Received: 21 February 2023 | Revised: 5 May 2023 | Accepted: 15 June 2023

https://doi.org/10.1016/j.jtha.2023.06.020

ISTH SSC COMMUNICATION

Survey on antiphospholipid syndrome diagnosis and antithrombotic treatment in patients with ischemic stroke, other brain ischemic injury, or arterial thromboembolism in other sites: communication from ISTH SSC Subcommittee on Lupus Anticoagulant/Antiphospholipid Antibodies

Hannah Cohen[1,2] | David J. Werring[3,4] | Arvind Chandratheva[4] | Prabal Mittal[1,2] | Katrien M. J. Devreese[5] | David A. Isenberg[6,7] | for the ISTH SSC Lupus Anticoagulant/Antiphospholipid Antibodies Subcommittee Study Group

[1]Department of Haematology, Cancer Institute, University College London, London, UK

[2]Department of Haematology, University College London Hospitals NHS Foundation Trust, London, UK

[3]Stroke Research Centre, Department of Brain Repair and Rehabilitation, University College London Queen Square Institute of Neurology, London, UK

[4]National Hospital for Neurology and Neurosurgery, Queen Square University College Hospitals NHS Foundation Trust, London, UK

[5]Coagulation Laboratory, Ghent University Hospital, Ghent, Department of Diagnostic Sciences, Ghent University, Ghent, Belgium

[6]Department of Rheumatology, University College London Hospitals NHS Foundation Trust, London, UK

[7]Centre for Rheumatology, Division of Medicine, University College London, London, UK

Correspondence
Hannah Cohen, Department of Haematology, Cancer Institute, University College London, 72 Huntley Street, London WC1E 6DD, UK.
Email: hannah.cohen@ucl.ac.uk

Abstract

Background: The optimal strategy for diagnosis and antithrombotic treatment of patients with antiphospholipid syndrome (APS)–associated acute ischemic stroke (AIS), transient ischemic attack (TIA), or other brain ischemic injury is poorly defined.

Objectives: The survey goal was to capture variations in diagnosis and antithrombotic treatment of APS-associated ischemic stroke and related disorders to inform guidance and clinical trials to define optimal management.

Methods: Professional colleagues, including key opinion leaders, were invited to complete a REDCap survey questionnaire initiated by the International Society on Thrombosis and Haemostasis Scientific and Standardisation Committee Subcommittee on Lupus Anticoagulant/Antiphospholipid Antibodies. The survey data were tallied using simple descriptive statistics.

Results: There was generally good agreement on several aspects, including which patients to test for antiphospholipid antibodies (aPL), use of a lifelong vitamin K antagonist for AIS or recurrent TIA, and formal cognitive assessment for suspected cognitive impairment. There was less agreement on other aspects, including aPL testing for brain ischemic injury other than AIS/TIA or if an alternative cause for AIS or TIA exists; choice of aPL tests, their timing, and age cutoff; the aPL phenotype to trigger antithrombotic treatment; management for patent foramen ovale; antithrombotic treatment for first TIA or white matter hyperintensities; head magnetic resonance imaging specifications; and low-molecular-weight heparin dosing/anti-Xa monitoring in pregnancy. The survey highlighted that approximately 25% practice at dedicated APS clinics and <50% have a multidisciplinary team structure for patients with APS.

Manuscript handled by: Kathleen Freson

Final decision: Kathleen Freson, 15 June 2023

Conclusion: Much of the variation in practice reflects the lack of evidence-based recommendations. The survey results should inform the development of a more uniform multidisciplinary consensus approach to diagnosis and antithrombotic treatment.

KEYWORDS
antiphospholipid syndrome, cerebral infarcts, ischemic stroke, survey, transient ischemic attack, white matter hyperintensities

1 | INTRODUCTION

Stroke is the second most common cause of death worldwide [1] and the most important cause of adult complex disability [2]. Systematic reviews estimate that 13.5% (range, 6.8%-23.3%) of patients with acute ischemic stroke (AIS) or transient ischemic attack (TIA) [3], and, in patients aged <50 years, approximately 17% (range, 2%-56%) and 12% (range, 2%-45%) of those with AIS or TIA, respectively, are associated with antiphospholipid antibodies (aPL) [4]. AIS and TIA are thus important and frequent clinical manifestations of thrombotic antiphospholipid syndrome (APS). Neuroimaging findings associated with APS include infarcts (both subcortical and cortical) [5], white matter hyperintensities (WMH) of presumed vascular origin [5], cerebral venous thrombosis [6], and cerebral microbleeds [5]. WMH have face validity, being associated with clinically important outcomes of disease features. A systemic review reported that WMH predict an increased risk of 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 also suggested [7].

Patients with APS are also at increased risk of myocardial infarction [8], with aPL reported in 11% of patients with myocardial infarction [3]. Other arterial thrombotic events, such as renal artery thrombosis [9] and peripheral arterial ischemia [10], can occur. Among patients with systemic lupus erythematosus (SLE), 30%-40% have aPL [11], with estimates of the incidence of APS ranging from 7% to 15% [12,13]. Patients with SLE and APS are often challenging to manage, with complex multisystem clinical problems [13]. The optimal antithrombotic strategy for APS-associated AIS, other brain ischemic injury, or arterial thromboembolism in other sites remains poorly defined due to the lack of appropriate, adequately powered randomized controlled trials (RCTs) to guide the most favorable antithrombotic treatment [14].

The identification of patients with thrombotic APS and their optimal management is of high clinical importance to prevent potentially avoidable recurrent arterial and venous thrombosis. The goal of our survey was to capture variations in the diagnosis and antithrombotic treatment of APS-associated ischaemic stroke and related disorders. This goal would inform guidance based on a more uniform multidisciplinary consensus approach and clinical trials to define optimal management.

Essentials

- Diagnosis and antithrombotic treatment of antiphospholipid syndrome–associated acute ischemic stroke are poorly defined.
- An international survey to define current practice was performed.
- Antiphospholipid antibody testing strategy and antithrombotic treatment lack uniformity.
- The survey results could inform a more uniform multidisciplinary consensus approach.

2 | METHODS

2.1 | Survey questionnaire

The survey questionnaire (Supplementary Methods), formulated by the authors by consensus was placed on the International Society on Thrombosis and Haemostasis (ISTH) website using REDCap, and all members registered on the ISTH Scientific and Standardization Committee Subcommittees for Lupus Anticoagulant/Antiphopholipid Antibodies, Control of Anticoagulation, and Women's Health Issues in Thrombosis and Haemostasis, which include clinical and laboratory-based investigators in the field of APS/aPL, were invited by email to participate. Additionally, investigators of the Antiphospholipid Syndrome Alliance for Clinical Trials and International Networking, British Association of Stroke Physicians, and other key opinion leaders and professional colleagues in the field of APS/aPL were invited to complete the questionnaire.

2.2 | Data analysis

Specific details of the returned information were entered into an Excel (Microsoft) spreadsheet that included all records and fields, and data were tallied using simple descriptive statistics.

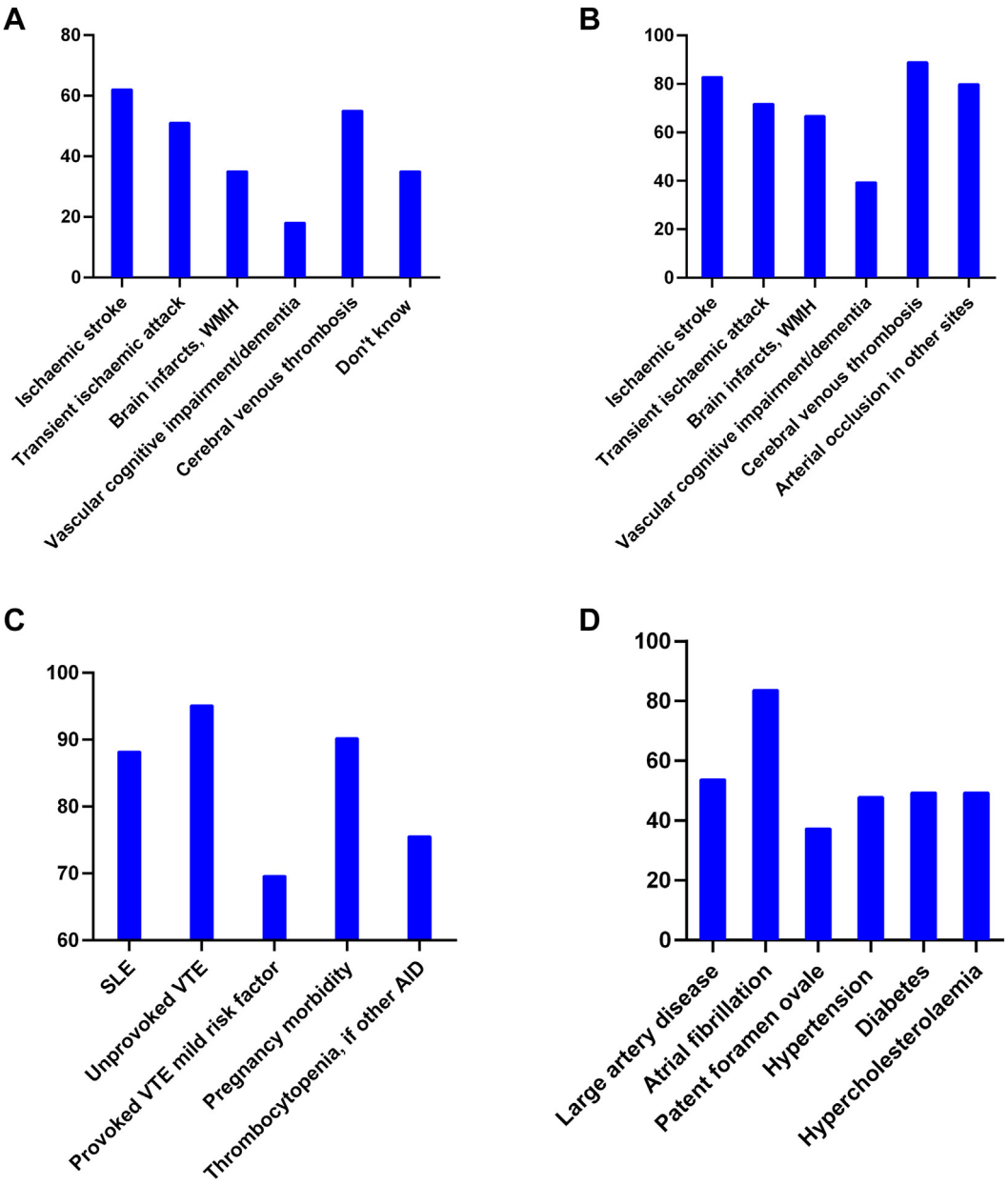

FIGURE 1 (A) Have local guidance that defines which patients with acute ischemic stroke (AIS), transient ischemic attack (TIA), head imaging findings (eg, brain infarcts and white matter hyperintensities [WMH]), vascular cognitive impairment or dementia, or cerebral venous sinus thrombosis should be tested for antiphospholipid antibodies (aPL) (100 respondents). (B) Test for aPL in patients with AIS, TIA, head imaging findings (eg, brain infarcts and WMH), vascular cognitive impairment, or dementia (99 respondents). The percentage for cerebral venous thrombosis and arterial occlusion in other sites are also included. (C) Test for aPL in patients with conditions recognized to be associated with aPL, regardless of a history of AIS, TIA, or other brain ischemic injury (102 respondents). (D) Exclude patients with alternative causes/risk factors for AIS or TIA from aPL testing (67 respondents). The y-axis indicates percentage of respondents. AID, autoimmune disease; SLE, systemic lupus erythematosus; VTE, venous thromboembolism.

3 | RESULTS

3.1 | General information

One hundred and seven responses to the survey were received (July 14, 2021, to December 19, 2021). The majority of respondents were clinical hematologists (43%), with rheumatologists and neurologists/stroke physicians comprising 23.4% and 14.9%, respectively, and those in other clinical specialties comprising 15.8%; 79.4% were based at a university hospital. A minority, 2.8%, were laboratory-based researchers. The clinical settings in which these specialists work and the clinics in which patients are seen highlight that this group of patients with APS impacts a broad range of clinical specialty services, mostly non–APS-dedicated (Supplementary Figure S1A, B).

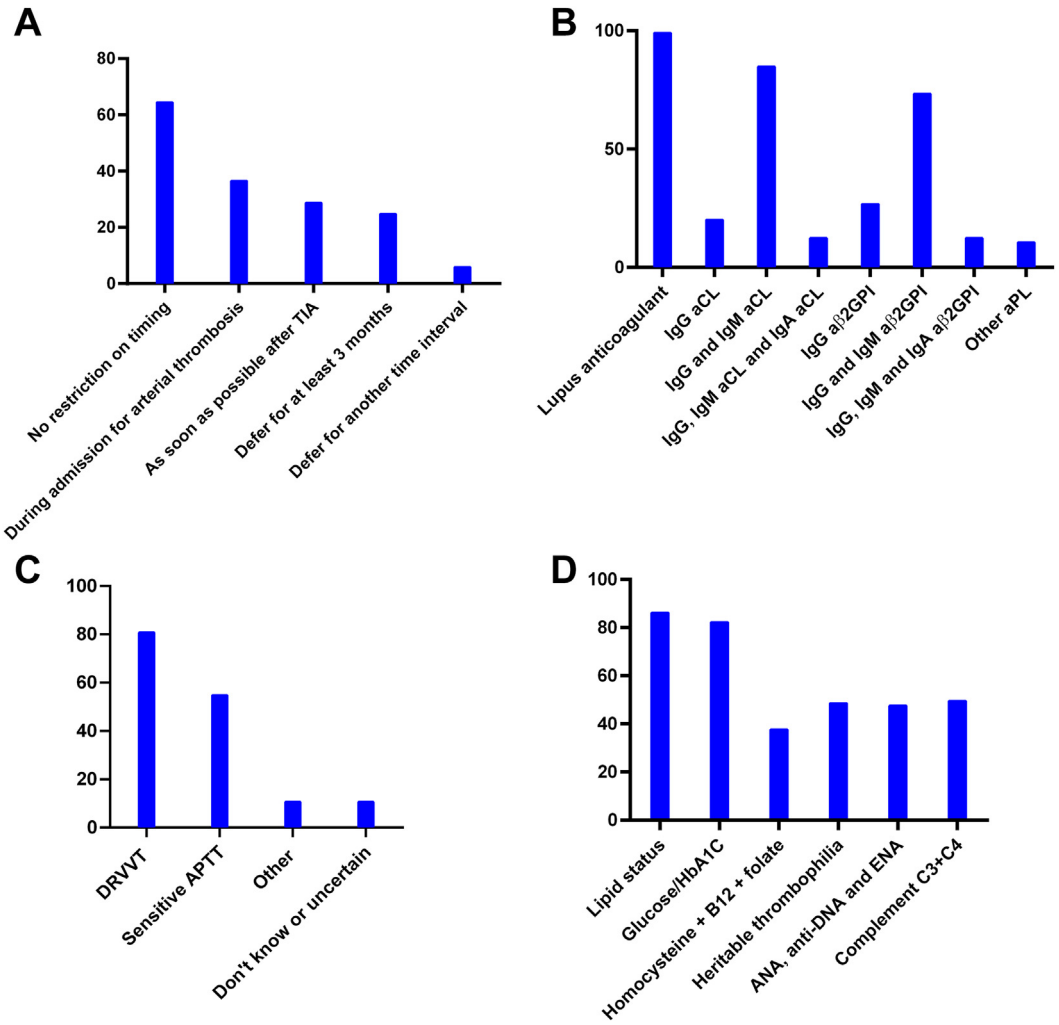

FIGURE 2 (A) Suggested options for timing of testing for antiphospholipid antibodies (aPL) after acute arterial thrombosis (101 respondents). (B) Repertoire of aPL tests requested (105 respondents). (C) Tests requested for LA in non-anticoagulated patients (104 respondents). (D) Laboratory tests other than aPL included in the routine assessment for patients with antiphospholipid syndrome-associated acute ischaemic stroke, transient ischaemic attack (TIA), or other brain ischaemic injury (101 respondents). The y-axis indicates percentage of respondents. aβ2GPI, anti-β2 glycoprotein I antibodies; aCL, anticardiolipin antibodies; ANA, antinuclear antibodies; APTT, activated partial thromboplastin time; C3 & C4, complement C3 and C4; dRVVT, dilute Russell's viper venom time; anti-DNA & ENA, antibodies to deoxyribonucleic acid and to extractable nuclear antigen; IgA, immunoglobulin A; IgG, immunoglobulin G; IgM immunoglobulin M.

Data pertaining to the numbers of adult patients (aged >18 years) assessed annually with AIS, TIA, brain infarcts on imaging not in the context of AIS, WMH, cognitive impairment, and dementia and the proportion of these who were tested for aPL, are shown in Supplementary Figures S2 and S3, respectively. Analogous data for the numbers of patients assessed annually with APS-associated AIS, TIA, brain infarcts on imaging not in the context of AIS, WMH, cognitive impairment, and dementia are also shown in the Supplementary Figure S4). The results include limited information on cerebral venous sinus thrombosis and arterial thromboembolism in sites outside the brain.

Survey responses are expressed as percentages followed by a fraction X/Y, where X is the number of affirmative responses for that option, and Y is the total number of responses to that question. Patients with APS and AIS, TIA, or other brain ischemic injury were seen in a dedicated APS clinic in 24.5% (26 of 106) of institutions. Forty-three percent (46 of 107) had a multidisciplinary team (MDT) structure in place; MDT composition was varied, with the majority including ≥2 from hematology, rheumatology, and neurology/stroke services.

3.2 | Testing for aPL and other laboratory parameters in adult patients with ischemic stroke, TIA, or other brain ischemic injury

In the majority of centers, aPL testing is performed in a specialist hemostasis laboratory in a university hospital (66.4%, 71 of 107) or nonuniversity hospital (15%, 16 of 107), with samples sent to another laboratory in 15% (16 of 107).

3.2.1 | Criteria for testing for aPL

The proportion of sites with local guidance or policy on testing for aPL according to presenting diagnosis (AIS, TIA, head imaging findings [eg, brain infarcts and WMH], vascular cognitive impairment, or dementia) was 18% to 62%, depending on the condition (Figure 1A). The percentage of clinicians who test for aPL in patients with AIS, TIA, other brain ischemic injury, or arterial occlusion in other sites is shown in Figure 1B. The majority tested for aPL in patients with conditions recognized to be associated with aPL, regardless of a history of ischemic stroke, TIA, or other brain ischemic injury (Figure 1C). Many clinicians excluded patients with alternative causes for stroke or TIA from aPL testing (Figure 1D).

3.2.2 | Age cutoffs and timing of testing for aPL

The majority of respondents (72.8%; 75 of 103) had no age cutoff for aPL testing in patients with AIS or TIA, or for conditions associated with APS (91%; 93 of 102). Of those who employ an age cutoff in the context of AIS or TIA, over half (57.1%, 16 of 28) use an age cutoff of 50 years, with the cutoff ranging from 40 to 75 years (Supplementary Figure S5). Many respondents (64.4%, 65 of 101) imposed no restriction on when to test for aPL after an acute arterial thrombotic event, advising to test at any time after the acute event, with suggested options shown in Figure 2A.

3.2.3 | Tests for aPL

The range of aPL tests requested is shown in Figure 2B. For LA testing in patients not undergoing anticoagulation, 66% (68 of 103) perform a coagulation screen: prothrombin time, activated partial thromboplastin time (APTT), thrombin time, and fibrinogen. In non-anticoagulated patients, 80.8% (84 of 104) request the dilute Russell's viper venom time test (dRVVT) and 54.8% (57 of 104) request a sensitive APTT (low phospholipids and silica as activator) (Figure 2C). In patients on low-molecular-weight heparin (LMWH), 78.6% (77 of 98) request dRVVT and 16.3% (16 of 98) request a sensitive APTT; 34% (34 of 100) temporarily omit LMWH/unfractionated heparin (UFH) routinely prior to blood sampling; and 42% (42 of 100) routinely aim to collect the blood sample during the trough period. Only 20% (20 of 100) request a concomitant LMWH/UFH anti-Xa level.

Warfarin/other vitamin K antagonist (VKA) is stopped prior to LA testing, with temporary heparin cover by 37.6% (38 of 101) of respondents whereas 50.5% (51 of 101) do not stop warfarin/VKA prior to LA testing. The dRVVT is the LA test performed in patients on warfarin/other VKA by 68.7% (68 of 99), with a concomitant international normalized ratio (INR) requested by only 36.6% (37 of 101) overall, and the range of INR cutoff for use of dRVVT ranging from <1.4 to 4.0, or no cutoff (Supplementary Figure S6). Sixty-six percent (42 of 64) perform the dRVVT on a 50:50 mix with normal plasma in patients on VKA. The Taipan/Ecarin test is performed by only 11.1% (11 of 99).

In patients on direct oral anticoagulants (DOACs), 35.6% (36 of 101) discontinue the DOAC for at least 48 hours, or longer in patients with renal impairment prior to testing for LA; 20% (20 of 101) ensure that the sample for LA testing is collected during the DOAC trough period and 8.9% (9 of 101) request a concomitant DOAC activity test. DOAC absorbent is used for LA testing by 11.9% (12 of 101). In patients on direct anti-Xa inhibitors, 55.9% (52 of 93) perform a dRVVT and 10.8% (10 of 93) a Taipan/Ecarin test, with alternative tests performed by 17.2% (16 of 93) and 34.4% (32 of 93) stating they did not know or were uncertain. Antiphosphatidylserine/prothrombin antibodies were performed by 6.7% (7 of 105) of respondents.

3.2.4 | Additional investigations

Laboratory tests other than aPL included in the routine assessment for APS-associated AIS, TIA or other brain ischemic injury are shown in Figure 2D. Seventy-five percent (75 of 100) advised that patients with APS and presumed cardioembolic stroke should be investigated for a patent foramen ovale (PFO), with investigation and management options advised in patients in whom a PFO was considered to be potentially causal shown in Figure 3B and 3C, respectively.

3.3 | Antithrombotic treatment

The decision to start antithrombotic treatment in patients with APS-associated AIS, TIA, other brain ischemic injury, or arterial thromboembolism in other sites was influenced by the aPL phenotype (Figure 4A). Over half (56.4%, 57 of 101) would start anticoagulation prior to establishing that aPL are persistently positive, with comments indicating that this might be contingent on clinical features (severity of event, antiplatelet therapy failure, evidence of an embolic source, and bleeding risk) and/or the laboratory aPL profile (perceived higher risk aPL profiles: triple positivity, a high titer of aPL, and LA positivity).

Indications for lifelong antithrombotic treatment are shown in Figure 4B. Lifelong antithrombotic treatment was advised by 83.5% (86 of 103) for a first APS-associated AIS and by 84.5% (87 of 103) for a recurrent APS-associated AIS. Antithrombotic treatment options for first APS-associated AIS are shown in Figure 3A. The majority (83.8%, 83 of 99) used standard-intensity warfarin/other VKA, with a target INR of 2.5 (range, 2.0-3.0), with (36.4%) or without (47.5%) low-dose aspirin (LDA) 75 to 100 mg once daily; 15.2% (15 of 99) used high-intensity warfarin/other VKA, with a target INR of 3.5 (range, 3.0-4.0).

For patients with APS-associated TIA, 80.4% (78 of 97) would consider anticoagulation if there is evidence of either acute ischemic

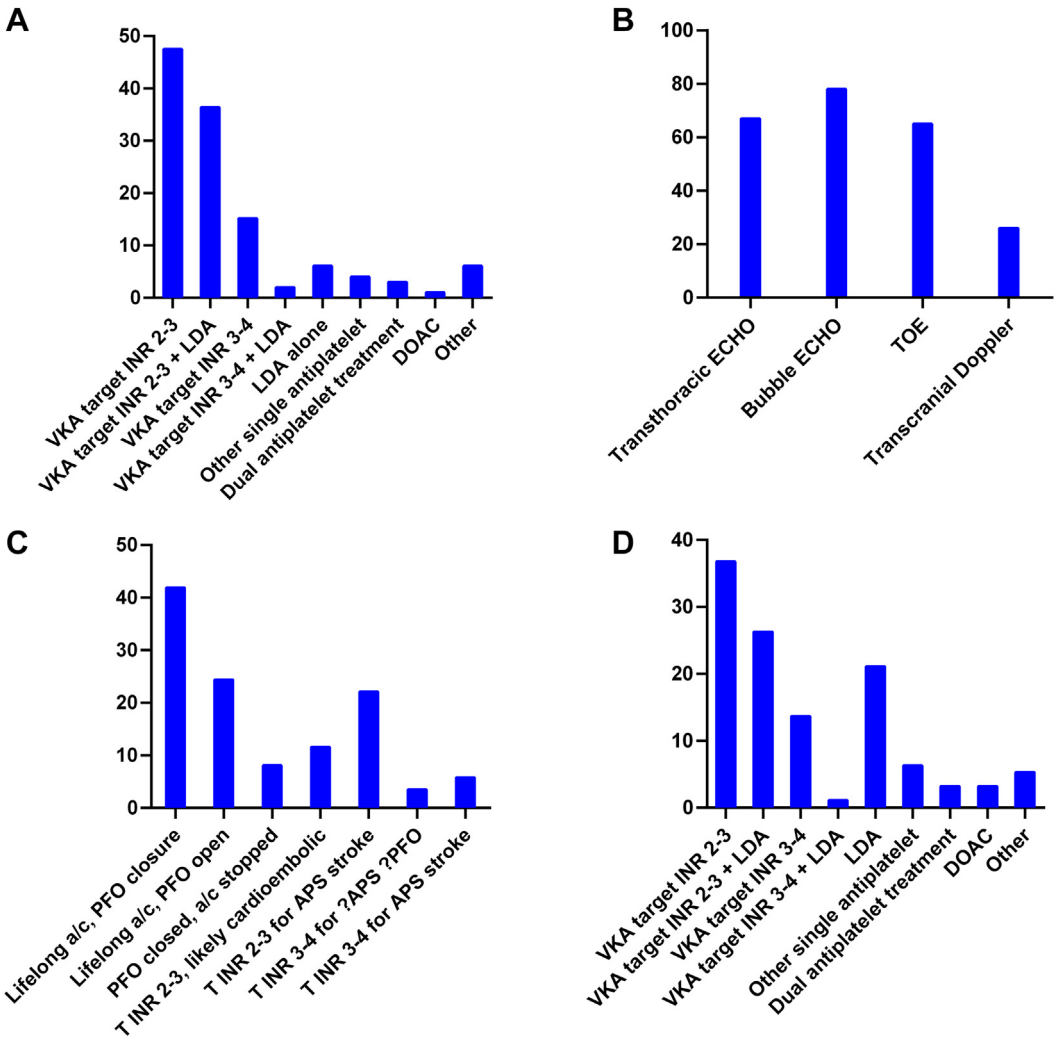

FIGURE 3 (A) Antithrombotic treatment for first antiphospholipid syndrome (APS)–associated acute ischemic stroke (99 respondents). Clopidogrel was the only single nonaspirin antiplatelet agent stated. (B) Investigations performed for patent foramen ovale (PFO): transthoracic echocardiography (ECHO), bubble ECHO, transesophageal echocardiography (TOE), and transcranial Doppler (100 respondents). (C) Management options advised in patients in whom a PFO was considered to be potentially causal (86 respondents). (D) Antithrombotic treatment options advised for APS-associated transient ischemic attack (95 respondents). Clopidogrel was the only single nonaspirin antiplatelet agent stated. The y-axis indicates percentage of respondents. DOAC, direct oral anticoagulant; INR, international normalized ratio; LDA, low-dose aspirin; T INR, target international normalized ratio; VKA, vitamin K antagonist.

or chronic ischemic injury (ie, established WMH, lacunae, or territorial cortical infarcts) on head magnetic resonance imaging (MRI), including diffusion-weighted imaging. Anticoagulation based on clinical history of confirmed TIA alone was advised by 26.8% (26 of 98). In patients with APS-associated TIA, 50.5% (52 of 103) advised antithrombotic treatment for the first APS-associated TIA, increasing to 72.8% (75 of 103) for recurrent TIA. Antithrombotic treatment options advised for APS-associated TIA are shown in Figure 3D. More than twice as many clinicians used single antiplatelet treatment as for AIS: 27.4% (26 of 95; 21.1% LDA) for TIA vs 10.1% (10 of 99) for ischemic stroke.

Antithrombotic treatments for patients with APS-associated established nonacute cerebral infarct(s) in the context of a history of AIS and for silent cerebral infarcts are shown in Figure 5A, B, respectively. Antithrombotic treatment for WMH of presumed vascular origin is shown in Figure 5C.

3.3.1 | Follow-up of patients with APS-associated ischemic stroke, TIA, other brain ischemic injury, and arterial thromboembolism outside of the brain

For the majority (87.8%, 86 of 98) of follow-up patients with APS-associated AIS, TIA, other brain ischemic injury, or arterial thromboembolism outside of the brain, long-term follow-up intervals varied: 3-monthly (21.2%, 18 of 85), 6-monthly (37.6%, 32 of 85), and annually (30.6%, 26 of 85). The majority (77.5%, 69 of 89) requested interval

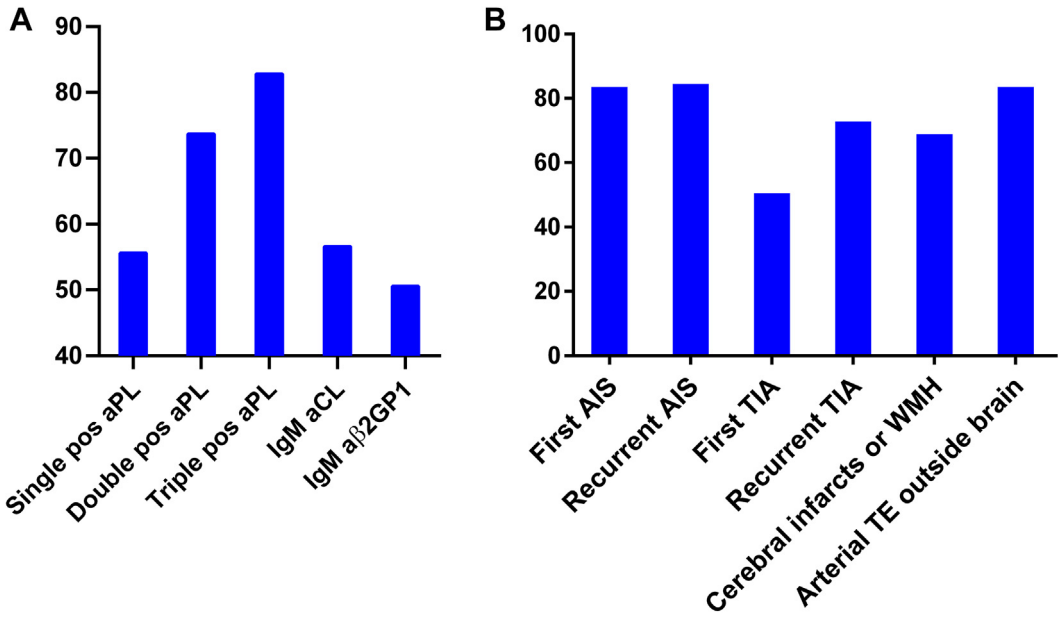

FIGURE 4 (A) Influence of antiphospholipid antibody (aPL) phenotype on the decision to start antithrombotic treatment in patients with antiphospholipid syndrome–associated acute ischemic stroke (AIS), transient ischemic attack (TIA), other brain ischemic injury, or arterial thromboembolism (TE) in other sites (99 respondents). (B) Indications for lifelong antithrombotic treatment for patients with antiphospholipid syndrome–associated AIS, TIA, cerebral infarcts or white matter hyperintensities (WMH), or arterial thromboembolism in sites outside the brain (103 respondents). The y-axis indicates percentage of respondents. aβ2GPI, anti-β2-glycoprotein I antibodies; aCL, anticardiolipin antibodies; IgM, immunoglobulin M; pos, positive.

head MRI only if the patient had neurologic symptoms to warrant this; 24.7% (22 of 89) requested head MRI to assess progress on the antithrombotic regimen, with the frequency of imaging generally between 6-monthly and 2-yearly, although some would scan only based on clinical features. Head MRI including susceptibility-weighted imaging and fluid-attenuated inversion recovery was requested by 47% (37 of 79). The majority (80.5%, 70 of 87) of nonneurologists referred patients with APS and suspected cognitive impairment for neurologic assessment and formal cognitive testing.

During pregnancy, the majority (61.9%, 60 of 97) use standard-intensity LMWH, with 19.6% (19 of 97) using high-intensity LMWH for AIS; and 56.3% (54 of 96) and 18.8% (18 of 96), respectively, using standard- and high-intensity LMWH for patients with previous AIS (Figure 6A, B). A generally similar approach as for AIS or previous AIS was used for patients with acute or previous arterial thromboembolism outside the brain, respectively (Supplementary Figure 7A, B). Two-thirds (66.7%, 64 of 96) used split (ie, divided dose administered twice daily) treatment dose LMWH during pregnancy. Almost half (46.9%, 45 of 96) monitored anti-Xa levels during pregnancy. The majority (81.7%, 76 of 93) used LDA during pregnancy (Figure 6C). The main reason given for aspirin use in addition to anticoagulation among respondents was prevention of pregnancy morbidity (preeclampsia, placental insufficiency, and pregnancy loss), with reduced thrombotic risk cited by a minority. Among those who do not routinely use LDA, reasons given included bleeding risk, lack of evidence, and need for guidance by specialists in obstetrics and gynecology.

4 | DISCUSSION

This survey has highlighted the diverse approaches to diagnosis and antithrombotic treatment of patients with APS and AIS, TIA, or other brain ischemic injury. The clinical importance of identifying these clinical manifestations of APS has been recognized in successive ISTH guidance documents [15,16] and the National Clinical Guideline for Stroke for the UK and Ireland [17]. The majority of clinicians (67%-83%, depending upon the indication) advised aPL testing in these patients, but this was not universal, and only 39% advised aPL testing in patients with vascular cognitive impairment or dementia. There was a general absence of local guidance defining criteria for aPL testing, with the greatest lack (82%) for cognitive impairment/dementia, with cognitive impairment common in patients with aPL, and associated with WMH, ischemic lesions, and cortical atrophy [5].

Many clinicians excluded patients with alternative risk factors for AIS or TIA, such as hypercholesterolemia, hypertension, atrial fibrillation, or PFO, from aPL testing. The adjusted global APS score suggests that traditional cardiovascular risk factors can exacerbate arterial thrombotic risk associated with aPL [18]. PFO, incidence approximately 25% in the general population and approximately 40% in patients with cryptogenic stroke [19], is addressed below.

Most respondents did not have an age cutoff for aPL testing. The suggested age cutoff of <50 years in the ISTH guidance [16] and the National Clinical Guideline for Stroke for the UK and Ireland [17] aims to limit aPL testing to those who are likely to have APS as APS is

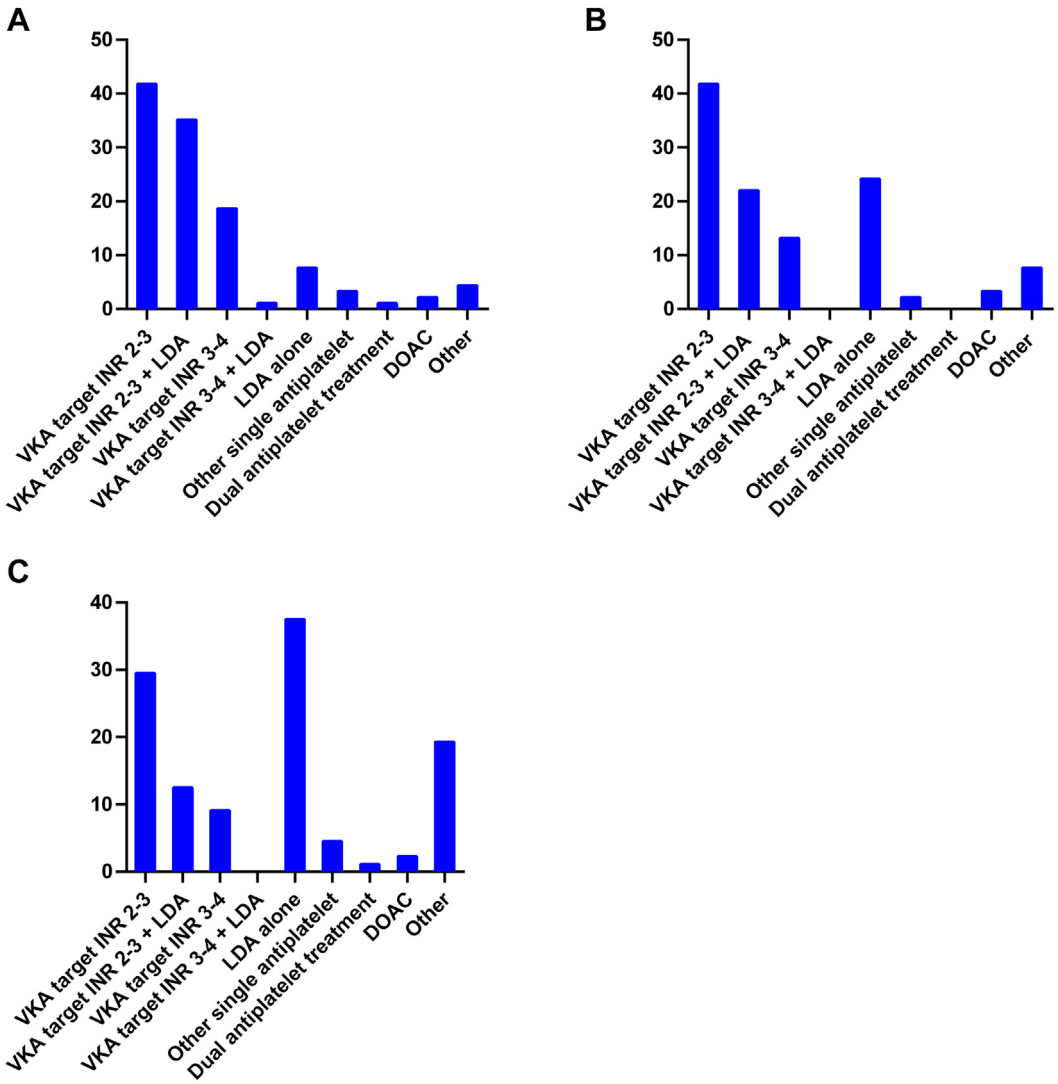

FIGURE 5 (A) Antithrombotic treatment advised for patients with antiphospholipid syndrome (APS)–associated established nonacute cerebral infarct(s) in the context of a history of acute ischemic stroke (91 respondents). (B) Antithrombotic treatment advised for APS-associated silent cerebral infarcts (91 respondents). (C) Antithrombotic treatment advised for APS-associated white matter hyperintensities of presumed vascular origin (88 respondents). The y-axis indicates percentage of respondents. DOAC, direct oral anticoagulant; INR, international normalized ratio; LDA, low-dose aspirin; VKA, vitamin K antagonist.

typically diagnosed in younger patients aged <50 years [6]. However, APS may occur in older individuals. In a population-based study, age-specific incidence rates of APS peaked at age ≥75 years and APS incidence increased significantly with age (P = .007) [20]. In the Elderly-Phospholipid study (n = 44), stroke was the most common manifestation at diagnosis (38.6%). Over a mean follow-up of 3.8 years, 20.5% (n = 8) had a new arterial event, despite antithrombotic treatment with antiplatelet agents and/or oral anticoagulants [21].

Testing for aPL did not conform to the ISTH guidance on many points. Testing for all three criteria aPL is required for accurate diagnosis [22,23], with LA, immunoglobulin G (IgG) and immunoglobulin M (IgM) anticardiolipin antibodies (aCL), and anti-β2-glycoprotein I antibodies (aβ2GPI) requested by 99%, 84.8%, and 73.3%, respectively. Notably, 20% and 26.7% tested only for IgG aCL and aβ2GPI, respectively, although over half would treat patients with only IgM aCL (56.6%) or aβ2GPI (50.5%) with antithrombotic treatment. In a multicenter study including 1008 individuals, IgM was reported to have no diagnostic value for thrombotic APS (the data supported testing in obstetric APS), although considered useful for risk stratification. However, patients who experience stroke were under-represented, comprising 55 of 259 patients with thrombotic APS [24]. A retrospective study reported that isolated IgM aPL (in 14.3%: 24 of 168 patients) showed an association with AIS [25]. *In vitro* and animal studies suggest that IgM aPL might be potentially thrombogenic [26–28]. A minority (12.4%) test for immunoglobulin A aCL or aβ2GPI, not included in the current guidance for aPL testing [22], although reported to add to thrombotic risk in patients with SLE [29].

The dRVVT was performed for LA detection in nonanticoagulated patients by the majority (80.8%), with a sensitive APTT performed by 54.8%. ISTH guidance on LA testing recommends 2 tests based on

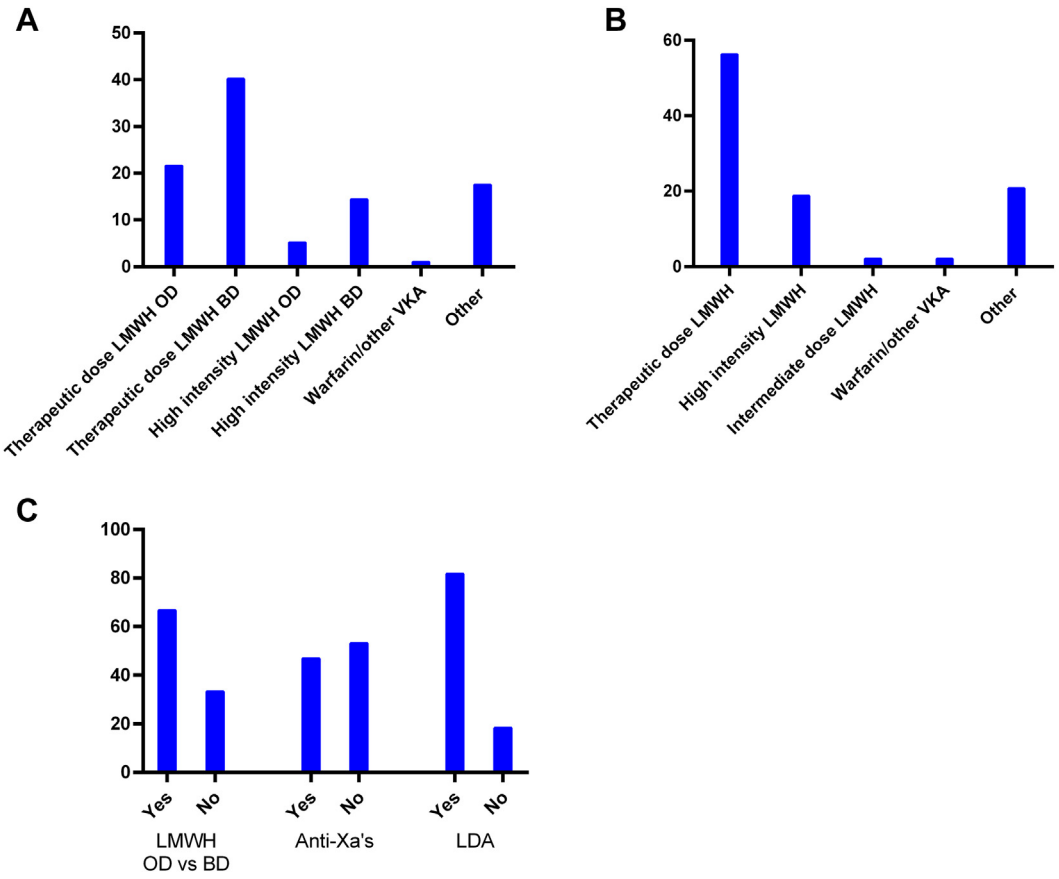

FIGURE 6 (A) Antithrombotic treatment during pregnancy for patients with antiphospholipid syndrome–associated acute ischemic stroke (97 respondents). (B) Antithrombotic treatment during pregnancy for patients with antiphospholipid syndrome–associated previous acute ischemic stroke (96 respondents). (C) Use of once daily (OD) vs split dose (twice daily [BD]) low-molecular-weight-heparin (LMWH) (97 respondents), use of anti-Xa monitoring tests (96 respondents), and use of low-dose aspirin (LDA) (93 respondents). The y-axis indicates percentage of respondents. VKA, vitamin K antagonist.

different principles [16]. In patients on LMWH or UFH, only 20% measure anti–factor Xa activity together with LA testing, as recommended in ISTH guidance [16]. The guidance states that in VKA-treated patients (INR, <3.0) LA testing is discouraged, and if attempted, results should be interpreted with care [16]. The dRVVT is the LA test performed in patients on VKAs by 68.7%, with a concomitant INR requested by only 36.6%. Should VKA be stopped prior to LA testing? There is no ideal option [30]. Notably, the Taipan/Ecarin test, performed by a minority (11.1%) of respondents, is validated for LA testing in patients on VKAs and DOAC anti-Xa inhibitors [31]. LA testing on DOACs did not conform to ISTH guidance. The dRVVT, used by 55.9% in patients on direct anti-Xa inhibitors, may produce false positive LA results in patients on these agents, unless performed after DOAC adsorption [32,33], with DOAC absorption used by only 11.9%. In patients on DOAC anti-Xa inhibitors, the Taipan/Ecarin test is performed in a minority (10.8%) of centers. Only 8.9% request a concomitant DOAC activity test, recommended by the ISTH [16]. The use of DOAC absorbent remains limited.

There is an uncertain relationship between heritable thrombophilia, screened for by 48.5%, and AIS or TIA, with a reported incidence of 6.8% in 628 patients [34], and no demonstrable influence in APS-associated thrombosis [35]. AIS is a major cause of morbidity, mortality, and disability in patients with SLE who have a 2-fold increase in the risk of stroke. This risk increases to up to 10-fold in patients aged <50 years. However, testing for SLE, important in patients with AIS [36], was undertaken by <50%. Approximately 38% measured plasma homocysteine. An RCT showed that lowering homocysteine with folic acid and vitamins B6 and B12 reduced the overall risk of stroke, but not stroke severity or disability [37].

There was variation with regard to aPL phenotype as a trigger to initiate antithrombotic treatment. Although triple aPL-positivity is associated with a high risk of recurrent thrombosis [38], thrombotic risk may not increase linearly with the number of positive aPL tests [39]. The timing of starting anticoagulation varied. Over half (56.4%) would start anticoagulation prior to establishing that aPL are persistently positive in patients with AIS or TIA. Early aPL assessment after AIS or TIA can ensure that testing patients is not missed, and might benefit patients through early institution of anticoagulation. However, the influence of early vs later initiation of anticoagulation on the outcome following acute stroke, is unknown [16]. LA results should be interpreted with caution in the acute phase after AIS: elevated factor VIII levels can shorten the APTT, leading to false negative results [40],

while elevated C-reactive protein levels may lead to false positive results [41].

The majority of respondents conformed to European Alliance of Associations for Rheumatology guidelines on antithrombotic treatment for APS-associated ischemic stroke [42]. This guidance, underpinned by a systematic review [14], recommends VKA, at a target INR of 2.5 (range, 2-3), with or without LDA, or VKA at a target INR of 3.5 (range, 3-4) for patients with a first arterial thrombosis, considering the individual's risk of bleeding and recurrent thrombosis [14,42]. In a prospective cohort study of 1000 patients with APS, in which approximately 20% of patients with APS had stroke and 11% of patients with APS had TIA at baseline, 25% of patients on antithrombotic treatment developed thrombosis over 5 to 10 years of follow-up (5.3% AIS and 4.7% TIA) [43]. Two RCTs comparing standard-intensity vs high-intensity warfarin in patients with thrombotic APS concluded that standard-intensity warfarin is appropriate for patients with thrombotic APS. However, in both studies, patients with arterial thrombotic APS were underrepresented: 44 of 109 (34 arterial only) in one [44] and 27 of 114 in the other [45]. A systematic review and meta-analysis reported that 22% of patients with initial stroke or other arterial occlusion on VKA or DOAC (95% CI, 0.15-0.31), and 21.6% of patients receiving antiplatelet therapy (95% CI, 0.18-0.26), developed recurrent thromboembolism over 2 years follow-up [46]. A further review and meta-analysis reported that combined antithrombotic therapy (VKA plus single antiplatelet treatment) may be more effective than single agents for secondary prophylaxis for APS-associated arterial thrombosis, and that dual antiplatelet treatment may be more effective than single agents [47].

DOACs (rivaroxaban and apixaban) at standard intensity are reported in some RCTs to be associated with recurrent arterial thrombosis in patients with APS, with a key risk factor being previous arterial thrombosis, [48–50], and their use is not recommended in patients with APS-associated AIS [51,52]. Approximately 10% of patients with a first venous thromboembolism (VTE) are estimated to have aPL [3,53,54], thus in the phase 3 trials in general population patients with VTE, where standard-intensity rivaroxaban and apixaban were noninferior to standard-intensity warfarin (target INR 2.5) with no increase in thrombosis recurrence [55], patients with undiagnosed APS were likely included. Systematic review of DOAC APS RCTs, which included the key DOAC trials in patients with APS [48–50,56] indicated that DOACs are not associated with an increased risk of VTE compared with warfarin [57]. However, there is no precedent to use standard-intensity DOACs in patients with APS and arterial thrombosis. Studies in animal models indicate that increased rivaroxaban anti-Xa activity is required to protect against arterial vs venous thrombosis [58]. The Rivaroxaban in Stroke Patients with APS RCT (RISAPS) is assessing the efficacy of high-intensity rivaroxaban 15 mg twice daily vs high-intensity warfarin (target INR, 3.5) in patients with APS and previous AIS or other brain ischemic injury (ClinicalTrials.gov Identifier: NCT03684564).

Views differed on PFO closure (41.9% opted for closure with lifelong anticoagulation and 24.4% opted for lifelong anticoagulation without PFO closure). Two observational studies on patients with cryptogenic stroke/TIA with thrombophilia (APS in 29.8% [n = 134] and 31% [n = 136]) found a decreased risk of recurrent stroke in patients with thrombophilia who underwent PFO closure (relative risk, 0.17; 95% CI, 0.07-0.44) [59,60]. Society for Cardiovascular Angiography and Interventions guidelines recommend that patients with thrombophilia and a prior PFO-associated stroke should be managed with PFO closure plus lifelong anticoagulation rather than anticoagulation alone [61].

In patients with a first APS-associated TIA, only 50.5% advised antithrombotic treatment. First TIA is associated with a high risk of subsequent TIA/AIS, estimated at up to 20% within 90 days [62] and is an important opportunity to institute secondary prevention therapy. For patients with APS-associated TIA, the majority (80%) based the decision to use antithrombotic treatment on evidence of acute or chronic brain ischemic injury on head MRI, including diffusion-weighted imaging, rather than clinical history alone. The diagnosis of TIA can be challenging, with significant interrater variability. TIAs are brief episodes of neurological disturbance caused by focal brain or retinal ischaemia with clinical symptoms typically lasting less than one hour and without evidence of acute infarction [63].

In patients with APS-associated silent cerebral infarcts, for whom approximately two-thirds advised VKA with or without LDA and approximately one-third advised single antiplatelet treatment, mainly aspirin, alone, there are no robust trial data on antithrombotic treatment for patients without APS. In patients with WMH of presumed vascular origin, approximately two-thirds based the decision to administer antithrombotic treatment on whether an expert clinical opinion (neurologist/stroke physician) would consider this a reasonable treatment option; approximately 20% would not base antithrombotic treatment decisions on WMH. As cognitive dysfunction is common in APS [5], if suspected, patients with APS should be referred for neurological assessment and formal cognitive testing, as was undertaken by the majority (80.5%) of nonneurologists. Long-term follow-up of patients in the aforementioned categories, undertaken by the majority (86.7%), usually 6-monthly to annually (68.2%), enables review of management after recurrent thrombotic episodes. Approximately one-quarter request interval head MRI scans to assess progress on the antithrombotic regimen. A retrospective study demonstrated development of new brain lesions, predominantly ischemic, in approximately 45% of individuals with aPL, with less progression in those with a target INR of >3.0 [64]. Almost half (46.8%) request head MRI with susceptibility-weighted imaging and fluid-attenuated inversion recovery, with the former being useful to detect hemorrhage/blood products, which may not be apparent on other brain MRI sequences, and the latter being particularly helpful in the detection of subtle changes at the periphery of the hemispheres and in the periventricular region.

The optimal dose regimen for LMWH during pregnancy in thrombotic APS is not established. Therapeutic-dose heparin during pregnancy, as recommended in European Alliance of Associations for Rheumatology guidelines (EULAR) [42], appears prudent. Limited data suggest that patients with a history of APS-related cerebrovascular events are at increased risk of recurrence during pregnancy [65,66].

Consequently, high-intensity adjusted dose LMWH may be required, as was used by 16.5% of respondents. The optimal dosage regimen of LMWH during pregnancy for treatment/secondary thromboprophylaxis of arterial and venous thrombosis and the value and role of anti-Xa monitoring merit further investigation [67].

This survey had several limitations. It is possible that there was bias with regard to the responding health care professionals, who were from diverse backgrounds, including hematologists, rheumatologists, and neurologists, with the majority being university hospital–based. However, it seems likely that the majority of patients with APS are managed in these settings. The survey did not include enquiry about the impact of concomitant VTE on decision making in patients with APS and arterial thromboembolism. We recognize that it is important to address this complex situation in a guidance document. The survey did not include questions about additional therapy for cardiovascular risk factors. Checking that lipid status and hypertension are optimized following stroke should be universal [68].

5 | CONCLUSIONS

This survey has provided a comprehensive overview of the current status of diagnosis and antithrombotic treatment of APS-associated AIS, TIA, or other brain ischaemic injury and limited information on arterial thromboembolism in other sites.

There was generally good agreement on several aspects, including which patients to test for aPL, use of lifelong VKA for AIS or TIA, and formal cognitive assessment for suspected cognitive impairment. There was less agreement on other aspects, including aPL testing for brain ischemic injury other than AIS/TIA or if an alternative cause for stroke or TIA exists; which aPL tests to perform, their timing and age cutoff; aPL phenotype to trigger antithrombotic treatment; management approach for PFO; antithrombotic treatment for first TIA or WMH; specifications for head MRI; LMWH dosing/anti-Xa monitoring in pregnancy. The survey highlighted that approximately 25% practice at dedicated APS clinics and <50% have an MDT for patients with APS. Much of the variation in practice reflects the lack of evidence-based recommendations. The survey results should inform the development of a more uniform multidisciplinary consensus approach to diagnosis and antithrombotic treatment.

ACKNOWLEDGMENTS

The authors thank the International Society on Thrombosis and Haemostasis Lupus Anticoagulant/Antiphospholipid Antibodies Scientific and Standardisation Committee Subcommittee (Chair: Hannah Cohen; Cochairs: M. Laura Bertolaccini, Katrien M. J. Devreese, Doruk Erkan, Johanna Gebhart, Sam Schulman, and Savino Sciascia) for their review and endorsement of this communication. We also thank Cary Clark and Shannon Brooks from the International Society on Thrombosis and Haemostasis team for helping us with the set-up and registration of the questionnaire.

AUTHOR CONTRIBUTIONS

H.C. devised and analyzed the survey questionnaire, wrote the first draft of the manuscript, and undertook critical revision of the manuscript. D.A.I, D.J.W., A.C., and K.M.J.D. devised the questionnaire and undertook critical revision of the manuscript. P.M. undertook critical revision of the manuscript.

DECLARATION OF COMPETING INTERESTS

H.C. reports lecture fees from Technoclone, paid to University College London Hospitals Charity. M.C. reports consulting for Bayer for products other than rivaroxaban. M.K. reports being GSK Global Medical Expert (Lupus), Dubai, United Arab Emirates. The other authors and remaining study group members have no competing interests to disclose.

REFERENCES

[1] World Health Organization. The top 10 causes of death. https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death; 2020 [accessed November 1, 2022].
[2] Adamson J, Beswick A, Ebrahim S. Is stroke the most common cause of disability? *J Stroke Cerebrovasc Dis*. 2004;13:171–7.
[3] Andreoli L, Chighizola CB, Banzato A, Pons-Estel GJ, Ramire de Jesus G, Erkan D. Estimated frequency of antiphospholipid antibodies in patients with pregnancy morbidity, stroke, myocardial infarction, and deep vein thrombosis: a critical review of the literature. *Arthritis Care Res*. 2013;65:1869–73.
[4] Sciascia S, Sanna G, Khamashta MA, Cuadrado MJ, Erkan D, Andreoli L, Bertolaccini ML, Action APS. The estimated frequency of antiphospholipid antibodies in young adults with cerebrovascular events: a systematic review. *Ann Rheum Dis*. 2015;74:2028–33.
[5] Donnellan C, Cohen H, Werring DJ. Cognitive dysfunction and associated neuroimaging biomarkers in antiphospholipid syndrome: a systematic review. *Rheumatology (Oxford)*. 2021;61:24–41.
[6] Cervera R, Piette JC, Font J, Khamashta MA, Shoenfeld Y, Camps MT, Jacobsen S, Lakos G, Tincani A, Kontopoulou-Griva I, Galeazzi M, Meroni PL, Derksen RH, de Groot PG, Gromnica-Ihle E, Baleva M, Mosca M, Bombardieri S, Houssiau F, Gris JC, et al. Antiphospholipid syndrome: clinical and immunologic manifestations and patterns of disease expression in a cohort of 1,000 patients. *Arthritis Rheum*. 2002;46:1019–27.
[7] Debette S, Markus HS. The clinical importance of white matter hyperintensities on brain magnetic resonance imaging: systematic review and meta-analysis. *BMJ*. 2010;341:c3666.
[8] Nazir S, Tachamo N, Lohani S, Hingorani R, Poudel DR, Donato A. Acute myocardial infarction and antiphospholipid antibody syndrome: a systematic review. *Coron Artery Dis*. 2017;28:332–5.
[9] Tektonidou MG. Antiphospholipid syndrome nephropathy: from pathogenesis to treatment. *Front Immunol*. 2018;9:1181.
[10] Gavier B, Vazquez F, Gandara E. Antiphospholipid antibodies and lower extremity peripheral arterial disease—a systematic review and meta-analysis. *Vasa*. 2016;45:325–30.
[11] Petri M. Epidemiology of the antiphospholipid antibody syndrome. *J Autoimmun*. 2000;15:145–51.
[12] Del Carmelo Gracio Tello B, Jones A, Raine C, Isenberg D. Systemic lupus erythematosus: detailed anatomy of a cohort (follow-up for more than 35 years). http://acrabstracts.org/abstract/systemic-lupus-erythematosus-detailed-anatomy-of-a-cohort-follow-up-for-more-than-35-years/; 2016 [accessed November 1, 2022].
[13] Ruiz-Irastorza G, Egurbide MV, Ugalde J, Aguirre C. High impact of antiphospholipid syndrome on irreversible organ damage and

survival of patients with systemic lupus erythematosus. *Arch Intern Med*. 2004;164:77–82.

[14] Tektonidou MG, Andreoli L, Limper M, Tincani A, Ward MM. Management of thrombotic and obstetric antiphospholipid syndrome: a systematic literature review informing the EULAR recommendations for the management of antiphospholipid syndrome in adults. *RMD Open*. 2019;5:e000924.

[15] Pengo V, Tripodi A, Reber G, Rand JH, Ortel TL, Galli M, De Groot PG. Subcommittee on Lupus Anticoagulant/Antiphospholipid Antibody of the Scientific and Standardisation Committee of the International Society on Thrombosis and Haemostasis. Update of the guidelines for lupus anticoagulant detection. Subcommittee on Lupus Anticoagulant/Antiphospholipid Antibody of the Scientific and Standardisation Committee of the International Society on Thrombosis and Haemostasis. *J Thromb Haemost*. 2009;7:1737–40.

[16] Devreese KMJ, de Groot PG, de Laat B, Erkan D, Favaloro EJ, Mackie I, Martinuzzo M, Ortel TL, Pengo V, Rand JH, Tripodi A, Wahl D, Cohen H. Guidance from the Scientific and Standardization Committee for lupus anticoagulant/antiphospholipid antibodies of the International Society on Thrombosis and Haemostasis: update of the guidelines for lupus anticoagulant detection and interpretation. *J Thromb Haemost*. 2020;18:2828–39.

[17] National Clinical Guideline for Stroke for the UK and Ireland. London: Intercollegiate Stroke Working Party; 2023 May 4. Available at: www.strokeguideline.org. [accessed July 19, 2023]

[18] Radin M, Sciascia S, Erkan D, Pengo V, Tektonidou MG, Ugarte A, Meroni P, Ji L, Belmont HM, Cohen H, Ramires de Jesús G, Branch DW, Fortin PR, Andreoli L, Petri M, Rodriguez E, Rodriguez-Pinto I, Knight JS, Atsumi T, Willis R, et al. The adjusted global antiphospholipid syndrome score (aGAPSS) and the risk of recurrent thrombosis: results from the APS ACTION cohort. *Semin Arthritis Rheum*. 2019;49:464–8.

[19] Atianzar K, Casterella P, Zhang M, Gafoor S. Update on the management of patent foramen ovale in 2017: indication for closure and literature review. *US Cardiology Review*. 2017;11:75–9.

[20] Duarte-García A, Pham MM, Crowson CS, Amin S, Moder KG, Pruthi RK, Warrington KJ, Matteson EL. The epidemiology of antiphospholipid syndrome: a population-based study. *Arthritis Rheumatol*. 2019;71:1545–52.

[21] Grimaud F, Yelnik C, Pineton de Chambrun M, Amoura Z, Arnaud L, Costedoat Chalumeau N, Hachulla E, Lambert M, Roriz M, Sibilia J, Papo T, Sacre K. Clinical and immunological features of antiphospholipid syndrome in the elderly: a retrospective national multicentre study. *Rheumatology (Oxford)*. 2019;58:1006–10.

[22] Devreese KMJ, Ortel TL, Pengo V, de Laat B. Subcommittee on Lupus Anticoagulant/Antiphospholipid Antibodies. Laboratory criteria for antiphospholipid syndrome: communication from the SSC of the ISTH. *J Thromb Haemost*. 2018;16:809–13.

[23] Miyakis S, Lockshin MD, Atsumi T, Branch DW, Brey RL, Cervera R, Derksen RHWM, de Groot PG, Koike T, Meroni PL, Reber G, Shoenfeld Y, Tincani A, Vlachoyiannopoulos PG, Krilis SA. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). *J Thromb Haemost*. 2006;4:295–306.

[24] Chayoua W, Kelchtermans H, Gris JC, Moore GW, Musiał J, Wahl D, de Groot PG, de Laat B, Devreese KMJ. The (non-)sense of detecting anti-cardiolipin and anti-β2glycoprotein I IgM antibodies in the antiphospholipid syndrome. *J Thromb Haemost*. 2020;18:169–79.

[25] Urbanski G, Yelnik CM, Maillard H, Launay D, Dubucquoi S, Hachulla E, Hatron PY, Lambert M. Antiphospholipid syndrome with isolated isotype M anticardiolipin and/or anti-B2GPI antibody is associated with stroke. *Stroke*. 2018;49:2770–2.

[26] Pierangeli SS, Liu XW, Barker JH, Anderson G, Harris EN. Induction of thrombosis in a mouse model by IgG, IgM and IgA immunoglobulins from patients with the antiphospholipid syndrome. *Thromb Haemost*. 1995;74:1361–7.

[27] George J, Blank M, Levy Y, Meroni P, Damianovich M, Tincani A, Shoenfeld Y. Differential effects of anti-beta2-glycoprotein I antibodies on endothelial cells and on the manifestations of experimental antiphospholipid syndrome. *Circulation*. 1998;97:900–6.

[28] Rikarni Dharma R, Tambunan KL, Isbagyo H, Dewi BE, Acang N, Setiabudy R, Aman AK. Prothrombotic effect of anti-beta-2 glycoprotein-1 antibodies on the expression of tissue factor, thrombomodulin, and plasminogen activator inhibitor-1 in endothelial cells. *Acta Med Indones*. 2015;47:31–7.

[29] Demir S, Li J, Magder LS, Petri M. Antiphospholipid patterns predict risk of thrombosis in systemic lupus erythematosus. *Rheumatology (Oxford)*. 2021;60:3770–7.

[30] Tripodi A, Cohen H, Devreese KMJ. Lupus anticoagulant detection in anticoagulated patients. Guidance from the Scientific and Standardization Committee for lupus anticoagulant/antiphospholipid antibodies of the International Society on Thrombosis and Haemostasis. *J Thromb Haemost*. 2020;18:1569–75.

[31] Moore GW, Jones PO, Platton S, Hussain N, White D, Thomas W, Rigano J, Pouplard C, Gray E, Devreese KMJ. International multicenter, multiplatform study to validate Taipan snake venom time as a lupus anticoagulant screening test with ecarin time as the confirmatory test: communication from the ISTH SSC Subcommittee on Lupus Anticoagulant/Antiphospholipid Antibodies. *J Thromb Haemost*. 2021;19:3177–92.

[32] Arachchillage DRJ, Mackie IJ, Efthymiou M, Isenberg DA, Machin SJ, Cohen H. Interactions between rivaroxaban and antiphospholipid antibodies in thrombotic antiphospholipid syndrome. *J Thromb Haemost*. 2015;13:1264–73.

[33] Ratzinger F, Lang M, Belik S, Jilma-Stohlawetz P, Schmetterer KG, Haslacher H, Perkmann T, Quehenberger P. Lupus-anticoagulant testing at NOAC trough levels. *Thromb Haemost*. 2016;116:235–40.

[34] Alakbarzade V, Taylor A, Scully M, Simister R, Chandratheva A. Utility of current thrombophilia screening in young patients with stroke and TIA. *Stroke Vasc Neurol*. 2018;3:231–6.

[35] Berman H, Ugarte-Gil MF, Espinosa G, Tàssies D, Monteagudo J, Reverter JC, Cervera R. Can inherited thrombophilia modulate the clinical phenotype of patients with antiphospholipid syndrome? *Clin Exp Rheumatol*. 2013;31:926–32.

[36] Nikolopoulos D, Fanouriakis A, Boumpas DT. Cerebrovascular events in systemic lupus erythematosus: diagnosis and management. *Mediterr J Rheumatol*. 2019;30:7–15.

[37] Saposnik G, Ray JG, Sheridan P, McQueen M, Lonn E. Heart Outcomes Prevention Evaluation 2 Investigators. Homocysteine-lowering therapy and stroke risk, severity, and disability: additional findings from the HOPE 2 trial. *Stroke*. 2009;40:1365–72.

[38] Pengo V, Ruffatti A, Legnani C, Gresele P, Barcellona D, Erba N, Testa S, Marongiu F, Bison E, Denas G, Banzato A, Padayattil Jose S, Iliceto S. Clinical course of high-risk patients diagnosed with antiphospholipid syndrome. *J Thromb Haemost*. 2010;8:237–42.

[39] Bertin D, Camoin-Jau L, Veit V, Resseguier N, Lambert M, Buffet Delmas P, Heim X, Mège JL, Morange PE, Bardin N. Single or triple positivity for antiphospholipid antibodies in "carriers" or symptomatic patients: untangling the knot. *J Thromb Haemost*. 2021;19:3018–30.

[40] Ten Boekel E, Böck M, Vrielink GJ, Liem R, Hendriks H, de Kieviet W. Detection of shortened activated partial thromboplastin times: an evaluation of different commercial reagents. *Thromb Res*. 2007;121:361–7.

[41] Schouwers SM, Delanghe JR, Devreese KM. Lupus anticoagulant (LAC) testing in patients with inflammatory status: does C-reactive protein interfere with LAC test results? *Thromb Res*. 2010;125:102–4.

[42] Tektonidou MG, Andreoli L, Limper M, Amoura Z, Cervera R, Costedoat-Chalumeau N, et al. EULAR recommendations for the management of antiphospholipid syndrome in adults. *Ann Rheum Dis*. 2019;78:1296–304.

[43] Cervera R, Serrano R, Pons-Estel GJ, et al, Euro-Phospholipid Project Group (European Forum on Antiphospholipid Antibodies). Morbidity and mortality in the antiphospholipid syndrome during a 10-year period: a multicentre prospective study of 1000 patients. *Ann Rheum Dis*. 2015;74:1011–8.

[44] Finazzi G, Marchioli R, Brancaccio V, Schinco P, Wisloff F, Musial J, Baudo F, Berrettini M, Testa S, D'Angelo A, Tognoni G, Barbui T. A randomized clinical trial of high-intensity warfarin vs. conventional antithrombotic therapy for the prevention of recurrent thrombosis in patients with the antiphospholipid syndrome (WAPS). *J Thromb Haemost*. 2005;3:848–53.

[45] Crowther MA, Ginsberg JS, Julian J, Denburg J, Hirsh J, Douketis J, Laskin C, Fortin P, Anderson D, Kearon C, Clarke A, Geerts W, Forgie M, Green D, Costantini L, Yacura W, Wilson S, Gent M, Kovacs MJ. A comparison of two intensities of warfarin for the prevention of recurrent thrombosis in patients with the antiphospholipid antibody syndrome. *N Engl J Med*. 2003;349:1133–8.

[46] Ortel TL, Meleth S, Catellier D, Crowther M, Erkan D, Fortin PR, Garcia D, Haywood N, Kosinski AS, Levine SR, Phillips MJ, Whitehead N. Recurrent thrombosis in patients with antiphospholipid antibodies and an initial venous or arterial thromboembolic event: a systematic review and meta-analysis. *J Thromb Haemost*. 2020;18:2274–86.

[47] Aibar J, Schulman S. Arterial thrombosis in patients with antiphospholipid syndrome: a review and meta-analysis. *Semin Thromb Hemost*. 2021;47:709–23. Erratum in: Semin Thromb Hemost 2021;47:e1e2.

[48] Pengo V, Denas G, Zoppellaro G, Jose SP, Hoxha A, Ruffatti A, Andreoli L, Tincani A, Cenci C, Prisco D, Fierro T, Gresele P, Cafolla A, De Micheli V, Ghirarduzzi A, Tosetto A, Falanga A, Martinelli I, Testa S, Barcellona D, et al. Rivaroxaban vs warfarin in high-risk patients with antiphospholipid syndrome. *Blood*. 2018;132:1365–71.

[49] Ordi-Ros J, Sáez-Comet L, Pérez-Conesa M, Vidal X, Riera-Mestre A, Castro-Salomó A, Cuquet-Pedragosa J, Ortiz-Santamaria V, Mauri-Plana M, Solé C, Cortés-Hernández J. Rivaroxaban versus vitamin K Antagonist in antiphospholipid syndrome: a randomized noninferiority trial. *Ann Intern Med*. 2019;171:685–94.

[50] Woller SC, Stevens SM, Kaplan D, Wang TF, Branch DW, Groat D, Wilson EL, Armbruster B, Aston VT, Lloyd JF, Rondina MT, Elliott CG. Apixaban compared with warfarin to prevent thrombosis in thrombotic antiphospholipid syndrome: a randomized trial. *Blood Adv*. 2022;6:1661–70.

[51] Zuily S, Cohen H, Isenberg D, Woller SC, Crowther M, Dufrost V, Wahl D, Doré CJ, Cuker A, Carrier M, Pengo V, Devreese KMJ. Use of direct oral anticoagulants in patients with thrombotic antiphospholipid syndrome: guidance from the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. *J Thromb Haemost*. 2020;18:2126–37.

[52] Cohen H, Cuadrado MJ, Erkan D, Duarte-Garcia A, Isenberg DA, Knight JS, Ortel TL, Rahman A, Salmon JE, Tektonidou MG, Williams DJ, Willis R, Woller SC, Andrade D. 16th International Congress on Antiphospholipid Antibodies Task Force Report on antiphospholipid syndrome treatment trends. *Lupus*. 2020;29:1571–93.

[53] Kearon C, Parpia S, Spencer FA, Baglin T, Stevens SM, Bauer KA, Lentz SR, Kessler CM, Douketis JD, Moll S, Kaatz S, Schulman S, Connors JM, Ginsberg JS, Spadafora L, Bhagirath V, Liaw PC, Weitz JI, Julian JA. Antiphospholipid antibodies and recurrent thrombosis after a first unprovoked venous thromboembolism. *Blood*. 2018;131:2151–60.

[54] Miranda S, Park J, Le Gal G, Piran S, Kherani S, Rodger MA, Delluc A. Prevalence of confirmed antiphospholipid syndrome in 18-50 years unselected patients with first unprovoked venous thromboembolism. *J Thromb Haemost*. 2020;18:926–30.

[55] van Es N, Coppens M, Schulman S, Middeldorp S, Büller HR. Direct oral anticoagulants compared with vitamin K antagonists for acute venous thromboembolism: evidence from phase 3 trials. *Blood*. 2014;124:1968–75.

[56] Cohen H, Hunt BJ, Efthymiou M, Arachchillage DR, Mackie IJ, Clawson S, Sylvestre Y, Machin SJ, Bertolaccini ML, Ruiz-Castellano M, Muirhead N, Doré CJ, Khamashta M, Isenberg DA. RAPS trial investigators. Rivaroxaban versus warfarin to treat patients with thrombotic antiphospholipid syndrome, with or without systemic lupus erythematosus (RAPS): a randomised, controlled, open-label, phase 2/3, non-inferiority trial. *Lancet Haematol*. 2016;3:e426–36.

[57] Dufrost V, Wahl D, Zuily S. Direct oral anticoagulants in antiphospholipid syndrome: meta-analysis of randomized controlled trials. *Autoimmun Rev*. 2021;20:102711.

[58] Perzborn E, Strassburger J, Wilmen A, Pohlmann J, Roehrig S, Schlemmer KH, Straub A. In vitro and in vivo studies of the novel antithrombotic agent BAY 59-7939—an oral, direct Factor Xa inhibitor. *J Thromb Haemost*. 2005;3:514–21.

[59] Liu K, Song B, Palacios IF, Inglessis-Azuaje I, Deng W, McMullin D, Wang X, Lo EH, Xu Y, Buonanno FS, Ning M. Patent foramen ovale attributable cryptogenic embolism with thrombophilia has higher risk for recurrence and responds to closure. *JACC Cardiovasc Interv*. 2020;13:2745–52.

[60] Buber J, Guetta V, Orion D, Lubetsky A, Borik S, Vatury O, Israel A. Patent foramen ovale closure among patients with hypercoagulable states maintained on antithrombotic therapy. *Cardiology*. 2021;146:375–83.

[61] Kavinsky CJ, Szerlip M, Goldsweig AM, Amin Z, Boudoulas KD, Carroll JD, Coylewright M, Elmariah S, MacDonald LA, Shah AP, Spies C, Tobis JM, Messé SR, Senerth E, Falck-Ytter Y, Babatunde I, Morgan RL. SCAI guidelines for the management of patent foramen ovale. *J Soc Cardiovasc Angiogr Interv*. 2022;1:100039.

[62] Coull AJ, Lovett JK, Rothwell PM, Oxford Vascular Study. Population based study of early risk of stroke after transient ischaemic attack or minor stroke: implications for public education and organisation of services. *BMJ*. 2004;328:326.

[63] Kernan WN, Ovbiagele B, Black HR, Bravata DM, Chimowitz MI, Ezekowitz MD, et al. American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, and Council on Peripheral Vascular Disease. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2014;45:2160–236.

[64] Efthymiou M, SvrKova P, Moll R, Nallamilli S, Alexandre AR, Isenberg D, Werring D, Jager RH, Cohen H. Progression of ischaemic and haemorrhagic brain lesions on MRI in APS patients on antithrombotic therapy. https://abstracts.isth.org/abstract/progression-of-ischaemic-and-haemorrhagic-brain-lesions-on-mri-in-aps-patients-on-antithrombotic-therapy/; 2021 [accessed November 1, 2022].

[65] Stone S, Hunt BJ, Khamashta MA, Bewley SJ, Nelson-Piercy C. Primary antiphospholipid syndrome in pregnancy: an analysis of outcome in a cohort of 33 women treated with a rigorous protocol. *J Thromb Haemost*. 2005;3:243–5.

[66] Fischer-Betz R, Specker C, Brinks R, Schneider M. Pregnancy outcome in patients with antiphospholipid syndrome after cerebral ischaemic events: an observational study. *Lupus*. 2012;21:1183–9.

[67] Royal College of Obstetricians and Gynaecologists. Reducing the risk of venous thromboembolism during pregnancy and the puerperium: green-top guideline no 37a. https://www.rcog.org.uk/media/qejfhcaj/gtg-37a.pdf; 2015 [accessed March 31, 2023].

[68] Sacco RL, Benjamin EJ, Broderick JP, Dyken M, Easton JD, Feinberg WM, Goldstein LB, Gorelick PB, Howard G, Kittner SJ, Manolio TA, Whisnant JP, Wolf PA. American Heart Association Prevention Conference. IV. Prevention and rehabilitation of stroke. Risk factors. *Stroke*. 1997;28:1507–17.

SUPPLEMENTARY MATERIAL

The online version contains supplementary material available at https://doi.org/10.1016/j.jtha.2023.06.020