GUIDELINES AND GUIDANCE

TITLE

Long term management and secondary prevention in patients with antiphospholipid syndrome-associated acute ischaemic stroke, transient ischaemic attack, or other brain ischaemic injury: Guidance from the International Society on Thrombosis and Haemostasis Scientific and Standardization Committee Subcommittee on Antiphospholipid Syndrome

SHORT TITLE: ISTH Guidance for management of patients with antiphospholipid syndrome-associated ischaemic cerebrovascular disease

WORD COUNT

Abstract: 155 words

Manuscript: 5654 words, 2 Tables, 3 Supplementary Appendices

KEYWORDS

antiphospholipid syndrome, antiphospholipid antibodies, cerebrovascular disease, acute ischaemic stroke, transient ischaemic attack, brain ischaemic injury, antithrombotic treatment

ABSTRACT

The diagnosis and optimal management of patients with antiphospholipid syndrome (APS)-associated ischaemic cerebrovascular disease: acute ischaemic stroke (AIS), transient ischaemic attack (TIA), or other brain ischaemic injury: silent cortical or subcortical/lacunar infarcts, or white matter hyperintensities of presumed vascular origin (indicating the presence of cerebral small vessel disease), are uncertain. These uncertainties are primarily due to lack of definitive data, derived mainly from observational studies that are subject to bias and confounding.

This communication from the International Society on Thrombosis and Haemostasis Scientific and Standardization Committee (ISTH-SSC) Subcommittee on

Antiphospholipid Syndrome (APS) provides guidance to healthcare professionals on the diagnosis and management of patients with APS who have AIS, TIA or other brain ischaemic injury.

The guidance includes clinical aspects of testing for antiphospholipid antibodies (aPL), alternative mechanisms for AIS/TIA in aPL-positive patients; and long-term management and secondary prevention, including antithrombotic treatment and other options. The guidance also provides a call and focus for research.

1. INTRODUCTION

The diagnosis and optimal management of patients with antiphospholipid syndrome (APS)-associated ischaemic cerebrovascular disease: acute ischaemic stroke (AIS), transient ischaemic attack (TIA), or other brain ischaemic injury, i.e. cerebral small vessel disease (CSVD): silent cortical or subcortical infarcts, or white matter hyperintensities (WMH) of presumed vascular origin (indicating the presence of cerebral small vessel disease), are uncertain. These uncertainties are primarily due to paucity of definitive data, derived mainly from observational studies subject to bias and confounding.

An International Society on Thrombosis and Haemostasis Scientific and Standardisation Committee (ISTH-SSC) Subcommittee survey highlighted that antiphospholipid antibody (aPL) testing strategy and antithrombotic treatment for patients with APS-associated cerebrovascular disease lack uniformity, and only 25% of healthcare professional respondents practice at dedicated APS clinics[1].

2. SCOPE AND METHODS

This ISTH-SSC Subcommittee guidance aims to achieve a more uniform, multidisciplinary, consensus approach to diagnosis, long-term management and secondary prevention in patients with APS-associated ischaemic cerebrovascular disease.

The guidance, for diagnosis and management of patients with APS-associated AIS, TIA confirmed by DWI (TIA-DWI) or other brain ischaemic injury, is based on systematic review of the literature (Supplementary Appendix S1), acknowledging the paucity of evidence, and expert consensus. The latter was achieved for all guidance

statements by a combination of a series of discussions between the coauthors, and document modification following coauthor comments in serial drafts.

Although the antithrombotic treatments discussed are widely available and affordable internationally, we acknowledge that some of the investigations, particularly brain MRI, are not easily available in low resource settings. For guidance statements informed by higher quality clinical studies with greater certainty of evidence, the term used is “we advise.” For guidance statements informed by lower quality clinical studies with lower certainty of evidence, the term used is “we suggest.” The guidance also provides a call and focus for research.

The authors followed the ISTH Guidelines and Guidance Committee COI Policy and disclosed any relevant financial relationships with industry within the past 12 months. Authors who reported more than $5,000 relevant direct financial conflicts and/or had major conflicts recused themselves from voting on the guidance statements.

3. ASSOCIATIONS BETWEEN AIS, TIA, OTHER BRAIN ISCHAEMIC INJURY, VASCULAR COGNITIVE IMPAIRMENT AND DEMENTIA, AND ANTIPHOSPHOLIPID ANTIBODIES

3.1 AIS and TIA

AIS and TIA with MRI diffusion-weighted imaging (DWI) evidence of acute ischaemic changes (TIA-DWI), are clinical classification criteria for thrombotic APS[2]. The diagnosis of TIA is challenging, with notable interrater variability[3], risk of misdiagnosis due to non-classical presentations, and challenges regarding availability, timing, and interpretation of DWI.

Analysis of 120 full-text papers showed 13.5% (range 6.8%-23.3%) of patients with AIS have aPL (ages and timing of aPL testing not included). The role of concomitant risk factors was evaluated in 45% of AIS/TIA studies. Other limitations were: 11% of studies included all three criteria aPL, many used a low-titre cutoff, and aPL persistence was confirmed in 19%[4]. A follow-up analysis of the association between criteria aPL and stroke in 14 studies, median number of patients and controls (interquartile range [IQR] 116.5 [81-189] and 121 [100-315], respectively), found a significantly higher prevalence of stroke in aPL-positive patients vs controls: 14% vs 5.5% (p=0.0002). Individual cohort studies showed positive associations between

incident stroke and anticardiolipin antibodies (aCL), anti-beta 2 glycoprotein I (aβ2GPI) antibodies, and lupus anticoagulant (LA) in 9/14, 2/4 and 3/3 studies, respectively[5].

The GBD (Global Burden of Disease) 2021 online database reports that ~15% of stroke events occur at 15-49 years[6]. A systematic review/meta-analysis noted that stroke rates have declined in older populations, but remain stable/increased among those <55y[7].

A systematic review (43 studies, 5,217 patients, <50y with AIS/TIA) reported that 17% and 12% of patients who had stroke or TIA, respectively, had aPL. Adequate population-based studies with appropriate controls, required to calculate odds ratios, were rarely included; and, although CVD risk-factors were reported in 88% of studies, their role was statistically evaluated in a minority, using heterogeneous methods. Furthermore, ~60% of studies reported a low cutoff value for aCL, with aPL persistence established in 30%[8]. A systematic review/meta-analysis (30 studies, 16,441 patients without systemic lupus erythematosus [SLE]) reported that LA, aCL and aβ2GPI were significantly associated with arterial thrombosis (AT)[9].

Thus, aPL are common in AIS/TIA, with the range of prevalence overlapping with healthy populations. The association between aPL and AIS/TIA is variable, confounded by methodological limitations. The prognostic significance of aPL in AIS/TIA is unclear.

3.2 Other brain ischaemic injury

The spectrum of APS-associated CSVD on neuroimaging includes ischaemic brain injury, i.e. silent cortical or subcortical/lacunar infarcts, or WMH, but whether APS-associated CSVD is the same as in sporadic CSVD (i.e. arteriosclerosis) is unclear. Lacunar infarcts (i.e. chronic subcortical infarcts, diameter <20mm noted radiographically during subacute/oedema phase and <10mm pathologically) and WMH are markers of CSVD, the presumed cause of 25% of AIS and most spontaneous intracerebral haemorrhage[10].

A systematic review reported that, in general or high-risk populations, WMH are associated with an increased risk of incident stroke (hazard ratio [HR], 3.3; 95% CI, 2.6-4.4), dementia (HR, 1.9; 95% CI, 1.3-2.8), and death (HR, 2.0; 95% CI, 1.6-2.7). An association of WMH with a faster decline in global cognitive performance, executive function, and processing speed was suggested[11]. Another systematic review/meta-

analysis reported that WMH, MRI-defined brain infarcts and cerebral microbleeds (manifestations of CSVD), were associated with incident stroke, intracerebral haemorrhage and death[12]. An imaging study (41,626 UK Biobank participants), 47% male, mean age (SD) 55y (7.5y) reported 32% of the variance in WMH volume was explained by CVD risk factors, sex, and age, suggesting other factors underlie WMH development[13].

Endothelial dysfunction is a central feature of CSVD[14,15] which may be relevant in APS. Endothelial nitric oxide (NO) plays a major role in vasodilation and blood flow regulation. Plasma endogenous NO synthase inhibitor and asymmetric dimethylarginine (ADMA) levels were elevated in patients with CSVD and correlated with cognitive impairment[16]. Hyperglycaemia and smoking cause vasodilatory dysfunction by downregulating endothelial NO synthase, affecting endothelium-dependent vasodilation[17]. A prospective mechanistic study showed that fluvastatin reduced significantly, and reversibly, proinflammatory and prothrombotic biomarkers[18].

Information on associations between aPL and CSVD is sparse and based on small studies. Among 44 patients with primary APS, 24 with aPL (no history of stroke), TIA, migraine, dementia, epilepsy or bipolar disorder, and 23 age and sex-matched healthy controls, 38 patients (56%) vs 1 control (4%) had abnormal brain MRIs ($p<0.001$). Vascular risk factors were infrequent and not significantly different in the two groups. Lacunar infarcts were the most frequent MRI abnormality (31/68 [45.6%]), followed by WMH (20/68 [29.4%]). Age (odds ratio [OR] 1.09, $p=0.016$) and LA positivity (OR 5.2, $p=0.002$) were independently associated with brain MRI abnormalities[19]. Sneddon syndrome, a noninflammatory thrombotic vasculopathy, is characterized by livedo racemosa/reticularis and recurrent CVE, with aPL reported in ~40% of patients[20].

The relationship of aPL to pathologically proven brain infarcts was assessed in 142/607 deceased subjects (mean age at death 89y, 66% females), with at least one aPL, persistently positive in 75%. In a logistic regression analysis, baseline aPL positivity did not increase the odds of cortical/subcortical brain infarcts (OR=1.08; 95% CI: 0.74, 1.58; $p=0.19$)[21].

3.3 Vascular cognitive impairment (VCI) and dementia

Neurological disorders other than AIS, including VCI, may be associated with aPL[22]. A systematic review (20 studies; 3,374 patients) reported VCI is common in patients with aPL, and associated with WMH, ischaemic lesions and cortical atrophy. There was no consistent cognitive profile or definite association with aPL. Most studies were based on single aPL testing and/or low titers[23]. There was confounding by inclusion of neuropsychiatric SLE, strokes, definitions, neuroimaging modalities, and protocols.

Of 60 patients with APS (39 primary, 21 SLE-related) and 60 healthy controls, matched for age, sex, and education, 25 (42%) had cognitive deficits versus 11 (18%) healthy controls (p=0.005). A significant association was noted between VCI and livedo reticularis (p=0.004), and WMH on brain MRI (p=0.01)[24]. In a systematic review/meta-analysis, aCL prevalence in patients with dementia was higher (33% of 372) than in healthy controls (9.5% of 337) (OR: 4.94, 95% CI: 2.66–9.16, p<0.00001). Potentially confounding CVD risk factors were not included[25].

4. GUIDANCE STATEMENTS

4.1 GENERAL SCOPE

The guidance statements herein for TIA with diffusion weighted imaging (TIA-DWI) evidence of acute cerebral ischaemia may be applied to all TIA, although diagnostic accuracy is likely to be much higher where ischaemia is confirmed on DWI. If DWI is unavailable, or in patients with a syndrome indicating a high probability of TIA and normal MRI, an individualized local approach for management should be developed.

4.2 CLINICAL ASPECTS OF aPL TESTING

4.2.1 We suggest aPL testing in individuals <60y with AIS or TIA-DWI, with acute brain ischaemic injury in the following situations:

a) lack of a well-defined alternative mechanism, including AF, extracranial/intracranial artery stenosis, cerebral artery dissection, non-aPL related cerebral vasculitis, sporadic or genetic cerebral small vessel diseases, RCVS, drug-associated stroke (e.g. cocaine, amphetamines), cardioembolism from a mechanical heart valve, infective endocarditis, or left ventricular thrombus;

b) in the absence of a high-risk CVD profile (Supplementary Appendix S2);

c) in those where positive aPL would directly affect the patient's management, e.g. AF associated with recurrent AIS while on a DOAC, with no alternative mechanism of stroke or other explanation for recurrent stroke identified.

4.2.2 We suggest consideration of early aPL testing, during the acute phase following AIS/TIA-DWI, where clinical judgement indicates a high probability that aPL are causal, with cognisance that aPL results may be affected by the acute phase post-thrombotic state for 3 months post-event. Positive aPL tests should be rechecked after >12 weeks to establish persistence, prior to determining the long-term antithrombotic plan.

4.2.3 We suggest aPL testing in individuals <60y with brain ischaemic injury other than AIS/TIA-DWI, i.e. CSVD: silent cortical or other site (subcortical/lacunar) infarcts or WMH of presumed vascular origin, or VCI, in the absence of a high-risk CVD profile.

4.2.4 We advise aPL testing in patients with major autoimmune rheumatic diseases, notably SLE.

4.3 Age cut-off for aPL testing in patients with AIS, TIA-DWI or other brain ischaemic injury

The mean age of APS diagnosis in population-based studies is ~50y[26-28]. The age-related peak incidence of APS varies in different populations: 55-64y, 55-59y and 70-79y in males in the US, UK and Korea, respectively[29]. IgG aCL were reported in 50% of healthy older individuals (mean age 81y)[30]. The prevalence of AIS/TIA in the general population increases with age[31,32], making a causal relationship with aPL in elderly individuals unlikely. A population study reported that the prevalence of aPL in the general population was 1/2000, with stroke/TIA in 45% of patients, and the incidence of aPL increased significantly with age (p=0.007), peaking at ≥75y, although confounding factors, e.g. atrial fibrillation (AF), were not accounted for[33].

The systematic review in patients <50y with AIS/TIA reported a significant association between aPL and cerebrovascular events (CVE) in a subanalysis of 13/15 studies (87%): cumulative OR 5.48; 95% CI: 4.42-6.79[8]. Another systematic review/meta-analysis (8 studies, 2,510 patients, 844 aPL-positive), reported a relative risk of aPL (versus no aPL) for recurrent AIS of 1.41 (95% CI, 0.91-2.17). In a subgroup analysis, age <50 years, ethnicity, and type of aPL did not increase the risk of recurrent AIS[34]. The mean age (SD) of 720/844 patients with baseline aPL positivity in the Antiphospholipid Antibodies and Stroke Study (APASS) study was

63.1 (11.4)y. However, many patients did not fulfil criteria for APS: single aPL assessment <30days of study entry (thus potential acute phase effects), low aCL titres and IgA non-criteria aCL included[35].

In the Elderly-Phospholipid retrospective study (n=44, 43% triple aPL-positive), 39% had AIS at diagnosis and 20.5% a new arterial event (mean follow-up 3.8y), despite antiplatelet treatment and/or vitamin K antagonist (VKA) anticoagulation. One or more CVD risk factors, smoking, hypertension, or dyslipidaemia, were present in 70%, and 11% had diabetes mellitus[36]. An age cutoff for aPL testing of <60y might be considered pragmatic, given the more prominent role of concomitant CVD risk factors in those over 60y[3].

4.4 Timing of aPL testing post AIS/TIA-DWI

The optimal timing for aPL testing post-thrombosis is not established. ISTH guidance highlighted that LA results during the early post-thrombotic state may be confounded by acute phase reactants, with false-positives/negatives[37-39]; and aβ2GPI levels vary around the time of thrombosis[40].

Data on serial aPL post AIS are lacking and the influence of early vs later initiation of anticoagulation on the outcome following AIS is unknown. Early aPL assessment following AIS could guide treatment, e.g. consideration of early anticoagulation initiation in patients with high-risk aPL phenotypes with no alternative aetiology may be appropriate. Positive aPL should be rechecked after >12 weeks to confirm persistence[3,37,38].

4.5 Consideration of aPL phenotype in patients with APS-associated AIS/TIA-DWI

Triple aPL-positivity (LA, aCL and anti-β2GPI) appears to be the highest-risk phenotype for recurrent thrombosis: 44.2% (95%CI, 38.6–49.8) after 10 years in a retrospective analysis in 160 patients, 69 (43.1%) with previous AT (42/69 stroke/TIA), with the incidence of events independent of the clinical manifestations at diagnosis [41].

Prospective studies demonstrate that LA is an independent risk factor for increased thrombotic risk [42], and new-onset thrombosis an independent risk factor for increased mortality in LA-positive individuals[43]. In the multicentre case-control RATIO study, the ORs for AIS in women <50y with LA or aß2GPI were 43.1 (12.2-

152) and 2.3 (1.4-3.7), respectively [44]. In a cross-sectional study (60 patients with APS, 390 controls), isolated LA was significantly associated with thrombosis (OR 7.3; 95% CI 3.3–16.1)[45]. Systematic reviews reported that LA is a stronger risk factor for thrombosis than aCL[46], and a weak association between isolated aβ2GPI and thrombosis[47].

In a multicentre study (n=1008), IgM aCL/aß2GPI had no diagnostic value for thrombotic APS, although it was useful for risk stratification. Patients with AT were under-represented: 55/259 with thrombotic APS[48]. A retrospective study reported that isolated IgM aPL (in 14.3%: 24/168 patients) was associated with AIS[49]. ISTH guidance recommends assessment for aPL should include testing for LA plus aCL and aβ2GPI, IgG and IgM isotypes; and the 99th percentile of a local normal population used to determine cut-off values[37,38].

Moderate- and high-positive ELISA titres (40U/80U) are used for diagnosis[38] and for classification in the 2023 ACR/EULAR criteria, to avoid overestimation of aPL contribution to thrombosis[2]. Harmonization of ELISA and non-ELISA solid phase aPL assays is required[50].

4.6 Coexistence of CVD risk factors in aPL-positive patients with AIS/TIA

The definitions for AT, with/without CVD risk factors, were graded in the ACR/EULAR classification criteria. These employ a weighting system for estimation of aPL contribution to thrombosis and avoidance of overdiagnosis of APS in patients with AT[2] (Supplementary Appendix S2).

Analysis of 379 patients with APS-associated arterial and/or venous thrombosis, in the APS ACTION (AntiPhospholipid Syndrome Alliance For Clinical Trials and InternatiOnal Networking) prospective Registry, showed significantly higher adjusted global APS scores (aGAPSS), based on hyperlipidaemia, hypertension, aCL, aβ2GPI and LA in patients with recurrent arterial, but not venous, thrombosis (8.1 ±SD 2.9 vs. 6±3.9; $p<0.05$)[51]. This highlights the importance of management of CVD risk factors, emphasised in secondary stroke prevention guidelines[52].

4.7 Coexistent alternative mechanisms and associations with AIS/TIA in aPL-positive patients

4.7.1 Alternative mechanisms for AIS/TIA may coexist with aPL-positivity, including atrial fibrillation (AF), extracranial or intracranial artery stenosis, cerebral

artery dissection, cerebral vasculitis, sporadic or genetic CSVD, reversible cerebral vasoconstriction syndrome (RCVS), drug-associated stroke (e.g. cocaine, amphetamines), cardioembolism from a mechanical heart valve, endocarditis, or left ventricular thrombus. Whether particular stroke mechanisms are more likely to be associated with aPL is undefined. Diagnostic testing and management depend upon the patient's age, pattern of cerebral ischaemia, cerebrovascular, cardiac and haematological tests, and other underlying comorbidities. Heritable thrombophilia, reported in 14% of 360 patients with AIS/TIA, showed no demonstrable influence on aPL-associated AIS/TIA[53]. Although elevated serum homocysteine has been linked to increased risk of AIS, RCTs of folate and B vitamin supplementation have not shown benefit in secondary prevention of AIS[54,55].

4.7.2 Systemic lupus erythematosus (SLE): Among patients with SLE, 30%-40% have aPL[56], with APS prevalence 7%-15%[57,58]. AIS is a major cause of morbidity, mortality and disability in these patients, who have a 2-fold increased risk of stroke, up to 10-fold in individuals <50y[59]. APS is rarely a presenting SLE feature[60]; and aPL are part of the diagnostic criteria and contribute to risk assessment[61]. AIS may rarely be associated with central nervous system vasculitis, primary[62] or secondary, e.g. SLE[63]. A Working Group for the American College of Rheumatology proposed that cerebral CNS lupus has 12 manifestations, some likely to be inflammatory, some not[64].

5. ANTITHROMBOTIC AND OTHER TREATMENT OPTIONS FOR PATIENTS WITH APS-ASSOCIATED AIS OR TIA-DWI

Critical review of key characteristics of studies of antithrombotic treatment for aPL-associated AIS/TIA and their limitations are summarised in Table 1[65-78]; and systematic reviews/meta-analyses in Supplementary Appendix S3[79-84].

A first TIA is associated with a 10% risk of subsequent TIA/AIS, within five years, based on a prospective registry (4789 patients with a TIA/minor AIS), thus TIA identification provides an opportunity to institute secondary prevention strategies[85]. While studies have focused on aPL-associated AIS, a similar treatment approach seems logical in aPL-positive patients with TIA-DWI.

5.1 GUIDANCE STATEMENTS: PATIENT MANAGEMENT

5.1.1 We suggest that patients with persistent aPL and AIS, TIA-DWI, or other brain ischaemic injury, are managed using a multidisciplinary team meeting (MDT) approach, including haematologists and neurologists or stroke physicians and review in a specialist APS clinic (if available), to optimize patient care and facilitate clinician decision-making.

5.1.2 We suggest long-term antithrombotic treatment for patients with a first APS-associated AIS or TIA-DWI, using one of the following options, in the absence of high-quality evidence of efficacy and safety for a single antithrombotic regimen. Advice on the individual regimens (listed below) is detailed in Table 2, with the following considerations:

a) The antithrombotic regimens are stratified based on aPL phenotype-associated thrombotic risk;
b) For all suggested antithrombotic regimens, particularly VKA plus antiplatelet or high-intensity VKA, it is important that risk factors for bleeding are taken into account, with ongoing assessment of thrombotic and bleeding risk;
c) Antithrombotic options (see Table 2 for detailed patient profiling):
    i. warfarin/other vitamin K antagonist (VKA), target INR (TINR) range 2.0-3.0;
    ii. warfarin/other VKA, TINR range 2.0-3.0, plus single antiplatelet treatment (SAPT);
    iii. warfarin/other VKA, TINR range 3.0-4.0;
    iv. SAPT or dual antiplatelet treatment (DAPT).
d) A TINR range of 2.5-3.5 is a pragmatic option, in view of the lack of definitive evidence regarding optimal anticoagulation intensity for APS-associated arterial thrombosis, and potential recurrent thrombosis and bleeding risks with lower or higher TINR ranges, 2.0-3.0 or 3.0-4.0, respectively.

5.1.3 We suggest antithrombotic treatment: SAPT, DAPT or VKA on an individualized basis, for patients with APS-associated CSVD.

5.1.4 We advise against the use of direct oral anticoagulants (DOACs) in patients with APS-associated AIS, TIA-DWI or CSVD.

5.1.5 We suggest consideration of anticoagulation initiation prior to establishing aPL persistence in patients with AIS or TIA-DWI, in the situations below, noting that aPL may be associated with an acute phase response post-AIS/TIA-DWI:

a) absence of high-risk CVD profile or alternative clear stroke mechanism identified, particularly in patients with a high-risk aPL profile, suggesting that aPL are causal with a likely increased risk of recurrent events without treatment; recurrent event in aPL-positive individuals while on SAPT/DAPT.
b) Other potential mechanisms for ischaemic events and risk factors for bleeding should be taken into account.

5.1.6 We advise control of CVD risk factors in all patients with AIS/TIA or CSVD, critical for secondary prevention, namely:

a) blood pressure target <130/80 mmHg;
b) LDL cholesterol target <1.8 mmol/l (<70 mg/dL);
c) HbA1C target <7%;
d) advice on modifiable lifestyle factors: cessation of cigarette smoking, maintaining a healthy weight, regular physical activity, a balanced diet, and limiting alcohol consumption.

5.1.7 We suggest vitamin D deficiency/insufficiency should be corrected as in general population guidelines.

5.1.8 We suggest patent foramen ovale (PFO) closure in patients with a potentially causal PFO, i.e. substantial and potentially causal degree of shunting, noting the paucity of evidence, after discussion at MDT (if available).

5.1.9 We suggest transitioning to high-intensity VKA (TINR range 3.0-4.0) if a patient develops recurrent AIS/TIA-DWI while the INR is between 2.0 and 3.0 (anticoagulant-refractory thrombotic APS).

5.1.10 We suggest the following options if recurrent AIS/TIA-DWI occurs on high-intensity VKA (INR between 3.0-4.0):

a) transition to low molecular weight heparin (LMWH), approximately 25% above standard therapeutic dose (split-dose, i.e. half total daily dose, 12 hourly), aiming for peak anti-Xa 0.8-1.2IU/mL, 3-4 hours post dose; or treatment dose fondaparinux;
b) other options to consider:
    i. addition of aspirin to VKA or LMWH;
    ii. adjunctive treatment with hydroxychloroquine and a statin;
    iii. immunomodulation, e.g. rituximab.

5.1.11 We advise that patients with aPL-associated AIS, TIA-DWI or other brain ischaemic injury are assessed for underlying autoimmune rheumatic diseases, notably

SLE, with standard SLE tests undertaken: ANA, anti-DNA, anti-ENA, complement C3 and C4.

5.1.12 We suggest that patients with suspected aPL-associated VCI should be referred for formal cognitive assessment.

5.2 Warfarin/other VKA: Recurrent thrombosis

Patients with thrombotic APS can develop recurrent thrombosis despite antithrombotic treatment. Two RCTs reported no significant difference in recurrent thrombosis between moderate-intensity warfarin, TINR (TINR) range 2.0-3.0, or high-intensity, TINR range 3.1-4.0/3.0-4.5, respectively[68,70]. Notably, in one of these RCTs, 6/8 recurrent thrombotic events (6/56 in the high-intensity, 2/58 in the moderate-intensity arm) occurred at INR <3.0[68]. In the other RCT, 7/109 patients had recurrent thrombosis, all arterial: AIS, 2/54 and 2/55; and TIA, 3/54 and 1/55, in the high-intensity and moderate-intensity arms, respectively. INRs associated with thrombosis were not specified. In addition, 5/54 and 3/55 thrombotic vascular deaths occurred in the high-intensity and moderate-intensity arms, respectively[70].

Conclusions from these RCTs are limited as: (a) patients with AT were under-represented, 31.8% (71/223) across both RCTs; and (b) there was frequent lack of TINR achievement in the high-intensity arms: subtherapeutic INRs 43% of the time in the high-intensity arm [68], and mean INR 3.2 in the high-intensity arm, consistent with a high proportion of INRs <3.0[70]. A systematic review that included these two RCTs and two retrospective studies reported no significant difference in thrombosis recurrences between moderate-intensity or high-intensity warfarin (RR 0.46 [0.06–3.52])[79].

In the Euro-Phospholipid prospective observational study (N=1000), 10% of 198/111 patients with APS-associated stroke/TIA at baseline, had recurrent stroke/TIA (5.3%/4.7%, respectively) over 10y of follow-up (FU). Forty percent of patients received VKA in the first 5y FU, 37% in the second 5y FU: 62% at TINR range 2.0-3.0, and 38%, TINR range 3.0-4.0. During the second 5y FU, 24.8% developed recurrent thrombosis despite antithrombotic treatment (20% antiplatelet, 45% anticoagulant, 35% both). Notably, stroke was the third leading cause of death, with severe thrombotic events, including MI, strokes and PE, accounting for 36.5% of the deaths[60].

In a UK-wide retrospective study (n=500, 2012-2021; 26.8% (134/500) with AT, 75.4% (101/134) AIS/TIA), the 10y recurrent thrombosis rate was high, 46%, with a significantly increased risk of recurrence in patients with AT (p=0.03). Antithrombotic treatment for 69% (345/500) of patients was VKA; TINR ranges were 2.0-3.0 in 80.6% (278/345), and 3.0-4.0 in the remainder (19.4%, 67/345), with a greater preference for higher intensity INR with VKA in this group compared with VTE (27.7% vs 14.7%)[86]. As indicated above, triple aPL-positivity appears to be the highest-risk phenotype for recurrent thrombosis[41], and isolated LA strongly associated with increased thrombotic risk[42,45], notably AIS[44], and mortality[43].

5.3 Warfarin/other VKA: Bleeding

The RCT by Crowther et al reported no difference in major bleeding between the two treatment arms: 3/56 at TINR 2.0-3.0 and 4/58 at TINR 3.0-4.0 (HR, 1.0; 95% CI, 0.2 to 4.8)[68]. The RCT by Finazzi et al also reported no difference in major bleeding between the two treatment arms, although an increase in minor bleeding on high-intensity warfarin was noted. Major and minor bleeding, respectively, occurred in 15 patients (two major) (27.8%) assigned to receive high-intensity warfarin and eight (three major) (14.6%) assigned to receive conventional treatment (hazard ratio 2.18; 95% CI 0.92–5.15)[70].

In the Euro-Phospholipid prospective study, during the 10yr prospective follow-up, 61 major bleeds occurred on antithrombotic treatment, a third of these on VKA target INR >3.0. The remainder (two-thirds) occurred on other antithrombotic treatment, including VKA at lower target INR. Of these, 50.8% of bleeds were musculocutaneous, 24.6% cerebral, 16.4% GI, 8.2% intra-abdominal); 10% (16.4%) were fatal[60].

In the retrospective UK multicentre observational study, major bleeding occurred in 6.7% (21/313) and clinically significant non-major bleeding in 15.3% (48/313). Of these, 82.6% (57/69) occurred on VKA, 71.9% (41/57) on standard-intensity VKA. Increasing age was the only factor significantly associated with bleeding on multivariate analysis (OR 1.05 (95%CI 1.01-1.1; p=0.02)[86]. The optimal warfarin/VKA anticoagulation intensity for individuals with APS-associated AIS/TIA remains undefined.

5.4 Antiplatelet, VKA, VKA plus antiplatelet, dual antiplatelet treatment

An international retrospective study analysed outcomes of 139 patients with APS and AT treated with antiplatelet (aspirin, clopidogrel or both) and/or VKA. Patients on antiplatelet plus VKA, TINR range 2.0–3.0, had a lower rate of recurrent thrombosis versus those on VKA or antiplatelet(s) alone: 16 (37.2%) on antiplatelet(s), 9 (23.7%) on VKA, and 4 (6.9%) on combined therapy[73]. A RCT of 20 patients with APS-associated AIS, using updated Sapporo criteria[77], except that aPL tests were repeated after >6 weeks[37,38,76], randomised patients to aspirin 100mg/day or aspirin 100mg/day plus warfarin TINR range 2.0-3.0. Results suggested that the cumulative incidence of stroke on warfarin plus aspirin was significantly lower than on aspirin alone: 2/9 versus 8/11, respectively (p=0.026)[77]. In a prospective study (N=27), 7/18 patients (39%) with ischaemic cerebrovascular disease on aspirin had stroke, whereas 1/7 (14%) on aspirin plus warfarin (TINR range unspecified) had retinal infarction, with no strokes (NS). Cerebral infarcts occurred in 74% and were recurrent in 37%.[65].

A review/meta-analysis concluded that VKA plus SAPT may be more effective than VKA for secondary prophylaxis for aPL-associated arterial thrombosis: VKA+SAPT vs VKA: RR 0.43; 95% CI: 0.22–0.85; and also that DAPT may be more effective than SAPT: RR 0.29; 95% CI: 0.09–0.99[87]. A retrospective cohort study (n=90) suggested that DAPT was effective and safe for prophylaxis of recurrent AT[82]. A Cochrane systematic review, in patients with prosthetic heart valves, noted that the risk of major bleeding was increased when antiplatelet agents were added to oral anticoagulation (OR 1.58, 95% CI 1.14 to 2.18; P=0.006)[87].

APASS compared warfarin (TINR range 1.4-2.8) vs aspirin (325 mg/day) for prevention of recurrent stroke/death), and reported no increase in thrombo-occlusive events associated with baseline aPL positivity in patients on warfarin (RR 0.99; 95% CI: 0.75-1.31; P=0.94), or aspirin (RR, 0.94; 95% CI, 0.70-1.28; P=0.71). The overall event rate was 22.2%/21.8% among aPL-positive/aPL-negative patients, respectively (NS). However, the median INR after 28 days in the warfarin-treated patients was 1.9, implying subtherapeutic anticoagulation (i.e. INR <2.0), which may have impacted on warfarin efficacy[35].

A systematic review/meta-analysis reported no significant difference in efficacy between anticoagulation versus antiplatelet therapy in patients with APS-associated AIS/other arterial occlusion: 19.7% of patients on VKA (95% CI 0.51-0.31), and 21.6% of patients receiving antiplatelet (95% CI 0.18-0.26) developed thromboembolism over

two years[80]. However, patients on VKA or DOAC were analysed as a single group, although the cited DOAC RCTs[74,76], as well as a further RCT[78] and systematic review/meta-analysis of 4 RCTs of DOACs versus VKA[84] reported a significant increase in AT, especially AIS, in patients with APS on DOAC versus VKA.

5.5 Direct oral anticoagulants (DOACs)

The systematic review/meta-analysis of 4 RCTs of DOACs versus VKAs showed that DOACs were associated with a significantly increased rate of AIS compared with warfarin/VKA (OR: 5.43; 95% CI: 1.87-15.75; P<0.001), but not of VTE (OR 1.20; 95% CI: 0.31-4.55; P=0.79). Major bleeding (OR: 1.02; 95% CI 0.42; p=0.97) was not significantly different on DOACs versus warfarin/VKA[74-76,78,84]. A Cochrane systematic review concluded that DOACs may increase the risk of stroke, compared with VKA (moderate-certainty evidence) [812]. ISTH and other guidance recommend against the use of DOACs in patients with APS-associated AT[88-90]. Notably, the DOAC doses associated with recurrent thrombosis were standard- or prophylactic-dose DOAC[74,76,78].

The RISAPS (RIvaroxaban in Stroke patients with APS) Phase 2b RCT is investigating high-dose rivaroxaban 15mg twice daily versus high-intensity warfarin, in patients with APS-associated AIS, TIA or other brain ischaemic injury[91].

5.6 Antithrombotic treatment for patients with APS-associated other brain ischaemic injury: cerebral small vessel disease

There is little evidence to guide management of general population patients who have CSVD on brain imaging. European Stroke Organisation (ESO) guidelines do not recommend antiplatelet drugs, e.g. aspirin, for CSVD in the general population, unless for another indication, such as ischaemic heart disease or after TIA/minor stroke[92]. In the Lacunar Intervention Trial-2 RCT, isosorbide mononitrate-cilastazol reduced the composite of adverse vascular, dependence, and cognitive outcomes in patients with lacunar stroke, with the conclusion that definitive trials are needed[93].

5.7. Patent foramen ovale

PFO is present in ~25% of adults and a common cause of stroke in young/middle-aged patients[94]. In a PFO prospective registry (n=591), PFO closure provided a lower risk for recurrent events compared with medical therapy (HR: 0.16;

95% CI: 0.09 to 0.30; p<0.001) in those with cryptogenic stroke/TIA and heritable thrombophilia or LA/aCL[95]. The PICSS-APASS study included patients with LA, aCL or both, within a month post-stroke. The two-year risk of recurrent stroke/TIA/death in 525 subjects with PFO and aPL, was 23.9% (HR 1.39, 95% CI 0.75–2.59) in the PFO-positive/aPL-positive group, 13.9% (HR 0.83, 95% CI 0.44–1.56) in PFO-positive/aPL-negative and 19.9% (HR 1.16 95% CI 0.68–1.90) in PFO-negative/aPL positive patients. Limitations included that many patients did not fulfil criteria for APS diagnosis[35,96].

There are no evidence-based recommendations for management of PFO in aPL-positive patients. Based on four class II RCTs, in patients <60y with a PFO, embolic-appearing infarct and no other mechanism of stroke identified, the potential benefits and risks of PFO closure were: absolute recurrent stroke risk reduction of 3.4% at 5y; periprocedural complication rate 3.9%; and increased absolute rate of non-periprocedural AF 0.33%/y[97].

The Society for Cardiovascular Angiography and Interventions made a conditional recommendation (very low certainty of evidence) that patients with thrombophilia and a prior PFO-associated stroke should have PFO closure plus lifelong anticoagulation[98]. Patients 18-60y with no other obvious cause of stroke, particularly those with a large right-to-left shunt and an atrial septal aneurysm, are likely to derive the greatest benefit from PFO closure, recommended in European Stroke Organisation (ESO) guidelines[99].

5.8 General considerations for secondary prevention of AIS, TIA-DWI or other brain ischaemic injury

Control of modifiable CVD risk factors in patients with AIS/TIA (Table 2) is critical in secondary prevention of AIS/TIA[100].

In patients with CSVD, ESO guidelines, which noted little direct evidence mostly low quality, advise that hypertension, a major risk factor for CSVD, should be well controlled, and healthy lifestyle interventions, particularly smoking cessation, aerobic exercise, a healthy diet and avoidance of obesity. The ESO Guideline Group was divided on lipid lowering with statins in covert CSVD, where evidence is limited[100]. In patients with APS, it seems appropriate to use statins in view of the additional APS-associated CVD risk.

Median vitamin D levels were significantly lower in patients with thrombotic APS compared with normal healthy donors ($p<0.01$)[101]. The immunomodulatory properties and central role of inflammation in aPL-mediated thrombosis, support a potential role for vitamin D in APS[102].

6. RECURRENT AIS OR PROGRESSION OF OTHER BRAIN ISCHAEMIC INJURY ON VKA

6.1 Antithrombotic treatment

Data are limited regarding the management of patients with recurrent AIS/progression of other brain ischaemic injury on VKA, i.e. anticoagulant-refractory thrombotic APS[103]. Whether the INR was subtherapeutic and INRs performed using an LA-insensitive thromboplastin should be checked[104], and alternative causes for progressive/recurrent thrombosis considered, e.g. malignancy.

Antithrombotic treatment is empirical. High-intensity VKA, target INR range 3.0-4.0, should be considered if thrombosis occurred at an INR of 2.0-3.0. Bleeding risk may limit intensification of antithrombotic treatment. In patients who re-thrombose on high-intensity VKA, limited retrospective/indirect data suggests LMWH may be useful: in two studies, of 14/24 and 9/23 patients who re-thrombosed on warfarin, four patients overall subsequently re-thrombosed on LMWH[105,106]. Utility of anti-Xa monitoring of LMWH is uncertain, with limitations including suboptimal reproducibility, lack of interlaboratory standardisation[107], or evidence of correlation of anti-Xa activity with efficacy and safety. LMWH at ~125% of standard dose may be used, aiming for peak anti-Xa levels of 0.8-1.20, with cognisance of the uncertainties. Addition of LDA to warfarin or LMWH may be considered.

Limited data suggest that fondaparinux, a synthetic analogue of heparin pentasaccharide, may provide an option[108,109]. Fondaparinux is eliminated exclusively by the kidneys (half-life ~17hours) and contraindicated in severe renal impairment[110].

6.2 Other therapeutic modalities

Other options, including immunomodulation and vascular approaches (e.g. vasodilators/epidermal skin grafting/digital sympathectomy/hyperbaric oxygen), may be considered, noting evidence is limited[103,111].

Hydroxychloroquine (HCQ) has pleotropic effects including suppression of pro-inflammatory cytokine release, increased nitric oxide availability and attenuation of antibody-production and antigen presentation[112]. Antithrombotic effects have been demonstrated in murine models and patients with APS. In a randomised pilot study (n=50), HCQ addition to anticoagulation achieved a lower risk of thrombosis at 2.6y (0.001 vs 0.007, log rank p=0.048), not significant after adjustment for covariates[113]. In another study, non-randomised and prospective (n=40), six patients re-thrombosed on warfarin alone, and none on HCQ with warfarin, at 6-36 months follow-up[114].

Small studies suggest that rituximab (a chimeric, B-cell depleting, anti-CD20 monoclonal) reduces recurrent thrombosis, improves non-criteria clinical APS manifestations, especially thrombocytopenia, and improves survival in patients with catastrophic APS[115-118].

7. CLINICAL RESEARCH AGENDA

We suggest:

1. Well-designed prospective cohort studies to define:

a) aPL prevalence, persistence and natural history of aPL-associated AIS, TIA, other brain ischaemic injury;

b) associations between brain MRI and aPL phenotypes;

c) optimal timing of aPL testing following AIS/TIA, and influence of early vs later initiation of antithrombotic therapy on clinical outcomes.

2. Further studies in aPL-positive patients, including RCTs, to:

a) establish optimal antithrombotic treatment;

b) define optimal management of aPL-positive patients with high-risk CVD risk factors or other potential mechanisms, including PFO;

c) clarify the role of aPL in CSVD, pathogenic mechanisms and optimal management;

d) define the role of immunomodulatory agents e.g. hydroxychloroquine, biologic agents;

e) define cognitive impairment prevalence, patterns, mechanisms and associations with neuroimaging biomarkers, to guide development of symptomatic/disease modifying treatment strategies.

3. All cases of aPL-associated AIS and TIA-DWI are reported to the international ISTH registry: https://redcap.isth.org/surveys/?s=9RC8EEDPX37

TABLES

Table 1: Antithrombotic treatment in patients with antiphospholipid syndrome-associated arterial thrombosis: Randomised controlled trials, prospective and retrospective studies
See separate document

Table 2: Suggested antithrombotic treatment options for patients with persistent antiphospholipid antibodies and first acute ischaemic stroke or transient ischaemic attack, or cerebral small vessel disease
See separate document

SUPPLEMENTARY APPENDICES

Supplementary Appendix S1: Systematic literature review
See separate document

Supplementary Appendix S2: Grading of CVD risk factors, adapted from ACR/EULAR Classification criteria
See separate document

Supplementary Appendix S3: Recurrent arterial thrombosis in patients with APS-associated arterial thrombosis: Systematic reviews and meta-analyses
See separate document

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Table 1: Antithrombotic treatment in patients with antiphospholipid syndrome-associated arterial thrombosis:

Randomised controlled trials, prospective and retrospective studies

Reference	Study design	Comparators/ treatment regimens	Population	Primary outcome	Number of patients	Follow up duration	Results	Comments, critical review and limitations
Verro et al, 1998[65]	Prospective cohort study	-Warfarin (generally transitioned from aspirin to warfarin if ischaemic event on aspirin) -Aspirin	Ischaemic cerebrovascular disease, IgG aCL >100 GPLU (on 1-13 occasions, average 4.4); LA present in 72%	Stroke	27	Mean 2.8y	-7/18 patients (39%) on aspirin alone had a stroke -1/7 patients (14%) on warfarin had a retinal infarct, none had a stroke (NS)	-Early prospective cohort study in patients with ischaemic cerebrovascular disease; several treatment options including aspirin alone and warfarin plus aspirin -Results suggest that warfarin may be associated with fewer recurrent strokes than aspirin -One patient had a minimally haemorrhagic infarct (on aspirin plus warfarin); no other information regarding bleeding complications -Conclusions limited by small number of patients and the following factors: a) Antithrombotic treatment non-randomised b) Aspirin dose and TINR not specified c) Persistent aPL not demonstrated in all patients (pre-Sapporo criteria; aPL testing 1-13 times, mean 4.4)

Ruiz-Irastorza et al, 2002 [66]	Retrospective cohort study	-Warfarin TINR range 3-4	-Arterial thrombosis (51/66), 38 stroke, -VTE 32/66 -Arterial thrombosis + VTE 15/66 -Sapporo criteria [67]	Recurrent thrombosis	66	12m	-6 patients had thrombotic recurrence, 4 arterial and 2 VTE -4 patients had major bleeding (2 retroperitoneal, 1 rectal, 1 intracranial	-Relatively small study -Retrospective, although all patients personally interviewed to review major bleeding and thrombotic events during previous 12m -INRs at time of thrombosis 2.1-2.6 (not determined in 1 patient) -Risk factors for bleeding events in the 4 patients: 2 retroperitoneal haemorrhages: -renal biopsy, INR 5.2; -aspirin and INR 1.9; 1 rectal haemorrhage (internal haemorrhoids, aspirin); 1 intracranial haemorrhage (head trauma, INR >20, aspirin) -3 of 4 patients who had recurrent arterial thrombosis had risk factors: hypertension, hyperlipidaemia, cigarette smoking
Crowther et al, 2003 [68]	RCT Double blind	-Warfarin T INR range 3.1-4.0 - Warfarin TINR range 2.0-3.0	-Venous or arterial thrombosis, Sapporo criteria [67]	Recurrent thrombosis	114	Mean 2.7y	No difference in recurrent thrombosis: -Thrombosis in 6/56 (10.7%) patients on warfarin TINR 3-4 -Thrombosis in 2/58 (3.4%) patients on warfarin TINR 2-3	-RCT in patients with thrombotic APS, compared efficacy of standard (TINR 2-3) versus high-intensity (TINR 3.1-4) warfarin -Results reported no difference in recurrent thrombosis on high-intensity versus standard-intensity warfarin

							No difference in major bleeding: -3 patients on high-intensity warfarin -4 patients on standard-intensity warfarin	-Conclusions with regard to efficacy for APS-associated AT limited by: a) Minority of patients (27/114, 23.7%) had arterial thrombosis, and b) Subtherapeutic INRs (<3) 43% of the time in high-intensity arm: c) 6 of 8 recurrent thrombotic events (6 in the high-intensity and 2 in the moderate-intensity arm) occurred at INR <3.0
Levine et al, 2004 [69]	Prospective cohort study (APASS) within WARSS RCT	-Warfarin TINR range 1.4-2.8 - Aspirin 325mg/d	Ischaemic stroke with -baseline aPL: single and/or dual positive; aCL IgG/IgM/IgA (low positive 53%) and/or LA on one occasion) -Cohort average age 60y	Composite endpoint of death from any cause, ischaemic stroke, TIA, MI, DVT, PE, and other systemic thrombo-occlusive events	720	2y	-22.2% aPL-positive/ 21.8% non-aPL positive patients had thrombo-occlusive event -No difference in thrombo-occlusive events in patients treated with warfarin or aspirin	-Nested prospective cohort study, results reported no difference in recurrent thrombo-occlusion on warfarin or aspirin in patients with ischaemic stroke and aPL -Conclusions limited by: a) Subtherapeutic anticoagulation, INR <2 in many patients: median INR after 28d on warfarin 1.9 b) Sapporo criteria [67] for diagnosis of APS not fulfilled: single aPL assessment <30d of study entry (i.e. results potentially confounded by acute phase response), low aCL titres and some IgA aCL only (not criteria aPL) included

Finazzi et al, 2005 [70]	RCT	-Warfarin TINR range 2-3 -Warfarin TINR range 3-4.5	Venous or arterial thrombosis, Sapporo criteria [67]	Recurrent thrombosis	109	Median 3.6y	No difference in recurrent thrombosis between the two groups: -2 AIS, 2 TIA, and 5 vascular deaths (thrombosis) among 54 patients on warfarin TINR range 3-4; -2 AIS, 1 TIA, and 3 vascular deaths (thrombosis) among 55 patients on warfarin TINR range 2-3 No difference in major bleeding, which occurred in: -2 patients on high-intensity warfarin -3 patients on standard-intensity warfarin	-RCT in patients with thrombotic APS, compared efficacy of standard versus high-intensity warfarin -Results showed no difference in recurrent thrombosis in the two arms of the trial: 7 patients had recurrent thrombosis: 4 had AIS (two in each arm) and three had TIA (two in the high-intensity arm). -Conclusions with regard to efficacy for APS-associated AT limited by: a) Relatively small number of patients with AT (44/109, 40.4%) b) Subtherapeutic INRs (<3) in many patients in high-intensity arm (mean INR 3.2): mean INR in the high-intensity arm was 3.2, consistent with a high proportion of INRs <3.0 and that recurrent AIS/TIA events probably occurred at moderate-intensity VKA
Okuma et al, 2010 [71]	RCT	-Aspirin 100mg OD + VKA TINR range 2-3 -Aspirin 100mg OD	Ischaemic stroke, updated Sapporo criteria [72], except repeat tests >6w apart	Stroke	20	Mean 3.9±2y	-Incidence of stroke significantly lower on VKA+aspirin vs aspirin alone (p=0.026): 2/9 on VKA+aspirin and 8/11 on aspirin had recurrent ischaemic stroke	-Small RCT that compared aspirin + VKA vs aspirin alone in patients with AIS -Conclusions limited by: a) aPL persistence based on repeat positive after >6 rather than >12w

								b) Information on level of achievement of target INR range in patients on VKA not provided
Jackson et al, 2017 [73]	Retrospective cohort study	-VKA TINR range 2.0-3.0 + SAPT (n=58) - VKA TINR range 2.0-3.0 (n=37); -Antiplatelet agent(s) (aspirin and/or clopidogrel) (n=43)	APS patients with arterial thrombotic event, updated Sapporo criteria [72]	Recurrent thrombosis	139	Median 4.3y	-Patients receiving combined therapy had a 70% lower hazard of a recurrent event than those on VKA or antiplatelet alone: 4/58 (7%) on VKA + SAPT; 9/37 (24%) on VKA alone; 16/43 (37%) on SAPT or DAPT	-Retrospective cohort study, concluded that there was a lower risk of recurrent thrombosis on VKA + antiplatelet vs VKA or antiplatelet alone Conclusions limited by: a) Retrospective design b) Information on level of achievement of target INR range in patients on VKA not provided
Pengo et al, 2018 [74]	RCT: TRAPS	-Rivaroxaban 20mg OD or 15mg OD based on renal function -Warfarin TINR 2-3.	Thrombotic APS: triple aPL-positive; 25 arterial (16 stroke); venous 77; arterial + venous 18; updated Sapporo criteria [72]	Recurrent thrombosis	120	Mean 1.5y	-7/57 patients on rivaroxaban had arterial thrombosis: 4 ischaemic stroke, 3 MI; no recurrent VTE -No thrombosis in patients on warfarin -Major bleeding in 4 pts on rivaroxaban, 2 on warfarin -The trial was discontinued prematurely	-DOAC RCT that showed an increased rate of arterial thrombotic events on rivaroxaban in triple aPL-positive thrombotic APS patients -The results indicate that high-risk patients with thrombotic APS should not be treated with rivaroxaban -NB: Patients with arterial thrombotic events were excluded in the prior RAPS RCT of rivaroxaban vs warfarin in patients with thrombotic APS (28% triple aPL positive), which was not associated with thrombosis over 7m follow up [75]

Ordi-Ros et al, 2019 [76]	RCT	-Rivaroxaban 20mg OD or 15mg OD, according to renal function -Warfarin TINR 2-3 or 3.1-4 for those with a history of recurrent thrombosis	Thrombotic APS (71 arterial, 139 VTE, 20 both arterial and VTE); updated Sapporo criteria [72]	Recurrent thrombosis	190	3y	-Recurrent thrombosis occurred in 11 patients (11.6%) in the rivaroxaban group and 6 (6.3%) in the VKA group (RR in the rivaroxaban group 1.83 [95% CI, 0.71 to 4.76]) -9 patients on rivaroxaban vs 0 on VKA had ischaemic stroke (corrected RR, 19.00 [CI, 1.12 to 321.9] -Post hoc analysis suggested an increased risk for recurrent thrombosis in rivaroxaban-treated patients with previous arterial thrombosis, livedo racemosa, or APS-related cardiac valvular disease	-This DOAC RCT showed a non–statistically significant near doubling of the risk for recurrent thrombosis vs VKA in patients with thrombotic APS -The results indicate that patients with thrombotic APS, particularly those with a history of arterial thrombosis, should not be treated with rivaroxaban -Of note, patients with a history of recurrent thrombosis were treated with higher intensity warfarin, target INR 3.1-4, but such patients randomised to rivaroxaban received standard dose, 20mg OD
Ohnishi et al, 2019 [77]	Retrospective cohort	Antithrombotic options: -Warfarin (n=13) -SAPT (n=41) -Warfarin + antiplatelet (n=21) -DAPT (n=15)	Thrombotic APS, history of arterial event, 81/90 cerebral infarction; updated Sapporo criteria [72]	Recurrent thrombosis	90	>2y	-Recurrent thrombotic events in 40 patients: 35/40 arterial thrombotic events, 29/35 cerebral infarction; 5/40 VTE -Thrombosis recurrence rate per 100 patient-years: Warfarin 11.6; SAPT 5.5, Warfarin + SAPT 3.7, DAPT 1.8	-Retrospective cohort study, concluded that DAPT might be an effective and safe option for the prophylaxis of recurrent arterial thrombosis in patients with APS -Conclusions limited by: a) Selection bias inherent to retrospective study design b) Small number of patients on DAPT precluded comparisons

							-Severe bleeding events in 9 patients -Serious adverse events in 20 patients: 14 deaths, 3 bleeding (aortic dissection [SAPT], alveolar haemorrhage [W + SAPT], aortic aneurysm rupture [DAPT], 2 cerebral infarction	between different antiplatelet regimens -Notably, a review/meta-analysis reported that DAPT may be more effective than single agents in patients with APS-associated arterial thrombosis: DAPT vs SAPT: RR 0.29; 95% CI: 0.09–0.99 [82]
Woller et al, 2022 [78]	RCT: ASTRO-APS	-Apixaban 2.5mg BD -Apixaban dose increased to 5mg BD after 3 patients had stroke on apixaban -Warfarin TINR range 2.0-3.0	Thrombotic APS (17 arterial [12 stroke], 38 VTE); 7 patients had an arterial thrombotic event and VTE -Updated Sapporo criteria [72]	Recurrent thrombosis	48	12m	-Stroke in 6/23 patients on apixaban: 3/6 on apixaban 2.5mg BD, 3/6 after apixaban dose increased to 5mg BD -No stroke or other site thrombosis on warfarin -The trial was discontinued prematurely	-The results of this DOAC RCT (ischaemic stroke in all 6 cases, in patients with thrombotic APS) indicate that apixaban is associated with arterial thrombotic events -4/6 patients who experienced stroke on apixaban had a previous stroke -Prophylactic dose apixaban, 2.5mg BD, was used in this trial -This apixaban dose was increased to treatment dose 5mg BD after the first 3 strokes -A further 3 strokes occurred on treatment dose apixaban -The results indicate that patients with APS, particularly those with a history of arterial thrombosis, should not be treated with apixaban

Abbreviations: aCL, anticardiolipin antibodies; AIS, acute ischaemic stroke; APASS (The Antiphospholipid Antibodies and Stroke Study), a prospective cohort study within the WARSS (Warfarin vs Aspirin Recurrent Stroke Study); aPL, antiphospholipid antibodies; APS, antiphospholipid syndrome; ASTRO-APS, Apixaban for the secondary prevention of thrombosis among patients with antiphospholipid syndrome; AT, arterial thrombosis; BD, twice daily; CI, confidence interval; DAPT, dual antiplatelet treatment; INR, International Normalised Ratio; OD, once daily; m, month(s); m, months; NS, not significant; RAPS, Rivaroxaban in Antiphospholipid Syndrome; RCT, randomised controlled trial; RR, relative risk; SAPT, single antiplatelet treatment; TINR, target INR; TRAPS, Trial on Rivaroxaban in AntiPhospholipid Syndrome; VTE, venous thromboembolism; VKA, vitamin K antagonist; W, warfarin; w, week(s); y, year(s).

TABLE 2: SUGGESTED ANTITHROMBOTIC TREATMENT OPTIONS FOR PATIENTS WITH PERSISTENT ANTIPHOSPHOLIPID ANTIBODIES AND FIRST ACUTE ISCHAEMIC STROKE OR TRANSIENT ISCHAEMIC ATTACK, OR CEREBRAL SMALL VESSEL DISEASE

A. ACUTE ISCHAEMIC STROKE (AIS) OR TRANSIENT ISCHAEMIC ATTACK CONFIRMED BY DIFFUSION-WEIGHTED IMAGING (TIA-DWI)

Antiphospholipid antibodies/antiphospholipid syndrome patient profiles	**Suggested antithrombotic options**
Single or double aPL-positive, excluding LA, i.e. aCL and/or aß2GPI antibodies, IgG and/or IgM	VKA target INR range 2.0-3.0
Positive LA alone or in combination with positive aCL or anti-ß2GPI antibodies, IgG and/or IgM	VKA target INR range 2.0-3.0 or VKA target INR range 3.0-4.0*
Triple aPL-positive, i.e. LA, aCL and anti-ß2GPI antibodies, IgG and/or IgM	VKA target INR range 2.0-3.0 or VKA target INR range 3.0-4.0*
All aPL phenotypes, with high-risk CVD profile (Supplementary Appendix 2) or specific indication for antiplatelet treatment e.g. coronary artery disease or stent	VKA target INR range 2.0-3.0 plus antiplatelet treatment**
All aPL phenotypes, if VKA not considered appropriate/patient preference	SAPT (e.g. aspirin or clopidogrel) or DAPT (e.g. LDA + clopidogrel)

Antithrombotic treatment initiation may be considered in some situations prior to establishing persistence of aPL (see Guidance Statements in guidance text)

Notes: AIS or TIA-DWI

-The antithrombotic regimens above are stratified based on antiphospholipid antibodies phenotype-associated thrombotic risk;

-For all the suggested antithrombotic regimens, particularly VKA plus antiplatelet or high-intensity VKA (target INR 3.0-4.0), risk factors for bleeding should be taken into account, with ongoing assessment of thrombotic and bleeding risks;

*A target INR range of 2.5-3.5 is a pragmatic option, in view of the lack of definitive evidence regarding optimal anticoagulation intensity for APS-associated arterial thrombosis, and potential recurrent thrombosis or bleeding with lower or higher target INR ranges, respectively;

**Duration of antiplatelet treatment should be based on the indication;

-DOACs should be avoided in patients with APS-associated AIS or TIA-DWI.

B. CEREBRAL SMALL VESSEL DISEASE (CSVD); SILENT CORTICAL OR SUBCORTICAL INFARCTS, OR WHITE MATTER HYPERINTENSITIES OF PRESUMED VASCULAR ORIGIN

All antiphospholipid antibody phenotypes	SAPT or DAPT or VKA, on an individualized basis

Notes: AIS/TIA-DWI and CSVD

-Suggested criteria for aPL testing in patients with AIS/TIA-DWI and CSVD are detailed in the Guidance Statements;
-Control of CVD risk factors is critical for secondary prevention of AIS/TIA or CSVD:
Blood pressure target <130/80 mmHg
LDL cholesterol target <1.8 mmol/l (<70 mg/dL)
HbA1C target <7%
Advice on modifiable lifestyle factors: cessation of cigarette smoking, maintaining a healthy weight, regular physical activity, a balanced diet, and limiting alcohol consumption.
-DOACs should be avoided in patients with APS-associated cerebrovascular disease, i.e. AIS/TIA-DWI and CSVD.

Abbreviations

aPL, antiphospholipid antibodies; APS, antiphospholipid syndrome; AIS: acute ischaemic stroke; aß2GPI, anti-ß2 glycoprotein I antibodies; aCL, anticardiolipin antibodies; CSVD, cerebral small vessel disease; CVD, cerebrovascular disease; DAPT, dual antiplatelet treatment; DOACs, direct oral anticoagulants; HBA1C, haemoglobin A1C; LDA, low dose aspirin; LDL, low density lipoprotein; SAPT, single antiplatelet treatment; TIA, transient ischaemic attack; TIA-DWI, transient ischaemic attack confirmed by diffusion-weighted imaging; VKA, vitamin K antagonist

Supplementary Appendix S1

Systematic literature review

The search terms for the review (below) focused on APS and aPL in combination with comorbidities (e.g., stroke) or interventions (e.g., warfarin). The search included references between 01-Jan-2000 and 31-Dec-2024. Narrative review articles, case studies, articles without abstracts and articles written in a language other than English were excluded. Articles were also identified by hand searches. The search identified a total of 249 articles, which were reviewed by 2 coauthors (HC, DAI), with 102 included in the final assessment. Management during pregnancy is outside the scope of this guidance.

Search terms

Antiphospholipid antibodies AND antiphospholipid syndrome 'diagnosis' WITH stroke, transient ischaemic attack, cerebrovascular disease, small vessel disease, brain infarcts, white matter hyperintensities, vascular cognitive impairment, dementia, age and sex

Antiphospholipid antibodies AND antiphospholipid syndrome 'treatment' WITH stroke, transient ischaemic attack (TIA), cerebrovascular disease, small vessel disease, brain infarcts, white matter hyperintensities, vascular cognitive impairment, dementia

Antiphospholipid antibodies AND antiphospholipid syndrome WITH stroke, transient ischaemic attack, cerebrovascular disease, small vessel disease, brain infarcts, white matter hyperintensities, vascular cognitive impairment, dementia AND hypertension, hyperlipidaemia, diabetes, hyperhomocysteinaemia, smoking

Antiphospholipid antibodies AND antiphospholipid syndrome WITH Sneddon syndrome

Prevalence of antiphospholipid antibodies WITH stroke and transient ischaemic attack (TIA)

Anticoagulants for antiphospholipid syndrome; warfarin, vitamin K antagonists, direct oral anticoagulants, rivaroxaban, apixaban, dabigatran, edoxaban, heparin, low molecular weight heparin, antiplatelet treatment WITH stroke, aspirin, clopidogrel, ticagrelor, dual antiplatelet, transient ischaemic attack (TIA), cerebrovascular disease, small vessel disease, brain infarcts, white matter hyperintensities, vascular cognitive impairment, dementia

Hydroxychloroquine, vitamin D, complement inhibitors, B-cell inhibition for antiphospholipid syndrome WITH stroke, transient ischaemic attack (TIA), cerebrovascular disease, small vessel disease, brain infarcts, white matter hyperintensities, vascular cognitive impairment, dementia

Antiphospholipid antibodies AND antiphospholipid syndrome with Patent foramen ovale WITH stroke, transient ischaemic attack (TIA)

Antiphospholipid antibodies AND antiphospholipid syndrome with autoimmune disease, systemic lupus erythematosus, rheumatoid arthritis

(((((((Antiphospholipid antibodies[Title/Abstract]) AND (antiphospholipid syndrome[Title/Abstract])) AND (stroke[Title/Abstract] OR transient ischaemic attack[Title/Abstract] OR transient ischemic attack[Title/Abstract] OR cerebrovascular disease[Title/Abstract] OR small vessel disease[Title/Abstract] OR brain infarcts[Title/Abstract] OR white matter hyperintensities[Title/Abstract] OR vascular cognitive impairment[Title/Abstract] OR dementia[Title/Abstract] OR Sneddon syndrome[Title/Abstract] OR patent foramen ovale[Title/Abstract] OR autoimmune disease[Title/Abstract] OR systemic lupus erythematosus[Title/Abstract] OR rheumatoid arthritis[Title/Abstract]))) OR ((((antiphospholipid syndrome[Title/Abstract]) AND (warfarin[Title/Abstract] OR vitamin K antagonists[Title/Abstract] OR direct oral anticoagulant[Title/Abstract] OR rivaroxaban[Title/Abstract] OR apixaban[Title/Abstract] OR dabigatran[Title/Abstract] OR edoxaban[Title/Abstract] OR heparin[Title/Abstract] OR antiplatelet treatment[Title/Abstract])) AND (stroke[Title/Abstract] OR asprin[Title/Abstract] OR clopidogrel[Title/Abstract] OR ticagrelor[Title/Abstract] OR dual antiplatelet[Title/Abstract] OR transient ischaemic attack[Title/Abstract] OR transient ischemic attack[Title/Abstract] OR cerebrovascular disease[Title/Abstract] OR small vessel disease[Title/Abstract] OR brain infracts[Title/Abstract] OR white matter hyperintensities[Title/Abstract] OR vascular cognitive impairment[Title/Abstract] OR dementia[Title/Abstract]))) OR ((((antiphospholipid syndrome[Title/Abstract]) AND (hydroxychloroquine[Title/Abstract] OR vitamin D[Title/Abstract] OR complement inhibitors[Title/Abstract] OR b-cell inhibition[Title/Abstract])) AND (stroke[Title/Abstract] OR transient ischaemic attack[Title/Abstract] OR transient ischemic attack[Title/Abstract] OR cerebrovascular disease[Title/Abstract] OR small vessel disease[Title/Abstract] OR brain infarcts[Title/Abstract] OR white matter hyperintensities[Title/Abstract] OR vascular cognitive impairment[Title/Abstract] OR dementia[Title/Abstract]) AND (("2000/01/01"[Date - Publication] : "3000"[Date - Publication])) AND ("english"[Language]) AND (fha[Filter]) AND ((fha[Filter]) AND (clinicalstudy[Filter] OR clinicaltrial[Filter] OR controlledclinicaltrial[Filter] OR guideline[Filter] OR meta-analysis[Filter] OR observationalstudy[Filter] OR practiceguideline[Filter] OR randomizedcontrolledtrial[Filter] OR systematicreview[Filter])))))

Supplementary Appendix S2

Grading of CVD risk factors, adapted from ACR/EULAR Classification criteria[1]

Definitions of high-risk cardiovascular disease (CVD) profiles based on current general population guidelines (refer to supplementary Section 8 at https://onlinelibrary.wiley.com/doi/10.1002/art.42624

High-risk CVD profile is defined based on 1 or more high CVD risk factors OR 3 or more moderate CVD risk factors, if timeline/severity is associated with the event based on investigator's judgment (timelines based on general population guidelines are provided when available).

a. High CVD risk factors (any of the following at the time of the event):
Arterial hypertension with systolic blood pressure (BP) ≥180 mm Hg or diastolic BP ≥110 mm Hg.
Chronic kidney disease with estimated glomerular filtration rate ≤60 ml/minute for more than 3 months.
Diabetes mellitus with organ damage* or long disease duration (type 1 for ≥20 years; type 2 for ≥10 years).
Hyperlipidemia (severe) with total cholesterol ≥310 mg/dl (8 mmoles/liter) or low-density lipoprotein (LDL)–cholesterol >190 mg/dl (4.9 mmoles/liter).

b. Moderate CVD risk factors (3 or more of the following at the time of the event):
Arterial hypertension on treatment, or with persistent systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg.
Current tobacco smoking.
Diabetes mellitus with no organ damage* and short disease duration (type 1 <20 years; type 2 <10 years).
Hyperlipidemia (moderate) on treatment, or with total cholesterol above normal range and <310 mg/dl (8 mmoles/liter), or LDL-cholesterol above normal range and <190 mg/dl (4.9 mmoles/liter).
Obesity (BMI ≥30 kg/m²).

* Diabetes mellitus diagnosis based on a hemoglobin A1c ≥6.5%, or a fasting plasma glucose ≥126 mg/dl (7.0 mmoles/liters), or symptoms of diabetes (e.g., polyuria, polydipsia, or unexplained weight loss) with a random plasma glucose concentration ≥200 mg/dl (11.1 mmoles/liter).
According to the 2019 ESC/EASD guidelines on diabetes, organ damage is defined by proteinuria, chronic kidney disease, left ventricular hypertrophy, or retinopathy [2].

References

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Table 1
Recurrent arterial thrombosis in patients with APS-associated arterial thrombosis: Systematic reviews and meta-analyses

First author	**Tektonidou**(79)	**Ortel**(80)	**Bala**(81)	**Aibar**(82)	**Attachaipanich**(83)	**Khairani**(84)
Year of publication	2019	2020	2020	2021	2023	2023
Design	Systematic literature review	Systematic review and meta-analysis	Cochrane database systematic review	Review and meta-analysis	Frequentist random-effects network meta-analysis	Meta-analysis
Total number of patients	440 (4 studies)	858 (8 studies)	811 (8 studies)	1767 (11 studies)	719 (13 studies)	472 patients (4 RCTs)
APS population	APS patients with arterial thrombosis 169 (38.4% of total) -Sapporo criteria met in 2/4 studies	aPL and initial ATE variable criteria for aPL in different studies	3/8 Sapporo criteria, 3/8 updated Sapporo criteria, 2 not defined	7 arterial thrombosis, 4 arterial or venous thrombosis, or microvascular (1 study); 9/11 used updated Sapporo criteria, 1 study: stroke+aPL, 1 not stated	APS patients with arterial thrombosis, criteria for APS not stated	Updated Sapporo criteria: Arterial or venous thrombosis with documented positivity of at least 1 aPL (LA, IgG and/or IgM aCL and abeta2GPI) and verified at least 12 weeks apart
Intervention	2 RCTs, warfarin TINR -3-4 vs 2-3 -3.1-4 vs 2-3 2 retrospective cohort studies -warfarin TINR 3-4 or 2-3 -warfarin TINR >3.0 or <3.0	488 patients chronic anticoagulant therapy (3 warfarin, 3 DOAC: 2 rivaroxaban, one dabigatran); 370 patients on LDA	3 studies compared rivaroxaban vs warfarin T INR range 2.0-3.0; 2 studies compared VKA T INR range 3.1-4.0/3.0-4.5 vs 2.0-3.0; 1 study VKA T INR 2.0-3.0 + LDA vs VKA TINR 2.0-3.0; 2 studies compared different combinations of VKA or antiplatelet drugs	Diverse antithrombotic treatments, including VKA with variable target INR ranges, VKA+SAPT, DAPT	antiplatelet agents, warfarin, DOACs, or a combination of these therapies	23 apixaban; 211 rivaroxaban; 240 warfarin/other VKA (145 warfarin T INR 2.0-3.0; 95 other VKA, T INR 2.0-3.0 and 3.1-4.0 if history of recurrent thrombosis

Primary endpoint	Recurrent thrombotic events	Recurrent thrombotic events	Recurrent thrombotic events	Recurrent arterial thrombosis, any thromboembolism (arterial or venous thromboembolism)	Recurrent thrombotic events	Main efficacy outcomes: composite of AT events; and VTE events; Other efficacy outcomes included AMI, IS or TIA, acute major limb events, PE, DVT, all-cause death, composite of any ATE or VTE events
PRIMARY RESULT	2 studies RCTs: -Recurrent thrombosis in 6/56 patients (10.7%) in high-intensity warfarin arm (RCT) - Recurrent thrombosis 2 AIS and 2 TIA, of 55 patients; and 5 vascular Deaths (RCT 2 studies retrospective cohorts: -Recurrent thrombosis 101/147 -recurrent thrombosis 37 patients	Recurrent TE in patients with ATE -anticoagulation 19.7% (95% CI 0.133, 0.282) -antiplatelet 21.6% (95% CI 0.177, 0.261)	2 studies of VKA -T INR 3--4 vs 2-3: no difference in rates of thrombosis -T INR 2-3+antiplatelet vs VKA T INR 2-3: more thrombosis with combined treatment 3 studies rivaroxaban vs VKA T INR 2-3: similar proportions with thrombosis, more strokes with DOAC vs VKA 2 studies using different combinations of VKA or antiplatelet drugs inconclusive	Recurrent AT reduced with -VKA+SAPT vs VKA (RR 0.43; 95% CI: 0.22–0.85) -DAPT vs SAPT (RR 0.29; 95% CI: 0.09–0.99) Any recurrent TE reduced with VKA+SAPT -vs VKA alone (RR: 0.41; 95%; CI 0.24–0.69) -vs SAPT alone (RR 0.36; 95% CI 0.13–0.96)	Recurrent TE reduced with -antiplt+warfarin vs SAPT (RR 0.41 (95% CI 0.20-0.85) -DAPT vs SAPT (RR 0.29 (95% CI 0.08-1.07), NS	DOACs compared with VKAs: -significantly increased subsequent ATE, especially stroke (OR 5.43; 95% CI: 1.87-15.75; P<0.001) -VTE not significantly increased (OR 1.20; 95% CI: 0.31-4.55; P=0.79)

Abbreviations: aPL, antiphospholipid antibodies; APS, antiphospholipid syndrome; ATE, arterial thromboembolism; CI, Confidence Interval; DAPT, dual antiplatelet therapy; DOAC, direct oral anticoagulant; INR, International Normalised Ratio; LDA, low dose aspirin; RR, relative risk; SAPT, single antiplatelet therapy; TINR, target International Normalised Ratio; TE, thromboembolism; VKA, vitamin K antagonist