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BSH GUIDELINE

Guidelines on the investigation and management of antiphospholipid syndrome

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METHODOLOGY

This guideline was compiled according to the British Society for Haematology (BSH) process at (https://b-s-h.org.uk/media/16732/bsh-guidance-development-process-dec-5-18.pdf). The Grading of Recommendations Assessment, Development and Evaluation (GRADE) nomenclature was used to evaluate the levels of evidence and to assess the strength of recommendations. The GRADE criteria can be found at http://www.gradeworkinggroup.org. A literature search was carried out using the terms given in the appendix up to April 2024.

REVIEW OF THE GUIDELINE

Review of the guideline followed the standard BSH guidelines procedure. Following review of the draft guideline by the BSH Haemostasis and Thrombosis Task Force and the BSH Guidelines Committee, it was placed on the members' section of the BSH website for comment (sounding board) and these comments were addressed and incorporated appropriately. The guideline was reviewed by the Royal College of Obstetricians and Gynaecologists, Thrombosis UK and APS Support UK. These organizations do not necessarily approve or endorse the contents.

INTRODUCTION

This guidance updates and replaces previous BSH guidelines.[1,2] Antiphospholipid syndrome (APS) is an autoimmune disease characterised by thrombosis (venous, arterial and/or microvascular) and/or pregnancy morbidity in association with persistently positive antiphospholipid antibodies (aPL).

APS can occur in isolation (primary APS) or in association with other autoimmune diseases, most commonly systemic lupus erythematosus (SLE) and rheumatoid arthritis (secondary APS).

The diagnosis of APS requires the presence of at least one clinical event (either an objectively confirmed thrombotic event and/or pregnancy complication) and detection of one or more aPL (lupus anticoagulant [LA], IgG/IgM anticardiolipin [aCL] and/or IgG/IgM anti-β_2 glycoprotein-1 [aβ_2GPI]) on two or more occasions at least 12 weeks apart.[3] Thrombosis in APS can occur in any organ or tissue. Deep vein thrombosis (DVT) with or without pulmonary embolism (PE) is the most common venous thrombosis (VTE) while transient ischaemic attack (TIA) and stroke are the most common arterial thromboses.[3] APS may also present with unusual site thrombosis such as portal, renal, mesenteric and cerebral venous sinus thrombosis. Microvascular thrombosis in APS is uncommon but may manifest as the potentially lethal catastrophic antiphospholipid syndrome (CAPS), which develops in <1% of patients with APS and where there is evidence of multiorgan failure commonly affecting the heart, lungs, brain and/or kidneys.[3]

In the updated Sapporo classification criteria, non-thrombotic clinical manifestations such as thrombocytopenia and heart valve disease were not included as diagnostic or defining features of definite APS.[3] However, recent American College of Rheumatology (ACR)/European Alliance of Associations for Rheumatology (EULAR) Antiphospholipid Syndrome Classification Criteria,[4] designed for uniformity of patient risk profiles in clinical studies, include several features not described in the revised Sapporo criteria.[3] The ACR/EULAR criteria (Table 1)[4] include a scoring system (score range 1–7 points each) divided into six clinical domains (macrovascular venous thromboembolism, macrovascular arterial thrombosis, microvascular thrombosis, obstetric, cardiac valve and haematological) and two laboratory domains similar to the revised Sapporo criteria. Patients are classified as having APS if they score ≥3 points in clinical domains and ≥3 points in laboratory domains (Table 1). The definition of aPL persistence has not altered, but the maximum time between a clinical event and persistently positive aPL has been shortened from 5 to 3 years (Table 1). Diagnosis of APS in routine clinical practice is less restrictive than the ACR/EULAR APS classification criteria; their strict application in routine practice to diagnose individual patients should be avoided. The diagnosis of APS should depend on careful clinical assessment, paying attention to alternative causes of thrombosis or pregnancy morbidity and critical evaluation of laboratory results considering the limitations of the laboratory assays. Current clinical practice is based on the evidence derived from the clinical studies from patients with APS diagnosed as per revised Sapporo criteria.[3]

Recommendations

- **To make the diagnosis of APS, patients should have at least one persistently (minimum 12 weeks apart) positive aPL with either thrombosis unprovoked or provoked by a minor risk factor, or pregnancy morbidity (1B).**
- **We suggest using ACR/EULAR Antiphospholipid Syndrome Classification Criteria when considering patients for research studies but not for routine clinical use (2C).**

PATHOPHYSIOLOGY OF APS

Thrombotic APS

aPL are heterogeneous and primarily directed against phospholipid-binding proteins, the best recognized being β2GPI (primarily domain-I of the open form of the molecule) and prothrombin. Their presence is necessary but insufficient for the development of the thrombotic manifestations of APS. It is hypothesized that this requires a second trigger, such as infection, pregnancy or surgery, which leads to a more pronounced thrombo-inflammatory response.[5–8] aPL-mediated thrombosis can occur through multiple mechanisms including endothelial dysfunction, activation of monocytes, platelets[9] and neutrophils, neutrophil extracellular traps (NETs) formation, complement activation[10] and impaired fibrinolysis.[11–15] Hypercoagulability is further enhanced by downregulation of natural anticoagulants including protein C[16] and tissue factor pathway inhibitor.[17,18]

The paradoxical prolongation of clotting times that define a positive LA is thought to be due to either binding of aβ_2GPI antibodies to factor (F)V and subsequent inhibition of the latter's activation by activated FX (FXa) and/or by competition with FXa for phospholipid-binding sites by anti-prothrombin antibody-prothrombin complexes.[19–21]

Obstetric APS

The pathophysiology of the obstetric manifestations of APS is similarly complex and probably varies according to stage of gestation, thereby contributing to the observed heterogeneity of clinical features. Inflammation, complement activation and placental thrombosis all have been proposed to play pathogenic roles in obstetric APS.

A systematic review of placental histopathology of women with aPL (93% of whom had received some form of treatment) identified a number of more common features including placental infarction, impaired spiral artery remodelling, decidual inflammation, an increase of syncytial knots and a decrease in vasculosyncytial membranes.[22] Intraluminal spiral artery thrombosis that would likely explain placental infarction was infrequently seen and may have been due to sampling location. Other lines of evidence support a thrombo-inflammatory process involving complement activation, neutrophil activation with tissue factor expression and formation of NETs in the intervillous spaces and reduced annexin-V on placental villi surfaces leading to phosphatidylserine exposure.[8,23,24]

TABLE 1 Comparison of the 2006 modified Sapporo and the 2023 ACR/EULAR APS classification criteria.[218]

Criteria	Revised Sapporo criteria	ACR/EULAR APS classification criteria		Comments
Clinical—thrombosis	≥1 episode of arterial, venous or small vessel thrombosis in any organ or tissue confirmed objectively (imaging/histology) Where histology used, thrombosis should be present without overt vessel wall inflammation	*Macrovascular VTE*		Although the supplementary guidance notes to the modified Sapporo criteria do suggest taking other risk factors for thrombosis into account, there is no formal downgrading in the presence of risk factors for CVD or VTE The Sapporo criteria provide no weighting to thrombotic manifestations (any thrombotic manifestation counts as towards the diagnosis equally in the appropriate clinical context) Both guidelines emphasise the need to confirm thrombosis objectively
		VTE with other high-risk VTE profile	1 point	
		VTE without other high-risk VTE profile	3 points	
		Macrovascular arterial thrombosis		
		Arterial thrombosis with high-risk CVD profile	2 points	
		Arterial thrombosis without high-risk CVD profile	4 points	
		Microvascular Thrombosis		
		Any one of:		
		Livedo racemosa, livedoid vasculopathy, aPL nephropathy, pulmonary haemorrhage		
		Suspected	2 points	
		Confirmed (e.g. histology/imaging)	5 points	
		Confirmed adrenal haemorrhage/microvascular myocardial disease	5 points	
Clinical—obstetric	≥1 unexplained death of a morphologically normal fetus at ≥10 weeks' gestation *AND/OR* ≥1 birth of a morphologically normal neonate <34 weeks' gestation due to: (i) Eclampsia or severe pre-eclampsia OR (ii) Placental insufficiency *AND/OR* ≥3 consecutive spontaneous miscarriages <10 weeks' gestation with alternative maternal/paternal factors excluded (anatomical, hormonal, chromosomal)	≥3 consecutive pre-fetal (<10 weeks gestation) and/or early fetal (10–15 weeks +6-day gestation) death	1 point	As for thrombotic manifestations, the Sapporo criteria do not provide a weighting to obstetric manifestations
		Fetal death (16–33 weeks +6-day gestation) in the absence of	1 point	
		Pre-eclampsia with severe features AND		
		Placental insufficiency with severe features		
		Pre-eclampsia with severe features (<34 w gestation) OR	3 points	
		Placental insufficiency with:		
		Severe features (<34-week gestation) with/without fetal death		
		Pre-eclampsia with severe features (<34-week gestation) AND	4 points	
		Placental insufficiency with:		
		Severe features (<34-week gestation) with/without fetal death		
Clinical—other	None counting toward diagnosis	*Cardiac Valve*		Previously termed non-criterion manifestations of APS are incorporated into the diagnostic algorithm in the ACR/EULAR guidelines. These features are mentioned in the revised Sapporo criteria, but it is suggested that they are insufficiently specific to count towards the diagnosis
		Thickening	2 points	
		Vegetation	4 points	
		Haematological		
		Thrombocytopenia	2 points	

(Continues)

TABLE 1 (Continued)

Criteria	Revised Sapporo criteria	ACR/EULAR APS classification criteria		Comments
Laboratory	Persistently positive LA detected according to ISTH guidelines. *AND/OR* Persistently positive IgG/IgM aCL at medium or high titre by ELISA *AND/OR* Persistently positive IgG/IgM aβ2GPI by ELISA	LA detected on:		The criteria for aPL persistence (detected on 2 occasions, 12 weeks apart) has not been altered Points are assigned for transient LA positivity in ACR/EULAR, but this by itself is insufficient for the diagnosis Weighting is applied to the combination of aPL seen to account for higher risk phenotypes (e.g. triple antibody positivity)
		One occasion	1 point	
		Persistently	5 points	
		Persistently positive aCL and/or aβ2GPI:		
		Moderate or high titre IgM aCL and/or aβ2GPI	1 point	
		Moderate (40–79 U/mL) titre IgG aCL and/or β2GPI	4 points	
		High titre (≥80 U/mL) IgG aCL OR aβ2GPI	5 points	
		High titre (≥80 U/mL) IgG aCL AND aβ2GPI	7 points	
Diagnosis	APS is classified as ≥1 clinical criterion and ≥1 laboratory criterion Clinical and laboratory criteria must be detected <5 years of each other	Single highest scoring feature from each domain is summed APS is classified as ≥3 points in clinical domains and ≥3 points in laboratory domains. Clinical and laboratory criteria must be detected <3 years of each other		

Abbreviations: aCL, anticardiolipin; aPL, antiphospholipid antibody; aβ2GPI, anti-beta2-glycoprotein I; CVD, cardiovascular disease; ELISA, Enzyme-linked immunosorbent assay; ISTH, International Society on Thrombosis and Haemostasis; LA, lupus anticoagulant; VTE, venous thromboembolism.

Recurrent early miscarriage may be the result of a strong local inflammatory response to aβ_2GPI antibodies interfering with implantation and inhibition of trophoblast proliferation.[25] Evidence suggests complement activation plays a major role in early miscarriages.[26,27] Later, pregnancy manifestations have been attributed to antibody-mediated complement activation with inhibition of trophoblast proliferation and differentiation, abnormal spiral artery development and a local inflammatory response with placental fibrin deposition including placental infarctions leading to placental dysfunction.[8,21,23,28]

CLINICAL MANIFESTATIONS OF APS AND TESTING FOR aPL IN CLINICAL PRACTICE

There is inconsistency in the reported frequency of clinical events (thrombosis or pregnancy morbidity) in patients with aPL. This could be due to inconsistency of the aPL testing methodology, for example, testing for only LA or only aCL, variation in timing of aPL testing in relation to clinical events or testing without confirmation of persistent positivity after 12 weeks. In an analysis which included 120 studies, the frequency of aPL was 6% for pregnancy complications, 13.5% for stroke, 11% for myocardial infarction (MI) and 9.5% for DVT.[29] However, 60% of the studies were published prior to 2000; hence, all three criteria aPL were tested in only 11% of the studies and 36% used low titre aCL cut-offs and heterogeneous aβ_2GPI cut-offs. Furthermore, persistence of aPL was confirmed in only 24% of the studies.[27] The mean age at APS diagnosis is around 50 years in recent population-based studies.[30–32] In patients aged <50 years, approximately 17% (range 2%–56%) and 12% (range 2%–45%) had stroke and TIAs, respectively, associated with aPL.[33]

Thrombocytopenia is a frequent finding in individuals with aPL with or without APS. The Euro-phospholipid project group, which included 1000 patients with APS, found that thrombocytopenia was present in 37% of patients,[34] but the incidence can vary from 20% to 53%.[35] The presence of thrombocytopenia could predict APS-related clinical events with a threefold increased risk for thrombotic events or obstetrical morbidity or all-cause deaths.[36] Furthermore, the presence of aPL with or without APS in patients with thrombocytopenia is important as this may influence the management of patients with autoimmune thrombocytopenia (ITP), since some treatment options for ITP may increase the risk of thrombosis more than others.[37] Thrombocytopenia in individuals with aPL is often mild ($100–150 \times 10^9$/L) but can be severe ($<50 \times 10^9$/L) in patients with other associated autoimmune disease such as SLE, or those presenting with acute thrombosis, especially CAPS.[36,38]

The British Society for Rheumatology guidelines[39] recommend testing for aPL at baseline in all adults with SLE, especially in those with an adverse pregnancy history or arterial/venous thrombotic events, with confirmatory tests after at least 12 weeks if positive.

Testing for aPL is recommended when clinical features are suggestive of APS as this may influence management decisions including the choice of antithrombotic agent as discussed below and in the BSH guideline on thrombophilia testing.[40]

Indications for aPL testing in clinical practice are summarised in Table 2.[41] Testing for aPL is not recommended in patients who develop thrombosis with strong provoking factors.[40]

Recommendations

- **Testing for aPL is recommended in patients with VTE in the absence of major provoking factors (1B).**
- **Testing for aPL is recommended in patients <50 years of age with arterial thrombosis in the absence of other vascular risk factors (1B).**
- **We suggest against testing for aPL in individuals with VTE associated with a transient reversible major risk factor such as surgery or immobilization, or active cancer (2B).**
- **We recommend testing for aPL in women who fulfil the clinical criteria for obstetric APS (1B).**
- **Testing for aPL is suggested at baseline in all adults with SLE, especially in those with an adverse pregnancy history or arterial/venous thrombotic events, with confirmatory tests after at least 12 weeks if positive (2B).**

LABORATORY DIAGNOSIS OF APS

To increase diagnostic utility, the same venepuncture should be used for solid phase and clotting tests for aPL.[42]

TABLE 2 Indications for testing for aPL in patients presenting with thrombosis or obstetric complications. Adapted from Arachchillage et al.[41]

Unprovoked VTE or minor provoking factors and VTE at unusual sites such as splanchnic vein thrombosis (which includes portal vein, mesenteric vein and splenic vein thrombosis, and the Budd–Chiari syndrome) and cerebral venous sinus thrombosis without clear risk factors
Arterial thrombosis in patients <50 years of age without clear risk factors
History of systemic lupus erythematosus (SLE) or other autoimmune disease developing thrombosis or pregnancy complications
Unexplained microvascular thrombosis
Presence of livedo reticularis/livedoid vasculopathy
Unexplained prolonged PT or APTT prior to starting anticoagulation
Recurrent thrombosis despite therapeutic anticoagulation not explained by non-adherence or other clear risk factors
Thrombocytopenia
Recurrent miscarriages/stillbirths/severe pre-eclampsia or evidence of placental insufficiency <34 weeks of onset
Cardiac valve abnormalities in the absence of other explanation

Abbreviations: aPL, antiphospholipid antibodies; APS, antiphospholipid syndrome; APTT, activated partial thromboplastin time; PT, prothrombin time; VTE, venous thromboembolism.

Pre-analytics

Sample preparation

Samples for LA assays should be collected into 0.105–0.109 M (3.2%) tri-sodium citrate and double centrifuged at 2000 *g* for 15 min[1,43,44] to achieve a platelet count (PLT) $<10\times10^9$/L. Local verification is suggested to ensure that, in a sample size of at least 20 double centrifuged plasmas, all have PLT $<10\times10^9$/L. Double centrifugation is always required for samples that are to be frozen, even if single centrifugation for a particular sample meets the criteria for PLT.[45]

Samples for LA assays should be double centrifuged ideally within 4 h of sample collection,[1,46,47] but transport times >4 h are common in many parts of the United Kingdom. Samples for dilute Russell's viper venom time (DRVVT) are stable at room temperature for up to 24 h before double centrifugation and freezing.[48] Although routine activated partial thromboplastin time (APTT) assays should be performed within 4 h of sample collection,[49,50] delays of up to 24 h in double centrifuging may not result in a change in classification (from negative to positive, or from positive to negative).[45] Therefore, if local transport times exceed 4 h, laboratories should verify sample stability and adapt their testing repertoire and/or reporting comments where necessary.

Frozen plasma for LA assays should be stored in a screw cap polypropylene tube with an 'O'-ring below −70°C,[49] although storage below −24°C in freezers without auto-defrost cycles can be used for up to 3 months.[51]

Plasma or serum can be used for solid-phase aPL assays, according to manufacturers' instructions for use.[52] If plasma is used, it should be prepared as for LA. Samples for solid phase assays can be stored at 2–8°C and tested within 2–3 days,[39,48] or stored below −30°C for up to 6 months.[53,54]

Frozen samples shipped to another laboratory should be sent on dry ice.[49] Frozen samples must be thawed in a temperature-controlled water bath at 37°C with the surface of the frozen sample at or below the surface of the water.[55] For plasma volumes <1 mL, a thaw of 5 min is sufficient, although that can be reduced if the sample is completely thawed sooner.[55,56] Samples should be mixed thoroughly by inversion prior to testing.[49] DRVVT, APTT and solid-phase aPL assays change significantly in samples that have been frozen and thawed more than once[54,57] and should not be used.

Haemolysis

Samples should be examined for haemolysis: APTT can be shortened in haemolysed samples,[57,58] which may lead to false-negative LA results. Haemolysed samples should be rejected for clotting and solid-phase aPL assays,[42,59] unless intravascular haemolysis is suspected,[46] for example in suspected CAPS, when results should be reported with a caveat stating that results are potentially unreliable.

Testing in acute phase or pregnancy

APTT assays may be shortened when FVIII is increased in acute phase or pregnancy, potentially leading to false negatives. They may also be prolonged to varying degrees in the presence of elevated levels of C-reactive protein in the acute phase,[60] potentially leading to false positives or negatives.

Assays

Reference intervals and cut-off values

Reference intervals (RI) and cut-off values for aPL assay positivity should be specific for the reagents and analysers in use,[1] and local validation is essential. Common practice in the United Kingdom is for laboratories to use 95% confidence intervals (2.5th–97.5th centiles) for RI calculations,[49] but the International Society on Thrombosis and Haemostasis[61] state that 99th centiles should be used, while highlighting that use of 95th centiles may be of use in investigating individuals with pregnancy morbidity. Sourcing >120 normal samples for approximation of the 97.5th or 99th centile[1,61] is problematic for many laboratories,[44] so a compromise is to verify manufacturer's cut-off values using 20–40 normal samples.[42,62] This is only applicable to specified reagent/analyser combinations (including the source of pooled normal plasma [PNP] for LA mixing studies) and assumes that analysis has been performed on a sufficiently large number of samples by the manufacturer. There is considerable variation of cut-offs in multicentre studies when using the same analyser and reagent combinations,[63] or when using the same reagents and normal donor plasmas.[64]

In-house cut-off values using the 99th percentile or verification of a manufacturer's cut-off (using the same reagent, analyser and PNP as used by the manufacturer) should be established for all reported aPL parameters.[42,61] Laboratories that cannot generate in-house cut-off values or verify a manufacturer's cut-off should refer samples to a centre that has done so.

Solid-phase tests for aPL

Screening for aPL should include assays for IgG and IgM aCL and aβ_2GPI.[42,65,66] These were previously assayed only by enzyme-linked immunosorbent assays (ELISA) with heterogeneity in analytical platforms and reagents resulting in method variability.[67,68] The increasing use of automated platforms[69] allows consistent application of protocols and may reduce inter-laboratory variation. Different assays are not interchangeable, and aCL/aβ_2GPI should be measured on the same solid-phase platform.[66] Assays for aCL should be β_2GPI dependent[69] and use human-derived β_2GPI as the β_2GPI source.[42,69] Calibration is an issue due to lack of uniformity of reference material,[70] so calibrators should be traceable to primary standards.[52] Rheumatoid factor may produce false-positive results in IgM assays; heterophile antibodies, intravenous immunoglobulins (IVIG) and human anti-animal antibodies can cause false positives.[42,49]

There are stronger associations of thrombosis with IgG than with IgM antibodies[71,72] and of pregnancy morbidity with IgM antibodies.[65] Testing of IgG and IgM can help reinforce clinical probability of APS[66] with triple-positivity (LA plus aCL [IgG and/or IgM] plus aβ_2GPI [IgG and/or IgM]) correlating most strongly with pregnancy morbidity and thrombosis.[40,73] Testing for IgA aCL/aβ_2GPI is not recommended for routine diagnostic use.[9,42]

Non-criterion aPL

Anti-phosphatidylserine/prothrombin antibodies (anti-PS/PT) may predict risk of recurrence in patients with previous thrombosis[74,75] and are frequently found in triple-positive patients.[76,77] However, their independent diagnostic utility in thrombotic and obstetric APS is uncertain.[78,79] Moreover, ELISAs for anti-PS/PT lack reference standards[80] and are not recommended for routine diagnostic use.

IgG-antibodies against β_2GPI-domain-1 are strongly associated with triple-positive APS,[81–84] but there is insufficient evidence to recommend them for routine diagnostic use.

Detection of LA

LA is detected when there is prolongation of a phospholipid-dependent clotting test that is corrected by the presence of an excess of phospholipid in a confirmatory step but is not corrected in mixing studies with normal plasma. If the confirmatory step does not correct the prolongation, the test is not indicative of the presence of a LA. Alternative causes of the prolongation should be considered, but if the effect of mixing with normal plasma is to further prolong the test, then the normal plasma may be providing a missing or reduced LA-cofactor, and combining mixing studies with a confirmatory step may then be useful in interpretation. This may also be the case when the presence of a very strong LA is suspected.

Two assays of different principles must be used,[1] the first of which should be the DRVVT. The second test will usually be an APTT using a reagent with proven LA responsiveness. In some cases, a Taipan snake venom time (TSVT) may be considered[85] (Table 3).

When a screening test is prolonged, a confirmatory step using the same method principle (using a higher phospholipid concentration, a platelet neutralizing reagent or an LA-unresponsive reagent) to demonstrate phospholipid dependence and a mixing study (test plasma mixed 1:1 with PNP) using the same method principle should be performed to demonstrate inhibition.

Individuals are regarded as having an LA if either of the two assays is positive.

TABLE 3 Suggested aPL testing algorithm for 2 patients on anticoagulants.

Anticoagulant	Laboratory assays	Laboratory notes	Clinical notes
Patient not anticoagulated, or anticoagulation status not known	PT, APTT, TT, Clauss fibrinogen DRVVT LAR-APTT aCL/aβ2GPI	If DRVVT raised, check for the presence of Xa-inhibitors by performing an anti-Xa assay If TT raised, check for liver coagulopathy, IIa-inhibitors or paraprotein	Results of LA testing during an acute phase response (e.g. in the setting of an acute thrombotic event) should be interpreted with caution
VKA	PT, APTT, Clauss fibrinogen DRVVT mixing studies LAR-APTT mixing studies aCL/aβ2GPI	DRVVT and LAR-APTT in neat plasma can be reported if INR <1.5 TSVT/ET can be considered if INR ≥1.5[87,95] ACP ineffective	If feasible, perform LA testing 1–2 weeks after discontinuation of the VKA, with consideration of LMWH bridging[56] False negatives are possible if only mixing studies are performed
LWMH	PT, APTT, Clauss fibrinogen Heparin-specific anti-Xa assay DRVVT LAR-APTT aCL/aβ2GPI	DRVVT and/or LAR-APTT can only be performed if heparin level below level acceptable in the assay TSVT/ET cannot be used ACP ineffective	If feasible, perform testing at least 12 h after the last dose of LMWH was administered and as near as possible to the next dose[56] Results of LA testing during an acute phase response (e.g. in the setting of an acute thrombotic event) should be interpreted with caution
UFH	PT, APTT, TT, Clauss fibrinogen Heparin-specific anti-Xa assay DRVVT LAR-APTT aCL/aβ2GPI	DRVVT and/or LAR-APTT can only be performed if heparin level below level acceptable in the assay and TT normal TSVT/ET cannot be used ACP ineffective	Results of LA testing during an acute phase response (e.g. in the setting of an acute thrombotic event) should be interpreted with caution
Direct FXa-inhibitors	PT, APTT, Clauss fibrinogen Drug-specific anti-Xa assay DRVVT LAR-APTT aCL/aβ2GPI	DRVVT can only be performed if drug-specific anti-Xa assay is below LLoQ TSVT/ET can be considered[87,95] if drug-specific anti-Xa assay is above LLoQ ACP effective	If feasible, temporarily interrupt DOAC anticoagulation for at least 48 h after the last dose (longer in patients with renal impairment)[56]
Dabigatran	PT, APTT, TT, Clauss fibrinogen Dabigatran assay DRVVT LAR-APTT aCL/aβ2GPI	DRVVT and LAR-APTT can only be performed if dabigatran assay and TT is below LLoQ TSVT/ET cannot be used ACP effective[78,85]	If feasible, temporarily interrupt DOAC anticoagulation for at least 48 h after the last dose (longer in patients with renal impairment)[56]
Argatroban Bivalirudin	PT, APTT, TT, Clauss fibrinogen Drug-specific anti-IIa assay DRVVT LAR-APTT aCL/aβ2GPI	DRVVT and LAR-APTT can only be performed if drug-specific anti-IIa assay is below LLoQ TSVT/ET cannot be used ACP partially effective[78,85]	Results of LA testing during an acute phase response (e.g. in the setting of an acute thrombotic event) should be interpreted with caution, as false-positive and -negative results can occur
Fondaparinux Danaparoid	PT, APTT, Clauss fibrinogen Drug-specific anti-Xa assay DRVVT LAR-APTT aCL/aβ2GPI	TSVT/ET cannot be used ACP ineffective	If feasible, perform testing as near as possible to the next dose, with drug-specific anti-Xa activity levels checked alongside the LA test[207]
Direct FXIa-inhibitors Direct FXIIa-inhibitors	PT, APTT, TT, Clauss fibrinogen DRVVT aCL/aβ2GPI	Effect on LAR-APTT or TSVT/ET not known Effectiveness of ACP not known	No data yet available

Abbreviations: aCL/aβ2GPI, solid-phase assays for anticardiolipin and anti-β2GPI antibodies; ACP, activated charcoal product effective; APTT, activated partial thromboplastin time; DRVVT, dilute Russell's viper venom time; ET, ecarin time; FXa, factor Xa; FXIa, factor XIa; FXIIa, factor XIIa; LAR-APTT, lupus anticoagulant responsive APTT; LLoQ, lower limit of quantification; LMWH, low molecular weight heparin; PT, prothrombin time; TSVT, Taipan snake venom time; TT, thrombin time; UFH, unfractionated heparin; VKA, vitamin K antagonist.

Routine coagulation screening tests

All samples should have a prothrombin time (PT) and APTT performed as an assessment of sample integrity.[49] Ideally, reagents used for routine PT and APTT screening should be lupus-unresponsive[43] to reduce unnecessary investigation of prolonged clotting times due to the presence of LA in asymptomatic individuals, although an 'LA-unresponsive' APTT reagent may give a prolonged APTT in the presence of a potent LA.

A thrombin time (TT) should be considered as a screen for the presence of thrombin inhibitors that have not been disclosed in clinical details.[61] A Clauss fibrinogen activity should be performed as an indicator of an acute phase

response[61] (and possible false-negative results in APTT-based LA assays).

Choice of PNP

In-house or commercially available PNP can be used for mixing studies, provided they have been obtained by double centrifugation[46] and have normal fibrinogen levels and >80 IU/dL of clotting factors.[43,61] For in-house pools, at least 40 donors should be used.[61] Most laboratories use a commercial PNP,[44] which can be lyophilised or frozen, if it fulfils the specifications outlined above; this may require local verification if information is not available from the manufacturer. If a commercial PNP is used, laboratories need to confirm that it gives the same clotting time as the RI mean before it can be used; differences can lead to erroneous results.

Normalised ratios

Results for LA screen and confirmatory assays (in neat plasma and mixing studies) should be expressed as a ratio (to two decimal points) by dividing the individual clotting times by the normal clotting time for each specific assay. Ratios can be calculated using the results of a PNP tested in the same batch as the denominator,[1,61] or using the RI mean determined per reagent lot number[43] (as is standard practice for International Normalised ratio [INR] calculations). The former approach does not consider measurement uncertainty, which may be ameliorated if the PNP is tested multiple times before being used in the calculation; the latter approach does not compensate for day-to-day variation, although day-to-day variation is taken into account if the RI is determined over several days as recommended.[59]

The method for calculating the degree of correction in the confirm step should either use percentage correction of ratio = (screen ratio − confirm ratio/screen ratio) × 100 or a normalized test/confirm ratio = screen ratio/confirm ratio.

Mixing studies should be interpreted with a mixing study-specific cut-off expressed as normalized ratio.[61,86,87]

DRVVT

Most manufacturers have paired reagents for DRVVT, the only difference between screen and confirm reagents being phospholipid concentration. These have been well validated and are widely used.[44]

LA-responsive APTT assays

When intentionally testing for LA, an LA-responsive APTT (LAR-APTT) reagent should be used as the screen reagent, with a paired confirm reagent (the only difference being phospholipid concentration). The sensitivity of APTT reagents to screen for LA is dependent on phospholipid composition more than activator,[88,89] and some reagents that are marketed as LAR-APTT may not be sufficiently responsive for LA detection.[90]

Despite previous recommendations[1,46] and evidence that as many as 13.9% of individuals with triple-positive APS may have an LA detectable only by LAR-APTT,[91] a 2024 survey by UKNEQAS for Blood Coagulation found that only 48/60 (80%) of respondents used more than one APTT reagent for LA detection, suggesting that at least 20% of laboratories do not perform a screen and confirm for APTT [personal communication]. Data from the Royal College of Pathologists of Australasia Quality Assurance Program found that up to two-thirds of laboratories do not use paired APTT reagents.[92]

Few manufacturers supply paired reagents for APTT despite previous recommendations[1,46]; exceptions include Silica Clotting Time (Werfen), Cephen LS/Cephen (Hyphen Biomed), Lupus Anticoagulant Test (Technoclone) and Intrinsin (Hematex), all using silica as activator. If paired reagents are not available, a raised LAR-APTT screen should be confirmed by the platelet neutralization procedure, unless the sample contains heparin[93]; the Staclot LA reagents (Diagnostica Stago) use hexagonal phospholipids in place of platelet neutralization. Alternatively, an LA-unresponsive reagent can be used for the confirmatory step, but caution in result interpretation is needed as reagent sensitivities to acute-phase proteins, anticoagulants and clotting factors may differ, and false-positive results may occur, especially if there are differences in sensitivities to contact factor deficiencies.[94]

Taipan snake venom test and ecarin time

TSVT and ecarin time (ET) assays have been validated for the detection of LA in both non-anticoagulated individuals and those anticoagulated with vitamin K antagonists (VKA) or direct FXa-inhibiting anticoagulants (DFXaI).[95] TSVT/ET cannot be used to identify LA in an individual anticoagulated with direct or indirect FIIa-inhibiting anticoagulants.[95] TSVT/ET tests are performed without mixing studies.[95]

Other tests for LAs

Some LA may be detectable in a PT but not by DRVVT or APTT (or TSVT/ET), but dilute PT is not recommended for routine use. Specialist laboratories may consider using it to investigate an isolated prolonged PT, particularly if there is interference in PT-based factor assays.

The kaolin clotting time is difficult to automate, particularly in systems that detect an optical end-point, and shows poor reproducibility compared to other assays.[46] An important limitation is the lack of a confirmatory test, thus not fulfilling the diagnostic criteria for LA,[96] and it is not recommended for routine use.

Textarin can be used as an alternative to taipan snake venom, but commercial preparations for textarin are difficult to obtain and the assays are likely to be laboratory-developed tests.[97]

Use of activated charcoal products

Commercial reagents containing activated charcoal, and collectively called 'DOAC neutralizers', have been developed to remove the effect of direct oral anticoagulants (DOAC) for ex vivo application to detect LA in patients on DOAC.[98] Activated charcoal products (ACP) for LA assays in samples from individuals on DFXaI and direct thrombin inhibitors (DTI) show promise.[85] They are not effective against heparinoids or VKAs.

Anticoagulant levels are reduced by ACP to varying degrees (Table 3), and interference in assays is removed.[99–104] Treatment with ACP may affect clotting times, even in normal samples,[105,106] suggesting the possibility of false negatives or positives in ACP-treated samples; some have shown no effect[107] and differences may be explained by intra-assay measurement uncertainty. Specific RIs established using ACP-treated normal plasmas may be required,[108] which would make their use problematic. Differences in interpretation in anticoagulated samples have been seen when comparing ACP treatment and TSVT/ET.[109] ACP may be considered in individual cases where anticoagulation cessation cannot be countenanced.

Interferences with LA testing

Acute phase and pregnancy

False-negative and false-positive LA results are seen in the acute phase, such as soon after a thrombotic event and in pregnancy.[61]

Anticoagulants

Testing for LA should ideally be postponed until anticoagulation has been discontinued for a suitable time period (Table 3), or samples should be collected at a treatment trough. However, laboratories are often asked to test for LA without knowing a patient is anticoagulated; measurement of anticoagulant levels in a suitably calibrated assay can determine the presence of an anticoagulant and may guide appropriate testing.

Individuals receiving unfractionated heparin (UFH), argatroban or bivalirudin are likely to be acutely ill, and testing during the acute phase should ideally be avoided. However, some anticoagulated individuals with suspected CAPS may require testing during this time.

Testing algorithms for patients on anticoagulants are summarised in Table 3.

Vitamin K antagonists

VKAs cause false-positive or negative LA results by DRVVT and APTT in neat plasma, and a negative result in mixing studies should be regarded with caution, as it does not exclude the presence of an LA because of the dilution effect.[85]

Indirect FIIa/FXa inhibiting anticoagulants

DRVVT reagents contain heparinase that will neutralise UFH or low molecular weight heparin (LMWH) up to defined limits (0.8–1.0 IU/mL, depending on the reagent manufacturer). Some APTT reagents intended specifically for LA assays may also contain heparinase, but potential false positives may occur if using unpaired reagents, or at supratherapeutic levels.[96] If a patient is known or suspected to be anticoagulated with UFH or LMWH, a heparin anti-Xa level should be measured to ensure that levels do not exceed the neutralization capacity of the reagent in use.[56]

Assays are relatively unaffected by fondaparinux[110] or danaparoid.[111]

Direct FIIa inhibiting anticoagulants

DRVVT, APTT and TSVT/ET are all affected by the presence of DTI, and testing in neat plasma or in mixing studies should be avoided if the TT in the routine coagulation screen is raised.

Direct FXa inhibiting anticoagulants

DRVVT ratios are prolonged in the presence of DFXaI: Results in confirm assays are often >10% lower than those in screening assay in samples containing even low levels of rivaroxaban or edoxaban, giving false-positive results.[112] The presence of apixaban gives variable results.[108,113,114] A DRVVT and/or LAR-APTT-screen within the RI can reliably be reported as negative for the presence of an LA, but a prolonged DRVVT-screen in a sample containing detectable levels of DFXaI should not be reported (Table 2) and should not be investigated further. Careful interpretation of LAR-APTT, confirm and mixing studies can avoid misinterpretation of LA.

If a patient is known or suspected to be receiving a DFXaI, a drug-specific anti-Xa assay should be measured, to ensure that the drug is not likely to interfere with the DRVVT assay.[56] In the absence of clinical details, this should be suspected when results of the DRVVT-confirm assay exceed the RI. If a drug-specific anti-Xa assay is not available, a heparin anti-Xa level may be used as a surrogate,[115] although the routine use of this approach is not advocated, and care must be taken in the interpretation of results.

Direct FXIa and FXIIa-inhibiting anticoagulants

Direct FXIa- and direct FXIIa-inhibiting anticoagulants show promise as potential anticoagulants.[116] No data yet exist on their influence on assays for LAs, although they are likely to affect APTT-based assays. DRVVT and TSVT/ET assays are less likely to be affected, but this will require validation.

Liver-related coagulopathy and coagulation factor deficiencies

False positives or negatives by DRVVT, LAR-APTT and TSVT/ET are likely in liver-related coagulopathy and testing for LA should be avoided.

Individuals with clotting factor deficiencies may have co-existing LA and positive results by DRVVT, APTT and/or TSVT/ET depending on the clotting factor involved, but false positives may occur if using unpaired LA reagents.

One-stage clotting assays may also yield misleading results if an LA interferes with the phospholipid in the reagent; this problem may be identified if the same reagent is used in routine coagulation screening.

Some individuals with autoimmune (acquired) haemophilia may also have LA detectable at presentation.[117,118] Interpretation is difficult and testing should be avoided until anti-FVIII inhibitors are no longer detectable.

Quality control

A negative and positive internal quality control (IQC) should be included with every batch of aPL assays.

If a PNP is used to adjust normalised ratios with each LA batch, then a separate negative IQC sample should also be tested. Commercial (lyophilised or frozen) negative and positive IQC materials are available, but these may vary in composition, so they should be matched with the reagents in local use and verified as acceptable for use, with target values locally assigned.

For aCL/aβ_2GPI assays, laboratories should target between run precision of <15% for ELISA and 10% for automated platforms.[52]

Laboratories should participate in accredited external quality assurance programmes.

Reporting and interpretation

For LA, laboratories should report detailed quantitative results (normalised ratios for screen, confirm and mixing studies for each test system, with a percentage correction or screen/confirm ratio) and an interpretation of the results. Reports should state clearly all the tests that gave a negative result, for example, 'No LA detected by DRVVT or APTT'. Positive results should state which assay(s) gave a positive result. Samples that give a positive result in neat plasma but are not detectable in mixing studies should be reported with a phrase such as 'Positive in neat plasma and negative in mixing studies; a weak LA cannot be excluded due to the dilution effect'.

For aCL/aβ_2GPI, numerical values should be reported based on assay calibration.

If a sample has been tested after addition of an ACP, this should be clearly stated in the report.[61]

Results should state whether results are positive or negative.[42,61]

A positive result for any aPL should prompt a request for repeat samples (for LA and aCL/aβ_2GPI) in a further 12 weeks; a confirmatory positive test after 12 weeks renders the initial test result more reliable and increases assurance of the test result.[61] An integrated report with results of all aPL assays should be issued, and a comment on single, double or triple positivity should be included for positive results.[61]

Results from individuals who are anticoagulated, pregnant or who are acutely ill should be reported with a caveat about the possibility of false LA negatives or false LA positives.[61] The presence of certain aPL increases with age and results need to be interpreted taking this into consideration with asymptomatic detection of aPS.[119]

Recommendations

- **We suggest against testing for LA in individuals receiving anticoagulation (2C).**
- **We suggest against testing for LA in patients who are acutely ill or within 3 months of an acute thrombotic event (2B).**
- **Samples for LA testing should be double centrifuged at 2000 *g* for 15 min (1B).**
- **A PT, APTT and Clauss fibrinogen should be performed as a screen on all LA requests (1B).**
- **Solid-phase aCL and aβ_2GPI IgG and IgM assays must be performed (1B).**
- **Two LA assays of different principles must be used, and individuals are regarded as having an LA if either test is positive. In patients who are not on anticoagulation, these should be a DRVVT and an APTT using a reagent with proven LA responsiveness (1B).**
- **When an LA screening test is prolonged, a confirmatory step using the same method principle to demonstrate phospholipid dependence and a mixing study using the same method principle should be performed to demonstrate inhibition (1B).**
- **Either in-house or commercially available PNP should be used for LA mixing studies, provided they have been obtained by double centrifugation and have normal fibrinogen levels and >80 IU/dL of clotting factors (1B).**
- **Laboratories should report detailed quantitative results for all aPL tested alongside an interpretation of results (1A).**

Monitoring response to VKAs in patients with APS

A minority of patients with APS (4.3%) may have a prolonged PT prior to starting anticoagulation depending on the LA sensitivity of the local laboratory's reagent.[120] In some patients, this may be linked to hypoprothrombinaemia secondary to the LA, but if FII levels are normal and the baseline PT is above normal, there is a potential for overestimation of the INR and under-anticoagulation of the patient. Therefore, it is suggested that a baseline PT is measured in all APS patients before commencing treatment with VKA. If a discrepancy is noted, an alternative LA-insensitive reagent that gives a normal baseline PT should be used to monitor INR, or response to VKA could be measured using an PT-based FII assay[121] or an amidolytic (chromogenic) FX (CFX) assay.[110] Levels of FII of 15–25 IU/dL[121] or of CFX of 20–40 IU/dL have been shown to be equivalent to an INR of 2.0–3.0.[122] However, CFX assays are not widely available: in a recent survey by UKNEQAS for Blood Coagulation, only one of 209 returns for FX assays was by a chromogenic method [unpublished data]. If a local laboratory is using an LA-sensitive PT reagent for PT, INR and FII assays, then testing for parallelism in the FII assay is essential.[49]

In their product literature, manufacturers of point of care (POC) devices for monitoring INR may make recommendations about the suitability of using their device in patients with APS. One recent study has shown that interference in POC INR for these patients correlates with $a\beta_2$GPI titre,[123] whereas another has shown that aPL profile does not influence the result.[124] In a recent comparison between POC- and laboratory-INR in 291 samples from 52 patients with APS, where agreement was defined as ±0.4 for laboratory-INR <2.0, ±20% for laboratory-INR 2.0–4.5, ±25% for laboratory-INR >4.6–6.0 and ±30% for laboratory-INR >6.0, 79% of paired results were within the agreement limits; 67% of the non-agreeing results were from a subset of five patients.[125] International Council for Standardization in Haematology (ICSH) guidance suggests that agreement is defined as results within 0.5 INR units,[126] although correlation between results is only likely to occur within the therapeutic range (2.0–4.0). POC may be suitable for INR monitoring in APS patients if a minimum of three paired POC and laboratory INR results show agreement, and that when there is no agreement, the INR is monitored by a suitable laboratory method.

Recommendations

- **We suggest assessing a baseline PT prior to starting VKA in patients with APS and if prolonged, an alternative PT reagent for which the baseline is normal should be used (1C).**
- **We suggest against use of POC measurement of INR for patients with APS unless a minimum of three paired POC and laboratory INR results show agreement (2C).**

MANAGEMENT OF THROMBOTIC APS

Venous thrombosis

Anticoagulation remains the mainstay of treatment for patients with APS who have had a proven thrombotic event. Most data for secondary prevention of thrombosis in APS involve the use of VKA, mainly warfarin in the United Kingdom. Patients with APS tend to have a higher incidence of recurrent events after cessation of anticoagulation at 3–6 months compared to non-APS patients.[127,128]

Two randomized clinical trials (RCT) have compared warfarin at an INR target range of 2.0–3.0 versus 3.0–4.0 in patients with APS.[129,130] The majority of patients included had VTE rather than arterial thrombosis. Both trials concluded that there was no benefit to a higher therapeutic target INR.

Role of DOACs in APS

Four open-label RCTs have assessed the safety and efficacy of rivaroxaban or apixaban versus warfarin in patients with thrombotic APS.[131–134]

A recent systematic review and meta-analysis that included these four RCTs reported that anticoagulation with rivaroxaban or apixaban was associated with an increased risk of arterial thrombosis (odds ratio [OR]: 5.43, 95% confidence interval [CI]: 1.87–15.75, $p < 0.001$), especially stroke, compared to warfarin.[135] The risk was significant whether the index event was venous or arterial.[135] There was no difference in the risk of subsequent venous thrombotic events (OR: 1.20, 95% CI: 0.31–4.55, $p = 0.79$) or major bleeding (OR: 1.02, 95% CI: 0.42–2.47, $p = 0.97$) between the two anticoagulant types.[135] An excess of thromboembolic events was also seen in those who continued rivaroxaban rather than continuing or switching to warfarin in a post-trial closure 2-year follow-up of Trial of Rivaroxaban in AntiPhospholipid Syndrome,[136] an RCT in which patients with triple-positive APS received warfarin or rivaroxaban, and that was terminated prematurely due to an excess rate of arterial thrombosis in those receiving rivaroxaban.

There is insufficient evidence to make a strong recommendation for patients with single- or double-positive APS with VTE who comprised <50% of those included in the systemic review and meta-analysis.[135] Furthermore, prespecified subgroup analysis of showed only a trend towards a higher risk of recurrent arterial thrombosis in single- or double-positive APS patients with rivaroxaban or apixaban compared to warfarin.[135]

The European Medicines Agency (EMA) (https://www.ema.europa.eu, 2019) and the Medicines and Healthcare Products Regulatory Agency (MHRA) (https://www.gov.uk/drug-safety-update, 2019) issued recommendations that DOACs should not be used for secondary prevention of thrombosis in patients with APS.

Recommendations

- **APS patients with an unprovoked venous thrombotic event should be offered indefinite anticoagulation (1B).**
- **We suggest long- term anticoagulation for patients with APS and high-risk antibody profiles (e.g. triple-positive) and VTE associated with minor provoking risk factors especially where the risk factor persists in the absence of risk factors for major bleeding (2C).**
- **We recommend VKA with a target INR range of 2.0–3.0 as the anticoagulant of choice for patients with APS and VTE requiring long-term anticoagulation (1B).**
- **We recommend against the initiation of DOACs for treatment or secondary prophylaxis in patients with VTE and known triple-positive APS (1B).**
- **We suggest against the initiation of DOACs for treatment or secondary prophylaxis in patients with VTE and known single- or double-positive APS (2C).**
- **For patients with triple-positive APS who are currently on a DOAC, we recommend switching from the DOAC to a VKA after discussion with patients regarding the available evidence. For those patients who do not wish to switch, we recommend continuation of the DOAC over no anticoagulation (1B).**
- **APS patients with single- or double-positive aPL who are already on a DOAC may continue or switch to a VKA after discussion with the patient considering their clinical history, treatment adherence and previous experience. For those patients who do not wish to switch, we recommend continuation of the DOAC over no anticoagulation (2C).**

Management of arterial thromembolism

Stroke is the most common arterial thrombotic complication of APS.[137–139] In a prospective study of outcomes of 1000 patients with APS meeting diagnostic criteria included in the Europhospholipid project, the most common arterial thrombotic events were stroke (5.3% of total cohort) and TIA (4.7% of total cohort) over 10 years.[137]

Other arterial thrombotic complications include renal arterial thrombosis and renal thrombotic microangiopathy. Thrombotic MI is an uncommon complication associated with aPL; coronary vessels in these patients are typically unaffected by atherosclerosis.[38] Patients may also present with peripheral arterial occlusions, mesenteric ischaemia, thrombosis of retinal artery or vein, or bone necrosis.

APS-associated microvascular thrombotic complications include involvement of cerebral, cardiac, renal and skin small vessels but require radiological and/or histological confirmation to meet current APS classification criteria.

Management of stroke in APS

Anticoagulation in APS-associated stroke remains controversial due to lack of good quality evidence in this area. The National Institute for Health and Care Excellence (NICE) guidelines on the management of acute stroke (https://www.nice.org.uk/guidance/ng128) advise that stroke in patients with APS should be managed as for any other stroke and specifically does not support any recommendation on the safety and efficacy of anticoagulants versus antiplatelet agents.

The RCTs comparing intensities of anticoagulation in patients with APS have only included a minority of patients with arterial thrombosis.[129,130] The AntiPhospholipid Antibodies and Stroke Study was a cohort study within the warfarin versus aspirin recurrent stroke study assessing the use of aspirin versus warfarin for prevention of recurrent stroke or death.[140] A total of 720/1770 patients were positive for aPL measured on only one occasion. There was no difference in outcomes between patients treated with aspirin or low-intensity anticoagulation (target INR 1.4–2.8), but patients were not tested for aPL persistence.

A retrospective review of outcomes of rates of recurrent thrombosis in 139 patients receiving antiplatelet and anticoagulation after an initial arterial event reported that patients taking combined warfarin and antiplatelet therapy had a 70% lower risk of recurrence compared to those treated with antiplatelet agents or anticoagulation alone (hazard ratio, 0.30; 95% CI, 0.08–0.83; $p = 0.025$).[141] Data for this review were gathered from antibody databases (New York Presbyterian Hospital and APS action databases) for patients with a median follow-up of 4.24 years. A systematic review and meta-analysis found that aspirin and warfarin were similarly effective in preventing recurrent events in APS patients with arterial thrombosis.[142] A network meta-analysis in 2023 which included 13 studies ($n = 719$ patients) reported that the use of antiplatelet plus warfarin conferred a significant reduction in the risk of recurrent thrombosis compared to single antiplatelet therapy alone (RR 0.41, 95% CI 0.2–0.85).[143] However, there was no difference in bleeding rates between different antithrombotic treatment.[143] Furthermore, there was no comparison between anticoagulant alone and anticoagulant plus antiplatelet in this study.[143]

Dual antiplatelet therapy (DAPT) may be more effective than single antiplatelet therapy for prevention of recurrent stroke in APS, but studies assessing the use of DAPT were retrospective and only included a small number of patients.[144]

Furthermore, in normal practice, when aPL are found in conjunction with stroke, the clinical picture is sometimes complicated by other vascular risk factors that may act as competing or complementary causative mechanisms. In cases where aPL are borderline or not fulfilling diagnostic criteria, and biochemistry, cardiac tests or vascular/brain imaging

suggest alternative causes for stroke, the case for standard management with VKA may not be clear cut. Joint working between haematologists and stroke physicians can help devise appropriate management strategies for such patients.

Recommendations

- **We suggest that patients with APS and stroke are managed jointly by haematologists and stroke physicians (2C).**
- **We suggest anticoagulation with VKA for all patients with APS and stroke (2C).**
- **We recommend against the initiation of DOACs for treatment or secondary prophylaxis in patients with APS with stroke (1B).**
- **We suggest VKA with a target INR of 2.5 (2.0–3.0) in patients with APS and a first episode of stroke (2C).**
- **We suggest considering the addition of an anti-platelet agent to VKA therapy in patients with APS and stroke if they have additional vascular risk factors but no significant risk factors for bleeding (2C).**
- **We suggest against use of a single antiplatelet agent and instead consider DAPT in patients with APS with stroke if there is a contraindication to use of VKA (2C).**

Management of TIA, migraines and asymtomatic cardiovascular disease in patients with persistently positive aPL

TIA and stroke share similar pathophysiology and risk factors; TIA increases the risk of subsequent stroke, highest in the first few days. In patients with TIA or with stroke, but without aPL, investigational and management strategies are broadly aligned, aiming to identify risk factors for recurrence, manage those risks and initiate antithrombotic or anticoagulant therapy.[145] Therefore, the management of TIA associated with aPL is similar to the management of stroke and APS, with VKA rather than DOAC.

Migraines are a common TIA mimic. Observational studies have found a significantly greater prevalence of at least one positive test for aPL in migraineurs than in controls (12% vs. 3%).[146] However, evidence is lacking as to whether cerebrovascular disease in general, aPL-positivity or aPL-associated cerebrovascular disease in particular is causally related to, rather than associated with, migraine.

There are anecdotal and case reports of patients with APS and migraine headaches improving with antithrombotic treatment.[147] However, there have been significant advances in non-antithrombotic migraine treatments, and recent migraine guidelines do not support the routine use of antithrombotics for symptom control.[148,149]

The spectrum of asymptomatic cerebrovascular disease (aCVD) includes white matter hyperintensities (or leukariosis—a marker of small vessel disease), lacunar infarction (together commonly referred to as cerebral small vessel disease) and large vessel infarcts. There is little evidence to guide management in cases of aPL-positive patients who are found to have aCVD on brain imaging.

Wan et al. compared the incidence of silent brain abnormalities on routine MRI in people under 50 years with stroke or TIA, including 44 patients with primary APS, 24 persistent aPL carriers (without clinical criteria for APS) and 23 healthy controls.[150] In a composite result of MRI abnormalities, they noted a prevalence of 56% of imaging abnormalities in the aPL-positive groups versus 4% in controls ($p < 0.001$).[150]

The high prevalence of these MRI abnormalities expected in aPL-positive individuals must be borne in mind when considering the existing literature which does not show a benefit for aspirin for primary prophylaxis of thrombosis in aPL individuals.[82,151] Although a meta-analysis which assessed the efficacy of aspirin for the primary prevention of thrombosis in individuals with aPL showed the risk of a first thrombotic event was significantly reduced in those treated with aspirin, when the analysis was restricted to prospective studies, this was no longer significant.[152]

Recommendation

- **For patients with aPL and suspected TIA, confirmation of TIA by specialist stroke services is recommended (1C).**
- **For patients with APS and confirmed TIA, after considering any ischaemic changes on brain imaging and specialist assessment, we suggest consideration of anticoagulation with VKA with a target INR of 2.5 (2.0–3.0) (2D).**
- **We do not suggest using antiplatelets or anticoagulation for migraine treatment alone in patients with aPL (2C).**

Management of patients with APS and non-cerebrovascular arterial thrombosis

Myocardial infarction and unstable angina are the next most common arterial thrombotic complications outside the cerebrovascular territory.[137–139] Evidence for the role of anticoagulation and for risk of recurrence in patients presenting with arterial thrombosis outside the cerebrovascular territory is scarce. Considering the reported increased risk of recurrence, anticoagulation to prevent further thrombotic events in patients with APS and an arterial thrombotic event is recommended.[133] It is important that APS patients with cardiac events are managed jointly with cardiologists where possible and some patients may require antiplatelet treatment in addition to anticoagulation based on cardiovascular interventions.

Recommendations

- **We suggest use of VKA with a target INR of 2.5 (2.0–3.0) for patients with arterial or microvascular thrombosis (2C).**

- **We suggest APS patients with cardiac events are managed jointly with cardiologists where possible (2C).**

Managment of recurrent thrombosis despite anticoagulation

Recurrent thrombosis despite adequate anticoagulation remains high in patients with APS, especially those with triple-positive aPL with up to a 30% reported risk of recurrent events over 10 years.[73] A recent UK-wide study found that the risk of recurrent thrombosis may be even higher with almost 40% across all patients with APS.[153] However, high-quality data to guide the management of recurrent thrombosis are lacking and the management approach to such patients is largely empirical.

If a patient with APS develops recurrent thrombosis while on a DOAC, switching to a VKA is recommended. However, there is no consensus on the target INR. As all non-APS RCTs compared DOACs to warfarin with a target INR of 2.5 (2.0–3.0),[41] some suggest aiming for a target INR of 3.0 (2.5–3.5) rather than 2.5 (2.0–3.0) in the setting of recurrent thrombosis on a DOAC.

For patients presenting with recurrent thrombosis while on a VKA, the accuracy of the INR should be established as described in the earlier section on monitoring response to VKAs in patients with APS. The time spent within the therapeutic range should be assessed and a time in therapeutic range of at least 60% regarded as acceptable. A review of any potential drug or food interactions that may interfere with warfarin should be undertaken.

For patients presenting with a recurrent thrombotic event despite a therapeutic INR with a target INR of 2.0–3.0, a higher target INR of 3.0–4.0 is recommended.[154]

The addition of an antiplatelet agent has been associated with a lower risk of recurrence.[125] Other potential targets for non-anticoagulant-based therapies such as hydroxychloroquine and statins have been proposed in patients with APS, particularly those with recurrent thrombosis despite adequate anticoagulation.[146,155]

Retrospective studies have shown hydroxychloroquine to be associated with a decreased risk of thrombotic events in patients with SLE,[156,157] and statins may also reduce the risk of venous thromboembolism in patients with APS.[158] Outside of this, data are limited to case reports and series, and therefore, there is insufficient evidence to support their use in APS. Use of hydroxychloroquine for over 5 years can be associated with an increased risk of retinal toxicity; a retrospective study of more than 2300 patients using a dose of >5 mg/kg for over 5 years showed 7.5% of patients had some form of retinal toxicity.[159]

Other possible treatments include complement inhibition (e.g. eculizumab), anti-CD20 inhibition (e.g. rituximab), peptide therapy, nuclear factor κB and p38 mitogen-activated kinase inhibitors, defibrotide, abciximab and mTOR inhibitors.

Recommendations

- **We suggest referring patients with APS with recurrent thrombosis despite adequate anticoagulation to a specialist centre (2C).**
- **We suggest switching to a VKA for patients with APS who develop recurrent thrombosis while on a DOAC or antiplatelet therapy (2C).**
- **We suggest assessing time in therapeutic range and the reliability of INR measurement if a patient with APS develops recurrent thrombosis while on a VKA (2C).**
- **We suggest increasing the target INR to 3.0–4.0 for patients with APS on a VKA who develop recurrence thrombosis despite an acceptable time in therapeutic range at a target INR of 2.0–3.0 or adding antiplatelet treatment and keeping a target INR of 2.5 (2.0–3.0) (2C).**
- **We suggest considering the addition of immunomodulatory agents such as hydroxychloroquine for patients with APS and recurrent thrombosis despite an acceptable time in the therapeutic range while on a target INR of 3.5 (3.0–4.0) or a target INR of 2.5 (2.0–3.0) with antiplatelet therapy (2C).**
- **We recommend ophthalmology review for patients with APS started on hydroxychloroquine after 12 months, then at 5 years and annual screening, thereafter, specifically screening for retinal toxicity (1A).**
- **We suggest considering other immunomodulatory agents such as rituximab in patients who develop recurrent thrombosis despite increasing the INR intensity and antiplatelet treatment (2C).**

Cardiovascular risk managment in patients with venous or arterial thrombosis

Cardiovascular risk reduction including smoking cessation, weight loss, exercise, blood pressure and glycaemic control are key management considerations for all patients with aPL with or without venous or arterial thrombosis. Control of hypertension is particularly important in patients who develop recurrent thrombosis as hypertension is associated with increased risk of progression of cerebrovascular ischaemic lesions.[160] Patients with aPL and stroke should start statins as in patients with stroke without aPL. Statins reduce endothelial dysfunction, enhance the stability of atherosclerotic plaques and reduce inflammation and oxidative stress.[161] A retrospective cohort study of 184 patients with APS found that statins reduced the risk of recurrent thrombosis when given in addition to standard therapy in a multivariable regression analysis (HR 0.24, 95% CI 0.09–0.63, $p = 0.004$).[162] This remained significant when adjusting for vascular risk factors, type of standard therapy and aPL profile.

Recommendations

- **We suggest that all patients with APS and thrombosis should have strict control of cardiovascular risk factors. This should include use of a statin unless there is a contraindication (2C).**

Managment of APS patients with previous APS associated thrombotic complications and fluctuating levels or disapperance of aPL

It is recognized that aPL levels can fluctuate over time, but evidence on outcomes of patients according to the degree of fluctuation is sparse. An observational study of 230 patients followed up over 2–4 years suggested that $a\beta_2$GPI-domain-I and $a\beta_2$GPI titres decrease significantly over time ($p < 0.0001$ and $p = 0.010$ respectively).[163] Following adjustment for age, sex and number of positive aPL tests, it was found that treatment with hydroxychloroquine was associated with 1.3-fold and 1.4-fold decreases in $a\beta_2$GPI-domain-I and $a\beta_2$GPI titres respectively. Both $a\beta_2$GPI-domain-I and $a\beta_2$GPI titres decreased around the time of thrombosis.[155] Some patients may subsequently become seronegative, and some case reports suggest withdrawal of anticoagulation may be appropriate. However, there is insufficient evidence to make recommendations for these patients.[164]

Recommendations

- **We suggest not changing the management of patients with APS whose aPL levels fluctuate or become negative over time and who have a previous history of APS-related thrombosis (2C).**

OBSTETRIC APS

The testing and management for APS in the context of recurrent miscarriage is covered in a Royal College of Obstetricians and Gynaecologists (RCOG) guideline.[165] It is well recognised that testing for APS can be affected by pregnancy itself and that testing should be performed between pregnancies wherever possible.[40,166] Clinicians working in women's health are guided to perform APS testing in women who have:

1. One unexplained death of a morphologically normal fetus at 10 or more weeks' gestation
2. One birth of a morphologically normal neonate at <34 weeks' gestation due to:
   (i) Eclampsia or severe pre-eclampsia OR
   (ii) Placental insufficiency
3. Three consecutive spontaneous miscarriages at <10 weeks' gestation with alternative maternal/paternal factors excluded (anatomical, hormonal, chromosomal).

This is based on current clinical practice adopted from revised Sapporo criteria for clinical classification of obstetric APS.[3] A meta-analysis reported that LA has the strongest association with recurrent miscarriage, followed by IgG and IgM aCL.[167]

Potential interventions that have been investigated in an attempt to reduce pregnancy complications in women with obstetric APS include heparin, aspirin, steroids and IVIG. A Cochrane review in 2012[168] found that only aspirin combined with UFH was effective, reducing the risk of miscarriage by 54% compared to aspirin alone. Other data have shown no difference in the effectiveness and safety of UFH and LMWH when combined with aspirin in the prevention of miscarriage in women with APS.[169]

An updated Cochrane review (2020) evaluated the efficacy of aspirin or heparin or both to reduce pregnancy complications in women with APS. The review included 11 studies (1672 women) and found that heparin plus aspirin increased the number of live births in women with APS compared to aspirin alone (RR1.27, 95% CI 1.09–1.49, 5 studies, 1295 women, low-certainty evidence). Additionally, the Cochrane review found that heparin plus aspirin may reduce the risk of miscarriage (RR 0.48, 95% CI 0.32– 0.71, 5 studies, 1295 women, low-certainty evidence).[170]

A high-quality systematic review and network analysis also found supporting evidence for the first-line use of low-dose aspirin (LDA) plus heparin for prevention of miscarriage in women with APS.[171]

Both Cochrane reviews and RCOG Recurrent Miscarriage guidance note that treatment with aspirin and heparin is not without risks of bleeding in all three trimesters in pregnancy. However, there appear to be no additional adverse risks to the fetus of maternal exposure to aspirin and heparin.[21] Heparin and aspirin in pregnancy do not increase the risk of fetal haemorrhage or have teratogenic effects.[172] LMWH is the preferred heparin treatment due to its ease of use without the risks of maternal bleeding and severe allergic reactions that are associated with UFH.[173]

Management of pregnant women with APS

Preterm delivery, pre-eclampsia and fetal growth restriction are known to be associated with women with APS.[174] NICE guidance for hypertension in pregnancy: diagnosis and management recommends women with APS take 75–150 mg aspirin daily from 12 weeks' gestation until delivery.[175] As many of these women will have started aspirin and LMWH at positive pregnancy test, there is a need to continue the antiplatelet and heparin therapy with consideration of increasing the dose of aspirin to 150 mg from 12 weeks' gestation.

There is a lack of data for the management of pregnant women with APS and a previous history of thrombotic events. Warfarin is teratogenic at 6–12 weeks' gestation and therefore is generally discontinued on confirmation of a positive pregnancy test and switched to LMWH. Women on anticoagulation prior to pregnancy due to previous history

of either arterial or venous events should receive treatment dose LWMH during pregnancy, but this is a controversial area. Both heparin and warfarin are safe for breastfeeding[176]; therefore, women on long-term warfarin can be switched back to warfarin following delivery. Women with obstetric APS who develop thrombosis during pregnancy despite being on prophylactic dose LMWH should be treated with therapeutic dose LMWH for the remainder of the pregnancy, for at least 6 weeks postnatally, and until at least 3 months of total treatment.[177,178] Following this, they should be risk assessed for the requirement for long-term anticoagulation.[178]

Other treatments for pregnant women with APS

Prednisolone

Prednisolone, either with or without aspirin, did not appear to improve pregnancy outcomes in early trials.[179,180] However, a more recent small study in women with refractory APS-associated pregnancy loss reported that low-dose prednisolone in the first trimester (10 mg daily until 14 weeks' gestation) in addition to aspirin and heparin was associated with an increase in live birth rates compared with historical self-controls (4% [4 of 97 pregnancies] live birth rate prior to use of prednisolone compared to 61% [14 of 23 pregnancies] using prednisolone).[181]

Intravenous immunoglobulins

A systematic review of observational studies reviewing outcomes for patients with use of IVIG concluded that its use appeared to be associated with an increased risk of pregnancy loss and premature birth.[160]

Hydroxychloroquine

Retrospective studies have reported better outcomes in patients with obstetric APS treated with hydroxychloroquine in addition to standard treatment. This included a higher rate of live births (67% vs. 57%; $p = 0.05$) and a lower prevalence of APS-related pregnancy morbidity (47% vs. 63%; $p = 0.004$).[182] However, the majority of women treated with hydroxychloroquine in this cohort had SLE.[182] A retrospective study assessing the effects of hydroxychloroquine in 87 women with refractory primary obstetric APS showed outcomes were significantly better in women treated with hydroxychloroquine (97.1% (67/69) vs. 62.5% (20/32); $p < 0.001$).[182] The HYPATIA trial, a prospective randomised controlled trial of hydroxychloroquine to improve pregnancy outcome in women with aPL antibodies, is currently recruiting and will provide further data on the role of hydroxychloroquine in this setting.[183]

Fetal growth monitoring in women with APS during pregnancy

Pregnant women with APS should undergo uterine artery Doppler scanning at 20–24 weeks. An abnormal uterine artery Doppler (defined as a pulsatility index [PI] >95th centile)[184] has been shown to be predictive of placental dysfunction in women with APS.[185–187] A study of 170 pregnant women with APS treated with aspirin and LMWH[187] found that a persistent abnormal uterine artery Doppler predicted pre-eclampsia and fetal growth restriction (FGR) (likelihood ratios 12.8 and 13.6 respectively). If an abnormal uterine artery Doppler is detected, serial growth scans should be performed to monitor for FGR.

Post-partum management

Women with APS who have had previous thrombosis are recommended to receive antenatal LMWH (dose adjusted according to the context) with continuation for 6 weeks postnatally. When aPL have been detected in women without a history of thrombosis or obstetric complications, they should be considered as a risk factor for thrombosis during pregnancy. If other risk factors are present[188] antenatal and 10 days or 6 weeks of postnatal LMWH should be considered. EULAR Guidelines recommended LDA in women with a history of obstetric APS for the primary prevention of thrombosis[189] based on a meta-analysis which showed the pooled OR for first thrombosis associated with use of LDA was 0.25 (95% CI 0.10–0.62) compared those did not have LDA.[152] However, this was not significant when analysis was restricted to prospective studies or studies that used good quality methodologies.[152] Long-term LDA may be considered on the basis of individual risk balance in women with a history of obstetric APS.

Management of women with APS undergoing assisted reproductive treatment

Few studies have investigated the association of APS with infertility or implantation failure in those undergoing assisted reproductive technology techniques (ART). There is significant heterogeneity in the definitions of aPL positivity and the study populations. A meta-analysis concluded that there was no association between aPL positivity and adverse outcomes of ART.[190]

Recommendations

- **We suggest that women with obstetric or thrombotic APS are managed in a joint haematology obstetric clinic with expertise in these areas (2C).**
- **We suggest that pregnant women with APS are monitored throughout pregnancy with a uterine artery**

Doppler scan at 20–24 weeks' gestation and serial growth scans (2C).

- **We suggest that women with obstetric or thrombotic APS have a clearly documented plan for delivery including the anticoagulant plan (2C).**
- **Women with APS should be recommended treatment with aspirin and LMWH from positive pregnancy test for the duration of the pregnancy (Grade 1B).**
- **Women with aPL should be recommended treatment with aspirin to reduce the risk of pre-eclampsia and fetal growth restriction (Grade 1B).**
- **Women with thrombotic APS who are anticoagulated with a VKA should switch to LMWH on confirmation of a positive pregnancy test (1B).**
- **Women with thrombotic APS who had been on a VKA, we suggest treatment dose LMWH throughout the pregnancy and post-partum period until switching back to VKA (2C).**
- **Women with APS who are breastfeeding and require anticoagulation should remain on either LMWH or warfarin (grade 1B).**
- **Prednisolone, IVIG and hydroxychloroquine treatments in women with obstetric complications despite aspirin and LMWH are suggested only on a case-by-case basis (1C).**
- **We suggest women with refractory obstetric APS who have poor pregnancy outcomes despite therapy should be referred to specialist centres with expertise in managing obstetric APS (2D).**
- **We suggest changing to treatment dose LMWH for women with obstetric APS who develop thrombosis during pregnancy despite prophylactic dose LMWH for the remainder of the pregnancy, for at least 6 weeks post-delivery and for a minimum 3 months of treatment in total (2C).**
- **We suggest detailed risk assessment after delivery of the need for long-term anticoagulation in women with obstetric APS who develop thrombosis during pregnancy (2C).**
- **We suggest long-term LDA be considered in women with obstetric APS without a history of thrombosis following assessment of individual risks and benefits (2C).**

CATASTROPHIC APS

The cardinal feature of CAPS is the rapid onset of small vessel thrombosis in multiple vascular beds.[8] There is often associated organ dysfunction, most commonly involving the kidneys, lung, brain, heart, skin and liver, and in some cases a thrombotic microangiopathy.[191] Bilateral adrenal infarction/haemorrhage and thrombosis in large vessels may also occur. CAPS is a medical emergency associated with a high mortality (approximately 30% despite optimal treatment).[192] A triggering factor such as infection, surgery, pregnancy, sub-therapeutic anticoagulation or cancer can often be identified.[193] Unregulated complement activation is thought to be important in its pathogenesis in many patients and rare germ-line mutations in complement regulatory proteins may play a predisposing role in some individuals.[10] Reduced C3 and C4 complement levels are frequently seen.[194]

Early consideration of the diagnosis is required so that appropriate and timely treatment can be initiated. Confirmation may be particularly challenging in those not known to have APS prior to their presentation. In practice, confirmation of CAPS may not be possible before treatment initiation because this requires as a minimum histopathology showing small vessel occlusion and/or laboratory confirmation of persistent aPL (Table 4). Other forms of thrombotic microangiopathy should be considered where appropriate including thrombotic thrombocytopenic purpura, haemolytic uraemic syndrome, heparin-induced thrombocytopenia, cancer-associated thrombosis, preeclampsia, HELLP syndrome, malignant hypertension and disseminated intravascular coagulation.[191,195]

The management of CAPS requires a multidisciplinary approach. After identification and correction where possible of triggering factors, the standard approach to the treatment of CAPS involves triple therapy with therapeutic dose heparin, high-dose corticosteroids and IVIG and/or plasma exchange as this combination is associated with improved survival.[189,192,196] Initial intravenous UFH is most often administered to ensure absorption and because many patients have impaired renal function, although LMWH can be considered. When UFH is used, monitoring should be done using heparin anti-Xa assays rather than APTT as the presence of LA may prolong the baseline APTT, leading to overestimation of the anticoagulant effect of UFH and increasing the risk of further thrombosis. Stronger consideration might be given to plasma exchange over IVIG in those with a thrombotic microangiopathy. Antiplatelet therapy

TABLE 4 Classification criteria for catastrophic antiphospholipid syndrome.[208]

1. Evidence of involvement of three or more organs, systems and/or tissues
2. Development of manifestations simultaneously or in less than a week
3. Confirmation by histopathology of small vessel occlusion in at least one organ or tissue
4. Laboratory confirmation of antiphospholipid antibodies (lupus anticoagulant, anticardiolipin antibodies and/or anti-β_2GP1 antibodies)
Definite CAPS requires all four criteria
Probable CAPS is based on any of the following:
All four criteria, except for only two organs, systems and/or tissues
All four criteria, except for the laboratory confirmation at least 6 weeks apart due to the early death of a patient never previously tested for antiphospholipid syndrome
Criteria 1, 2 and 4
1, 3 and 4 and the development of a third event in more than a week but less than 1 month, despite anticoagulation

can be considered in addition to anticoagulation, accepting the increased risk of bleeding from the combination.[196]

In the absence of a rapid response, additional approaches can be considered although robust evidence is lacking. Cyclophosphamide is recommended in patients with SLE.[191] Rituximab, which has been used with apparent success,[197] can be considered and may be most beneficial in those with thrombocytopenia or non-criteria manifestations of APS. In view of the importance of the complement pathway to the pathogenesis of CAPS in many patients, the C5 complement inhibitor eculizumab can be considered and has been used with success, particularly in those with a thrombotic microangiopathy.[198] The optimal dosing regimen should be discussed where possible with a local expert and with meningococcal vaccination 2 weeks in advance in line with national guidance where possible. It may be possible to discontinue eculizumab after clinical improvement and disappearance of the laboratory features of the thrombotic microangiopathy.[198] Other immune modulators discussed in the management of recurrent thrombosis despite anticoagulation may be beneficial long term and it would be reasonable to consider them in the CAPS setting.

Limited evidence suggests that the majority of those who recover from CAPS remain symptom-free on anticoagulation but a significant minority develop further APS-related thrombosis.[199]

Recommendations

- **CAPS should be suspected in a patient with APS presenting with multiple sites of thrombosis including microvascular thrombosis leading to organ failure (1A).**
- **We suggest anticoagulation initially with intravenous UFH with monitoring of the anticoagulant effect using heparin anti-Xa levels rather than APTT in patients presenting with CAPS (2C).**
- **Patients presenting with CAPS should be managed with a multidisciplinary approach involving the haematologist, intensive care clinician and other relevant specialists (2C).**
- **Identification and correction where possible of triggering factors should be an essential part of the management of patients presenting with CAPS (2B).**
- **We suggest use of triple therapy with therapeutic dose heparin, high-dose corticosteroids, and IVIG and/or plasma exchange in patients presenting with CAPS (2C).**
- **We suggest considering rituximab and seeking specialist centre input in patients with CAPS who fail to respond to first-line therapy (2C).**

MANAGEMENT OF PATIENTS WITH LA DURING CARDIOPULMONARY BYPASS SURGERY

Patients with LA, with or without APS, requiring cardiopulmonary bypass (CPB) present a unique set of clinical challenges. In addition to interference by LA with the activated clotting time (ACT), there is a risk of both circuit and systemic thrombosis due to the presence of aPL. In general, the ACT correlates poorly with the plasma heparin level measured by anti-Xa activity and does not accurately predict the dose of protamine sulphate required for reversal of UFH following termination of CPB.[200,201] Although the monitoring of heparin anti-Xa levels is considered more accurate than the APTT for measuring the anticoagulant effect of UFH, this test may not be available in a timely manner in hospital laboratories for patients undergoing CPB.

Case reports and cohort studies used different approaches to monitoring UFH during CPB in patients with LA with or without APS. In a single-centre cohort study of 19 patients with LA with or without APS, it was demonstrated that the correlation between heparin anti-Xa level and the ACT was poor ($r = 0.16$, $p = 0.46$). The median heparin anti-Xa level and ACT prior to administration of protamine sulphate were 4.5 IU/mL (range: 4.0–6.2) and 630 s (540–910) respectively.[202] There was no circuit thrombosis or significant bleeding requiring transfusion, or death within 12 months. Postoperatively, all patients received standard thromboprophylaxis or therapeutic anticoagulation if the patients had a confirmed diagnosis of APS prior to surgery. In another study of 19 patients with APS undergoing cardiovascular surgery, 84% (16/19) had major postoperative complications including coronary graft thrombosis, MI, stroke, PE and/or major bleeding events.[203]

The heparin anti-Xa level required for CPB is >4.0 IU/mL, but standard heparin anti-Xa assays become nonlinear at levels above 1.5–2.0 IU/mL (depending on the assay); serial dilutions of the sample in PNP are required to obtain accurate levels. Alternatively, a point-of-care device is available to monitor heparin anti-Xa levels in this setting although this approach has not been used in patients with LA.[204,205]

Several approaches have been used to monitor anticoagulation in patients with LA undergoing cardiac surgery including no change to standard ACT goals for CPB (usually 400–480 s) if the baseline ACT is not affected by the presence of LA or is increased by only few seconds; maintaining an ACT level that is twice the normal range; creating a patient-specific ACT titration curve; or using heparin anti-Xa levels.[194,202]

Recommendations

- **We suggest that patients with LA with or without APS undergoing CPB have a baseline ACT in advance and prior to CPB to plan for heparin monitoring during CPB (2C).**
- **We suggest that patients with LA with or without APS undergoing CPB have preplanned heparin monitoring during the procedure and a postoperative anticoagulant plan (thromboprophylaxis or treatment dose depending on pre-procedure thrombotic history) (2C).**
- **We suggest that where possible patients with LA with or without APS undergoing CPB have heparin monitoring using heparin anti-Xa assays rather than ACT (2C).**

- **If facilities are not available to monitor heparin with heparin anti-Xa assays in a timely manner during CPB, we suggest use of patient adjusted ACTs (based on individual baseline ACT without heparin) (2C).**

MANAGEMENT OF PERSISTENTLY POSITIVE aPL CARRIERS

In a prospective observational study of 258 asymptomatic individuals with aPL and a median follow-up of 35 months, the annual incidence of thrombosis was 1.86% versus 0.1% in the general population. In univariate analysis, hypertension and LA were significantly predictive of thrombosis (both at $p < 0.05$) while thromboprophylaxis was significantly protective during high-risk periods ($p < 0.05$). In multivariate analysis, hypertension and LA remained as independent risk factors for thrombosis (HR 3.8, 95% CI 1.3–11.1, $p < 0.05$, and HR 3.9, 95% CI 1.1–14, $p < 0.05$, respectively).[206] In another prospective nationwide cohort study, which included 119 aPL carriers, it was found that the annual rate of first thrombotic event in individuals with single-positive aPL was 0.65%, similar to that in individuals without aPL in the Caucasian population while risk of thrombosis was doubled in carriers of double or triple positivity (1.27%). All who developed a thrombotic event had an underlying autoimmune disease. Twenty per cent (16/79) of the women had pregnancy complications.[207]

In the antiphospholipid antibody acetylsalicyclic acid study, 98 individuals with aPL and no history of thrombosis were randomised to receive aspirin (48 individuals) or placebo (50 individuals). At a mean 2.3-year follow-up, there was no difference between the groups in the rate of acute thrombosis (2.75 for aspirin vs. 0 per for placebo per 100 patient-years; hazard ratio 1.04, 95% CI 0.69–1.56, $p = 0.83$).[151] In a further prospective study of 104 individuals with high-risk aPL (triple-positive), an annual thrombotic incidence of 5.3% was observed with a cumulative incidence of 37.1% (95% CI: 19.9–54.3%) at 10 years. Aspirin had no significant benefit in reducing the incidence of thromboembolic events.[82] Despite the lack of evidence of benefit of aspirin in primary prevention of thrombosis, EULAR guidelines recommend LDA for individuals with a high-risk aPL profile with or without traditional risk factors.[189]

There is some evidence from animal models,[208–210] in vitro[211,212] and human studies that hydroxychloroquine may prevent thrombosis in individuals with aPL and no prior thrombotic history due to its anti-inflammatory, antithrombotic and antiplatelet effects.[213] Hydroxychloroquine is a standard first-line treatment for patients with SLE with or without aPL.[214] In a small, randomized study of 20 individuals (9/20 on hydroxychloroquine and 11/20 no hydroxychloroquine) with persistently positive aPL and no history of thrombosis, none developed thrombosis or a significant adverse event after a mean follow-up of 1.7 years.[215] However, the study was terminated early due to the low recruitment rate, lack of availability of hydroxychloroquine and substantial price increase of hydroxychloroquine in the United States.[215] Therefore, the evidence is insufficient to recommend hydroxychloroquine for primary prevention of thrombosis in asymptomatic carriers without other autoimmune disease such as SLE or RA. Whether individuals with a triple-positive aPL profile should receive hydroxychloroquine as primary prophylaxis remains to be determined.

Irrespective of the aPL profile, all individuals should be given advice to improve modifiable risk factors for thrombosis, such as smoking, hypertension and diabetes, which should be addressed adequately in all patients. Hypercholesterolaemia should be treated with statins and dietary modification. Pregnancy and the puerperium are well-known risk factors for thrombosis. The risk of thrombosis further depends on the mode of delivery with women undergoing caesarean section having a higher risk of thrombosis than following vaginal delivery.[216] Women with persistently positive aPL with no previous thrombotic or obstetric history, especially if triple positive or with additional vascular risk factors, may be at higher risk of thrombosis during pregnancy and the puerperium than those without persistently positive aPL. The RCOG Green-top Guideline recommendation is that women with persistent aPL without previous VTE be risk assessed and considered for antenatal and/or postnatal (10 days or 6 weeks) thromboprophylaxis.[217]

Recommendations

- **Routine use of LDA or hydroxychloroquine for primary prevention of thrombosis in asymptomatic aPL carriers is not recommended (2B).**
- **We suggest assessing individuals with high-risk aPL profiles (triple positive) with or without additional vascular risk factors but no history of other autoimmune disease on a case-by-case basis to consider hydroxychloroquine as primary thromboprophylaxis (2D).**
- **We suggest that all individuals found to have persistently positive aPL with or without additional vascular risk factors receive thromboprophylaxis in high-risk situations such as following surgery or prolonged immobility (2C).**
- **We suggest that irrespective of the aPL profile, all individuals receive advice to improve modifiable risk factors for thrombosis (1C).**
- **We suggest that all asymptomatic individuals with aPL be risk assessed for cardiovascular risk factors including hypertension and hyperlipidaemia, and standard interventions including diet, lifestyle modifications and statins should be considered when these are detected (2B).**
- **We suggest counselling asymptomatic individuals with aPL regarding the risks versus benefits of oestrogen-containing contraceptive pills or oral hormone replacement therapy (2C).**
- **We suggest antenatal and/or postnatal (10 days or 6 weeks) thromboprophylaxis be considered based on risk assessment and mode of delivery for women with persistent aPL without previous thrombosis or obstetric complications (2C).**

AUTHOR CONTRIBUTIONS

DJA chaired the writing group. All authors contributed to writing, editing and reviewing the manuscript including the final submission.

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REVIEW PROCESS

Members of the writing group will inform the writing group chair if any new evidence becomes available that would alter the strength of the recommendations made in this document or render it obsolete. The document will be reviewed regularly by the relevant Task Force and the literature search will be re-run every 3 years to search systematically for any new evidence that may have been missed. The document will be archived and removed from the BSH current guidelines website if it becomes obsolete. If new recommendations are made, an addendum will be published on the BSH guidelines website (www.b-s-h.org.uk/guidelines).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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