intravenous immunoglobulins or the combination of placebo with LDA and LMWH, intravenous immunoglobulins did not show a benefit on obstetrical or neonatal outcomes over LDA and LMWH[195]. However, women randomly assigned to the intravenous immunoglobulins arm had a lower rate of fetal growth restriction (14% versus 33%, $P>0.05$) and neonatal intensive care admission (14% versus 44%, $P>0.05$), which led some clinicians to consider intravenous immunoglobulins as adjuvant in refractory cases[196].

A case–control study in patients with established antiphospholipid antibody-related pre-eclampsia and/or intrauterine growth restriction suggests a role for pravastatin (a drug of the statin family)[197]. Eleven patients treated with pravastatin in combination with LDA and LWMH were compared with women receiving only LDA and LMWH. In all patients in the pravastatin group, signs of pre-eclampsia and placental perfusion remained static, whereas the control group progressed[197].

Lastly, some studies suggest that hydroxychloroquine reduces the rate of antiphospholipid antibody-related adverse pregnancy outcomes[198,199]. In a retrospective, multicentre cohort of women with refractory obstetrical APS, fewer first-trimester miscarriages (81% to 19%, $P<0.05$) and improved live birth rates to 78% ($P<0.05$) were reported when women received hydroxychloroquine compared with previous pregnancies in which most received LDA and LMWH[199]. In another retrospective review of 96 women with persistent antiphospholipid antibodies with 170 pregnancies, hydroxychloroquine use was associated with a higher rate of live births of 67% versus 57% in women treated with LDA and LMWH ($P<0.05$) and a lower prevalence of pregnancy morbidity in women treated with hydroxychloroquine in addition to standard of care (LDA and LMWH) compared with those who only received standard of care (47% versus 63%; $P=0.004$)[198]. The HYPATIA study, a multicentre RCT of hydroxychloroquine versus placebo in addition to standard of care in women with persistent antiphospholipid antibodies planning for pregnancy, is about to start[200].

Late obstetrical complications. There is limited evidence on the prevention of recurrent antiphospholipid antibody-related complications in the second and third trimesters. One RCT involving women with a previous history of antiphospholipid antibody-related delivery at <34 weeks of gestation with hypertensive disorder and/or small-for-gestational-age baby comparing LDA with LMWH plus LDA showed no benefit of LMWH; however, the study was underpowered[201]. The TIPSS trial, an open-label multicentre trial of 292 women with various thrombophilias, assessed the efficacy of an LMWH, dalteparin, versus no dalteparin in the prevention of a composite outcome of pregnancy-related venous thromboembolism, pregnancy loss and ischaemic placental complications, such as severe pre-eclampsia, intrauterine growth restriction and placental abruption. This study showed that dalteparin did not alter the primary composite outcome but was also underpowered[202].

Quality of life

Data from the European multicentre cohort, which included 820 individuals of different ethnicities from 13 European countries who were prospectively followed-up for 10 years, showed that individuals with APS had a mortality of 9.3%, but the severity of APS and the treatment during this period were unclear. Thrombosis and its consequences, such as ischaemic stroke, myocardial infarction, pulmonary embolism and catastrophic APS, were the predominant cause of death, causing one-third of all deaths[52].

A history of previous thrombosis has been associated with a reduced quality of life (QOL), irrespective of a diagnosis of APS[203], and thrombosis is the best-studied

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Box 3 | **The Global Anti-Phospholipid Syndrome Score**

The Global Anti-Phospholipid Syndrome Score (GAPSS)[210] is a scoring system to predict the risk of thrombosis (either first or recurrent) and pregnancy morbidity. The system consists of a combination of independent risk of thrombosis and pregnancy loss, including the antiphospholipid antibody profile and conventional cardiovascular risk factors. The GAPSS can be calculated for each patient by adding the points corresponding to the different risk factors, including presence of

- Anticardiolipin antibodies (immunoglobulin G (IgG) or IgM isotype): 5 points
- Anti-β2-glycoprotein antibodies (IgG or IgM isotype): 4 points
- Lupus anticoagulant: 4 points
- Anti-prothrombin/phosphatidylserine complex antibodies (IgG or IgM isotype): 3 points
- Hyperlipidaemia: 3 points
- Arterial hypertension: 1 point

clinical manifestation in terms of QOL in individuals with APS. A case–control study of 826 individuals with SLE with previous thrombosis, of whom 143 had antiphospholipid antibodies, reported a lower score on the mental and physical domains of the 36-Item Short-Form Health Survey[204]. These findings were similar to an online survey assessing QOL in 270 individuals with APS who were members of the Hughes Foundation, which showed that health-related QOL is significantly lower in individuals with APS than in healthy, age-matched controls[205]. Another study using this online survey also showed that insufficient social support was linked to a reduced health-related QOL and highlighted the importance of disease-specific patient education[206].

Recurrent pregnancy loss, intrauterine growth restriction, pre-eclampsia and/or late fetal loss have an impact on QOL, but to the best of our knowledge no published data have assessed QOL in individuals with obstetrical APS.

Finally, the warfarin treatment itself might have an impact on QOL owing to food interactions and the need for INR monitoring. The RAPS trial collected data on QOL as a secondary outcome, and patients assigned to the rivaroxaban arm reported better QOL than the warfarin group[158].

Outlook

Diagnosis and classification

To increase the future comparability of clinical studies of APS, better standardization of both clinical and laboratory criteria is required. Indeed, the lack of standardization of testing for antiphospholipid antibodies remains a great concern. Furthermore, validation of antibodies directed against prothrombin, the phosphatidylserine–prothrombin complex, specific protein domains such as domain 1 of β2-glycoprotein 1 and proteins that affect the anticoagulant activity of annexin A5 is required, as is validation of the IgA isotype of anticardiolipin antibodies and anti-β2-glycoprotein 1 antibodies. Additional tests may offer subclassification of APS and better characterization of future risk of thromboses. As we learn more about APS, the clinical criteria included in the diagnostic categories may also change[207]. Future classification criteria may include several APS-associated manifestations that are not currently included in the criteria[2,208,209], including heart valve lesions, renal manifestations, livedo reticularis and thrombocytopenia.

Risk stratification and recurrence risk

Several antiphospholipid antibodies have been identified and weighted with respect to their ability to predict thrombosis and pregnancy loss, resulting in the development of the Global Anti-Phospholipid Syndrome Score (GAPSS)[210] (BOX 3), which has been validated in APS[211] and SLE with antiphospholipid antibodies[212]. High GAPSS predicted incident thrombosis better than just the presence of the classical antiphospholipid antibodies and, consequently, may guide treatment decisions in clinical practice[213]. The GAPPS also includes non-APS risk factors, acknowledging the clinically important point that thrombosis risk in individuals with APS is also influenced by concomitant cardiovascular thrombotic risk factors such as arterial hypertension and hyperlipidaemia. It is of interest to stratify for the risk of a first thrombotic event as well as the risk of recurrent thrombosis. The GAPPS is useful in predicting the risk of recurrent thrombosis[211,214].

Management

As traditional cardiovascular risk factors add to the thrombotic risk associated with the presence of antiphospholipid antibodies, future treatment strategies should ensure modification of concomitant risk factors. The role of statins is of particular interest because they have the dual functionality of inhibiting cholesterol synthesis and modulating inflammatory responses. In the general population, statin treatment also reduces the rates of venous thromboembolism[215]. Fluvastatin reduces pro-inflammatory and prothrombotic markers in individuals who are positive for antiphospholipid antibodies[216] and pravastatin improves pregnancy outcomes in a cohort of pregnant women with refractory APS[197].

The positive outcomes associated with statin treatment support the notion that the pathogenesis of APS involves inflammatory and thrombogenic pathways. Thus, cell activation and complement activation mediated by antiphospholipid antibodies play a central part in APS pathology. Accoringly, it is of great interest that in a murine model of obstetrical APS, hydroxychloroquine was able to prevent placental and fetal abnormalities in parallel to lowering serum C5a levels[154]; we await the results of a trial of hydroxychloroquine in pregnant women with antiphospholipid antibodies (HYPATIA study)[200].

Future management trials may include B cell-directed therapy and complement inhibition with rituximab and eculizumab[217]. In a systematic review of haematopoietic stem cell transplantation in refractory APS, 32 of 44 (73%) individuals were able to discontinue anticoagulation after transplantation[218]. Although this procedure carries a considerable mortality risk, it is still of interest that remission could be induced in APS. As our knowledge of the pathogenesis of APS steadily increases, we will gain a better understanding of APS and will be able to identify opportunities to investigate new paradigm-shifting therapeutic targets.

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Introduction (G.R.-I.); Epidemiology (S.S.); Mechanisms/pathophysiology (J.E.S. and P.G.d.G.); Diagnosis, screening and prevention (K.D., Y.S. and O.S.); Management (K.S. and B.J.H.); Quality of life (K.S. and S.S.); Outlook (S.J.); Overview of Primer (K.S. and B.J.H.).

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CORRECTION

Antiphospholipid syndrome

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In the version of the article originally published, Guillermo Ruiz-Irastorza was incorrectly stated as Guillermo Ruiz-Irastroza. The article has now been corrected.

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