

Síndrome Antifosfolípido: Áreas de consenso y áreas grises

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Consensus

Definition

- **Clinical Features**

- Thrombosis

- Venous/arterial

- Pregnancy morbidity

- Early loss (<12w)

- Foetal death (>12w)

- Prematurity

- Pre-eclampsia

- **Antibodies**

- anti- β 2 GP1

- aCL

- **LA: Not an Ab**

Other clinical features

Microangiopathy: Also Criteria

- **Renal**
- **Heart**
- **Skin: Legs ulcers**
Skin necrosis
Livedo Reticularis

Other clinical features

- **Trombocytopenia**
- **Hemolytic Anemia**
- **Hypertension**
- **Cardiac Valve**
- **Chronic headache**
- **Epilepsy**
- **Corea**
- **Transverse Myelitis**

No thrombotic mechanism proven

Thrombotic APS

- **Venous Thrombosis**
- **Arterial Thrombosis**
- **Recurrent Thrombosis**
- **TMA**
- **Others**

Venous thromboembolism

American College of Chest Physicians VTE treatment

- Malignancy related**
- Provoked: Trigger factor identifiable**
- No Provoked: Genetic or acquired thrombophilia**

Venous thrombosis in APS

- **No provoked: Long-term anticoagulation**
- **Provoked: Stratification:**
 - Trigger factor**
 - Localization**
 - Doppler: Thrombi status**
 - D-Dimers level one month later**
 - Venous insufficiency**
 - aPL profile**

Recommendations:

Secondary thromboprophylaxis

- Patients with either arterial or venous thrombosis and aPL who do not fulfil criteria for definite APS should be managed in no different way than the general population.**

Definite APS and first venous thrombosis

- **VKA with a target INR 2-3 is recommended**
- **Unprovoked first venous thrombosis, VKA be continued long-term**
- **Provoked first venous thrombosis, therapy should be continued for a duration recommended for non-APS patients according to international guidelines**
- **Longer anticoagulation could be considered in patients with high-risk aPL profile in repeated measurements or other risk factors for recurrence**

Recurrent venous thrombosis on VKA therapy

- **Investigation of, and education on, adherence to VKA treatment, along with frequent INR testing**
- **If target INR 2-3 had been achieved, addition of LDA, increase of INR target to 3-4, or change to LMWH**

Definite APS and first arterial thrombosis

- Treatment with VKA is recommended over treatment with LDA only
- VKA with INR 2-3 plus LDA or INR 3-4 is recommended, considering the individual's risk of bleeding
- **Recurrent** arterial thrombosis, despite adequate treatment, after evaluating for other potential causes, an increase of target to INR 3-4, addition of LDA

Pregnancy: Conventional Treatment

- Low-dose aspirin \pm S.C. injections of unfractionated or low molecular weight heparin**
- Around 70% of pregnant women with APS will deliver a viable live infant.**

Grey areas

“Seronegative APS”

- **Patients with recurrent thrombosis or pregnancy morbidity**
- **No other diseases identifiable**
- **Other non-criteria features of APS**
- **Negative for aCL, anti- β 2 GPI and LA**

Antiphospholipid antibodies

- **Anti- β 2-glycoprotein 1**
- **Anti-cardiolipin**
- **Lupus anticoagulant**

**Coagulation times prolonged
(DRVVT and/or APTT)**

Non-criteria aPL

- **Phosphatidylserine (PS)**
- **Phrothrombin (PT)**
- **Phosphatidylserine/Phrothrombin (PS/PT)**
- **β -2 Glycoprotein IgA isotype**
- **β -2 Glycoprotein I Domain I (β -GPI-DI)**

Phrothrombin (PT)

- **aPT detected by ELISA, using PT or aPS/PT, as antigen.**
- **aPT and aPS/PT can co-exist but seem to belong to different populations of autoantibodies.**
- **Potential antigenic targets for the lupus anticoagulant (LA)**

Systematic review on aPTT and aPTT and aPS/PT

- **7,000 patients and controls from 38 studies analysing aPTT and 10 aPS/PT**
- **aPTT: OR 1.82; 95%CI 1.44-2.75**
- **aPS/PT: OR 5.11; 95%CI 4.2-6.3**

Sciascia S et al. Systematic review. Thromb Haem 2014

Phosphatidylserine/Prothrombin

- **Prothrombin/Phosphatidylserine**

Specificity: 51%

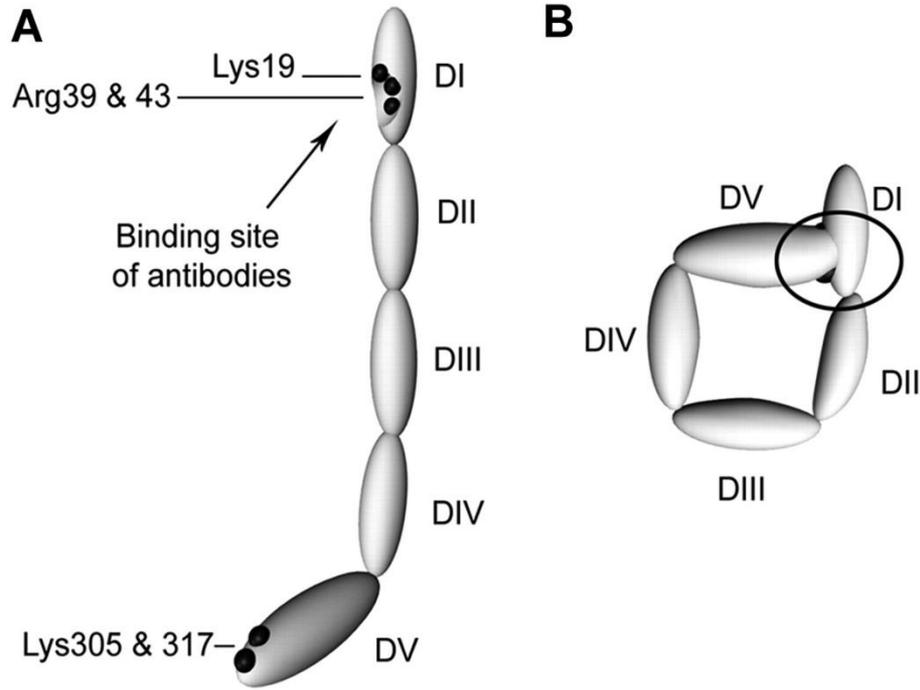
Sensitivity: 91%,

PPV: 5.9

NPV:0.5

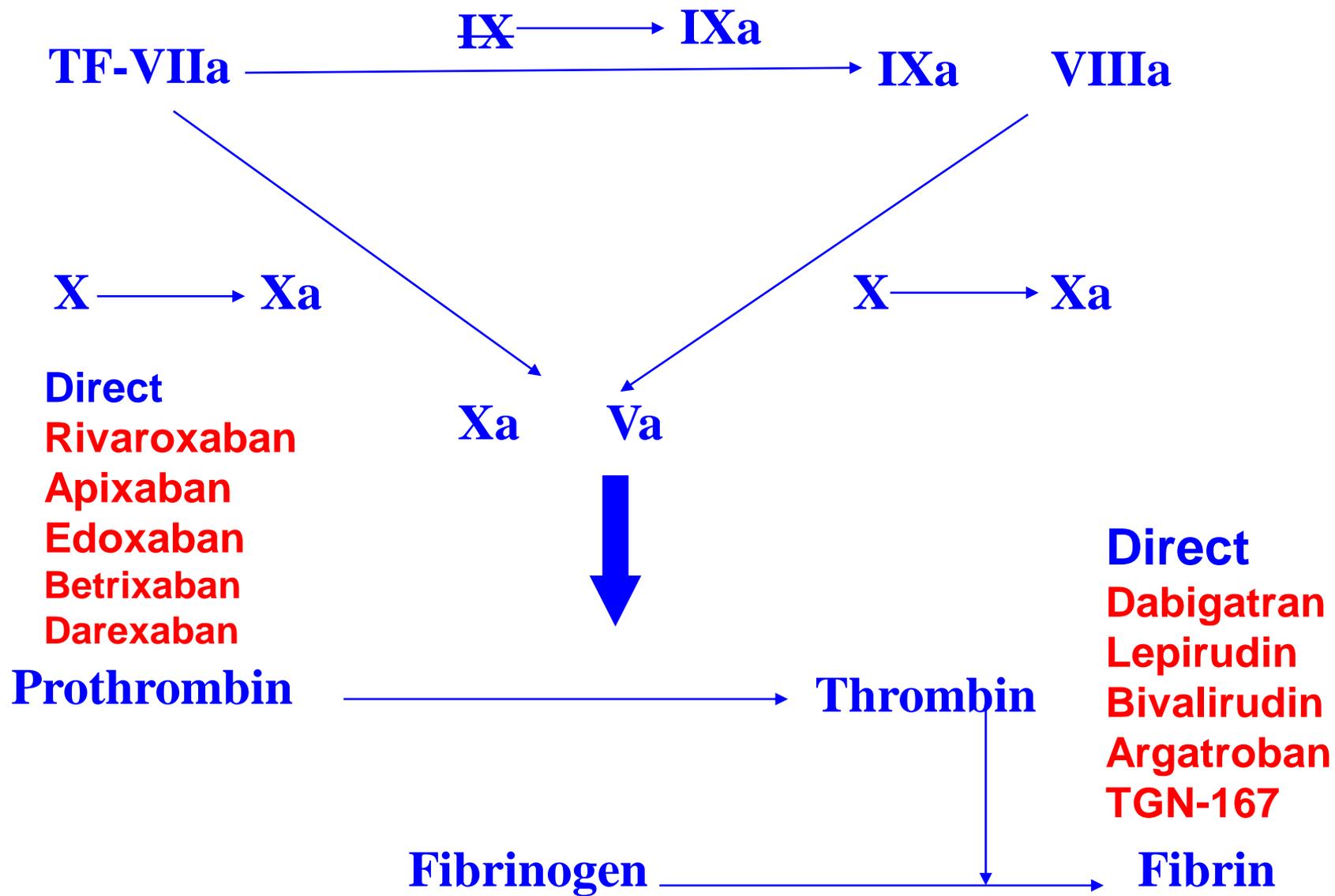
- **IgG aPS/PT detection might contribute to a better identification of patients with APS**

β -2 Glycoprotein I Domain I



The presence of aDI raised the hazard ratio for APS by 3–5 fold. IgG a β_2 GPI aDI were associated with thrombotic but not obstetric complications in patients with APS.

Target of direct oral anticoagulant



Which are the DOACs advantages?

- **Simplified dosing regimen**
- **No dietary restrictions**
- **Predictable anticoagulation and no need for routine coagulation monitoring**
- **Can be given at fixed doses**

Reduced potential for food and drug interactions

No Monitoring

Less impact on patient's life

Improved compliance

Reduced costs

Improved QoL

Improved benefit-risk profile

Mavrakanas T et al. Pharmacol Ther 2011;130:46–58

DOACs and APS

- **Rivaroxaban should not be used in patients with high risk of thrombosis (triple aPL positivity) and venous thrombosis.**
- **Based on the current evidence, we do not recommend use of DOACs in patients with definite APS and arterial events, due to high risk of recurrent thrombosis**

Thrombotic Microangiopathy

- **97 patients with SLE renal TMA**
- **Review of outcome with different treatments: VKA or LDA**
- **Adjusted for other factors such as IS treatment:**
 - Acute lesions in histopathology: VKA**
 - Chronic lesions: LDA**
- **Pathologist should describe histological changes in details**

Pregnancy Treatment: Other Approaches

- **Low dose prednisolone**
- **Hydroxychloroquine**
- **Pravastatin**

Low-Dose Prednisolone

- **Low-dose prednisolone improved the rate of live births in refractory aPL -related pregnancy loss(es) up to 61%**

Bramham et al. Blood 2011

- **Rationale: Inflammatory mechanisms such as complement activation**

Hydroxychloroquine

A new mouse model of obstetric APS:

- aPL antibodies induce metabolic changes in placenta and fetal brain measured by proton magnetic resonance spectroscopy.
- Using radiolabeled aPL antibodies and SPECT/CT the placenta and fetal brain were identified as target organs in APS *in vivo*.
- Hydroxychloroquine (HCQ) prevents placental and neurodevelopmental abnormalities in APS.
- HCQ inhibits complement *in vitro* and *in vivo*.

Hydroxychloroquine

- **Total: 180 pregnancies (96 women)**
- **Group A: HCQ before and during pregnancy:
65 pregnancies (31 women)**
- **Group B: NO HCQ
115 pregnancies (65 women)**

HCQ--Multivariate analysis

- The association of HCQ use with a reduction on aPL-related complications in pregnancy was confirmed (OR 2.2; 95% CI 1.2, 136.1; $p=0.04$).
- Previous pregnancy morbidity (OR 12.1; 95% CI 1.4, 134.3; $p=0.03$) and triple aPL positivity (OR 2.6; 95% CI 1.9, 21.8; $p=0.04$) were confirmed as independent factors for poor pregnancy outcome

Statins in pregnancy

- **Classified as drug X by the FDA**
- **Recent observational studies did not report an increased risk of congenital anomalies with statin exposure in pregnancy when compared to control groups or the prevalence of congenital anomalies in the general population”.**

The risks of statin use in pregnancy: A systematic review. Karalis DG et al. J Clin Lipidol, 2016

Pravastatin and pregnancy

- **Patients who received pravastatin exhibited increased placental blood flow and improvements in PE features.**
- **In the control group, all deliveries occurred preterm and only 6 of 11 neonates survived. Out of the 6 surviving neonates, 3 showed abnormal development.**

Conclusions

- **Consensus:**

Clinical features

Laboratory: aCL, anti-Beta2 GPI, LA

Treatment: Guidelines

- **Grey:**

Laboratory: aPS/PT, new criteria?

Treatment: DOAC use

Myicroangiopathy

Conclusions

Consensus: Conventional treatment

Grey: Refractory Obstetric APS

- **Low dose prednisolone**
- **Hydroxychloroquine**
- **Pravastatin**