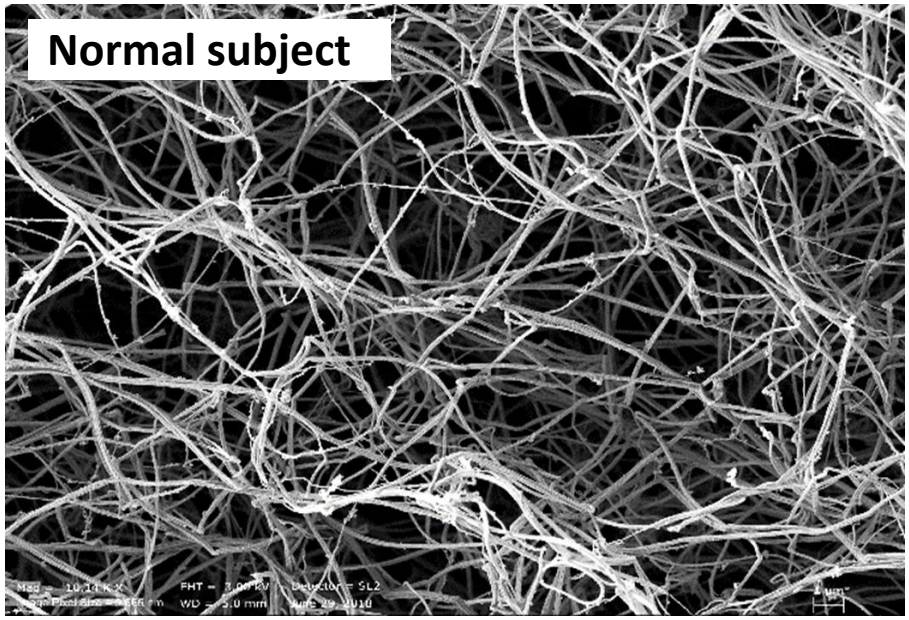
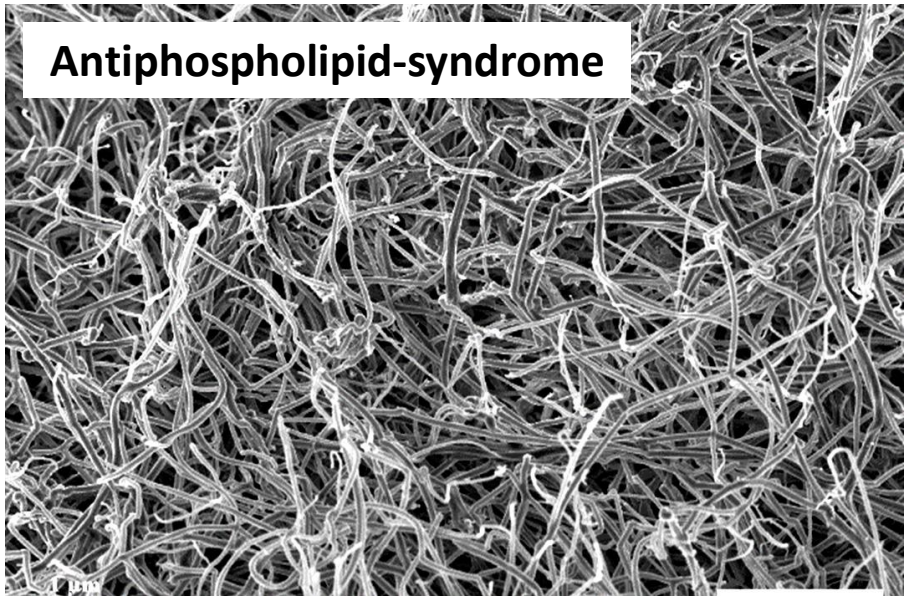




Fibrin clot density by EM (Svenungsson, *J Intern Med* 2020)

AIU

Grindelwald

2020

Anti-phospholipid syndrome

Camillo Ribi

Médecin adjoint, PD-MER

Immunologie & Allergie

CHUV

Why talk about antiphospholipid antibodies ?

Increased awareness of morbidity related to anti-phospholipid antibodies (APL)

Several high risk profiles (for both thrombosis and pregnancy complications):

- triple APL positivity
- positivity of lupus anticoagulant
- antibodies targeting domain 1 (the tail) of the beta-2GP1 molecule…

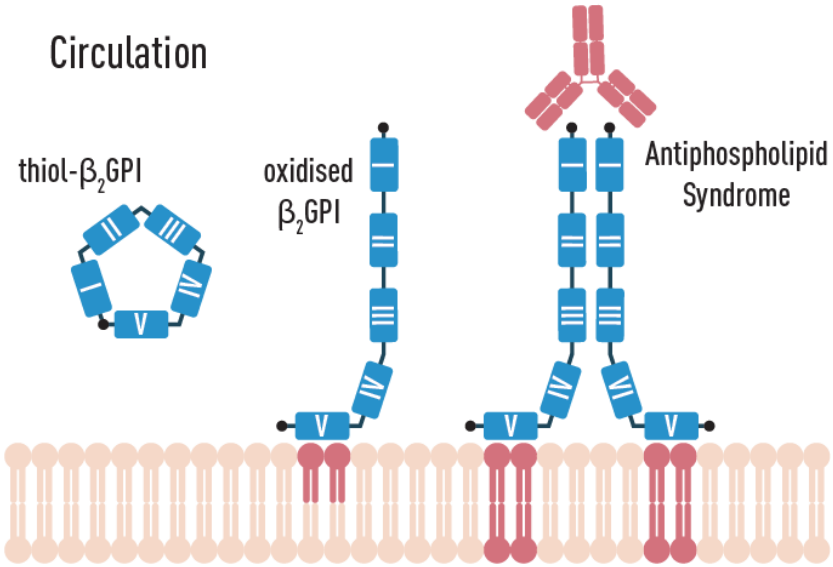
APL associated with features other than thrombosis and obstetrical complication

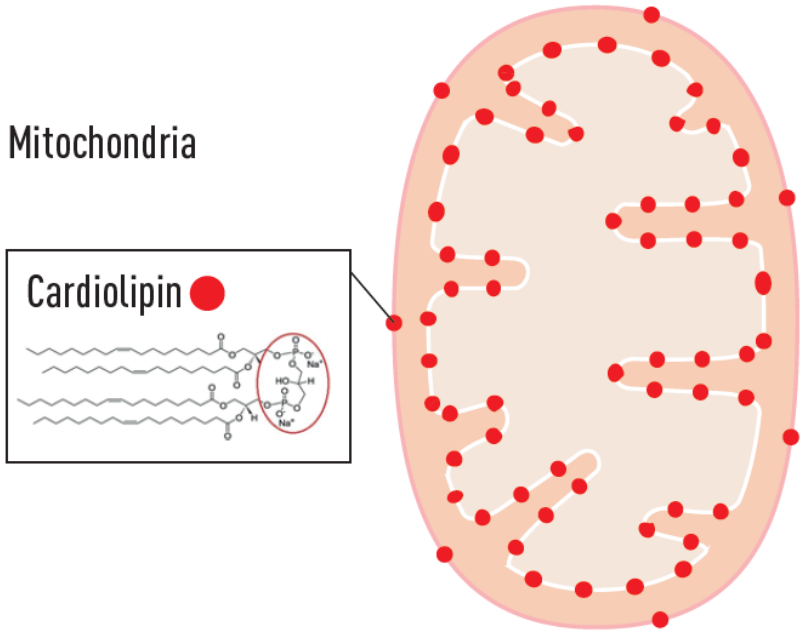
- epilepsy and other neurological diseases
- accelerated atheromatosis

Updated recommendations regarding 1° and 2° prophylaxis of APL morbidity

Much deception regarding NOAC, which are not safe in APL-syndrome

The main antigens targeted by APL antibodies





β_2 Glycoprotein-1 (β_2GPI)

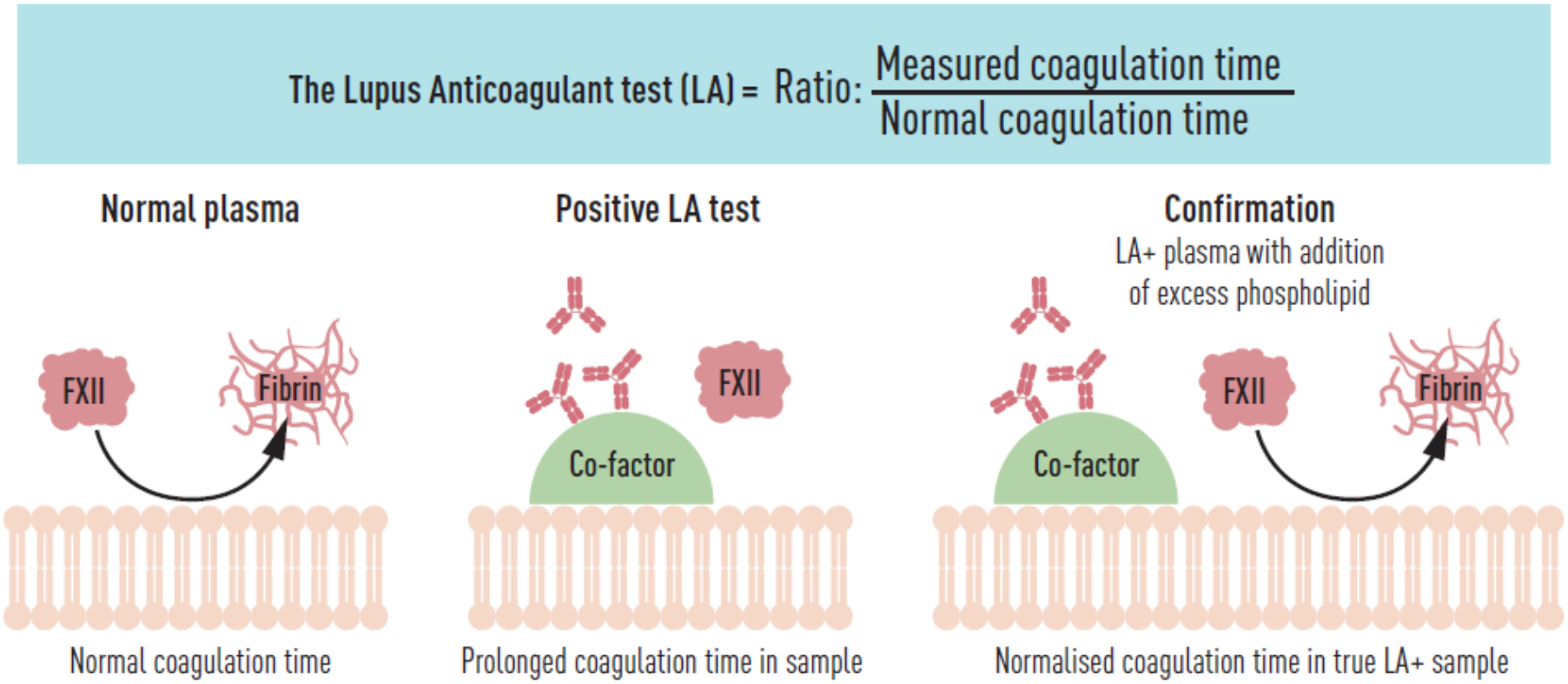
Also called apolipoprotein H
Synthesized mainly by hepatocytes
Abundant plasma protein
Scavenger molecule binding to phospholipids
Reduced (circular) and oxidized (J-shaped) conformational state

Cardiolipin (CL)

Negatively charged phospholipid
Synthesized in inner mitochondria membrane
A major constituent of inner mitochondrial membrane
Also common in bacterial membranes
Role in electron transport chain and ATP production
Role in cytochrome C release and induction of apoptosis
Conserves mitochondrial pH by trapping protons

E. Svenungsson and A. Antovic *J Intern Med* 2020

Lupus anticoagulant – ill-famed and ill-named

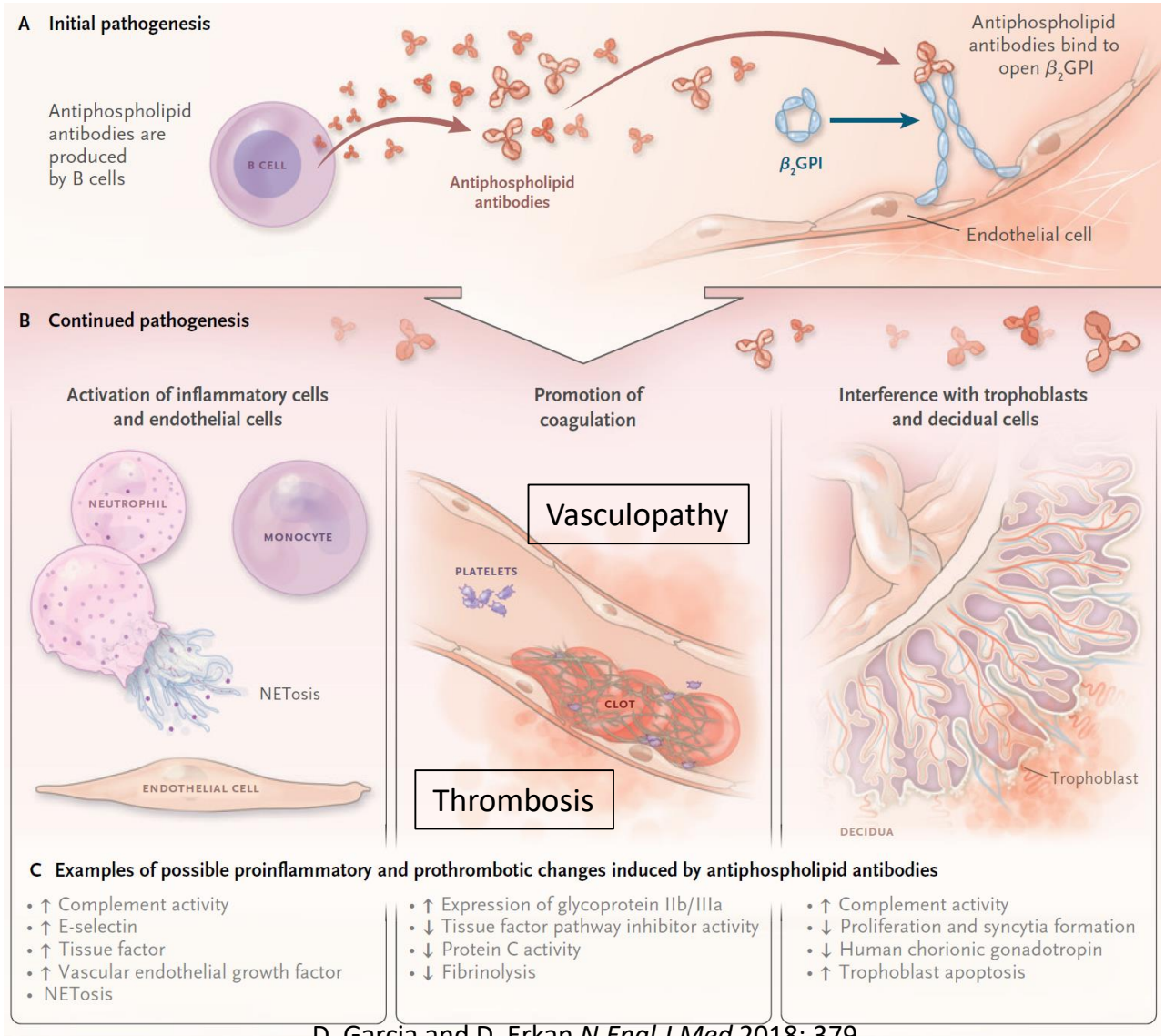


Lupus anticoagulant = functional test (interference AVK, heparine, NOAC)

Ratio ‘tested/normal coagulation time positive & not corrected by adding plasma

Normalization by adding excess phospholipids (saturation of antibodies)

Pathogenesis of anti-phospholipid syndrome



Inflammation

Adverse pregnancy outcomes

D. Garcia and D. Erkan *N Engl J Med* 2018; 379

Anti-phospholipid antibodies & - syndrome

Anti-phospholipid syndrome (APS) is characterized by:

- (recurrent) venous or arterial thrombosis and/or fetal loss
- persistently elevated levels of antibodies directed against membrane anionic phospholipids (i.e. anti-cardiolipin antibody, anti-phosphatidylserine)
- or their associated plasma proteins (i.e. β-2 glycoprotein I)
- or evidence of a circulating [in vitro] anticoagulant (lupus anticoagulans)

Distinction between APS with or without associated auto-immune diseases

- approximately half of cases are “primary” APS

Up to 5% of healthy individuals have aPL antibodies

Revised Sapporo criteria for the diagnosis of APS (2006)

Clinical criteria:

- **vascular thrombosis**:

  ≥ 1 clinical episodes of **arterial, venous, or small-vessel thrombosis** in any tissue or organ by findings from imaging studies, Doppler studies, or histopathology (superficial thrombophlebitis doesn't count)

- **pregnancy morbidity**:

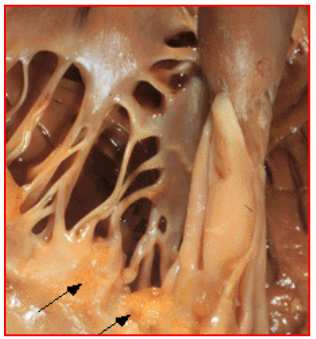
≥ **1 late-term (>10 weeks' gestation) spontaneous abortion**

≥ **1 premature births** of a morphologically healthy neonate at or before 34 weeks' gestation because of **severe preeclampsia/eclampsia** or **severe placental insufficiency**

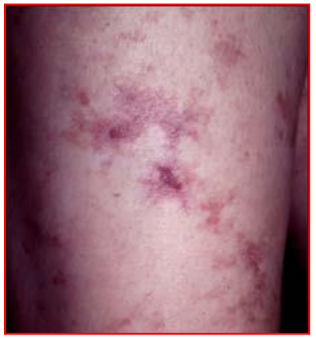
≥ **3 unexplained, consecutive, spontaneous abortions < 10 weeks' gestation**

Other classical aPL–associated clinical features

cardiac valve disease

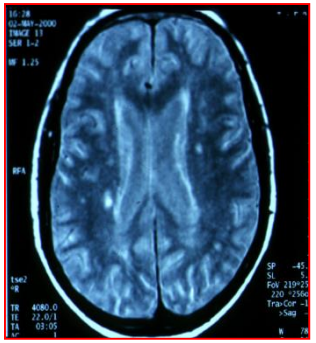


livedo reticularis



thrombocytopenia

nephropathy



neurologic manifestations

Revised criteria for the diagnosis of APS (2006)

Laboratory criteria:

(1) medium to high levels of IgG or IgM anticardiolipin (aCL); OR

(2) anti–beta-2 glycoprotein I; OR

(3) lupus anticoagulant (LA)

on **at least 2 occasions at least 12 weeks** apart

Testing for novel antibodies not recognized in the 2006 criteria can be considered if clinical suspicion is high (some are not commercially available), e.g.

- antibodies against the phosphatidylserine-prothrombin complex (PS-PT)
- antibodies recognizing the domain I epitope of beta-2 glycoprotein I
- IgA beta-2 glycoprotein I (?), anti-phosphatidylethanolamine, Annexin A5…

Prevalence of SAPL in the general population

In patients 18-50 years old,

with unprovoked first episode of venous thromboembolism (VTE)

how many fulfill the revised Sapporo criteria for anti-phospholipid syndrome ?

A ~ 1%

B ~ 5%

B ~ 10%

C ~ 20%

Prevalence of SAPL in the general population

Venous thromboembolism (VTE) most common manifestation of APS

Often also the first symptom

The risk for VTE rises when several aPL tests are positive (especially if LA+)

APL+ patients with VTE have a higher risk of VTE recurrence and mortality

Estimated prevalence of APS in venous thromboembolism 9.5%*

*based on 2013 meta-analysis on 21 studies including 5859 VTE patients)

Recent Canadian study on 491 patients 18-50 years old with 1st unprovoked VTE

- 44 (9%) fulfilling rev. Sapporo criteria (59% single +, 25% double+, 16 triple+)
- 23% with known autoimmune diseases

S. Miranda, et al. *J Thromb Haemost* 2019

Case 1: 29-year old patient of Chinese origin

Obese, no other known health issues

Family is alerted in early morning by loud crash in his bedroom

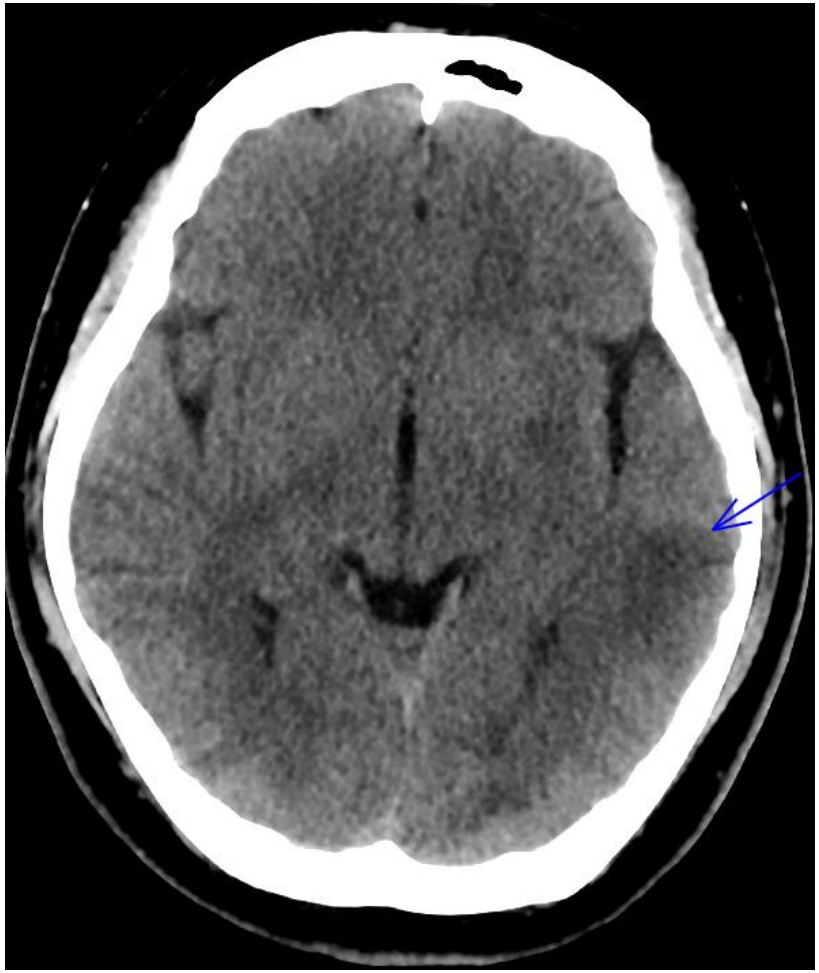
Found patient unable to speak and to stand up

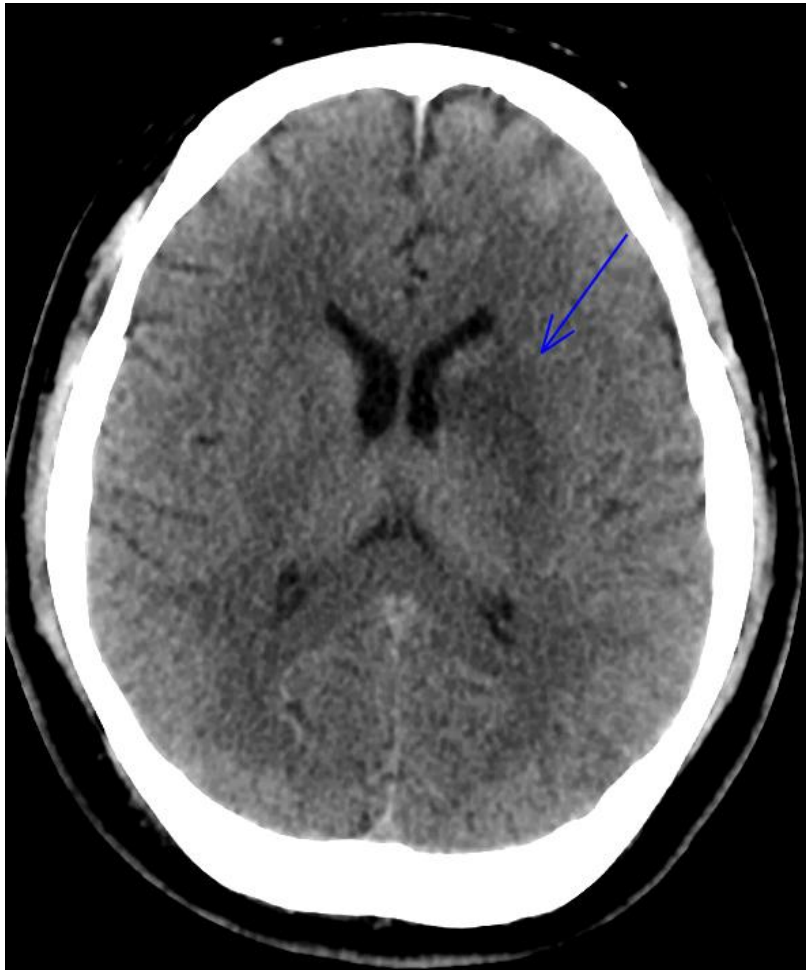
Admitted to the ER with right hemisyndrome, hemianopsia and aphasia

Apart from neurologica deficits normal physical examination

Lab workup :	Normal blood count	
	Quick	100%
	aPTT	23'' (normal 26-37'')
	Fibrinogen	normal
	Creatine kinase	235 U/l (25-190)
	CRP	2 mg/l

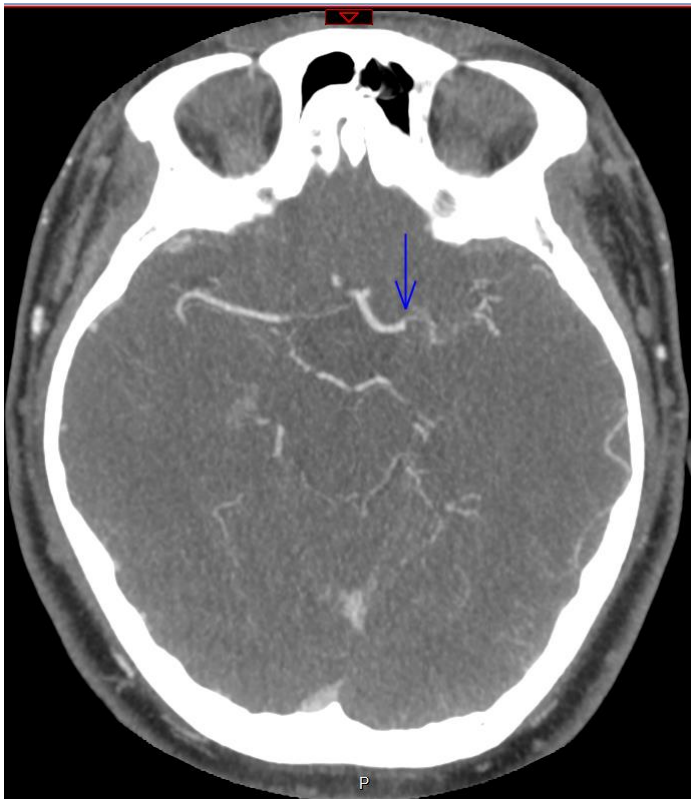
Case 1





Multiples signs of subacute ischemia left temporal lobe, Wernicke area, insula, internal capsule, globus pallidus

Case 1



Occlusion of the arteria cerebri media (M1 segment)

Mechanical thrombectomy failed

Constitution of a lage ischemic stroke without hemorragic transformation

Case 1

No arguments for carotid dissection, vasculitis or paradoxical embolism

Further lab work-up:

Moderate hypercholesterolemia	
Antithrombine III, factor V Leiden, protein S etc.	normal
Screen for anticardiolipin antibodies	negative
Screen for anti-beta2-GPI	negative
Lupus anticoagulant	positive

What would you consider in this case of acute stroke ?

A. LA test is false positive, given aPTT in the normal range at presentation

B. LA test is false positive, given absence of anti-cardiolipin / beta-2-GPI

C. Stroke sufficently explained by obesity/hypercholesterolemia

D. Higly suspicious of antiphospholipid syndrome: anticoagulate immediatly

E. Diagnosis of antiphospholipid syndrome only possible if LA+ in 12 weeks

Arterial events in APS

Reported prevalence of APL in arterial events*

14% of all strokes

11% of myocardial infarctions

*most studies based on older criteria and without repeated APL measurement

Ischemic stroke is the most common presentation of arterial APS

May arise from accelerated atheromatosis/thrombosis/embolism (Libman-Sacks)

Strong association between LA+ and stroke, especially in women < 50 years

Strokes especially frequent in Asian patients with APS

Arterial APS: higher risk of recurrence compared with those with venous APS

CAVE: do not diagnose APS on the basis of the classification criteria

normal aPTT or absence of anti-CL / anti-beta-2-GPI does not exclude LA

Secondary prevention of venous APL-related events

Unprovoked 1st venous thrombosis -> long-term anticoagulation (1b/B)

After initial therapy with unfractionated heparine or LMWH and bridging therapy:

- **treatment with VKA** with target INR 2-3 is recommended (1b/B)

Patients with **provoked first** venous thrombosis:

- anticoagulation for the duration recommended for patients without APS (5/D)

Longer anticoagulation after provoked 1st venous event could be considered in

- patients with **high-risk aPL profile**
- other risk factor for recurrence (5/D)

CAVE: APL (LA) may cause artificial prolongation of the prothrombin time leading to falsely elevated INR results (and sub therapeutic VKA dose)

Prefer INR by veinopuncture and confirm VKA efficacy by factor X activity

Direct Oral Anticoagulants (DOAC) in APS

Limited evidence about effectiveness and safety

Use of DOACs **not recommended in patients with arterial APS events** (5/D)

Rivaroxaban **not to be used if triple APL positivity** (1b/B): high risk of recurrence-

- RCT rivaroxaban vs warfarin (TRAPS trial) prematurely terminated

  Pengo V, et al. Blood 2018

- Open-label randomized trial rivaroxaban vs VKA: doubling of thrombotic risk

  Ordi-Ros J, Ann Intern Med 2019

DOACs may be considered in case of venous events:

- in patients unable to achieve target INR despite good adherence to VKA (5/D)
- those with CI to VKA in case of venous events (5/D)

Ongoing trial of apixaban (ASTRO-APS) modified to exclude arterial APS

Secondary prevention of arterial events in APS

In patients with definite APS and first arterial thrombosis:

- treatment with VKA is recommended over treatment with LDA only (2b/C)

Recommended target INR 2-3 (or INR 3-4*) considering the individual's risk (1b/B)

* no hard evidence that INR > 3 is beneficial in arterial APS

Alternatively VKA with INR 2–3 plus LDA may also be considered (4/C)

Krnic-Barrie S, et al. A. Arch Intern Med 1997;157:2101–8. and Okuma H, et al. Int J Med Sci. 2009;7:15-8

Recurrent arterial thrombosis despite adequate treatment with VKA:

1. evaluate for other potential causes
2. consider increase target INR target to 3–4

   OR addition of LDA

   OR switch to LMWH (4–5/D).

Case 2

34-year old patients followed in your practice for undifferentiated connective tissue disease with lupus traits, stable in the past years under Plaquenil.

She would like to conceive.

Lab work-up in February:	Anticardiolipin IgG 40.0 CU (N<20)
	Anticardiolipin IgM negative
	Anti-beta-2-GPI negative
	LA absent
repeated in September:	Anticardiolipin IgG 45.7 CU
	Rest negative

No history of thrombotic events; never pregnant

Case 2

What would you do in this patient with connective tissue disease, moderately positive IgG to cardiolipin, and no history of adverse events related to APL ?

A. No need to treat

B. Aspirine cardio

C. Aspirine cardio only if pregnant

D. Aspirine cardio now and prophylactic LMWH if pregnant

Primary prophylaxis in patients tested positive for APL

Evidence for a protective effect of LDA in APL+ individuals is low

- Cochrane review 2018 (9 trials, > 1000 patients): no proof of efficacy or harm
- Metaanalysis 2014: OR 1st venous/arterial thrombosis with LDA 0.5 (0.27-0.93)
  but mostly observational/retrospective studies
- RDBPC APLASA study (98 APL+ patients, 2/3 with SLE) : no benefit of LDA

Latest recommendation (expert-based): EULAR 2019

Stratification based on aPL risk profile:

High risk	LA+ with/without moderate-to-high titre aCL or a-β2GPI IgG or IgM
Moderate	Moderate-to-high titre aCL or anti-β2GPI IgG or IgM without LA
Low risk	Low-titre aCL or anti-β2GPI IgG or IgM and absent LA

Primary prophylaxis with LDA (EULAR)

1. Asymptomatic APL+ with **high-risk APL profile** with or without traditional risk factors -> prophylactic LDA is recommended (2a/B)
2. SLE patients APL+ and no history of thrombosis or pregnancy complications
   A. with **high-risk APL profile** -> prophylactic LDA is **recommended** (2a/B)
   B. with **low-risk aPL profile** -> prophylactic LDA **may be considered** (2b/C)
3. Non-pregnant women with/without SLE and **history of obstetric APS only** -> prophylactic LDA after risk/benefit evaluation recommended (2b/B)

Level of evidence: 1a: systematic review of RCTs; 1b: individual RCT; 2a: systematic review of cohort studies; 2b: individual cohort study (and low-quality RCT); 3a: systematic review of case–control studies; 3b: individual case-control study; 4: case series and poor-quality cohort and case-control studies; 5: expert opinion without explicit critical appraisal, or based on physiology, bench research or 'first principles'.

Grade of recommendation: A: consistent level 1 studies; B: consistent level 2 or 3 studies, or extrapolations from level 1 studies; C: level 4 studies or extrapolations from level 2 or 3 studies; D: level 5 evidence or troublingly inconsistent or inconclusive studies of any level.

Special situations beyond LDA

Asymptomatic APL+ individuals with APL and no underlying autoimmune disease

- strict control of cardiovascular risk factors
- prophylactic LMWH in high-risk situation (surgery, immobilization, puerperium)

Task force 13th Int. Congress on Antiphospholipid Antibodies. Ruiz-Irastorza G, Lupus 2011;20:206-18

Asymptomatic APL+ patients with SLE

- control of traditional risk factors (smoking cessation, oestrogen avoidance)
- adding LDA to HCQ treatment seem to offer additional benefit (low LoE)

Arnaud L, et al. Autoimmun Rev 2015;14:192–200

Asymptomatic APL-positive patients without SLE

- Some evidence of a protective effect of HCQ against thrombosis
- Controlled trial (APS ACTION HCQ trial) terminated for logistic reasons

Erkan D, et al. Lupus 2018

Hydroxychloroquine in APL-syndrome

APS associated with SLE

HCQ may reduces the risk of thrombosis

Thromboprotective effect possibly confounded by concomitant use of ASA

Lumina study: Hos KT, Rheumatology 2005; Greek cohort: Tektonidou MG, Arthritis Rheumatism 2009; Kaiser R, Ann Rheum Dis 2009

Petri M, Curr Rheumatol Rep 2011; Schmid-Tanguy A, et al. J Thromb Haemost 2013

Improved pregnancy outcomes in APL-related pregnancy complications with HCQ

Sciascia S, et al. Am. J. Obstet. Gynecol 2016. Retrospective data only

Ongoing randomised controlled trial in pregnancy (HYPTIA)

APS without SLE

Thromboprotective effect of HCQ in primary APL syndrome

Schmidt-Tanguy A, J Thromb Haemost, 11 (2013), pp. 1927–1929

Case 3

40-year old patient of Portuguese origin

Gave birth 3 years ago to a girl with intrauterine growth retardation

Neonatal thrombopenia (9 G/l)

Maternal anti-thrombocyte antibodies (« compatible with allo-immunization »)

In the following 2 years 3 consecutive fetal losses (4, 8 and 11 weeks of gestation)

Positive for anticardiolipin antibodies

Patient is in good health and does not smoke

No history of thromboembolic or autoimmune diseases

Physical examination normal

Case 3

Routine lab:

ESR 7mm/h, Full blood count normal

Chemistry normal

Urine sediment: slight hematuria and leucocyturia, without proteinuria

ANA 1:320 with homogenous immunofluorescence

Positive ENA screen with anti-SSA

Anti-TPO and anti-thyreoglobulin Ab strongly positive, TSH 8.5 mU/l

Complement C3 **0.63** g/l (N: 0.75-1.4), C4 normal (confirmed)

Anticardiolipin IgM **16** (N<12.5 MPL), no IgG, no anti-B2-GPI, LA absent

Antiphospholipid workup 3 months later: negative

Case 3

What would you propose to this person who wants a 2nd child ?

Obstetrical APS

Most frequent acquired risk factor for treatable cause of recurrent pregnancy loss

Risk for adverse pregnancy outcomes highest:

- in women with isolated positive LA
- in patients having simultaneous presence of aCL, aβ2GPI and LA

Other risk factors for adverse obstetrical outcomes:

- SLE
- History of vascular thrombosis
- Prior adverse obstetrical outcome

Management of APL positivity in pregnancy

High-risk APL profile, no history of thrombosis or adverse pregnancy outcomes (with/without SLE)	Before conception	LDA	
	During pregnancy	LDA	5/D
	Postpartum period	LDA	
APL+ and a history of 'non-criteria adverse pregnancy outcomes (eg. two consecutive miscarriages < 10 week or delivery > 34 weeks due to severe pre-eclampsia/eclampsia)	Before conception	-	
	During pregnancy	LDA +/- prophylactic LMWH	5/D
	Postpartum	No recommendations	
APL+ and previous preterm delivery without severe placental insufficiency	During pregnancy	LDA to be considered	
Intermediate/low-risk APL and **negative history**	During pregnancy	LDA to be considered	

Level of evidence: 4 = case series and poor quality control or case-control studies; 5`= expert opinion without explicit critical appraisal, or based on physiology, bench research or 'first principles'. Grade of recommendation: C = level 4 studies or extrapolations from level 2 or 3 studies; D = level 5 evidence or troublingly inconsistent or inconclusive studies of any level.

Management of APS in pregnancy

Obstetrical APS	Before conception	LDA	
	During pregnancy	LDA + pro. LMWH	2b/B
	Postpartum period	LDA + LMWH (6w)	4/C
Obstetrical APS and history of thrombosis OR **Vascular APS without obstetrical APS**	Before conception	AVK	
	During pregnancy	LDA + adjusted LMWH	4/C
	Postpartum period	AVK	
Obstetrical APS and adverse pregnancy outcomes despite LDA + prophyl. LWMH	During pregnancy	LDA + adjusted LMWH OR Hydroxychloroquine OR Prednisolone 1st trimester OR IVIG	5/D 4/D 4/D 5/D

Level of evidence: 4 = case series and poor quality control or case-control studies; 5`= expert opinion without explicit critical appraisal, or based on physiology, bench research or 'first principles'. Grade of recommendation: C = level 4 studies or extrapolations from level 2 or 3 studies; D = level 5 evidence or troublingly inconsistent or inconclusive studies of any level.

When to look for anti-phospholipid antibodies ?

- Thrombosis (e.g. VTE, stroke/TIA, myocardial infarction), especially if recurrent, at an earlier age, or in the absence of risk factors
- Miscarriage (especially late trimester or recurrent)
- Premature birth – preeclampsia
- Heart murmur, cardiac valvular vegetations or pulmonary hypertension
- Thrombocytopenia or hemolytic anemia
- Unexplained nephropathy
- Non-thrombotic neurologic symptoms (e.g. migraine headaches, seizures, chorea, transverse myelitis, polyradiculoneuritis, dementia with autoimmunity)
- Unexplained adrenal insufficiency
- Avascular necrosis of bone in the absence of other risk factors…

Essential points in anti-phospholipid syndrome

APL+ may be more common in general population than previously thought

Transient APL+ common after infections and not associated with clinical APS

Search for APL in case of recurrent/severe thrombotic episodes, in the young

Every patient with SLE should be screened for anti-phospholipid antibodies

Weak evidence supporting primary prophylactic low dose aspirine in APL+

APL persistence may be associated with increased CV risk (beyond thrombosis)

APS usually means lifelong anti-coagulation

However, one has to look beyond the mere coagulation problematic

No evidence to support target INR > 3 in APS (excluding refractory cases)

Novel oral anticoagulants (NOAC) are not safe in the setting of APS

HCQ may prevent APS events by anti-aggregant and immunologic mechanisms