SSC Subcommittee Project/Collaborative Project

NAME OF PROJECT

Survey on APS diagnosis and antithrombotic treatment in patients with ischaemic stroke, other brain ischaemic injury or arterial thromboembolism in other sites

Subcommittee
Lupus Anticoagulant/Antiphospholipid Antibodies of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis

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Description of project

Background

Stroke is the second most common cause of death worldwide,(1) and the most important cause of adult complex disability.(2) It is estimated from systematic reviews that 13.5% (range 6.8%–23.3%) of patients with stroke or transient ischaemic attack (TIA) overall (3) and, in patients under 50 years, approximately 17% (range 2%–56%) of those with stroke and 12% (range 2%–45%) of those with TIA, are associated with antiphospholipid antibodies (aPL).(4) A recent systematic review showed that the prevalence of cognitive impairment in APS patients ranged between 11-60.5%.(5) Stroke, TIA and cognitive impairment are thus important and frequent clinical manifestations of thrombotic antiphospholipid syndrome (APS). Neuroimaging findings associated with APS include infarcts (both subcortical and cortical), white matter hyperintensities (WMH) of presumed vascular origin, cerebral venous sinus thrombosis and cerebral microbleeds.

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).(7) An association of WMH with a faster decline in global cognitive performance, executive function, and processing speed was also suggested.(6)

APS patients are also at increased risk of myocardial infarction (MI),(7) with aPL reported in 11% of patients with MI.(3) Other arterial thrombotic events such as renal artery thrombosis(8) and peripheral arterial ischaemia(9) can occur.

Among systemic lupus erythematosus (SLE) patients, 30-40% have aPL,(10) with estimates of the prevalence of APS ranging from 7% to 15%.(11,12) SLE patients with APS are often difficult to manage, with complex multi-system clinical problems.(12)

Thrombotic APS is reported to be associated with recurrent thromboembolism (arterial, venous or microvascular) in about one-fifth of patients despite anticoagulation or antiplatelet treatment. In a prospective cohort study on 1000 APS patients, in which approximately 20% of APS patients

had stroke and 11% had TIA at baseline, 25% of patients on antithrombotic treatment developed thrombosis over 5-10 years follow up, with 5.3% developing stroke and 4.7% TIA. Eighty percent of these patients re-thrombosed while on anticoagulation (vitamin K antagonist; VKA), with or without antiplatelet treatment, and 20% while on antiplatelet treatment alone.(13) A recent systematic review and meta-analysis of 17 studies reported that 22% of patients with initial stroke or other arterial occlusion and taking anticoagulants (95% CI 0.15-0.31), and 21.6% of patients taking antiplatelet therapy (95% CI 0.18-0.26) developed recurrent thromboembolism.(14) The numbers of patients on VKA vs. direct oral anticoagulants (DOACs) was not clarified. The authors concluded that patients with aPL and arterial thromboembolism may benefit from a different antithrombotic approach than patients with aPL and VTE.(14)

The clinical importance of identifying APS patients with arterial thromboembolism has been recognised in successive ISTH guidance documents,(15,16) and the UK National Clinical Guideline for Stroke,(17) with testing for aPL recommended in younger patients (under 50 years) with ischaemic stroke (15-17), TIA,(16,17) other evidence of brain ischaemia,(16) or arterial thrombosis in other sites.(15,16)

Two randomised controlled trials (RCTs),(18,19) comparing standard-intensity (target INR 2.5, range 2.0-3.0) with high-intensity (target INR 3.5, range 3.0-4.0) warfarin, concluded, based on the low rate of recurrent thrombosis in patients on warfarin target INR 2.5, that standard-intensity warfarin is appropriate for patients with thrombotic APS. Notably, in both studies, patients with arterial thrombotic APS were under-represented, accounting for 44/109 (34 arterial only) in one (18) and 27/114 in the other.(19)

A third study, the Antiphospholipid Antibodies and Stroke Study (APASS), was a prospective cohort study, within the Warfarin vs Aspirin Recurrent Stroke Study (WARSS) RCT that reported no thrombo-occlusive events associated with aPL in patients with aPL at baseline treated with either warfarin (target INR range 1.4–2.8) vs. aspirin (325 mg/day) in stroke prevention.(20) However, the warfarin target INR range would have resulted in subtherapeutic anticoagulation (i.e. INR <2.0), and laboratory criteria for aPL did not fulfil the international consensus criteria for a diagnosis of APS.(20) A systematic review of 16 studies on secondary thromboprophylaxis in patients with aPL found that most recurrent thromboses (venous and arterial) occur in patients not receiving anticoagulation (VKA), or on antiplatelet treatment alone. Recurrent events were least likely to occur in those on warfarin, INR >3.0.(21)

The TRAPS (Rivaroxaban in Thrombotic APS) RCT compared rivaroxaban 20 mg once daily with warfarin, target INR 2.5, in 120 triple aPL-positive thrombotic APS patients [22]. Seven patients in the rivaroxaban arm (annualised recurrent thrombosis rate 7.6%) had new ischaemic vascular events (four ischaemic stroke and three myocardial infarctions) compared with 0% in the warfarin arm. Four of the seven patients had previous arterial occlusion.(22) International guidance from the International Society on Thrombosis and Haemostasis (ISTH) and International Congress on Antiphospholipid Antibodies Task Force on Treatment Trends guidance recommends against the use of DOACs in APS patients with arterial thrombosis.(23,24) Table 1 summarises arterial and venous thromboembolic events in APS patients on antithrombotic treatment reported in randomised controlled trials (RCTs) and systematic reviews.

The standard doses of DOACs reported in the literature in APS patients have been shown to be efficacious vs. standard-intensity warfarin in the prevention of arterial thromboembolism in phase 3 RCTs in general population patients with atrial fibrillation.(25) These doses may not however, be effective to prevent APS-associated arterial occlusion.(26) The RISAPS (Rivaroxaban in Stroke Patients with APS) phase 2/3 RCT aims to assess the efficacy of high-intensity rivaroxaban

15 mg twice daily versus high-intensity warfarin, target INR 3.5 (range 3.0–4.0) in patients with APS with previous ischaemic stroke or other brain ischaemic injury (ClinicalTrials.gov Identifier: NCT03684564).

Antithrombotic treatment in APS-associated ischaemic stroke, other brain ischaemic injury or arterial thromboembolism in other sites

The optimal antithrombotic strategy for APS-associated ischaemic stroke, other brain ischaemic injury or arterial thromboembolism in other sites is undefined due to the lack of appropriate, adequately powered RCTs to guide optimal antithrombotic treatment. The lack of definitive data to guide the optimal management of APS patients in these categories is reflected in variable national and international guidelines. Recommendations include standard VKA, (target INR 2.5),(24,29-31) with or without low dose aspirin,(24,29) high-intensity VKA (target INR 3.5).(24,29) or a range of options: aspirin (75-100 mg once daily), clopidogrel (75 mg once daily), aspirin/extended-release dipyridamole (25 mg/200 mg bid), or cilostazol (100 mg bid) over no anti-platelet therapy, oral anticoagulants, the combination of clopidogrel plus aspirin, or triflusal.(32)

Diagnosis of APS patients with ischaemic stroke, other brain ischaemic injury or arterial thromboembolism in other sites

The optimal strategy for diagnosis of APS in patients with ischaemic stroke, TIA or other clinical or radiological findings indicating brain ischaemic injury, and arterial thromboembolism in sites outside the brain, is also undefined. Results of testing for lupus anticoagulant (LA) during the acute phase of stroke, notably soon after a thrombotic event, should be interpreted with caution.(16) This is because of possible interference with the test result due to raised levels of factor VIII shortening the activated partial thromboplastin time(27), or C-reactive protein by interference with phospholipid in the reagent, prolonging phospholipid-dependent clotting tests;(28) the former may mask LA and the latter may yield false-positive results. The optimal timing of initial and subsequent aPL testing after acute ischaemic stroke is not established. Nevertheless, LA testing, together with testing for anticardiolipin (aCL) and anti-beta 2 glycoprotein I antibodies (aß2GPI), may be useful in new stroke patients in whom APS is clinically suspected, to inform whether the patient might benefit from an anticoagulant rather than long-term treatment with a single antiplatelet agent, to potentially prevent APS-related recurrent stroke.(16)

The identification of thrombotic APS patients and their optimal management is of high clinical importance, to prevent potentially avoidable recurrent thrombo-occlusion. We therefore now propose to conduct a survey of the diagnosis and antithrombotic treatment in APS patients with the main focus on ischaemic stroke, TIA or other ischaemic brain injury.

Purpose of the proposed survey

1. We aim to collate/capture the views of experienced investigators with regard to their perception of the optimal:
   i) approach to the antithrombotic treatment of patients with APS-associated ischaemic stroke, TIA or other brain ischaemic injury and associated cognitive impairment
   ii) strategy for diagnosis of APS in these patients

2. The survey will also address APS-associated arterial thromboembolism in sites outside the brain. In clinical practice, APS-associated arterial thromboembolism other than

ischaemic stroke or TIA are less common, however, information on APS-associated arterial occlusion in other sites will be sought, recognising that clinical evidence will be more limited.

As the respondents to the survey will include haematologists, rheumatologists, neurologists and stroke physicians with a special interest/expertise in the area, the responses will be very helpful to identify the current status with regard to the diagnosis and antithrombotic treatment of APS patients with ischaemic stroke, other brain ischaemic injury or arterial thromboembolism in other sites. They will also inform the development of a multidisciplinary consensus approach to the care of these patients.

Methods

A survey questionnaire designed to capture relevant information with the main focus on the diagnosis and management of APS patients with ischaemic stroke, TIA or other ischaemic brain injury (Appendix 1) will be circulated to members of the LA/aPL and Control of Anticoagulation ISTH SSCs.

To ensure wide and appropriate consultation, the survey questionnaire will also be circulated to members of the American College of Rheumatology (ACR), European League Against Rheumatic Diseases (EULAR), American Society of Haematology (ASH) and Antiphospholipid Syndrome Alliance for International Collaboration, Trials and Networking (APS ACTION), and we will aim to involve the European Stroke Organisation and World Stroke Organisation.

We anticipate that >100 clinicians will respond to the survey, which would enable a meaningful analysis of clinical practice and assessment of consensus.

Expected timeline

Conversion of survey questionnaire to RedCap format and circulation by ISTH team: by 1 April 2021 at the latest
Deadline for responses: six weeks after circulation of the survey (reminder after 3-4 weeks)
Analysis: by mid-June 2021
Presentation at ISTH LA/aPL SSC: 17 July 2021

Expected outcomes (ie. publications)

1. The completed manuscript would be submitted as an original article to the Journal of Thrombosis and Haemostasis with a view to an ISTH SSC communication.
2. The results of the survey will inform the development of ISTH SSC guidance based on a multidisciplinary consensus approach to the care of these patients.

Table 1: APS Previous and recurrent arterial and venous thromboembolism (RCTs and systematic reviews)

Study (reference)	Design	Population	Previous arterial occlusion	RCTs: Intervention / Comparator SR: Treatment	N	Outcomes: Recurrent thromboembolic events				
						Total (%)	Length of FU (y)	Total %/y	Arterial	Venous
Ortel(14)	SR	Thrombotic APS	44%	Anticoagulants, Antiplatelet therapy	In 488/ 1101 with initial ATE	22 22	2	11 11	NS	NS
Ordi Ros(33)	RCT	Thrombotic APS	38%	Rivaroxaban 20mg od / Warfarin T INR 2-3 or 3.1-4	95 95	11.6 6.3	3	3.9 2.1	9 2	3 3
Sanchez-Redondo(34)	SR	Thrombotic APS	17.4%*	DOACs	728	13.9%**	Mean 1.3	11	44***	43
Pengo(21)	RCT	Thrombotic APS	21%	Rivaroxaban 20mg od / Warfarin Target INR 2-3	59 61	12% 0%	Mean 1.6	7.6 0	7 0	0 0
Dufrost(35)	SR	Thrombotic APS	23%	DOACs	447	73 (16%)	Mean 1.4	11.7	31	28
Cohen(36)	RCT	Thrombotic APS	0%	Rivaroxaban 20mg od / Warfarin T INR 2-3	56 54	0 0	0.6	0 0	0 0	0 0

Okuma(37)	RCT	Thrombotic APS: all ischaemic stroke	100%	Aspirin 100mg od / VKA T INR 2-3 + Aspirin	11 9	18 11	Mean 3.9	2 1	2 1	0 0
Finazzi(19)	RCT	Thrombotic APS	31%	Warfarin T INR 3-4 vs. Warfarin T INR 2-3	54 55	6 (11% 3 (5%)	Mean 3.6	1.5	4 3	2 2
Crowther(18)	RCT	Thrombotic APS	24%	Warfarin T INR 3-4 vs. Warfarin T INR 2-3	56 58	6 (11%) 2 (3%)	Mean 2.7	1.3	4 1	2 1
Ruiz-Irastorza(38)	SR	Thrombotic APS	58%	Warfarin T INR 2-3, 3-4 Aspirin No antithrombotic Aspirin Warfarin Warfarin INR at time of thrombosis <3	1020[+]	180 104 27 49 42	NS	NS	50[++]	73[++]

Abbreviations: APS, antiphospholipid syndrome; ATE, arterial thromboembolism; FU, follow up; INR, international normalised ratio; N, number; NS, not stated; RCT, randomised controlled trial; SR, systematic review; T, target.
*9.2% arterial plus venous, **courses of DOAC treatment (102/731); ***2 arterial plus venous; [+]excluding Levine et al(20); [++]Not stated for remainder (N=57)

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Appendix 1

INTERNATIONAL SOCIETY ON THROMBOSIS AND HAEMOSTASIS SCIENTIFIC AND STANDARDIZATION COMMITTEE (ISTH): LUPUS ANTICOAGULANT/ ANTIPHOSPHOLIPID ANTIBODIES

Survey on APS diagnosis and antithrombotic treatment in patients with ischaemic stroke, other brain ischaemic injury or arterial thromboembolism in other sites

The optimal approach to the management of patients with antiphospholipid syndrome (APS)-associated ischaemic stroke, other brain injury or arterial thromboembolism in sites outside the brain is undefined, due to a lack of definitive data. This uncertainty is reflected in variable national and international guidance. The optimal strategy for diagnosis of APS in patients in these categories is also undefined.

The main focus of this survey is the diagnosis and antithrombotic treatment in patients with APS-associated ischaemic stroke or other brain ischaemic injury. Information on APS-associated arterial occlusion in sites outside the brain will also be sought, recognising that clinical evidence will be more limited.

We would greatly value your opinion. Your response will be very helpful to define the current status with regard to the diagnosis and antithrombotic treatment of APS patients with ischaemic stroke, other brain ischaemic injury or arterial thromboembolism in other sites. Your response will also inform the development of a multidisciplinary consensus approach to the care of these patients.

We thank you for completing this survey.

Katrien Devreese, Chair, ISTH SSC Lupus Anticoagulant/Antiphospholipid Antibodies
Hannah Cohen, Co-chair, ISTH SSC Lupus Anticoagulant/Antiphospholipid Antibodies
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Please indicate your responses to each question in your opinion.

PART A: APS DIAGNOSIS AND ANTITHROMBOTIC TREATMENT IN PATIENTS WITH ISCHAEMIC STROKE, OTHER BRAIN ISCHAEMIC INJURY OR ARTERIAL THROMBOEMBOLISM IN OTHER SITES

1. GENERAL INFORMATION

i. **Are you a:**
   A. Clinical haematologist
   B. Rheumatologist
   C. Neurologist
   D. Stroke Physician

E. Other specialist clinician, please specify
……..……
F. Other healthcare professional, please specify
……
G. Laboratory based researcher, with specialist interest in APS

ii. Type of institution that you are working in (tick all that apply)

A. University hospital
B. Non-university hospital
C. Private hospital
D. University Research unit, please specify
……
E. Other, please specify
……

iii. Type of clinical setting that you are working in (tick all that apply)

A. Haematology thrombotic APS clinic
B. Other haematology clinic, please specify
……..
C. Haematology APS/other thrombotic disorders acute inpatient service
D. Anticoagulation clinic
E. Rheumatology SLE clinic
F. Rheumatology APS clinic
G. Rheumatology acute inpatient service
H. Acute stroke unit
I. Stroke outpatient clinic
J. TIA clinic
K. Neurology clinic
L. Emergency department
M. Memory clinic
N. Other specialist clinic, please specify
……
O. Joint clinic, please specify specialties participating
……..
……..
P. Other healthcare professional, please specify
……..
Q. Laboratory based researcher with specialist interest in APS

iv. Which clinic(s) are patients with APS-associated ischaemic stroke, TIA or other ischaemic brain injury seen in at your institution? (tick all that apply)

A. Dedicated APS clinic
    a. Haematology
    b. Rheumatology
    c. Neurology
    d. Other, please specify specialty
    ……
    e. Joint clinic, please specify specialties participating

……
……..

B. Other Haematology clinic, please specify
……
C. Other Rheumatology clinic, please specify
……
D. Stroke clinic
E. TIA clinic
F. Other Neurology clinic, please specify
……
G. Other, please specify
……..
H. Don‘t know or uncertain

v. Arrangements for the care of patients with ischaemic stroke:

At your institution, what are the arrangements for the care of acute ischaemic stroke patients admitted to hospital?

A. Admitted to a specialist Hyperacute Stroke Unit
B. Admitted to an Acute Stroke Unit
C. Admitted to hospital under the care of the admitting medical team
D. Other – please specify
……
……
E. Don’t know or uncertain

vi. At your institution what are the arrangements for the care of patients with suspected TIA?

A. Seen in a specialist TIA clinic
B. Seen in the Emergency department
C. Other, please specify
……
……
D. Don’t know or uncertain

vii. Arrangements for laboratory testing for antiphospholipid antibodies (aPL) at your institution (tick all that apply)

A. Specialist haemostasis laboratory in University hospital
B. Laboratory in non-University hospital
C. Samples sent to another laboratory for aPL testing
D. aPL testing for lupus anticoagulant (LA) and IgG and IgM anticardiolipin (aCL) available
E. aPL testing for anti-beta 2 glycoprotein I antibodies (aß2GPI) also available
F. Other, please specify
……
G. Don’t know or uncertain

viii. Number of patients with stroke or other brain ischaemic injury that you assess each year (tick all that apply)

A. How many adult patients (>18 years) with APS-associated ischaemic stroke do you assess each year?

<5
5-10
10-20
>20 and <50
>50 and <100
Other number, please specify
……

B. How many adult patients (>18 years) with APS-associated TIA do you assess each year?

<5
5-10
10-20
>20 and <50
>50 and <100
Other number, please specify
……

C. How many adult patients (>18 years) with APS-associated cerebral infarcts, seen on brain imaging but not in the context of acute stroke, do you assess each year?

<5
5-10
10-20
>20 and <50
>50 and <100
Other number, please specify
……

D. How many adult patients (>18 years) with APS-associated white matter hyperintensities (WMH), seen on brain imaging but not in the context of acute stroke seen on brain imaging but not in the context of acute stroke, do you assess each year?

<5
5-10
10-20
>20 and <50
Other number, please specify
……

E. How many adult patients (>18 years) with APS-associated cognitive impairment do you assess each year?

<5
5-10
10-20
>20 and <50

>50 and <100
Other number, please specify
……

ix. What proportion (%) of the adult patients (>18 years) with thrombotic APS that you assess each year have APS-associated arterial thromboembolism in sites outside the brain? (tick all that apply)

a. Overall proportion (%)
<1
<5
5-10
Other proportion (%), please specify
……

b. Coronary arteries (%)
<1
<5
5-10
Other proportion (%), please specify
……

c. Upper limb arteries
<1
<5
5-10
Other proportion (%), please specify
……

d. Lower limb arteries
<1
<5
5-10
Other proportion (%), please specify
……

e. Renal arteries
<1
<5
5-10
Other proportion (%), please specify
……

f. Splanchnic arteries
<1
<5
5-10
Other proportion (%), please specify
……

g. Other arteries, overall proportion (%)

<1
<5
5-10
Other arterial sites - proportion (%), please specify
……
Please specify these other sites with arterial occlusion
……
……
……

Comments
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x. THE QUESTIONS IN THIS SECTION (x) ARE AIMED AT NEUROLOGISTS/STROKE PHYSICIANS (tick all that apply)

A. How many adult patients (>18 years) with ischaemic stroke do you assess each year?

10-20
>20 and <50
>50 and <100
>100 and <200
>200 and <300
Other number, please specify
……

B. What proportion of ischaemic stroke patients do you test for aPL? (%)

<5
>5 and <10
>10 and <20
>20 and <40
Other proportion (%), please specify
……

C. How many adult patients (>18 years) with TIA do you assess each year?

10-20
>20 and <50
>50 and <100
>100 and <200
>200 and <300
Other number, please specify
……

D. What proportion of TIA patients do you test for aPL? (%)

<5
>5 and <10

>10 and <20
>20 and <40
Other proportion (%), please specify
……

E. How many adult patients (>18 years) with cerebral infarcts, seen on brain imaging but not in the context of acute stroke, do you assess each year?

10-20
>20 and <50
>50 and <100
>100 and <200
>200 and <300
Other number, please specify
……

F. What proportion of patients with cerebral infarcts, seen on brain imaging but not in the context of acute stroke, do you test for aPL? (%)

<5
>5 and <10
>10 and <20
>20 and <40
Other proportion (%), please specify

G. How many adult patients (>18 years) with WMH, seen on brain imaging but not in the context of acute stroke, do you assess each year?

10-20
>20 and <50
>50 and <100
>100 and <200
>200 and <300
Other number, please specify
……

H. What proportion of patients with WMH, seen on brain imaging but not in the context of acute stroke, do you test for aPL? (%)

<5
>5 and <10
>10 and <20
>20 and <40
Other proportion (%), please specify
……

I. How many adult patients (>18 years) with cognitive impairment do you assess each year?

10-20
>20 and <50
>50 and <100
>100 and <200
>200 and <300
Other number, please specify
……

J. What proportion of patients with cognitive impairment do you test for aPL? (%)

<5
>5 and <10
>10 and <20
>20 and <40
Other proportion (%), please specify
……

K. How many adult patients (>18 years) with dementia do you assess each year?

10-20
>20 and <50
>50 and <100
>100 and <200
>200 and <300
Other number, please specify
……

L. What proportion of patients with dementia do you test for aPL? (%)

<5
>5 and <10
>10 and <20
>20 and <40
Other proportion (%), please specify
……

2. TESTING FOR ANTIPHOSPHOLIPID ANTIBODIES

ALL SPECIALTIES - PLEASE RESPOND TO THIS SECTION AND THE REMAINDER OF THE QUESTIONNAIRE

i. Do you have a protocol that outlines which patients should be tested for aPL for the following patient groups? (tick all that apply)

A. Ischaemic stroke
B. TIA
C. Brain imaging findings (e.g. brain infarcts, white matter hyperintensities)
D. Vascular cognitive impairment or dementia
E. Cerebral venous sinus thrombosis
F. Don't know or uncertain

ii. Criteria for aPL testing in patients with ischaemic stroke or TIA

A. Do you have an age cut-off for aPL testing? Yes/No

If 'Yes', please state your age cut-off:
……...

Comments

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B. Do you advise aPL testing in the following patient groups? (tick all that apply)

a. Ischaemic stroke
b. TIA
c. Brain imaging findings (e.g. brain infarcts, white matter hyperintensities)
d. Vascular cognitive impairment or dementia
e. Cerebral venous sinus thrombosis
f. Arterial occlusion in other sites
g. Don't know or uncertain

Comments
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C. Do you exclude patients with the following alternative causes for stroke or TIA from aPL testing (tick all that apply)

a. Large artery disease
b. Atrial fibrillation
c. Patent foramen ovale
d. Hypertension
e. Diabetes
f. Hypercholesterolaemia
g. Other, please specify
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Comments
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D. Do you test for aPL in patients if they have any of the following, regardless of regardless of a history of ischaemic stroke, TIA, or other brain ischaemic injury? (tick all that apply)

a. Systemic lupus erythematosus (SLE)
b. Autoimmune rheumatic disease
c. History of one or more episodes of unprovoked venous thromboembolism (VTE)
d. History of provoked VTE, where the environmental risk factors was disproportionally mild
e. Pregnancy morbidity (history of three early miscarriages (<10 weeks gestation), and/or one fetal death (>10 weeks gestation), and/or one intra-

uterine growth restriction or a premature birth before 34 weeks gestation due to preeclampsia, or eclampsia or placental insufficiency)

f. Thrombocytopenia, if any evidence of other autoimmune disease

iii. Do you have an age cut-off for testing patients in the categories a-f listed under ii. D. above? Yes/No

If 'Yes', please state your age cut-off:

……..……

Comments

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iv. Timing of aPL testing in relation to ischaemic stroke or TIA: Please state what advice you give in this regard (tick all that apply)

A. No restriction – i.e. test any time after acute thrombotic arterial event
B. Test acute stroke patients during their hospital admission with ischaemic stroke (i.e. during acute phase)
C. Test new TIA patients at their initial clinic visit, as soon as possible after the TIA
D. Defer initial aPL testing for at least 3 months after acute thrombotic arterial event
E. Defer initial aPL testing for another time interval after acute thrombotic arterial event, please specify

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Comments

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v. In patients with positive aPL on initial testing, what is your practice with regard to repeat aPL testing (tick all that apply

A. Repeat aPL testing after at least 12 weeks
B. Repeat aPL testing on a third occasion, regardless of whether the repeat aPL result was positive or negative
C. Further repeat aPL testing at least annually
D. Further repeat aPL testing at least every two years
E. No further aPL testing unless for specific reason, e.g. planned surgery
F. Other, please specify

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Comments

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vi. Which aPL tests do you routinely request? (tick all that apply)

A. Lupus anticoagulant
B. IgG anticardiolipin antibodies
C. IgG and IgM anticardiolipin antibodies
D. IgG, IgM and IgA anticardiolipin antibodies
E. IgG aß2 glycoprotein I antibodies
F. IgG and IgM aß2 glycoprotein I antibodies
G. IgG, IgM and IgA aß2 glycoprotein I antibodies
H. Other antiphospholipid antibodies, please specify

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vii. Requesting LA testing in patients not on anticoagulation (tick all that apply)

A. You also request a concomitant coagulation screen
B. The coagulation screen comprises prothrombin time, activated partial thromboplastin time (aPTT), thrombin time and fibrinogen Yes/No/Uncertain
   If No, please give details……..
   ……..
C. Please specify which LA test(s) is/are performed
   a. Dilute Russell's Viper Venom Time test (dRVVT)
   b. Sensitive aPTT (low phospholipids and silica as activator)
   c. Other, please specify
      ……..

Comments

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viii. Requesting LA testing in APS patients while on low molecular weight heparin (LMWH) or unfractionated heparin (UFH)? (tick all that apply)

A. You temporarily stop the LMWH/UFH routinely prior to taking the sample for LA
B. You routinely aim to take the sample during the trough period in patients on LMWH?
C. You request a concomitant LMWH/UFH anti-Xa level
D. Please specify which LA test(s) is/are performed
   a. Dilute Russell's Viper Venom Time test (dRVVT)
   b. Other, please specify
      ……

B. Don't know or uncertain

Comments

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ix. Requesting LA testing in APS patients while on warfarin/other vitamin K antagonists (VKAs) (tick all that apply)

A. You stop warfarin/VKA prior to testing for LA, with temporary heparin cover
B. You do not stop warfarin prior to testing for LA
C. You request a concomitant INR
D. Please specify which LA test(s) is/are performed
    a. dRVVT
       Please specify, if used, INR cut-offs for use of dRVVT
       ……
       Please specify if dRVVT performed on 50:50 mix with normal plasma in patients on VKA Y/N/Uncertain
    b. Taipan/Ecarin test
    c. Other, please specify
       ……..

E. Don't know or uncertain

Comments
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x. Requesting LA testing in APS patients while on a direct oral anticoagulant (DOAC) (tick all that apply)

A. You stop the DOAC for at least 48 hours or longer if renal impairment prior to testing for LA
B. You do not stop the DOAC prior to testing for LA
C. You ensure that the sample for LA testing is taken during the DOAC trough period
D. You request a concomitant DOAC activity level
E. Please specify which LA test(s) is/are performed for patients on direct anti-Xa inhibitors
    a. dRVVT
    b. Taipan/Ecarin test
    c. Other, please specify
       ……..
F. DOAC adsorbent is used for LA testing in patients on DOACs Yes/No/Uncertain

Comments
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3. OTHER BLOOD INVESTIGATIONS

i. Which of the following are included in your routine assessment of APS patients with ischaemic stroke or other brain ischaemic injury? (tick all that apply)

A. Lipid status
B. Glucose/HbAIC
C. Total homocysteine
D. Total homocysteine with B12 and folate
E. Thrombophilia screen for heritable defects
F. ANA
G. ANA and anti-DNA
H. ANA and anti-ENA
I. ANA, anti-DNA and ENA
J. Complement C3 and C4
K. Other, please specify

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Comments

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4. ANTITHROMBOTIC TREATMENT

i. Do you advise long-term antithrombotic treatment in patients in the following categories? (tick all that apply)

A. First APS-associated stroke
B. Recurrent APS-associated stroke
C. First APS-associated TIA
D. recurrent APS-associated TIA
E. APS-associated cerebral infarcts or WMH
F. APS-associated cognitive impairment
G. APS-associated arterial thromboembolism in sites outside the brain

Comments

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ii. If you opt for antithrombotic treatment in patients with ischaemic stroke, other brain ischaemic injury or arterial thromboembolism in other sites, which of the following aPL phenotypes would you regard as an indication to use antithrombotic treatment, assuming persistent aPL and, if present, moderate positive anticardiolipin and/or aß2 glycoprotein I antibodies (tick all that apply)

A. IgG anticardiolipin antibodies
B. IgM anticardiolipin antibodies
C. IgA anticardiolipin antibodies
D. IgG aß2 glycoprotein I antibodies
E. IgM aß2 glycoprotein I antibodies
F. IgA aß2 glycoprotein I antibodies
G. Single positive aPL
H. Double positive aPL
I. Triple positive aPL

Comments
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iii. Would you start antithrombotic treatment prior to establishing that aPL are persistently positive? Yes/No

Comments
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iv. If you opt for antithrombotic treatment in patients with a first APS-associated ischaemic stroke, which treatment do you advise? (tick all that apply)
A. Warfarin (or other vitamin K antagonist [VKA]) target INR range 2-3
B. Warfarin (or other vitamin K antagonist [VKA]) target INR range 2-3 with low dose aspirin (LDA) 75-100mg once daily
C. Warfarin (or other VKA) target INR range 3-4
D. warfarin (or other VKA) target INR range 3-4 with LDA
E. LDA alone
F. Other antiplatelet treatment alone. If you choose this option, please specify agents used
G. Dual antiplatelet treatment. If you choose this option, please specify:
   a. The antiplatelet agents used and doses
……
……
   b. Whether you continue the dual antiplatelet agents for 21 days
   c. Whether you continue the dual antiplatelet agents long-term
   d. Other regimen, please specify
……...
H. Direct oral anticoagulant
I. Other, please specify

Comments
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v. Do you advise that all APS patients with presumed cardioembolic stroke should be investigated for a patent foramen ovale? Yes/No

vi. Which investigations are done at your institution to identify the presence of a patent foramen ovale? (tick all that apply)

A. Transthoracic echocardiogram
B. Bubble echocardiography
C. Transoesophageal echocardiography

vii. In an APS patient in whom a patent foramen ovale is considered to be potentially causal, which of the following options do you recommend (tick all that apply)

A. That the patient should have long-term anticoagulation and the patent foramen ovale is closed
B. That the anticoagulation is continued long-term and the patent foramen ovale therefore does not need to be closed
C. That the patent foramen ovale is closed and the anticoagulation is stopped
D. The target INR range should be 2-3 (standard-intensity) as the stroke was likely cardioembolic
E. The target INR range should be 2-3 (standard-intensity) as this is the appropriate target INR for patients with APS-associated ischaemic stroke
F. The target INR range should be 3-4 (high-intensity) as the contribution of APS and the PFO to the stroke cannot be ascertained with certainty
G. The target INR range should be 3-4 (high-intensity) as this is the appropriate target INR for patients with APS-associated ischaemic stroke

Comments
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viii. In patients with a history of APS-associated TIA, when do you consider anticoagulation: (tick all that apply)

A. If there is evidence of either acute ischaemia or chronic ischaemic injury (i.e. established white matter intensities, lacunes or territorial cortical infarcts) on brain magnetic resonance imaging (MRI) (including diffusion-weighted magnetic resonance imaging [DWI])
B. Other criteria, please specify

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Comments
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ix. Which antithrombotic treatment do you advise for patients with acute APS-associated TIA(s)?

A. Warfarin (or other VKA) target INR range 2-3
B. Warfarin (or other VKA) target INR range 2-3 with low dose aspirin (LDA) 75-100mg once daily
C. Warfarin (or other VKA) target INR range 3-4
D. Warfarin (or other VKA) target INR range 3-4 with LDA 75-100mg once daily
E. LDA alone (75-100mg once daily)
F. Other single antiplatelet agent. If you choose this option, please specify
……
H. Dual antiplatelet treatment. If you choose this option, please specify
    a. The antiplatelet agents used and doses
    ……
    ……
    b. Whether you continue the dual antiplatelet agents for 21 days
    c. Whether you continue the dual antiplatelet agents long-term
    d. Other regimen, please specify
……
I. Direct oral anticoagulant
J. Other, please specify
……

Comments
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x. Which antithrombotic treatment do you advise for patients with APS-associated established (non-acute) cerebral infarct(s) associated previously with an acute stroke syndrome?

A. Warfarin (or other VKA) target INR range 2-3
B. Warfarin (or other VKA) target INR range 2-3 with low dose aspirin (LDA) 75-100mg once daily
C. Warfarin (or other VKA) target INR range 3-4
D. Warfarin (or other VKA) target INR range 3-4 with LDA 75-100mg once daily
E. LDA alone (75-100mg once daily)
F. Other single antiplatelet agent. If you choose this option, please specify agent used
G. Dual antiplatelet treatment. If you choose this option, please specify agents used and doses
……
……
H. Direct oral anticoagulant
I. Other, please specify
……

Comments
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xi. Which antithrombotic treatment do you advise for patients with APS-associated established (non-acute) cerebral infarct(s) *NOT* associated previously with an acute stroke syndrome?

A. Warfarin (or other VKA) target INR range 2-3
B. Warfarin (or other VKA) target INR range 2-3 with low dose aspirin (LDA) 75-100mg once daily
C. Warfarin (or other VKA) target INR range 3-4
D. Warfarin (or other VKA) target INR range 3-4 with LDA 75-100mg once daily
E. LDA alone (75-100mg once daily)
F. Other single antiplatelet agent. If you choose this option, please specify agent used
G.Dual antiplatelet treatment. If you choose this option, please specify agents used and doses
……
……
H.Direct oral anticoagulant
I.Other, please specify

Comments
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xii. In patients with APS-associated white matter hyperintensities of presumed vascular origin on brain MRI, what criteria do you use to decide on whether to advise antithrombotic treatment (tick all that apply)

A. Your clinical judgement
B. An expert clinical opinion (Neurologist or Stroke Physician) that anticoagulation is a reasonable treatment option (with the aim of preventing ischaemic brain injury)
B. Cognitive impairment
C. Regardless of presence of cognitive impairment

Comments
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xiii. Which antithrombotic treatment do you advise for patients with APS-associated white matter intensities?

A. Warfarin (VKA) target INR range 2-3
B. Warfarin (VKA) target INR range 2-3 with low dose aspirin (LDA) 75-100mg once daily
C. Warfarin (or other VKA) target INR range 3-4
D. Warfarin (or other VKA) target INR range 3-4 with LDA 75-100mg once daily
E. LDA alone (75-100mg once daily)
F. Other single antiplatelet agent. If you choose this option, please specify
……
G. Dual antiplatelet treatment. If you choose this option, please specify agents used and doses
……
……
H. Direct oral anticoagulant
I. Other, please specify
……..

Comments
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5. FOLLOW UP OF PATIENTS WITH APS-ASSOCIATED ISCHAEMIC STROKE, TIA, OTHER BRAIN ISCHAEMIC INJURY OR ARTERIAL THROMBOEMBOLISM IN SITES OUTSIDE THE BRAIN

i. Do you follow up all APS patients in the above categories long-term:
Yes/No

ii. If your answer to i. was 'Yes', how often do you follow up these patients for their thrombotic APS?

A. Three-monthly
B. Six-monthly
C. Annually
D. Other, please specify
……..

iii. If you do not follow up all APS patients long-term, please specify the arrangements for the patient's further management from the thrombotic APS perspective

……
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Comments
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iv. Interval MRI brain scans to assess progress on the antithrombotic regimen (tick all that apply)

A. You request interval MRI brain scans to assess progress on the antithrombotic regimen
B. If you request interval MRI brain imaging, please state the frequency:

……

C. You request MRI brain scans only if the patient has neurological symptoms to warrant this, i.e. there is a clinical indication
D. If you do MRI brain imaging in an APS patient (interval scanning or based on clinical indications), you request:
   a. MRI brain scan with SWI
   b. MRI brain scan with FLAIR
   c. MRI brain scan with SWI and FLAIR

Comments

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v. Do you refer APS patients with cognitive impairment for neurological assessment?

Yes/No

PART B: CONSIDERATION OF ANTITHROMBOTIC TREATMENT DURING PREGNANCY

i. Which anticoagulant treatment do you advise during pregnancy in APS patients with acute ischaemic stroke?

A. Standard therapeutic dose LMWH once daily
B. Standard therapeutic dose LMWH twice daily (split dose)
C. High intensity LMWH once daily
D. High intensity LMWH twice daily (split dose)
E. Intermediate dose LMWH
F. Warfarin (or alternative VKA)
G. Other, please specify

……

ii. Which anticoagulant treatment do you advise during pregnancy in APS patients with a history of previous ischaemic stroke?

A. Standard therapeutic dose LMWH once daily
B. Standard therapeutic dose LMWH twice daily (split dose)
C. High intensity LMWH once daily
D. High intensity LMWH twice daily (split dose)
E. Intermediate dose LMWH
F. Warfarin (or alternative VKA)
G. Other, please specify

……

iii. Which anticoagulant treatment do you advise during pregnancy in APS patients with acute arterial thrombosis outside the brain?

A. Standard therapeutic dose LMWH once daily
B. Standard therapeutic dose LMWH twice daily (split dose)
C. High intensity LMWH once daily
D. High intensity LMWH twice daily (split dose)
E. Intermediate dose LMWH
F. Warfarin (or alternative VKA)
G. Other, please specify

……

iv. Which anticoagulant treatment do you advise during pregnancy in APS patients with previous arterial thromboembolism outside the brain?

A. Standard therapeutic dose LMWH once daily
B. Standard therapeutic dose LMWH twice daily
C. High-intensity LMWH once daily
D. High-intensity LMWH twice daily
E. Intermediate dose LMWH
F. Warfarin (or alternative VKA)
G. Other, please specify

……

v. Which anticoagulant treatment do you advise during pregnancy in APS patients with acute cerebral venous sinus thrombosis?

A. Standard therapeutic dose LMWH once daily
B. Standard therapeutic dose LMWH twice daily (split dose)
C. High intensity LMWH once daily
D. High intensity LMWH twice daily (split dose)
E. Intermediate dose LMWH
F. Warfarin (or alternative VKA)
G. Other, please specify

……

vi. Which anticoagulant treatment do you advise during pregnancy in APS patients with a history of previous cerebral venous sinus thrombosis? Standard therapeutic dose LMWH once daily

A. Standard therapeutic dose LMWH twice daily
B. High-intensity LMWH once daily
C. High-intensity LMWH twice daily
D. Intermediate dose LMWH
E. Warfarin (or alternative VKA)
F. Other, please specify

……

vii.Do you give split dose (i.e. divided dose administered twice daily) treatment dose LMWH during pregnancy Yes/No

viii. Do you monitor anti-Xa levels in APS patients receiving therapeutic dose LMWH during pregnancy? Yes/No

ix. Use of low dose aspirin during pregnancy in thrombotic APS patients:

A. Do you advise low dose aspirin (75-150mg once daily) in addition to anticoagulation in all thrombotic APS patients during pregnancy
Yes/No

B. Please comment on why you responded "Yes" or "No" to question ix.A

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Comments on antithrombotic treatment during pregnancy

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COMMENTS – Please detail below any comments, either about the points covered above or any further issues

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Please state the country that you work in……..

Please fill in your email address……..……