Survey on APS diagnosis and antithrombotic treatment in patients with ischaemic stroke, other brain ischaemic injury or arterial thromboembolism in other sites: Communication from the International Society on Thrombosis and Haemostasis Scientific and Standardisation Committee (ISTH SSC) Subcommittee on Lupus Anticoagulant/Antiphospholipid Antibodies (LA/aPL)

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ESSENTIALS

- Diagnosis and antithrombotic treatment of APS-associated acute ischaemic stroke are poorly defined
- An international survey to define current practice has been performed
- Antiphospholipid antibody testing strategy and antithrombotic treatment lack uniformity
- The survey results could inform a more uniform multidisciplinary consensus approach

ABSTRACT

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

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

Methods: Key opinion leaders/workers were invited to complete a REDCap survey questionnaire initiated by the ISTH SSC 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 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 ischaemic injury other than AIS/TIA, or if an alternative cause for AIS or TIA exists; choice of aPL tests, their timing and age cut-off; 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; low-molecular-weight heparin dosing/anti-Xa monitoring in pregnancy. The survey highlighted that approximately 25% do dedicated APS clinics and <50% have a multidisciplinary team structure for APS patients.

Conclusions: 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, ischaemic stroke, transient ischaemic attack, cerebral infarcts, white matter hyperintensities, survey

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 ischaemic stroke (AIS) or transient ischaemic attack (TIA) overall,[3] and, in patients under 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 (CVT)[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), 95% confidence interval (CI): (3.3, 2.6 to 4.4), dementia (1.9, 1.3 to 2.8); and death (2.0, 1.6 to 2.7). An association of WMH with a faster decline in global cognitive performance, executive function, and processing speed was also suggested.[7]

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

The identification of thrombotic APS patients 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 diagnosis and antithrombotic treatment of APS-

associated ischaemic stroke and related disorders, to inform guidance based on a more uniform multidisciplinary consensus approach, and clinical trials to define optimal management.

METHODS

Survey questionnaire

The survey questionnaire (Appendix 2), 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 Standardisation Committees (SSCs) for Lupus Anticoagulant/Antiphospholipid Antibodies, Control of Anticoagulation, and the Women 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, participants of the Antiphospholipid Syndrome Alliance for International Collaboration, Trials and Networking (APS ACTION), British Association of Stroke Physicians (BASP) and other key opinion leaders and workers in the field of APS/aPL were invited to complete the questionnaire.

Data analysis

The specific details of returned information were entered onto an Excel spreadsheet that included all records and fields, and data tallied, using simple descriptive statistics.

RESULTS

General information

One-hundred and seven responses to the survey were received (14 July 2021-19 Dec 2021). The majority of respondents were clinical haematologists (43%, with rheumatologists and neurologists/stroke physicians comprising 23.4% and 14.9%, respectively, and those in other clinical specialties, 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 APS patients impact a broad range of clinical specialty services, mostly non-APS dedicated (Supplementary Appendix Figures (SF) s1A and s1B).

Data pertaining to the numbers of adult patients (>18 years age) 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 are tested for aPL, are shown in the Supplementary Appendix (SF 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 Appendix (SF 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. APS patients with AIS, TIA or other brain ischaemic injury were seen in a dedicated APS clinic in 24.5% (26/106) of institutions. Forty-three percent (46/107) had a multidisciplinary team (MDT) structure in place; MDT composition was varied, with the majority including two or more from haematology, rheumatology, and neurology/stroke services.

Testing for antiphospholipid antibodies and other laboratory parameters in adult patients with ischaemic stroke, TIA or other brain ischaemic injury

In the majority of centres, aPL testing is performed in a specialist haemostasis laboratory in a University hospital (66.4%, 71/107) or non-University hospital (15%, 16/107), with samples sent to another laboratory in 15% (16/107).

Criteria for testing for antiphospholipid antibodies

The proportion of sites with local guidance or policy on testing for aPL according to presenting diagnosis (AIS, TIA, head imaging findings (e.g. brain infarcts, 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 ischaemic injury, or arterial occlusion in other sites is shown in Figure 1B. The majority tested for aPL in patients with conditions recognised to be associated with aPL, regardless of a history of ischaemic stroke, TIA or other brain ischaemic injury (Figure 1C). Many clinicians excluded patients with alternative causes for stroke or TIA from aPL testing. (Figure 1D).

Age cut-offs and timing of testing for antiphospholipid antibodies

The majority (72.8%; 75/103) had no age cut-off for aPL testing in patients with AIS or TIA, or for conditions associated with APS (91%; 93/102). Of those who employ an age cut-off in the context of AIS or TIA, over half (57.1%, 16/28) use an age cut-off of 50 years, with the cut-off ranging from 40 to 75 years (SF s5). Many respondents (64.4%, 65/101) 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.

Tests for antiphospholipid antibodies

The range of aPL tests requested is shown in Figure 2B. For LA testing in patients not on anticoagulation, 66% (68/103) perform a coagulation screen: prothrombin time, activated

partial thromboplastin time, thrombin time and fibrinogen. In non-anticoagulated patients, 80.8% (84/104) request the dilute Russell's viper venom time test (dRVVT) and 54.8% (57/104), a sensitive aPTT (low phospholipids and silica as activator) (Figure 2C). In patients on low molecular weight heparin (LMWH), 78.6% (77/98) request the dRVVT and 16.3% (16/98) a sensitive aPTT; 34% (34/100) temporarily omit LMWH/unfractionated heparin (UFH) routinely prior to blood sampling; and 42% (42/100) routinely aim to take the blood sample during the trough period. Only 20% (20/100) request a concomitant LMWH/UFH anti-Xa level.

Warfarin/other VKA is stopped prior to LA testing, with temporary heparin cover by 37.6% (38/101) of respondents whereas 50.5% (51/101) 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% (68/99), with a concomitant INR requested by only 36.6% (37/101) overall, and the range of INR cut-off for use of the dRVVT ranging from <1.4 to 4.0, or no cut-off (SF s6). Sixty-six percent (42/64) 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% (11/99).

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

Additional investigations

Laboratory tests other than aPL included in the routine assessment for APS-associated AIS, TIA or other brain ischaemic injury are shown in Figure 2D. Seventy-five percent (75/100) advised that APS patients with 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 4B and 4C, respectively.

Antithrombotic treatment

The decision to start antithrombotic treatment, in patients with APS-associated AIS, TIA or other brain ischaemic injury, or arterial thromboembolism in other sites was influenced by the aPL phenotype (Figure 3A). Over half (56.4%, 57/101) 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 laboratory aPL profile (perceived higher risk aPL profiles: triple positivity, high titre aPL, and LA positivity).

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

For patients with APS-associated TIA, 80.4% (78/97) would consider anticoagulation if there is evidence of either acute ischaemia or chronic ischaemic injury (i.e. established WMH, lacunae or territorial cortical infarcts) on head magnetic resonance imaging (MRI), including

diffusion-weighted imaging (DWI). Anticoagulation, based on clinical history of confirmed TIA alone was advised by 26.8% (26/98). In patients with APS-associated TIA, 50.5% (52/103) advised antithrombotic treatment for a first APS-associated TIA, increasing to 72.8% (75/103) for recurrent TIA. Antithrombotic treatment options advised for APS-associated TIA are shown in Figure 4D. More than twice as many clinicians used single antiplatelet treatment as for AIS: 27.4% (26/95; 21.1% LDA) for TIA vs 10.1% (10/99) for ischaemic stroke.

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

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

The majority (87.8%, 86/98) follow up patients with APS-associated AIS, TIA or other brain ischaemic injury, and arterial thromboembolism outside of the brain long-term. Follow up intervals varied: three-monthly (21.2%, 18/85), six-monthly (37.6%, 32/85) and annually (30.6%, 26/85). The majority (77.5%, 69/89) requested interval head MRI only if the patient had neurological symptoms to warrant this; 24.7% (22/89) requested head MRI to assess progress on the antithrombotic regimen, with the frequency of imaging generally between 6-monthly to 2-yearly, although some would scan only based on clinical features. Head MRI including susceptibility weighted imaging (SWI) and fluid attenuated inversion recovery (FLAIR) were requested by 47% (37/79). The majority (80.5%, 70/87) of non-neurologists referred APS patients with suspected cognitive impairment for neurological assessment and formal cognitive testing.

During pregnancy, the majority (61.9%, 60/97) use standard-intensity LMWH, with 19.6% (19/97) using high-intensity LMWH for AIS; and 56.3% (54/96) and 18.8% (18/96),

respectively, using standard- and high-intensity LMWH for patients with previous AIS (Figures 6A and 6B). 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 Appendix: SF s7A, s7B). Two-thirds (66.7%, 64/96) used split (i.e. divided dose administered twice daily) treatment dose LMWH during pregnancy. Almost half (46.9%, 45/96) monitored anti-Xa levels during pregnancy. The majority (81.7%, 76/93) used LDA during pregnancy. (Figure 6C). The main reasons given for aspirin use in addition to anticoagulation among respondents was prevention of pregnancy morbidity (preeclampsia, placental insufficiency, 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/gynaecology.

DISCUSSION

This survey has highlighted the diverse approaches to diagnosis and antithrombotic treatment of APS patients with AIS, TIA, other brain ischaemic injury. The clinical importance of identifying these clinical manifestations of APS has been recognised in successive ISTH guidance documents[15,16] and the UK National Clinical Guideline for Stroke.[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, ischaemic lesions and cortical atrophy.[5]

Many clinicians excluded patients with alternative risk factors for AIS or TIA, such as hypercholesterolaemia, hypertension, atrial fibrillation or patent foramen ovale, from aPL

testing. The adjusted global APS score (aGAPSS) suggests that traditional cardiovascular risk factors can exacerbate arterial thrombotic risk associated with aPL.[18] PFO, prevalence, ~25% in the general population and ~40% in patients with cryptogenic stroke,[19] is addressed below.

Most respondents did not have an age cut-off for aPL testing. The suggested age cut-off of under 50 years in ISTH guidance[16] and RCP guidelines[17] aims to limit aPL testing to those who are likely to have APS, as APS is typically diagnosed in younger patients under 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=0.007).[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 ISTH guidance on many points. Testing for all three criteria aPL tests is required for accurate diagnosis,[22,23] with LA and IgG and IgM aCL and ab2GPI 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 multicentre 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, stroke patients were under-represented, comprising 55/259 thrombotic APS patients.[24] A retrospective study reported that isolated IgM aPL (in 14.3%: 24/168 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 IgA aCL or aβ2GPI, not included in current guidance for aPL testing,[22] although reported to add to thrombotic risk in SLE patients.[29]

The dRVVT was performed for LA detection in non-anticoagulated patients by the majority (80.8%), with a sensitive aPTT performed by 54.8%. ISTH guidance on LA testing

recommends two tests based on different principles.[16] In patients on LMWH or UFH, only 20% measure anti-FXa 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 centres. Only 8.9% request a concomitant DOAC activity test, recommended by the ISTH.[16] 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 prevalence 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 SLE patients who have a two-fold increase in the risk of stroke, increasing to up to 10-fold in patients <50 years, however, testing for SLE, important in AIS patients,[36] was undertaken by <50%. Approximately 38% measured plasma homocysteine. A randomised controlled trial (RCT) showed that lowering homocysteine with folic acid, vitamins B6 and B12 reduced the risk of overall stroke, but not its 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 versus later initiation of anticoagulation on the outcome following acute stroke, is unknown.[16] LA results should be interpreted with caution in the acute phase post-AIS: raised factor VIII can shorten the aPTT, leading to false negative results,[40] while raised C-reactive protein may lead to false positives.[41]

The majority of respondents conformed to EULAR guidelines on antithrombotic treatment for APS-associated ischaemic stroke.[43] This guidance, underpinned by a systematic review,[14] recommends for patients with a first arterial thrombosis: VKA, target INR 2.5 (range 2–3), with or without LDA, or target INR 3.5 (range 3–4), considering the individual's risk of bleeding and recurrent thrombosis:[14,42] In a prospective cohort study of 1000 APS patients, in which approximately 20% of APS patients had stroke and 11% TIA at baseline, 25% of patients on antithrombotic treatment developed thrombosis over 5-10 years 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 under-represented: 44/109 (34 arterial only) in one[44] and 27/114 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 taking antiplatelet therapy (95% CI 0.18-0.26), developed recurrent thromboembolism.[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 APS patients, 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 9-10% of patients with a first 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 non-inferior to standard-intensity warfarin (target INR 2.5) with no increase in thrombosis recurrence,[55] undiagnosed APS patients were likely included,. Systematic review of DOAC APS randomised RCTs, which included the key DOAC trials in APS patients,[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 APS patients with arterial thrombosis. Studies in animal models indicate that increased rivaroxaban anti-Xa activity is required to protect against arterial versus venous thrombosis.[58] The RISAPS (Rivaroxaban in Stroke Patients with APS) RCT is assessing the efficacy of high-intensity rivaroxaban 15 mg twice daily versus high-intensity warfarin (target INR 3.5) in APS patients with previous AIS or other brain ischaemic injury (ClinicalTrials.gov Identifier: NCT03684564).

Views differed on PFO closure (41.9% opted for closure with lifelong anticoagulation, 24.4% for lifelong anticoagulation without PFO closure). Two observational studies on patients with cryptogenic stroke/TIA with thrombophilia (APS in 29.8% [n=134][59] and 31% [n=136])[60] found a decreased risk of recurrent stroke in patients with thrombophilia who underwent PFO closure (RR, 0.17; 95% CI, 0.07-0.44). The Society for Cardiovascular Angiography and Interventions (SCAI) guidelines has recommended 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 TIA, the majority (80%) based the decision to use antithrombotic treatment on evidence of acute or chronic brain ischaemic injury on head MRI, including DWI, rather than clinical

history alone. The diagnosis of TIA can be challenging, with significant inter-rater variability. In the European Stroke Association guidelines TIA is clinically diagnosed and based on symptom duration of less than 24 hours.[63]

In patients with APS-associated silent cerebral infarcts, where approximately two-thirds advised VKA with/without LDA and approximately one-third, mainly single, antiplatelet treatment alone, there are no robust trial data on antithrombotic treatment for non-APS patients. In patients with WMH of presumed vascular origin, approximately two-thirds based the decision to give antithrombotic treatment on whether an expert clinical opinion (Neurologist/Stroke Physician) would consider this a reasonable treatment option; ~20% would not base antithrombotic treatment decisions on WMH. As cognitive dysfunction is common in APS,[5] if suspected, APS patients should be referred for neurological assessment and formal cognitive testing, as was undertaken by the majority (80.5%) of non-neurologists. Follow-up of patients in the above categories long-term, undertaken by the majority (86.7%), usually six to twelve monthly to annually (68.2%) enables review of management following 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 ischaemic, in approximately 45% of individual with aPL, with less progression in those with a target INR of >3.0.[64] Almost half (46.8%) request head MRI with SWI and FLAIR, the former being useful to detect haemorrhage/blood products, which may be inapparent on other brain MRI sequences, and the latter 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 EULAR guidelines,[43] 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 healthcare professionals, who were from diverse backgrounds, including haematologists, rheumatologists and neurologists, with the majority university hospital based. However, it seems likely that the majority of APS patients are managed in these settings. The survey did not include enquiry about the impact of concomitant VTE on decision making in APS patients with arterial thromboembolism. We recognise that it is important to address this complex scenario in a guidance document. The survey did not include questions about additional therapy for cardiovascular risk factors. Checking that lipid status and hypertension are optimised following stroke should be universal.[68]

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 ischaemic injury other than AIS/TIA or if an alternative cause for stroke or TIA exists; which aPL tests to perform, their timing and age cut-off; aPL phenotype to trigger antithrombotic treatment; management approach for patent foramen ovale; antithrombotic treatment for first TIA or white matter hyperintensities; specifications for head MRI; LMWH

dosing/anti-Xa monitoring in pregnancy. The survey highlighted that ~25% do dedicated APS clinics and under 50% have a MDT for APS patients. 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.

AUTHOR CONTRIBUTIONS

H. Cohen devised and analyzed the survey questionnaire, wrote the first draft of the manuscript, and undertook critical revision of the manuscript. D.A. Isenberg, D.J. Werring, A. Chandratheva and K.M.J. Devreese devised the questionnaire and undertook critical revision of the manuscript. P. Mittal undertook critical revision of the manuscript.

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CONFLICTS OF INTEREST

H. Cohen reports lecture fees from Technoclone, paid to University College London Hospitals Charity. D. J. Werring, A. Chandratheva, P. Mittal, K. M. J. Devreese and D. A. Isenberg have no relevant conflicts of interest to declare.

LEGENDS TO FIGURES

In all figures (1-6), the y-axis indicates percentage of respondents.

Figure 1

1A Have local guidance that defines which patients with AIS, TIA, head imaging findings (e.g. brain infarcts, WMH), vascular cognitive impairment or dementia, or cerebral venous sinus thrombosis, should be tested for aPL (100 respondents)

1B Test for aPL in patients with AIS, TIA, or head imaging findings (e.g. brain infarcts, WMH), vascular cognitive impairment or dementia (99 respondents). The percentage for cerebral venous thrombosis and arterial occlusion in other sites are also included.

1C Test for aPL in patients with conditions recognised to be associated with aPL, regardless of a history of AIS, TIA or other brain ischaemic injury (102 respondents)

1D Exclude patients with alternative causes/risk factors for AIS or TIA from aPL testing (67 respondents)

Figure 2

2A Suggested options for timing of aPL testing after an acute arterial thrombosis (101 respondents)

2B Repertoire of aPL tests requested (105 respondents)

2C Tests requested for LA in non-anticoagulated patients (104 respondents)

2D Laboratory tests other than aPL included in the routine assessment for patients with APS-associated AIS, TIA or other brain ischaemic injury (101 respondents)

Figure 3

3A Influence of aPL phenotype on decision start antithrombotic treatment, in patients with APS-associated AIS, TIA or other brain ischaemic injury, or arterial thromboembolism in other sites (99 respondents)

3B Indications for lifelong antithrombotic treatment for patients with APS-associated AIS, TIA, cerebral infarcts or WMH, or arterial thromboembolism in sites outside the brain (103 respondents)

Figure 4

4A Antithrombotic treatment for first APS-associated AIS (99 respondents). Clopidogrel was the only single non-aspirin antiplatelet agent stated.

4B Investigations performed for patent foramen ovale: transthoracic echocardiography, bubble echocardiography, transoesophageal echocardiography and transcranial doppler (100 respondents)

4C Management options advised in patients in whom a patent foramen ovale was considered to be potentially causal (86 respondents).

4D Antithrombotic treatment options advised for APS-associated TIA (95 respondents). Clopidogrel was the only single non-aspirin antiplatelet agent stated.

Figure 5

5A Antithrombotic treatment advised for patients with APS-associated established non-acute cerebral infarct(s) in the context of a prior history of AIS (91 respondents)

5B Antithrombotic treatment advised for APS-associated silent cerebral infarcts (91 respondents)

5C Antithrombotic treatment advised for APS-associated WMH of presumed vascular origin (88 respondents)

Figure 6

6A Antithrombotic treatment during pregnancy for patients with APS-associated AIS (97 respondents)

6B Antithrombotic treatment during pregnancy for patients with APS-associated previous AIS (96 respondents)

6C Use of once daily vs. split dose (twice daily) low molecular-weight-heparin (LMWH) (97 respondents), use of anti-Xa monitoring tests (96 respondents), and use of low dose aspirin (LDA) (93 respondents)

Figure 1A **Figure 1B**

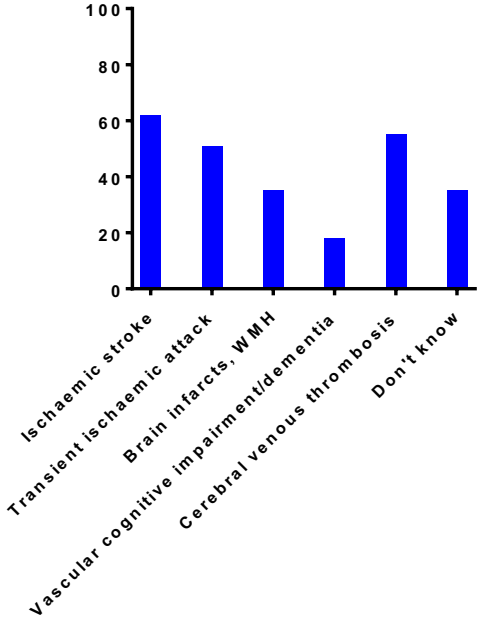
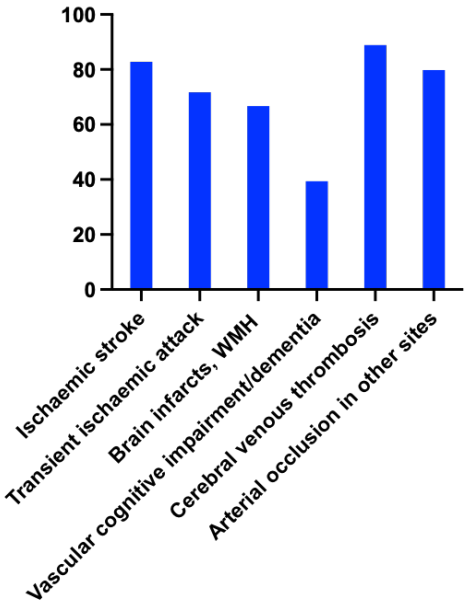


Figure 1C



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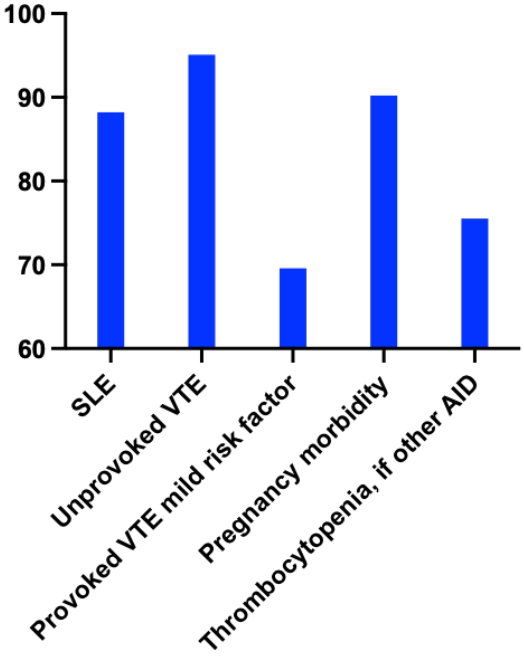

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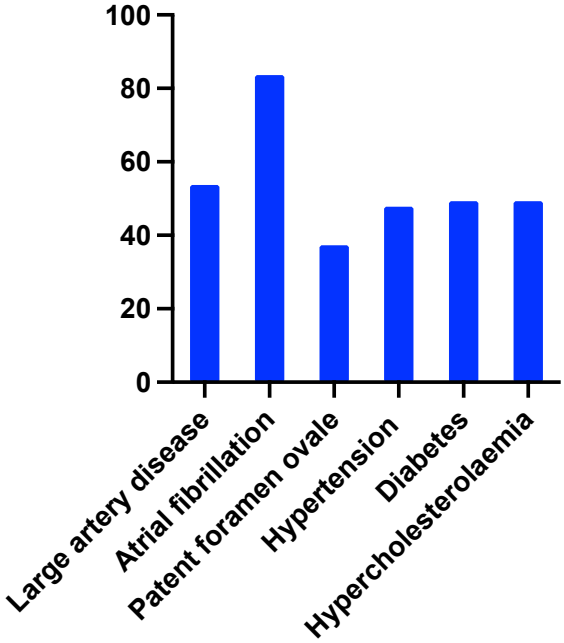

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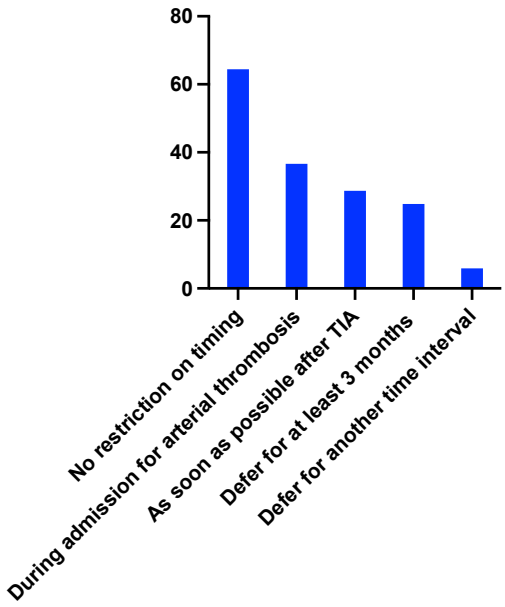

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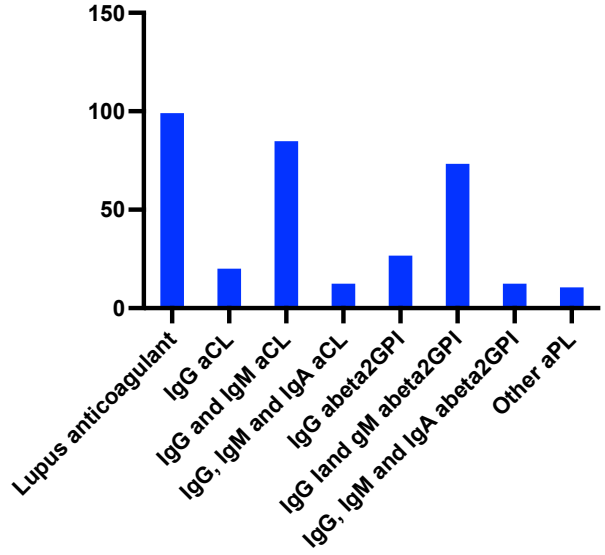

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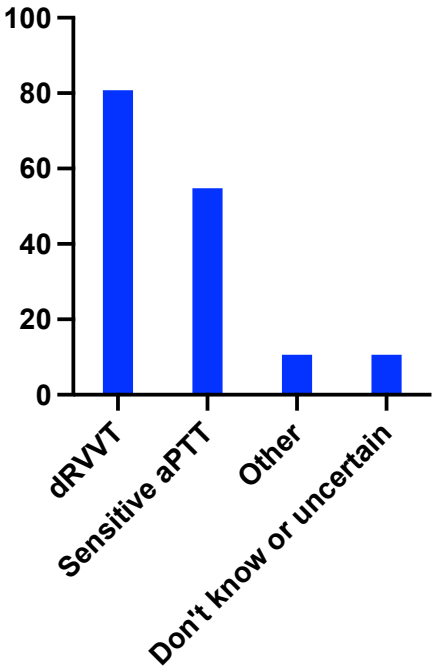

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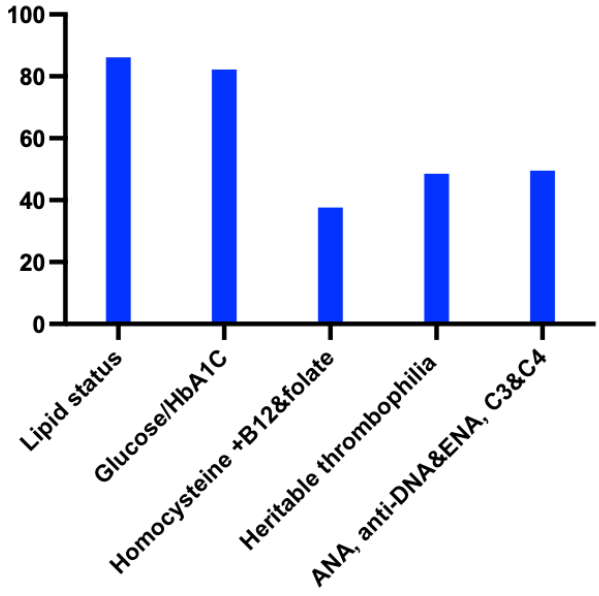

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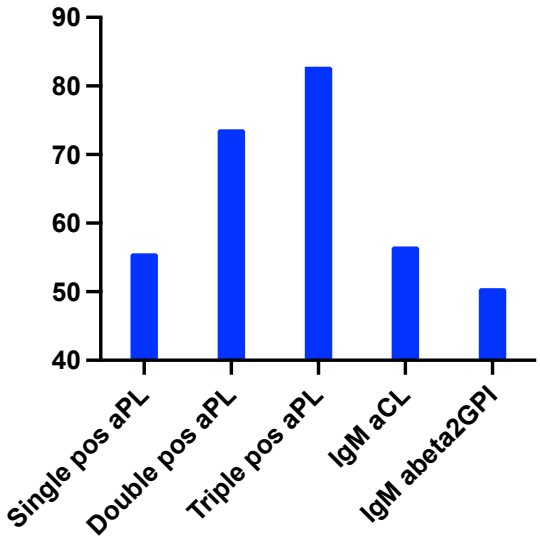

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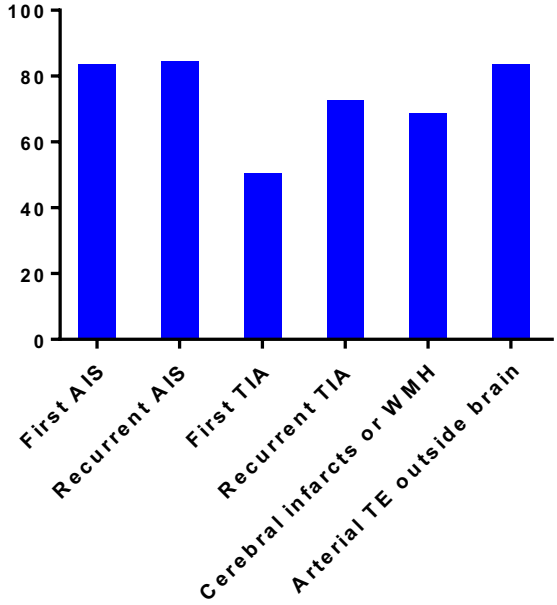

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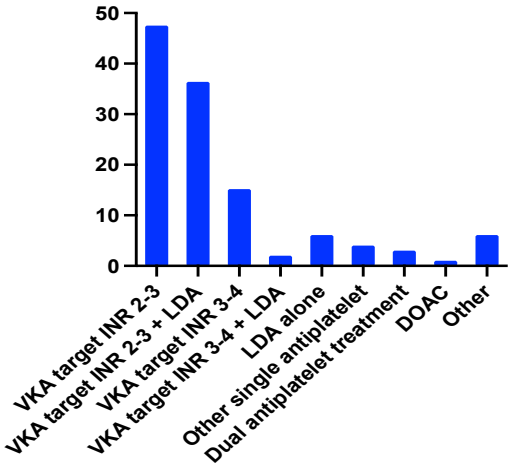

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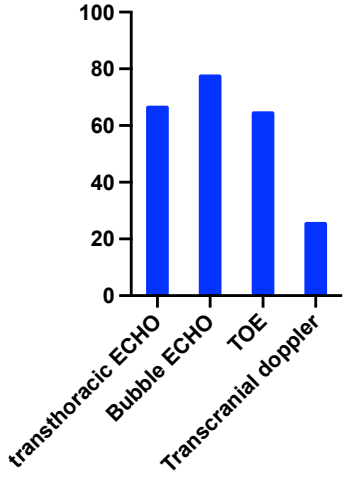

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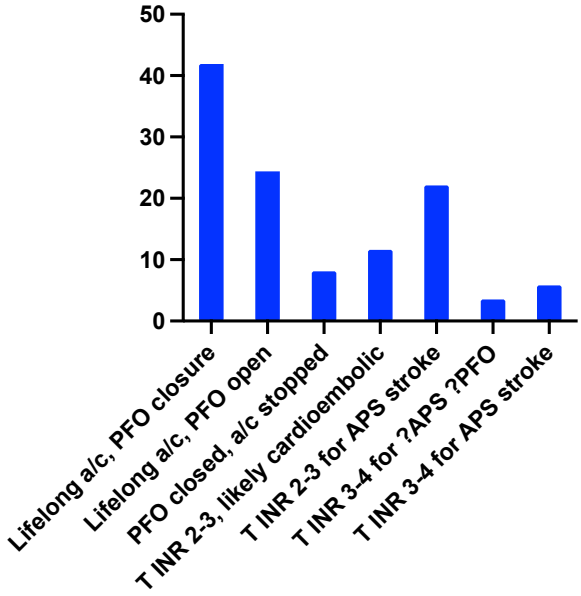

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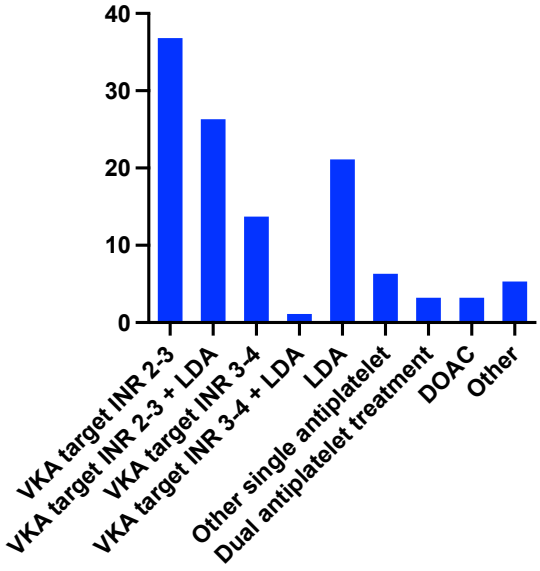

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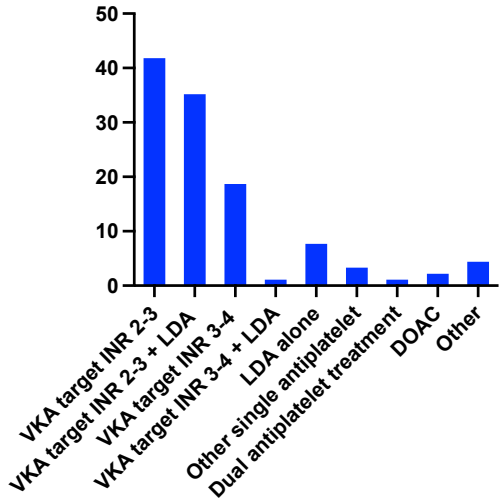

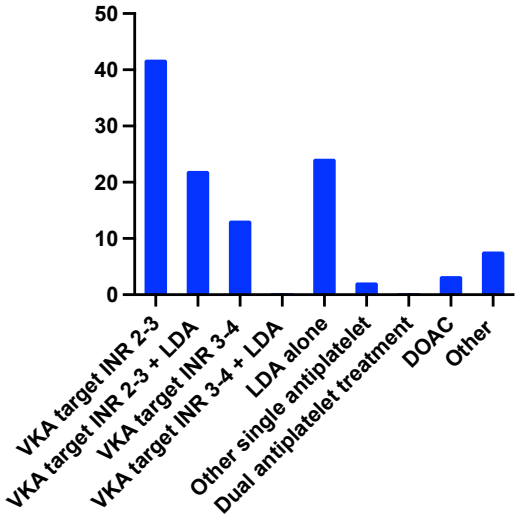

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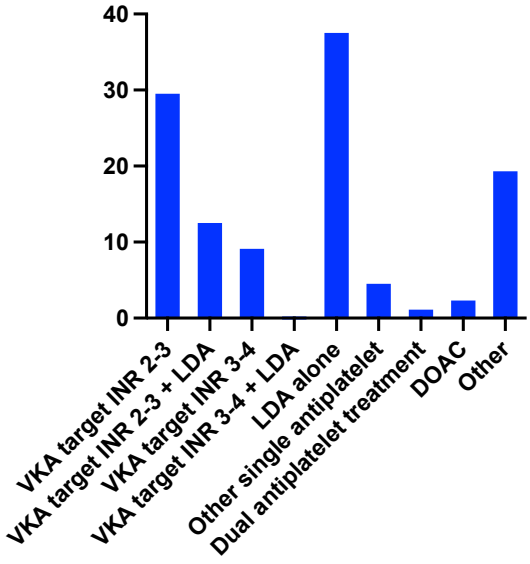
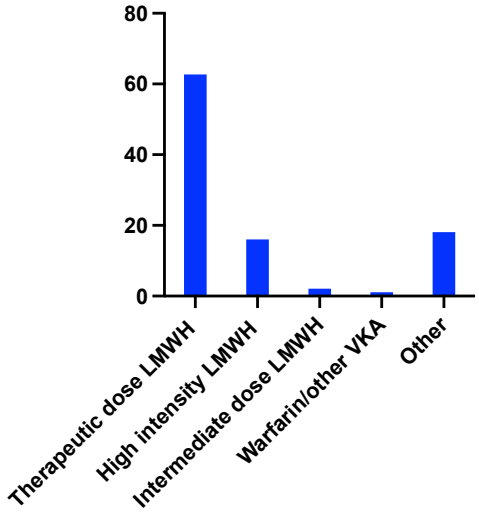


Figure 6A



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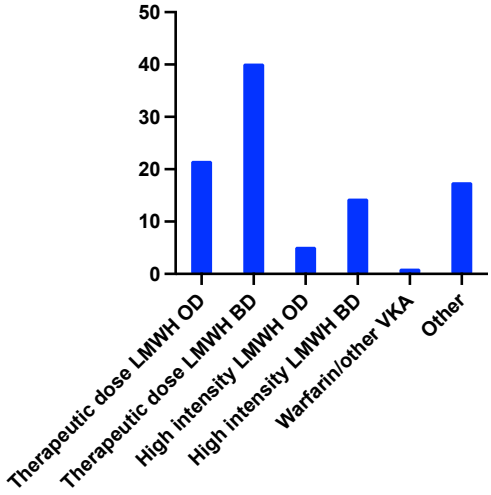

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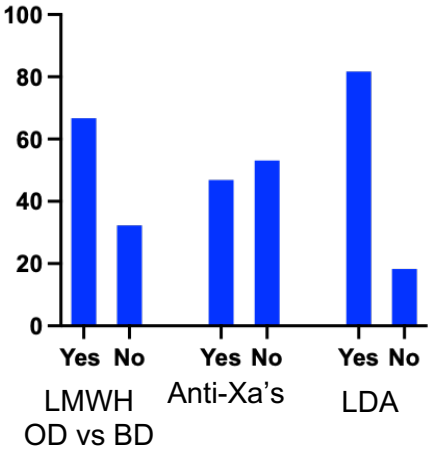

Abbreviations: aCL, anticardiolipin antibodies; aβ2GPI, a aβ2 glycoprotein I antibodies; AID, autoimmune disease; AIS, acute ischaemic stroke; aPL, antiphospholipid antibodies; ANA, antinuclear antibodies; aPTT, activated partial thromboplastin time; BD, twice daily; C3&C4, complement C3 and C4; DOAC, direct oral anticoagulant; dRVVT, dilute Russell's viper venom time; ECHO, echocardiography; OD, once daily; INR, International Normalised Ratio; LDA, low dose aspirin; LMWH, low-molecular-weight heparin; LA, lupus anticoagulant; PFO, patent foramen ovale; SLE, systemic lupus erythematosus; TE: thromboembolism; TIA, transient ischaemic attack; TOE, transoesophageal echocardiography; VKA, vitamin K antagonist; VTE, venous thromboembolism; WMH, white matter hyperintensities.

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