National and Kapodistrian
University of Athens

EULAR Centre of Excellence
Joint Academic Rheumatology Program

ΑΝΤΙΦΩΣΦΟΛΙΠΙΔΙΚΟ ΣΥΝΔΡΟΜΟ

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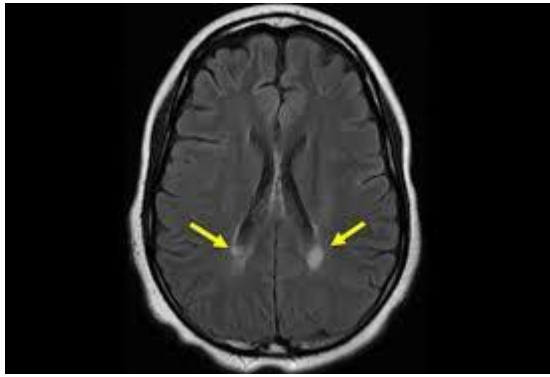
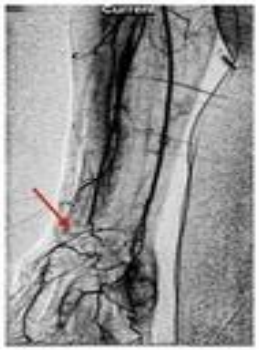
Υπεύθυνη Ρευματολογικής Μονάδας
Α' Προπαιδευτική Παθολογική Κλινική, ΓΝΑ 'Λαϊκό', ΕΚΠΑ

Περίγραμμα ομιλίας

- ΠΑΘΟΓΕΝΕΙΑ
- ΕΠΙΔΗΜΙΟΛΟΓΙΑ
- ΔΙΑΓΝΩΣΗ
- ΚΛΙΝΙΚΗ ΕΙΚΟΝΑ
- ΘΕΡΑΠΕΙΑ



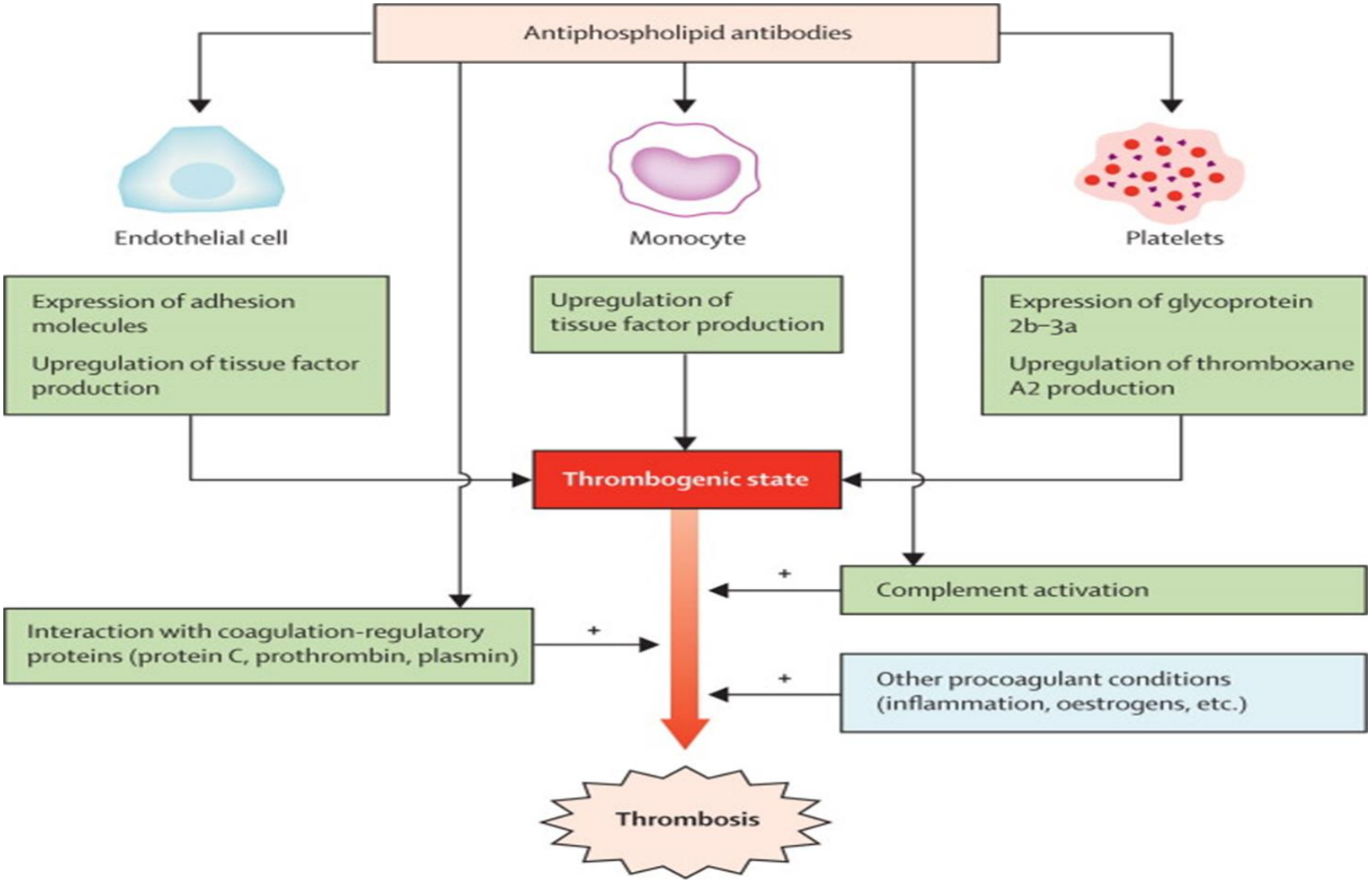


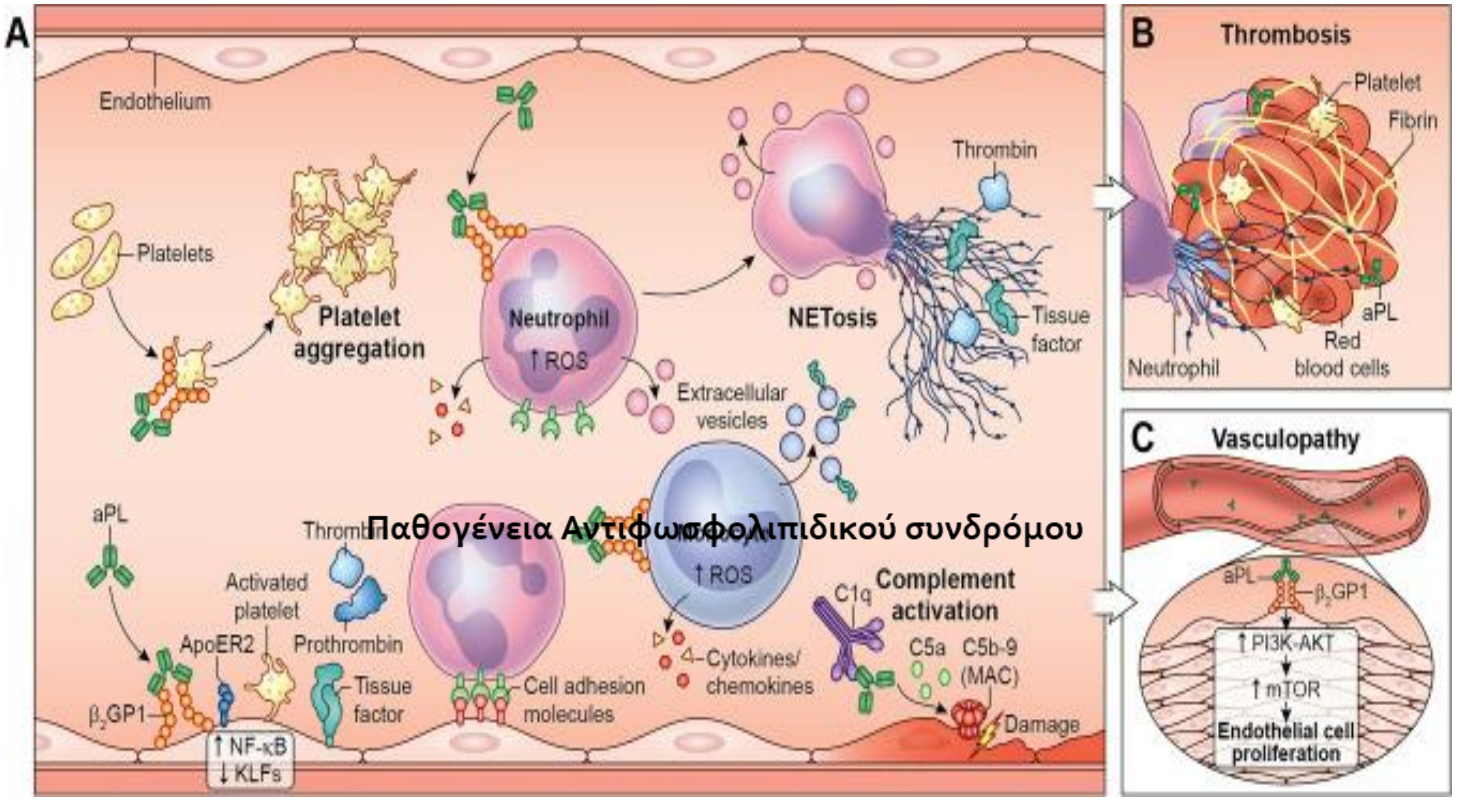
ΑΝΤΙΦΩΣΦΟΛΙΠΙΔΙΚΟ ΣΥΝΔΡΟΜΟ (APS)

Χρόνια αγγειοαποφρακτική νόσος με επεισόδια αρτηριακής ή/και φλεβικής θρόμβωσης, εμβρυϊκό θάνατο και θετικά αντιφωσφολιπιδικά αντισώματα (aPL)”

Hughes G, Br Med J 287:1088-1089, 1983

Παθογένεια Αντιφωσφολιπιδικού συνδρόμου





A. Endothelial cells increase expression of tissue factor (TF) and adhesion molecules. Complement damages the endothelium via the membrane attack complex (MAC) and acts as a chemoattractant via C5a. Monocytes express TF and cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and type I interferons (IFNs), and release microparticles. Neutrophils produce reactive oxygen species and release neutrophil extracellular traps (NETs).
B. NETs form an intravascular scaffold that promotes thrombus accretion.
C. Chronic activation of the endothelium by aPL can result in progressively occlusive vasculopathy

Knight S, Semin Immunopathol. 2022

Journal of Autoimmunity 128 (2022) 102813

Contents lists available at ScienceDirect

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journal homepage: www.elsevier.com/locate/jautimm

Cardiovascular disease risk in antiphospholipid syndrome: Thrombo-inflammation and atherothrombosis

Maria G. Tektonidou *

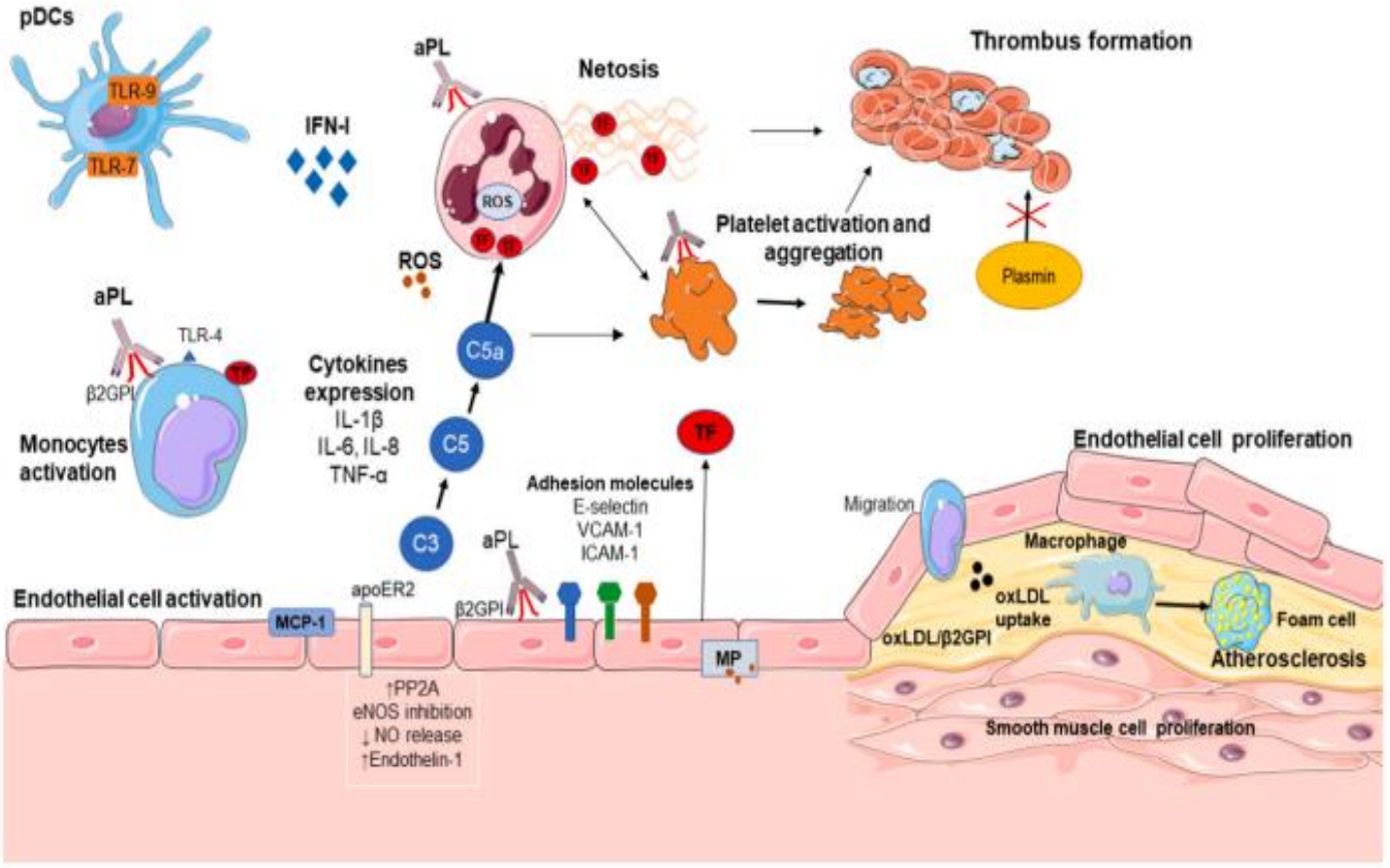


Fig. 1. Immuno-thrombo-atherogenic pathogenetic pathway in Antiphospholipid syndrome

Some mechanistic highlights of APS pathophysiology

Cell or pathway	In vitro, aPL…	In patients, we can find…
Endothelial cells	Increase expression of tissue factor and adhesion molecules [33, 34]	More endothelium-derived microparticles [35, 36]
Platelets	Induce activation under shear stress [37]	Increased platelet-leukocyte aggregates [38]
Monocytes	Trigger expression of tissue factor [39–42] and pro-inflammatory cytokines [43–45]	Increased tissue factor-expressing monocytes [46–48]
Neutrophils	Promote release of prothrombotic neutrophil extracellular traps (NETs) [49]	High levels of circulating NETs [49] and anti-NET antibodies [50]
Complement	Trigger cell lysis as measured by modified Ham test [51]	High levels of complement split products [52–54]
Coagulation	Interfere with coagulation inhibitors, especially protein C and antithrombin [55, 56]	High levels of the active free thiol form of factor XI [57]
Fibrinolysis	Interfere with activity of tissue plasminogen activator [58]	High levels of plasminogen activator inhibitor-1 (PAI-1) [59–61]

Knight S, Semin Immunopathol. 2022

Type I IFN pathway

- ✓ *Type I interferon signature* in primary APS patients

  Grenn RC, ARD 2017

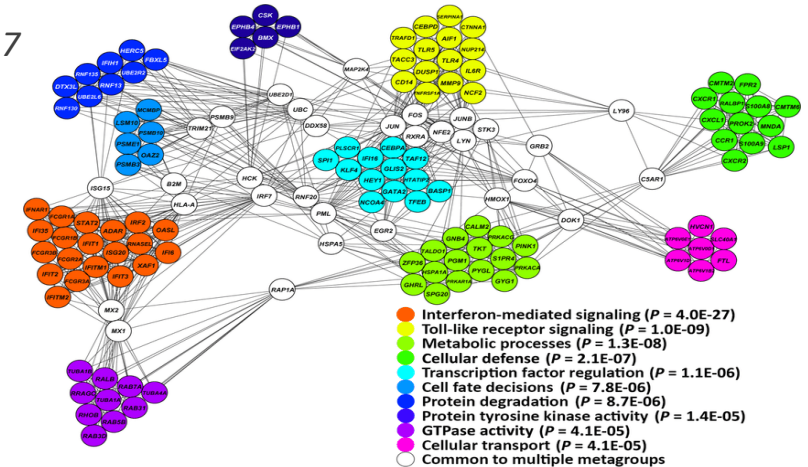
  van den Hoogen LL, ARD 2017

- ✓ ↑Galectin-9 levels in patients with SLE, SLE+APS and PAPS ($p<0.05$)
  correlated with IFN-score, disease activity and tissue factor expression

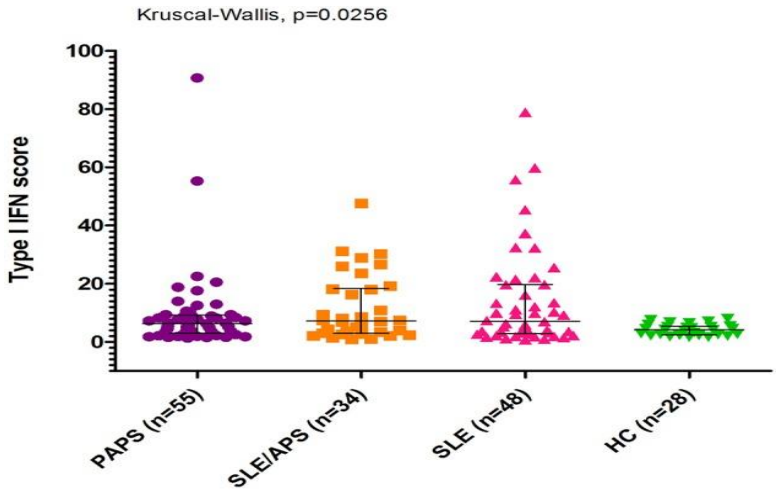
  van den Hoogen LL, ARD 2018

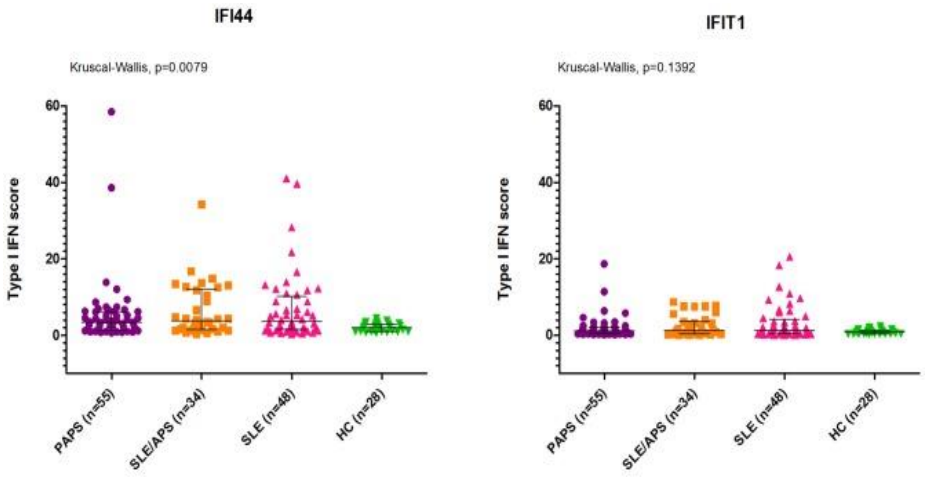
- ✓ *Transcriptome analysis of neutrophils* from 9 PAPS patients:
  overexpression of genes relevant to IFN signaling

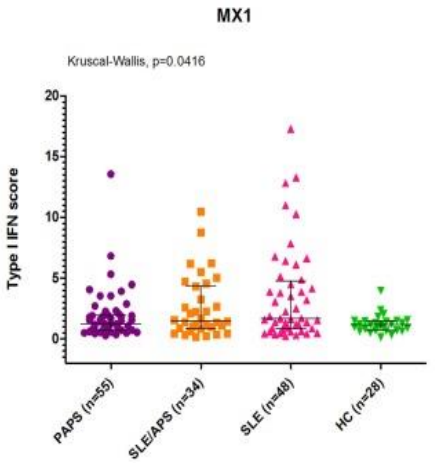
Knight J, JCI insight 2017

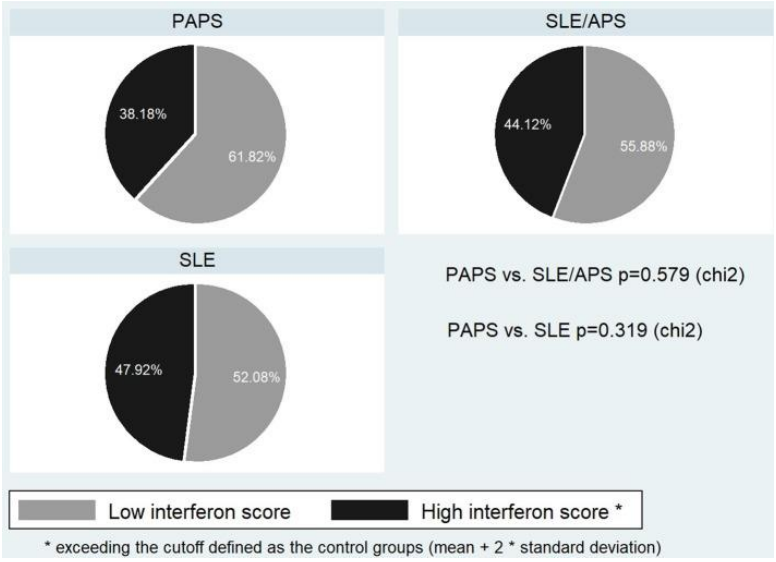


Type I IFN pathway









Palli E, Kravvariti E, Tektonidou MG. Front Immunol 2019

Journal of Autoimmunity 104 (2019) 102311

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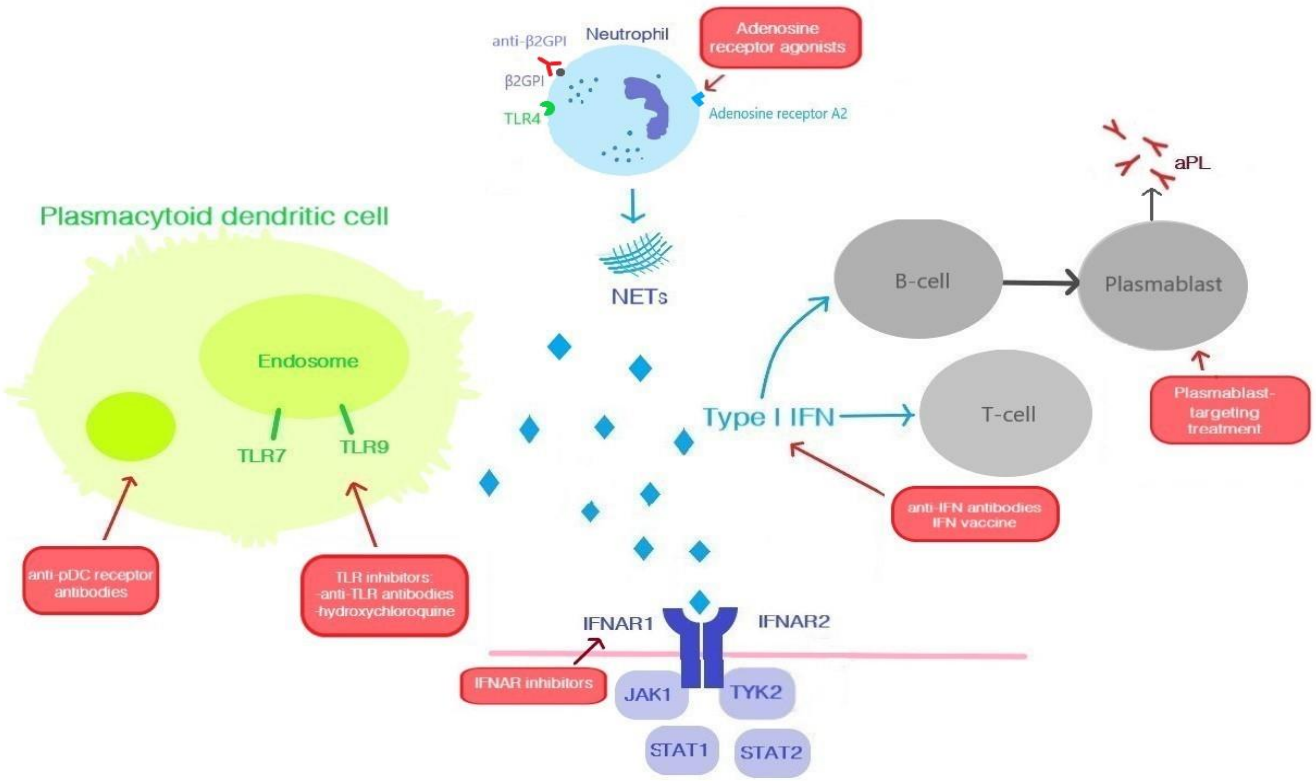
journal homepage: www.elsevier.com/locate/jautimm

Type I interferon gene expression in antiphospholipid syndrome: Pathogenetic, clinical and therapeutic implications

Eleni Xourgia, Maria G. Tektonidou*



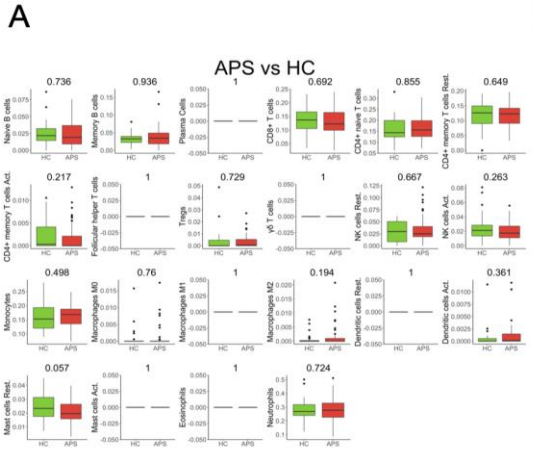
ThrPAPS vs HCs

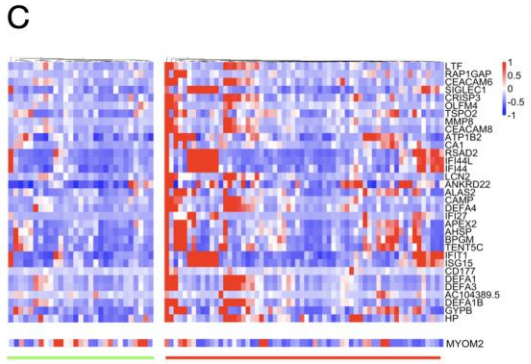
Whole blood RNA Sequencing

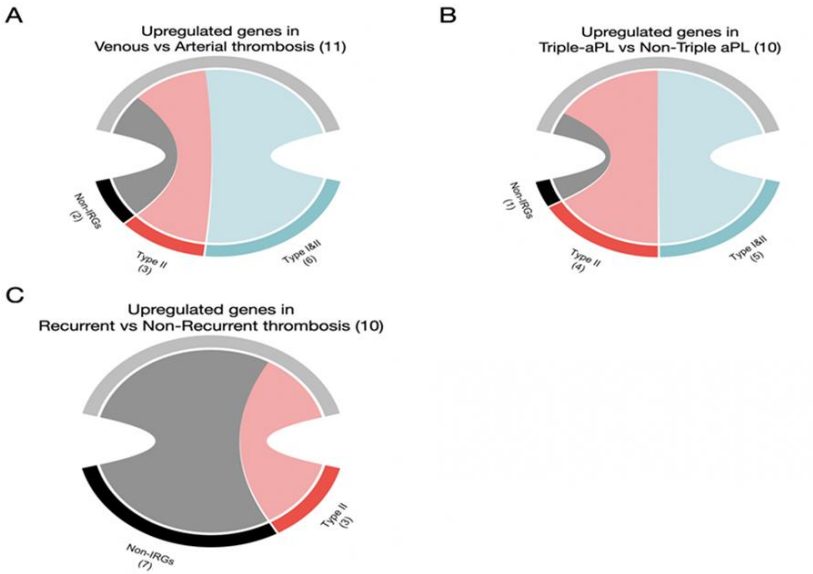
- Differential gene expression analysis (DEGA) of 12.306 genes --34 deregulated genes
- 33 were upregulated by at least 2-fold

>40% were type I and II interferon-regulated genes (IRGs)

Machine learning: 79% accuracy to discriminate thrPAPS from HCs, 82% when only IRGs were analyzed







Verrou K, Sfikakis PP, Tektonidou MG. Journal of Autoimmunity (in press)

ΤΑΞΙΝΟΜΗΣΗ ΤΟΥ APS

- APS χωρίς υποκείμενο ρευματικό νόσημα (πρωτοπαθές)
- APS σχετιζόμενο με υποκείμενο ρευματικό νόσημα (κυρίως ΣΕΛ)
- Καταστροφικό APS (πολυοργανική ανεπάρκεια εξαιτίας πολλαπλών αποφρακτικών συμβαμμάτων των αγγείων)

Κατηγορίες APS/aPL

- - Θρομβωτικό APS
- - Μαιευτικό APS
- - Θρομβωτικό+Μαιευτικό APS
- - Εκτός κριτηρίων APS εκδηλώσεις

aPL+/non APS

- ΣΕΛ/aPL+
- Ασυμπτωματικοί aPL+ ασθενείς

Επιπολασμός των Αντιφωσφολιπιδικών αντισωμάτων (aPL)

Υγιή άτομα(< 2%)

Λοιμώξεις

- Σύφιλη
- Νόσος Lyme
- ΤΒ
- Λοιμώδης ενδοκαρδίτιδα
- Ελονοσία
- HAV, HBV, HCV
- HTLV-I, CMV, VZV,HIV
- Λεπτοσπείρωση, λεϊσμανίαση

Φάρμακα

- Φαινοθειαζίδες
- Φαινυντοίνη
- Υδραλαζίνη
- Προκαϊναμίδη
- Κινιδίνη
- Προπρανολόνη

Νεοπλασίες

Επιπολασμός των aPL

Αυτοάνοσα ρευματικά νοσήματα

- Συστηματικός ερυθηματώδης λύκος (SLE)
- Ρευματοειδής αρθρίτιδα
- Σύνδρομο Sjogren
- Σκληρόδερμα

Επιπολασμός των aPL

Ασθενείς με SLE

- **20-40%** των ασθενών με SLE έχουν θετικά αντιφωσφολιπιδικά αντισώματα

Mok C , Arthritis Rheum 2005: 2774,
Kaiser L, Ann Rheum Dis 2009;68:238

Ποιοι θα εμφανίσουν τελικά σύνδρομο?

Risk of thrombosis in patients with antiphospholipid antibodies(aPL)

- Underlying autoimmune disorders (mainly SLE)
- aPL profile
- Traditional risk factors for thrombosis
- Genetic factors
- Other hypercoagulable states (protein C and protein S deficiency, factor V Leiden/prothrombin20210 gene mutation)

‘High risk’ aPL profile

- Lupus Anticoagulant (LA) test: strongest risk factor for thrombosis and pregnancy morbidity

Ruffatti A, Ann Rheum Dis. 2011;70:1083-6

Buyon J, Ann Intern Med 2015

- Persistently positive aPL at medium/high titres

Martinez-Berriotxoa A, Lupus. 2007;16:810-6

Tektonidou M, Arthritis Rheum 2009;61:29-36

- IgG isotype of aCL and anti-β2GPI (more specific than IgM isotype)

Ottomo K, Arthritis Rheum. 2012 ;64:504-12

- Triple positivity (LA and aCL και anti-ß2GPI): ↑risk of arterial /venous thrombosis and pregnancy morbidity, 30% recurrent thrombotic events

Pengo R, J Thromb Haemost 2010;8:237-42

Bazzan M, Autoimmun Rev 2013 ;12:826-31

aPL profile

- Anti-phosphatidylserine/prothrombin abs(anti-PS/PT):

  significant association with LA test/dRVVT ($p < 0.0001$) and arterial/venous thromboses in SLE

- **Systematic review:** aPS/PT: higher risk than anti-PT for arterial and/or venous thrombosis (**OR 5.11**; 95%CI 4.2-6.3 and OR 1.82; 95%CI 1.44-2.75, respectively).
- 62% sensitivity και 97% specificity for APS (in-house assay)

*Sciascia S, Thromb Haemost. 2014;*111:354-64

aPL Score

- aPL-Score (according to aPL type, isotype (IgG, IgM) and titre): higher in patients with thrombosis/pregnancy morbidity(P< 0.00001)

- aPL-Score of ≥30: independent risk factor for thrombosis in SLE (**HR 3.14** [95% CI 1.383-7.150], P= 0.006) .

Ottomo K, Arthritis Rheum. 2012 ;64:504-12

- **Global Anti-Phospholipid Syndrome Score**: (aPL, HT, lipidemia) : higher in patients with history of thrombosis vs those without [*GAPSS 9.5 vs 3.9 respectively, P < 0.001*]
- GAPSS> 16: the only significant predictor of thrombosis [**HR = 6.17** (95% CI 1.70, 22.40)].

Sciascia S, Arthritis Care Res 2014 ;66:1915
Zuily S, Rheumatology 2015

Thrombosis risk in patients with positive aPL
Traditional risk factors

- Hypertension (mainly arterial thrombosis)

Zuily S, Thromb Res. 2013;132:e1-7

- Hyperlipidemia

Matyja-Bednarczyk A, Thromb Res. 2014;133:173-6

- Diabetes, obesity, estrogens, family history (recurrent thrombosis)

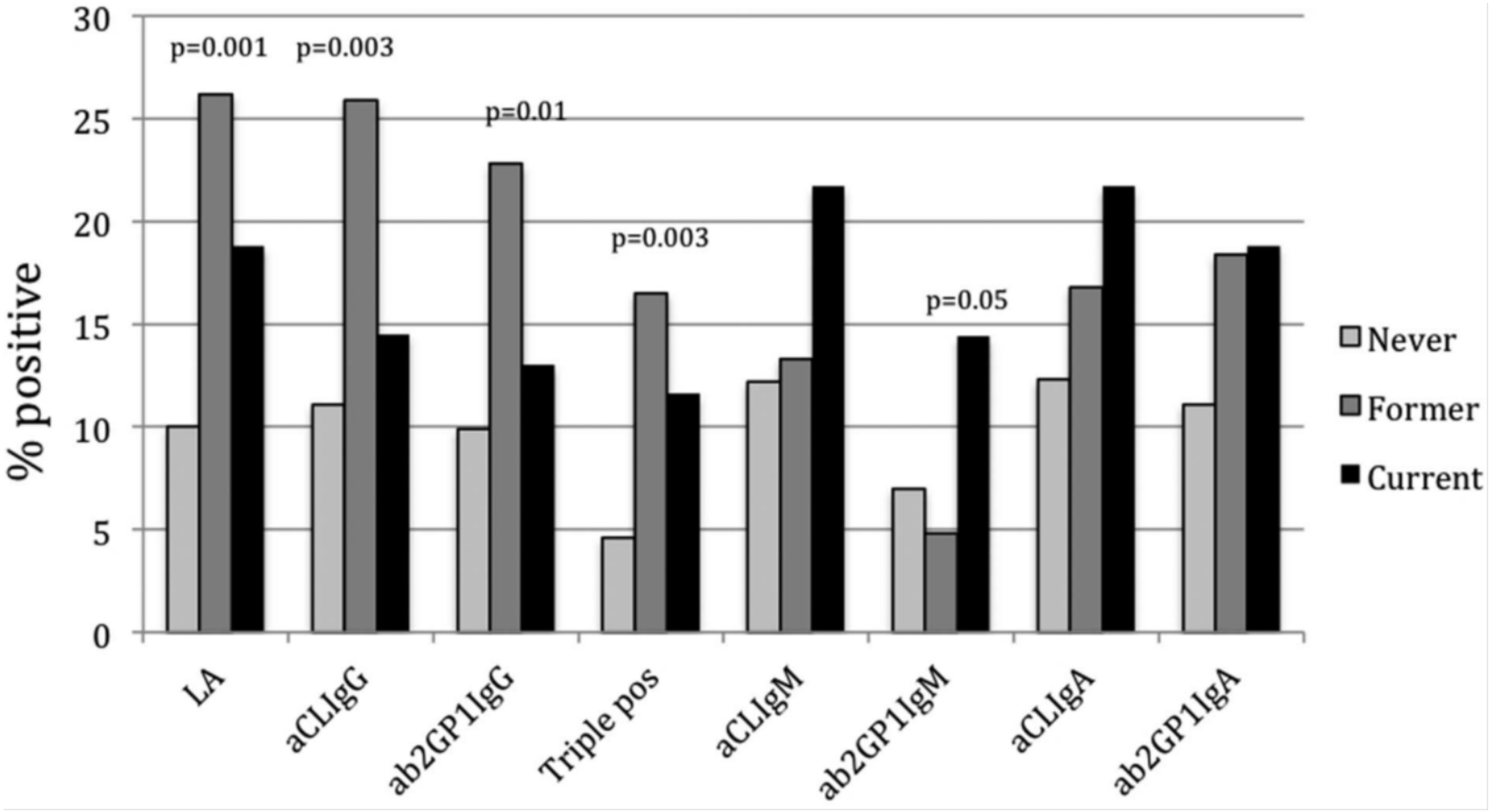
Bazzan M, Autoimmun Rev. 2013;12:826-31

- Smoking

Gustaffson J, Ann Rheum Dis 2014

Cigarette smoking, antiphospholipid antibodies and vascular events in Systemic Lupus Erythematosus.

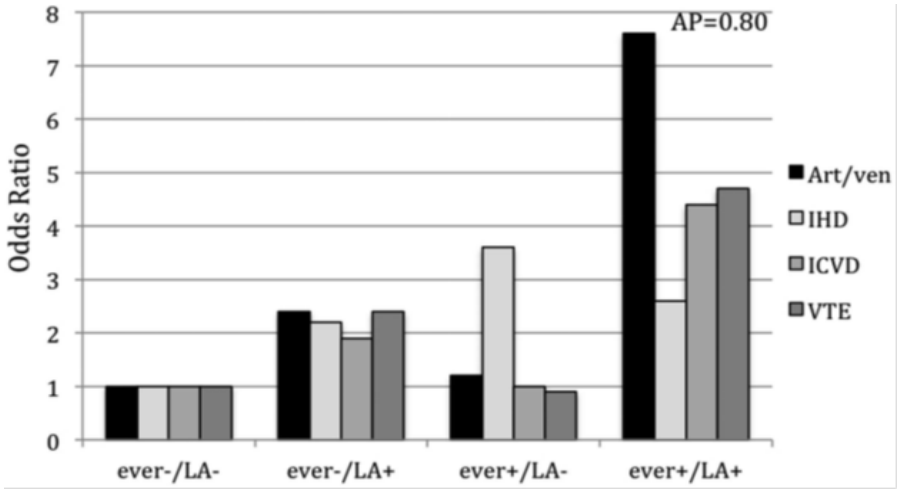
Gustafsson JT, Gunnarsson I, Källberg H, Pettersson S, Zickert A, Vikerfors A, Möller S, Rönnelid J, Elvin K, Svenungsson E. *Ann Rheum Dis. 2014 Apr*

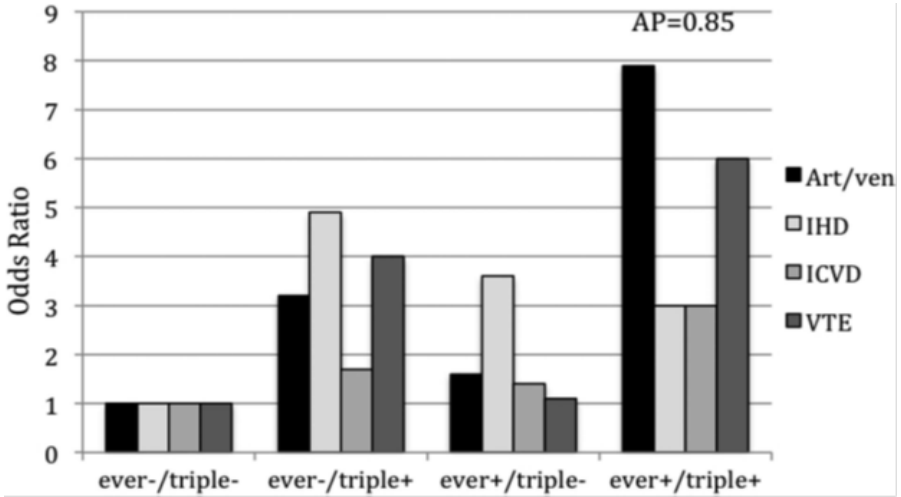


Cigarette smoking, antiphospholipid antibodies and vascular events in Systemic Lupus Erythematosus.

Gustafsson JT, Gunnarsson I, Källberg H, Pettersson S, Zickert A, Vikerfors A, Möller S, Rönnelid J, Elvin K, Svenungsson E. *Ann Rheum Dis. 2014 Apr*

- Combination of smoking (ever regular) and aPL (LA/triple positivity): strongly associated with vascular events





Thrombosis risk in patients with positive aPL

Genetic factors

- HLA-DRB1*04: more frequently in SLE patients with ischemic cerebrovascular events /associated with all specificities of aPL
- HLA-DRB1*13 : associated with any vascular event in SLE and with IgG aPL
- Combined HLA-DRB1*04/*13: significant additive interaction for any vascular events.

	Meta-analyses		
	N (%)	OR (95% CI)	p Value
DRB1*04			
aβ_2GP1 IgG	67 (46.5)	2.66 (1.81 to 3.91)	<0.00001
aCL IgG	60 (41.4)	1.99 (1.35 to 2.93)	0.0005
aCL IgM	59 (39.1)	1.76 (1.20 to 2.58)	0.004
aPT IgG†	32 (40.0)	1.69 (1.04 to 2.76)	0.03
≥2aPL‡	63 (44.4)	2.33 (1.58 to 3.44)	<0.00001
LAC§	40 (47.1)	2.57 (1.53 to 4.32)	0.0003
DRB1*13			
aβ_2GP1 IgG	48 (33.3)	1.69 (1.13 to 2.52)	0.01
aCL IgG	47 (32.4)	1.60 (1.07 to 2.40)	0.02
aCL IgM	43 (28.5)	1.25 (0.83 to 1.88)	0.28
aPT IgG†	28 (35.0)	1.66 (1.01 to 2.75)	0.05
≥2aPL‡	45 (31.7)	1.51 (1.00 to 2.28)	0.05
LAC§	28 (32.9)	1.65 (0.96 to 2.86)	0.06

ΕΠΙΠΤΩΣΗ ΚΑΙ ΕΠΙΠΟΛΑΣΜΟΣ

Data on APS incidence and prevalence around the world

Author	Country/geographical area	Study period	Case definition	Sample	Number of cases	Incidence per 100,000 (F/M)	Prevalence per 100,000 (F/M)	Incidence peak age (F/M)
Duarte-Garcia [6••]	USA/Midwestern Olmsted county	2000–2015	Sydney 2006 criteria	Population-based Record-linkage system	33	2.1 (2.1/2.0)	50 (51/48)	75+/55–64
Hwang [8]	South Korea	2008–2017	Diagnostic and utilization codes combination	Nationwide claims database	3088	0.75 (0.91/0.59)	6.19 (7.62/4.76)	30–39 and 70–79/70–79
Luissi [7]	Argentina	2000–2015	Sydney 2006 criteria	Health management organization	53 (50 definite)	2.6 (2.9/2.0)	40.5 (NA/NA)	30–39/60–69
Radin [9]	Northwest Italy (Piedmont and Aosta Valley)	2010–2019	Definite APS diagnoses	Regional rare disease registry	740	1.1 (NA/NA)	16.8 (NA/NA)	NA
Rodziewicz	UK	1990–	Diagnostic	Nationwide	2606	1.8	43	35–

Revised Sapporo (Sydney) classification criteria (2016)

Definite APS: 1 clinical + laboratory

1. **Vascular thrombosis**

One or more clinical episodes of arterial, venous, or small-vessel thrombosis in any tissue or organ confirmed by imaging, Doppler studies, or histopathology, with the exception of superficial venous thrombosis.
For histopathologic confirmation, thrombosis should be present without significant evidence of inflammation of the vessel wall.

2. **Pregnancy morbidity**

(a) ≥3 unexplained consecutive spontaneous abortions <10th week of gestation, with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded,

or

(b) ≥ 1 unexplained deaths of a morphologically normal fetus ≥10th week of gestation, with normal fetal morphology documented by ultrasound or by direct examination of the fetus,

or

(c) ≥ 1 premature births of a morphologically normal neonate <34th week of gestation because of severe preeclampsia or eclampsia or severe placental insufficiency

Laboratory criteria - Antiphospholipid antibodies

	Sapporo criteria	Sydney criteria
Lupus Anticoagulant (LA)	Screening, mixing, and confirmation tests (ISTH guidelines)	Screening, mixing, and confirmation tests (ISTH guidelines)
	Two or more occasions at least 6 weeks apart	Two or more occasions at least 12 weeks apart
Anticardiolipin (aCL) antibodies	Detected by standardized β2GPI-dependent ELISA	Detected by standardized ELISA
	IgG and/or IgM	IgG and/or IgM
	Medium or high titer	Medium or high titer (>40 units IgG or IgM antiphospholipid antibody titer or >99th percentile)
	Two or more occasions at least 6 weeks apart	Two or more occasions at least 12 weeks apart
Anti-β2GPI antibodies	–	IgG and/or IgM
		Titer >99th percentile
		Two or more occasions at least 12 weeks apart

Κλινικές εκδηλώσεις στην έναρξη της νόσου (Ευρωπαϊκό Registry)

Εν τω βάθει φλεβοθρόμβωση	32%
Θρομβοπενία	22%
Livedo reticularis	20%
Α.Ε.Ε	13%
Πνευμονική εμβολή	9%
Εμβρυϊκός θάνατος	8%
Παροδικό ισχαιμικό Α.Ε.Ε	7%
Αιμολυτική αναιμία	7 %

Cervera R, Piette J, Font J. Arthritis Rheum 2002

Revised Sapporo (Sydney) classification criteria (2016)

Κάποιες εκδηλώσεις σχετιζόμενες με το APS είναι αδιαμφισβήτητα συχνές αλλά όχι ειδικές για τους ασθενείς με APS (**non-criteria APS manifestations**):

- Νεφροπάθεια σχετιζόμενη με APS
- Βλάβες των βαλβίδων της καρδιάς
- Θρομβοπενία
- Livedo reticularis
- Νευρολογικές εκδηλώσεις (επιληψία, γνωσιακές διαταραχές)

Miyakis S, Lockshin MD, Atsumi T, et al. J Thromb Haemost 2006;4:295-306.

Αρτηριακή ή/και φλεβική θρόμβωση στο APS

- Η θρόμβωση μπορεί να συμβεί σε οποιοδήποτε αγγείο, οποιουδήποτε μεγέθους (μεγάλου, μέσου ή μικρού μεγέθους)

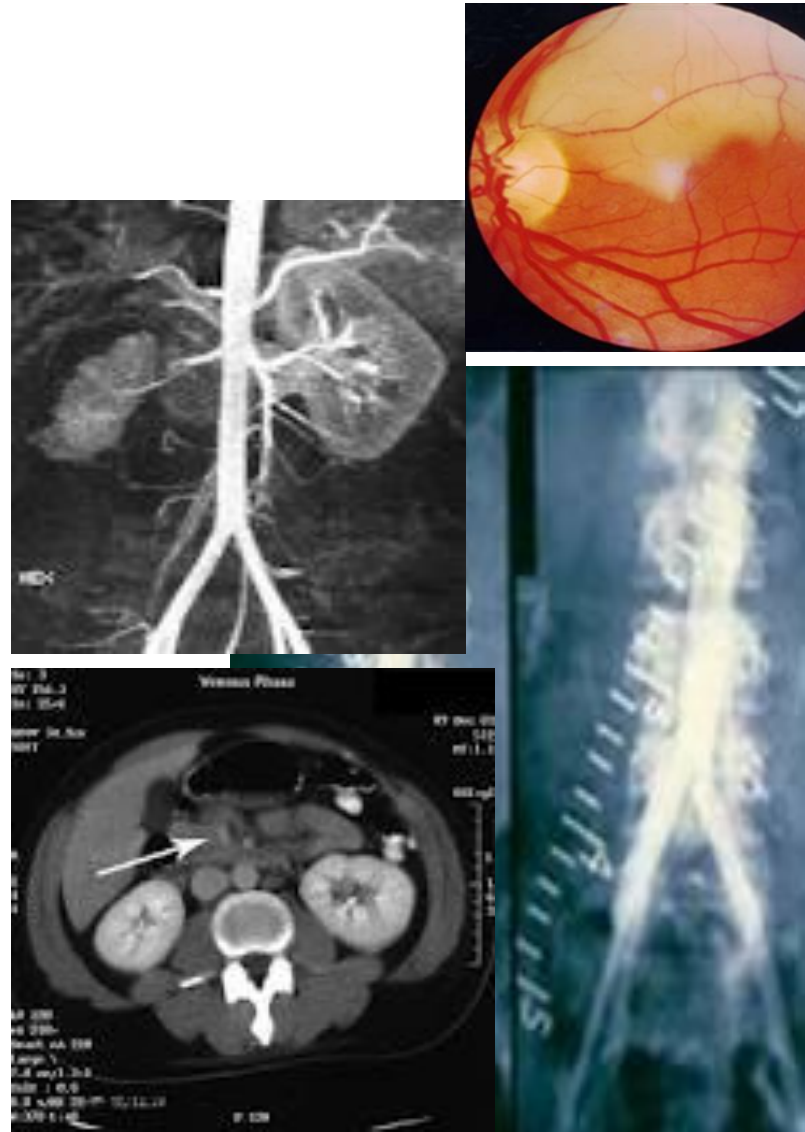
- Φλεβική θρόμβωση= συχνότερη από την αρτηριακή

- Εν τω βάθει φλεβοθρόμβωση (DVT)=πιο συχνή θρομβωτική εκδήλωση

- 1/3 ασθενών με DVT → πνευμονική εμβολή
- Υποτροπιάζουσες πνευμονικές εμβολές → πνευμονική υπέρταση (σπάνια).

Αρτηριακή ή/και φλεβική θρόμβωση στο APS

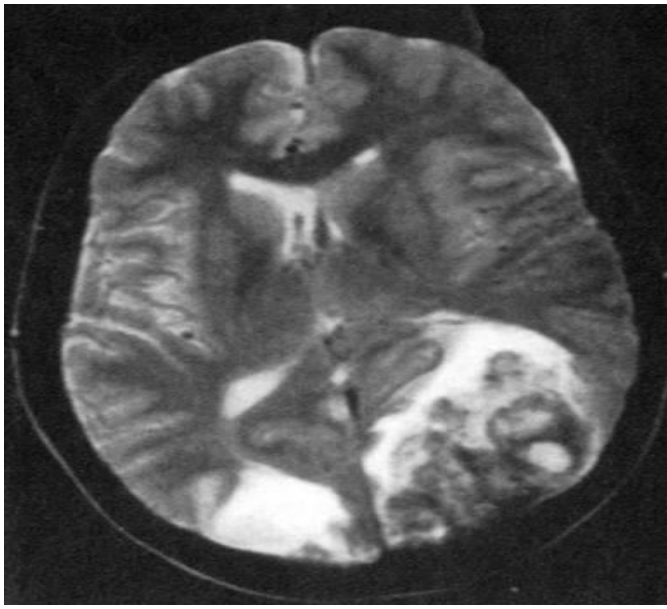
- Α.Ε.Ε και ΤΙΑ: η πιο συχνή αρτηριακή θρομβωτική εκδήλωση
- Άλλες εντοπίσεις αρτηριακής θρόμβωσης: αμφιβληστροειδική, στεφανιαία, βραχιόνιες, μεσεντέριες, νεφρικά αρτηριόλια
- Υψηλή υποψία σε νέους ασθενείς χωρίς προδιαθεσικούς παράγοντες για αθηροσκλήρυνση

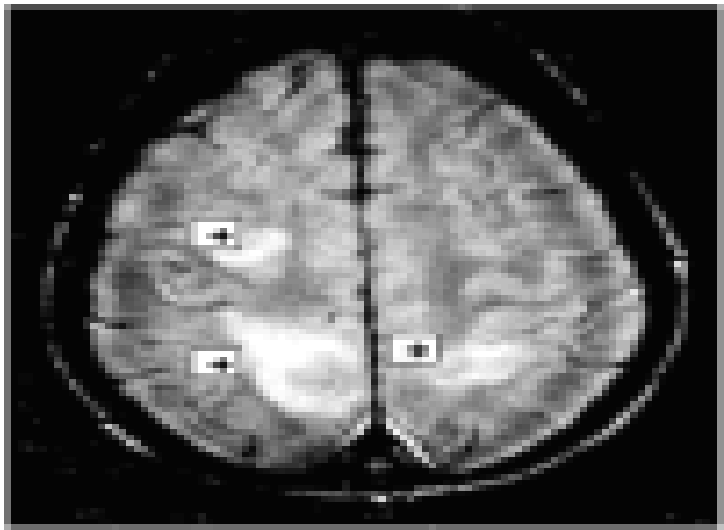


Νευρολογικές εκδηλώσεις

- Α.Ε.Ε και ΤΙΑ= οι πιο συχνές νευρολογικές επιπλοκές

→ εκδηλώσεις in situ θρόμβωσης ή εμβόλων από βαλβιδική καρδιακή νόσο.





The estimated frequency of antiphospholipid antibodies in young adults with cerebrovascular events: a systematic review.

- Μετα-ανάλυση -Medline 1970-2013

- Θετικά aPL σε νέους ασθενείς <50 ετών με θρομβωτικά εγκεφαλικά επεισόδια κάθε τύπου : 17%
- 22% για ΑΕΕ.

- θετικά aPL: **5 –πλάσιο κίνδυνο εκδήλωσης ΑΕΕ, ΤΙΑ**
- Σημαντικά μεθοδολογικά προβλήματα (ορισμός φυσιολογικών ορίων /αναπαραγωγή αποτελεσμάτων)

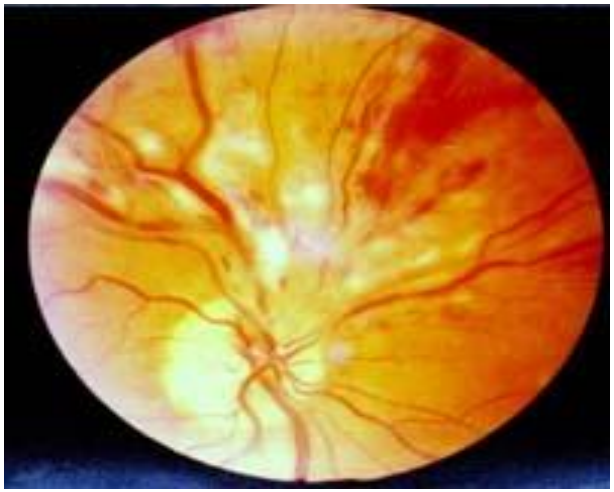
Νευρολογικές εκδηλώσεις εκτός των Α.Ε.Ε?

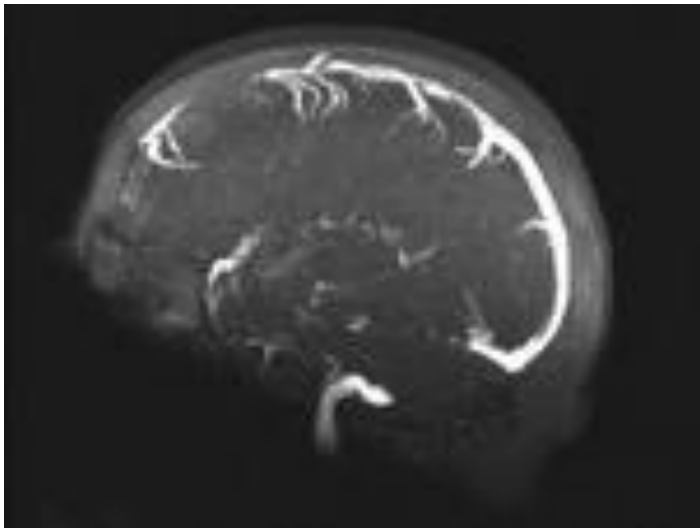
- Επιληψία
- Ψύχωση
- Χορεία
- Ημικρανία
- MS-like βλάβες ΚΝΣ

Rodrigues CE, Carvalho JF, Shoenfeld Y. Eur J Clin Invest. 2010 ;40:350-9.
Hughes GRV. Lupus 2010;19:343

Νευρολογικές εκδηλώσεις εκτός των Α.Ε.Ε?

- Θρόμβωση αμφιβληστροειδικής αρτηρίας ή φλέβας
- Θρόμβωση φλεβικών κόλπων
- Νευροαισθητηριακή απώλεια ακοής
- Εγκάρσια μυελίτιδα
- Γνωσιακές διαταραχές





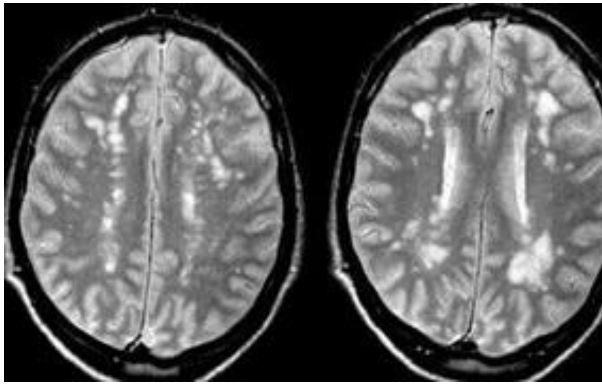
EULAR recommendations for the management of systemic lupus erythematosus with neuropsychiatric manifestations: report of a task force of the EULAR standing committee for clinical affairs.

Bertsias GK, Ioannidis J, Aringer M, Bollen E, Bombardieri S, Bruce IN, Cervera R, Dalakas M, Doria A, Hanly JG, Huizinga TW, Isenberg D, Kallenberg C, Piette JC, Schneider M, Scolding N, Smolen J, Stara A, Tassiulas I, Tektonidou M, Tincani A, van Buchem MA, van Vollenhoven R, Ward M, Gordon C, Boumpas DT. *Ann Rheum Dis. 2010 ;69(12):2074-82*

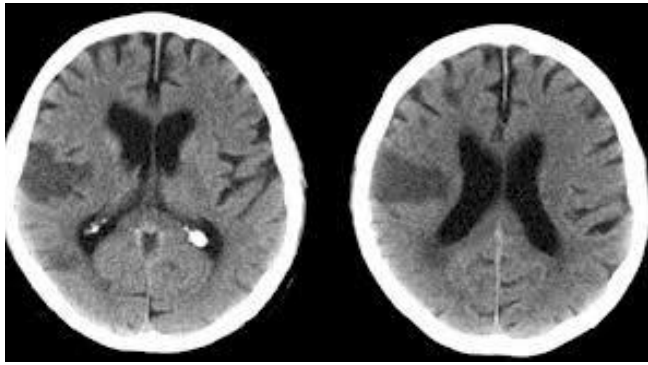
NPSLE syndrome	Risk factor- aPL antibodies	Evidence level
Seizure disorder	OR 3.7–6.1 (aCL-IgG), 2.9; 95% CI 1.0–8.5 (aCL-IgM), 6.2; 95% CI 1.7–22.5 (LA)	**1**
Cognitive dysfunction	OR 1.9–4.9 (for severe cognitive dysfunction)	**2**
Myelopathy	OR 9.6; 95% CI 1.8–50.7 (LAC)	**2**
Cranial neuropathy	OR 1.07; 95% CI 1.00–1.14 (aCL-IgG)	**3**

Μαγνητική τομογραφία εγκεφάλου

- Συχνότερα σε ασθενείς με SLE/APS vs SLE/non APS: Κενοτοπιώδη έμφρακτα (lacunar infarcts) εν τω βάθει λευκής ουσίας



- Φλοιϊκά έμφρακτα κατανομής μέσης εγκεφαλικής αρτηρίας
- Έμφρακτα μεταβατικής ζώνης
- Βλάβες πρόσθιων βασικών γαγγλίων



Καρδιακές εκδηλώσεις-βαλβιδική νόσος

- Βαλβιδική νόσος: 20-30% των ασθενών με APS σε Doppler U/S καρδιάς (συνήθως ασυμπτωματικοί)
- Η μιτροειδής προσβάλλεται πιο συχνά, ακολουθούμενη από την αορτική.
- Βαλβιδική ανεπάρκεια= η πιο συχνή αιμοδυναμική ανωμαλία
- Libman-Sacks

Myocardial dysfunction

Ann Rheum Dis 2001;**60**:43–48

Right ventricular diastolic dysfunction in patients with anticardiolipin antibodies and antiphospholipid syndrome

M G Tektonidou, J P A Ioannidis, I Moyssakis, K A Boki, V Vassiliou, P G Vlachoyiannopoulos, M K Kyriakidis, H M Moutsopoulos

Contents lists available at ScienceDirect

Seminars in Arthritis and Rheumatism

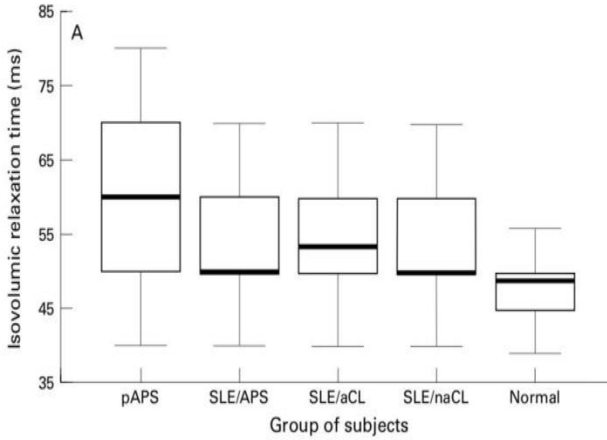
journal homepage: www.elsevier.com/locate/semarthrit

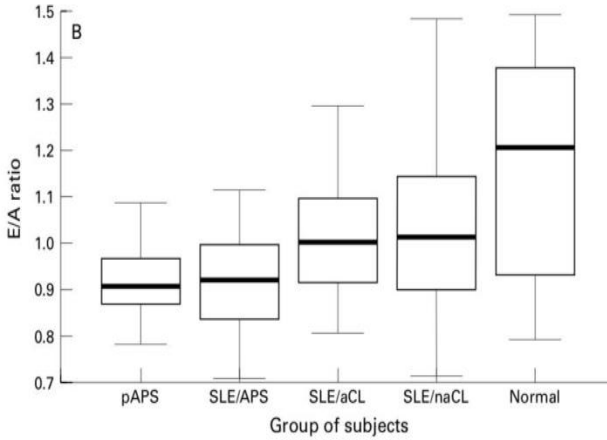
Evolution of cardiac dysfunction in patients with antiphospholipid antibodies and/or antiphospholipid syndrome: A 10-year follow-up study

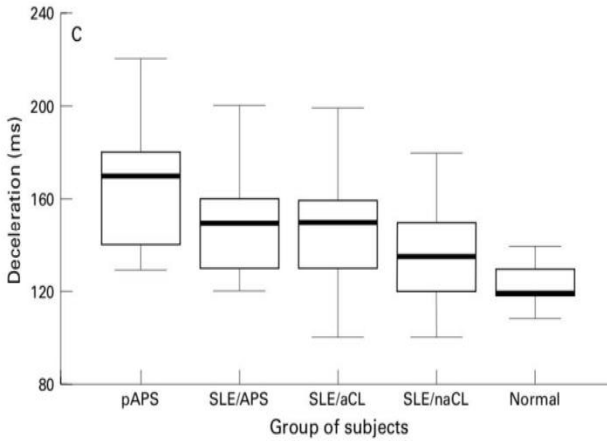
Christos Kampolis, MD[a,1], Maria Tektonidou, MD[b,1], Ioannis Moyssakis, MD[c], George E. Tzelepis, MD[a], Haralampos Moutsopoulos, MD, FACP, FRCP[a], Panayiotis G. Vlachoyiannopoulos, MD[a,*]

[a] Department of Pathophysiology, University of Athens Medical School, 75 Mikras Asias St, Athens 11527, Greece
[b] First Department of Internal Medicine, University of Athens Medical School, Laiko Hospital, Athens, Greece
[c] Laiko Hospital, Athens, Greece

- Left ventricular diastolic dysfunction similarly progresses in PAPS, SLE/APS, SLE/aPL(+)/non APS and SLE/non aPL patients.
- Right ventricular diastolic dysfunction progresses mainly in the SLE/APS group.







Silent myocardial ischemic disease

ARTHRITIS & RHEUMATISM
Vol. 62, No.7, July 2010, pp 2093–2100
DOI 10.1002/art.27488

Asymptomatic Myocardial Ischemic Disease in Antiphospholipid Syndrome

A Controlled Cardiac Magnetic Resonance Imaging Study

Karim Sacré,[1] Benoit Brihaye,[1] Fabien Hyafil,[1] Jean-Michel Serfaty,[1] Brigitte Escoubet,[2] Maria-Christina Zennaro,[3] Olivier Lidove,[1] Jean-Pierre Laissy,[1] and Thomas Papo[1]

CMR study

27 APS patients vs 81 HC:

- higher prevalence of late gadolinium enhancement, *consistent with subclinical coronary microvascular dysfunction*

ORIGINAL PAPERS

Adv Clin Exp Med 2016, **25**, 6, 1199–1205
DOI: 10.17219/acem/63753

ISSN 1899–5276

Agnieszka Padjas[1, A, B, D, F], Wojciech Płazak[2, B–D, F], Magdalena Celińska-Lowenhoff[1, B], Adam Mazurek[2, B], Carlo Perricone[3, E], Piotr Podolec[2, E], Jacek Musiał[1, A, E, F]

Myocardial Ischaemia, Coronary Atherosclerosis and Pulmonary Pressure Elevation in Antiphospholipid Syndrome Patients*

[1] Department of Internal Medicine, Allergy and Immunology, Jagiellonian University Medical College, Kraków, Poland
[2] Department of Cardiac and Vascular Diseases, John Paul II Hospital, Jagiellonian University Medical College, Kraków, Poland
[3] Rheumatology Unit, Department of Medicine, Sapienza University, Rome, Italy

PET study

Journal of Clinical Medicine

MDPI

Article

Silent Myocardial Perfusion Abnormalities Detected by Stress Cardiovascular Magnetic Resonance in Antiphospholipid Syndrome: A Case-Control Study

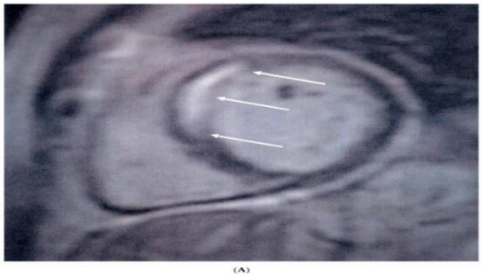
Sophie I. Mavrogeni [1], George Markousis-Mavrogenis [1], Olga Karapanagiotou [1], Konstantinos Toutouzas [2], Panagiotis Argyriou [3], Stella Velitsista [3], George Kanoupakis [3], Dimitrios Apostolou [3], David Hautemann [4], Petros P. Sfikakis [5] and Maria G. Tektonidou [5,*]

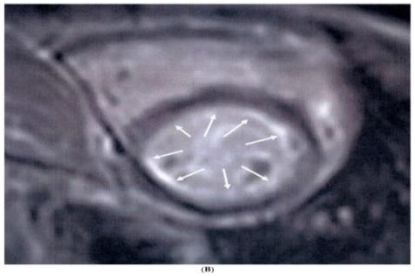
Late gadolinium enhancement (LGE): 16 (**36%**)of 44 asymptomatic APS patients *(mean age=44, 64% women)* vs none of 44 age/sex-matched HC ($p<0.001$). Only 2/16 abnormal coronary angiography

Myocardial perfusion reserve index (MPRI): significantly lower in APS vs HC [1.5 (0.9-1.9) vs. 2.7 (2.2-3.2), $p<0.001$] independently of any LGE presence

Mult. Analysis: no associations with APS-related or classic CVD risk factors, hs-CRP and hs-TnT {*trend for LDA for MPRI, no of CVD events for LGE in univ. analysis*).

1-year f-up: 3 patients experienced CAD complications *(1 MI, 2 unstable angina),* notably those with the lowest MPRI





(A) Septal myocardial scar following the distribution of the left anterior descending artery
(B) Diffuse subendocardial scar

Νεφρική προσβολή στο APS

- Θρόμβωση/στένωση της νεφρικής αρτηρίας
- Θρόμβωση της νεφρικής φλέβας
- Αυξημένη πιθανότητα θρόμβωσης νεφρικού μοσχεύματος
- Αγγειοαποφρακτική νεφροπάθεια των μικρών αγγείων (APS νεφροπάθεια)

Tektonidou MG., Clin Rev Allergy Immunol 2009;36:131-40.

Alchi B, Nephrol Dial Transplant 2010;25:3147-54.

Νεφροπάθεια σχετιζόμενη με APS

Nochy D et al, Am. Soc. Nephrol 1999 (primary APS)

*Daugas E et al, J Am Soc Nephrol 2002;13:42-52 (*SLE/APS)

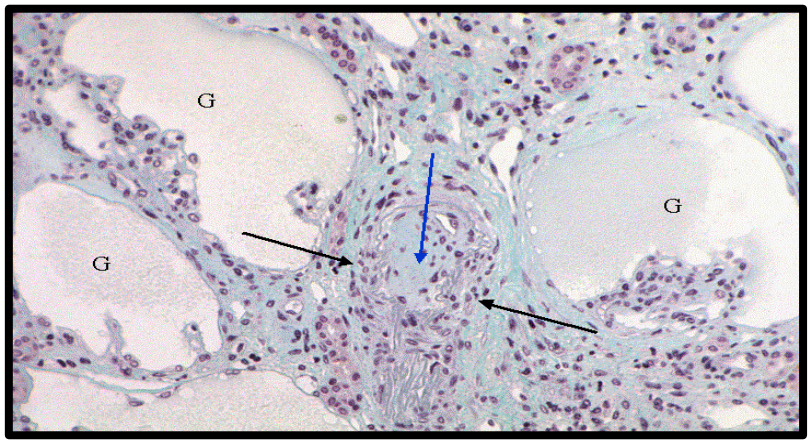
Tektonidou M, et al. Arthritis Rheum 2004;50:2567-79 (SLE/APS. SLE/aPL+)

Tektonidou M, et al. J Rheumatology 2008; 35:1983-8 (PAPS, SLE/APS, CAPS)

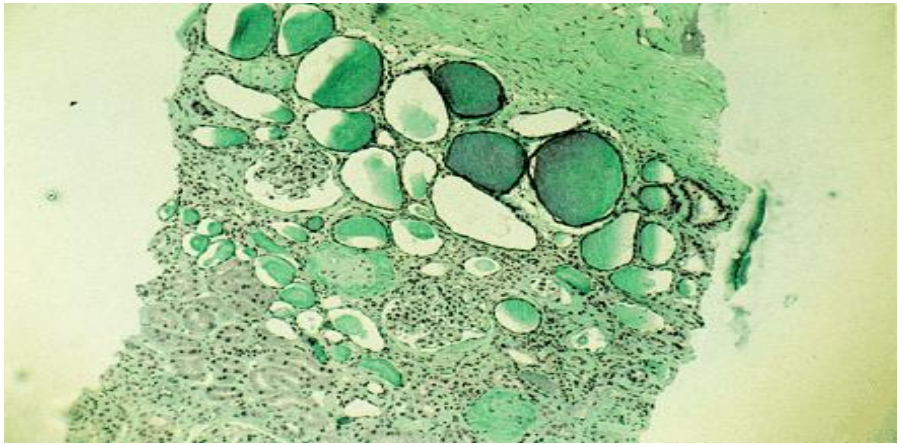
- Θρομβωτική μικροαγγειοπάθεια (TMA) *οξεία βλάβη*

- Ινώδης υπερπλασία της εσωτερικής στοιβάδας
- Οργανωμένοι θρόμβοι με επανασυρραγκοποίηση
- Ινώδης απόφραξη αρτηριών και αρτηριολίων
- Εστιακή ατροφία του φλοιού

} *χρόνιες βλάβες*



Fibrous intimal hyperplasia



Focal cortical atrophy

Νεφροπάθεια σχετιζόμενη με APS

- Ιστολογικές βλάβες–Νεφρικές εκδηλώσεις παρόμοιες σε:

  - Πρωτοπαθές APS
  - SLE/APS
  - SLE/aPL/non-APS
  - Καταστροφικό APS

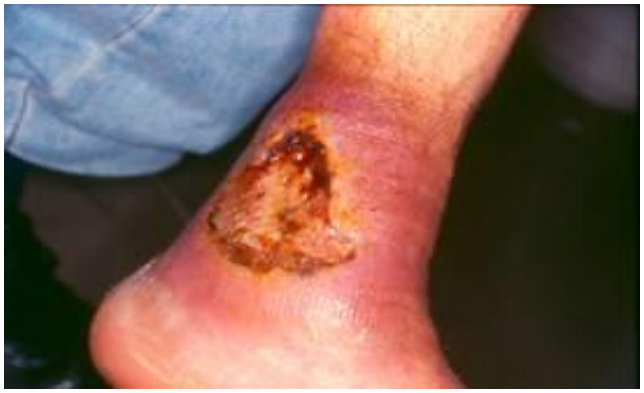
- Εκδηλώνεται με:

  - Συστηματική υπέρταση (ήπια ως κακοήθη)
  - Πρωτεϊνουρία (ήπια μέχρι νεφρωσικού τύπου), μικροσκοπική αιματουρία
  - Νεφρική ανεπάρκεια (συνήθως ήπια)

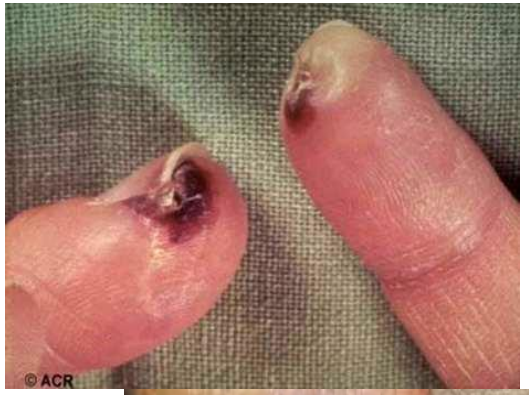
Θρομβοπενία

- Από τις πιο συχνές εκδηλώσεις του APS: 30%- 46% των ασθενών με APS.
- Αριθμός αιμοπεταλίων: 50.000- 140.000/microL.
- Ισχυρή συσχέτιση μεταξύ aPL και θρομβοπενίας στους ασθενείς με ΣΕΛ
- Η θρομβοπενία δεν αποκλείει την εμφάνιση θρομβωτικών επιπλοκών στο APS

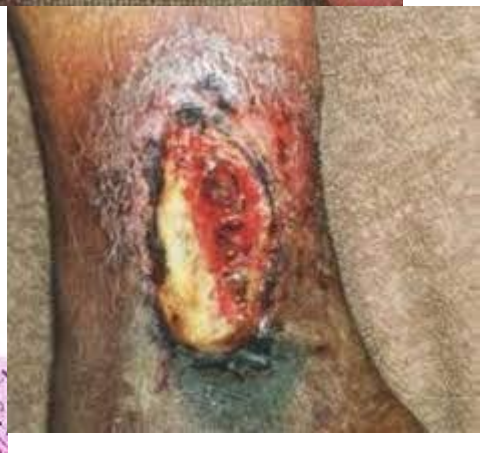
Δερματικές εκδηλώσεις



- 30-50% των ασθενών με APS
- Livedo reticularis

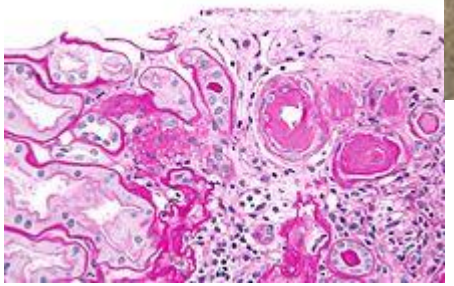


- Livedo racemose
- Δερματικά Έλκη (μεταφλεβιτιδικά, αρτηριακό σκέλος- μικροαγγειοπάθεια)



- Ισχαιμία, νέκρωση, γάγγραινα
- Livedoid vasculitis

ιστολογική επιβεβαίωση: *intraluminal thrombosis, endothelial proliferation, and subintimal hyaline degeneration (smooth muscle is replaced by fibrous connective tissue)*

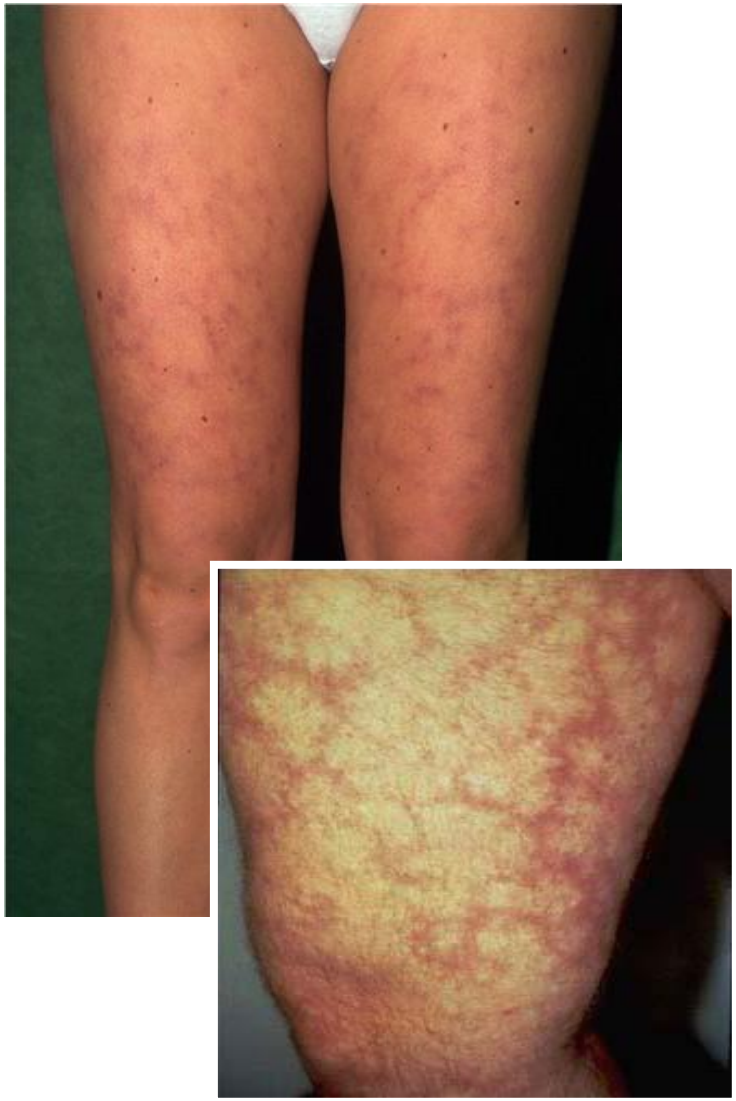


Livedo reticularis και livedo racemosa

- μπορεί να αποτελείται από κανονικούς κλειστούς κύκλους (livedo reticularis) ή από ακανόνιστους σπασμένους κύκλους (livedo racemosa).

- Livedo reticularis και livedo racemosa: αυξημένο κίνδυνο για αρτηριακή θρόμβωση, Α.Ε.Ε και νοσηρότητα της κύησης.

Task force for CAPS and non-criteria APS manifestations



CATASTROPHIC APS
International consensus for classification criteria

1. Clinical evidence of vessel occlusions affecting 3 or more organs or systems.
2. Development of the manifestations simultaneously or in less than a week.
3. Confirmation by histopathology of small vessel occlusion in at least one organ.
4. Laboratory confirmation of the presence of aPL (LA, ACL, anti-β2GPI).

Definite catastrophic APS: All 4 criteria.

-Probable catastrophic APS:

-1, 2 & 4

-1, 3 & 4 and the development of the third event in more than a week but less than a month, despite anticoagulation

Morbidity and mortality in the antiphospholipid syndrome during a 10-year period: a multicentre prospective study of 1000 patients.
Cervera R, Serrano R, Pons-Estel GJ, Ceberio-Hualde L, Shoenfeld Y, de Ramón E, Buonaiuto V, Jacobsen S, Zeher MM, Tarr T, Tincani A, Taglietti M, Theodossiades G, Nomikou E, Galeazzi M, Bellisai F, Meroni PL, Derksen RH, de Groot PG, Baleva M, Mosca M, Bombardieri S, Houssiau F, Gris JC, Quéré I, Hachulla E, Vasconcelos C, Fernández-Nebro A, Haro M, Amoura Z, Miyara M, Tektonidou M, Espinosa G, Bertolaccini ML, Khamashta MA; on behalf of the Euro-Phospholipid Project Group (European Forum on Antiphospholipid Antibodies).
Ann Rheum Dis. 2014 Jan 24.

- 10-ετής επιβίωση: 91% (παρόμοια σε πρωτοπαθές APS και SLE/APS)

<u>Πιο συχνά αίτια θανάτου</u> σε ασθενείς με APS:

- σοβαρά θρομβωτικά επεισόδια (ΟΕΜ, ΑΕΕ, Πν. εμβολή (36%)
- λοιμώξεις (27%)
- αιμορραγίες (10 %)

- Καταστροφικό APS=0.9%. Θάνατος: 55% ασθενών

ΠΡΟΦΥΛΑΞΗ - ΘΕΡΑΠΕΙΑ

Evidence-based recommendations for the management of APS

Evidence-based recommendations for the prevention and long-term management of thrombosis in antiphospholipid antibody-positive patients: Report of a Task Force at the 13th International Congress on Antiphospholipid Antibodies

G Ruiz-Irastorza[1], MJ Cuadrado[2], I Ruiz-Arruza[1], R Brey[3], M Crowther[4], R Derksen[5], D Erkan[6], S Krilis[7], S Machin[8], V Pengo[9], S Pierangeli[10], M Tektonidou[11] and M Khamashta[2]

Recommendation

EULAR recommendations for the management of antiphospholipid syndrome in adults

Maria G Tektonidou,[1] Laura Andreoli,[2] Marteen Limper,[3] Zahir Amoura,[4] Ricard Cervera,[5] Nathalie Costedoat-Chalumeau,[6] Maria Jose Cuadrado,[7] Thomas Dörner,[8] Raquel Ferrer-Oliveras,[9] Karen Hambly,[10] Munther A Khamashta,[11] Judith King,[12] Francesca Marchiori,[13] Pier Luigi Meroni,[14] Marta Mosca,[15] Vittorio Pengo,[16] Luigi Raio,[17] Guillermo Ruiz-Irastorza,[18] Yehuda Shoenfeld,[19] Ljudmila Stojanovich,[20] Elisabet Svenungsson,[21] Denis Wahl,[22] Angela Tincani,[2] Michael M Ward[23]

Ann Rheum Dis. 2019 Oct;78(10):1296-1304

RMD Open
Rheumatic & Musculoskeletal Diseases

REVIEW

Management of thrombotic and obstetric antiphospholipid syndrome: a systematic literature review informing the EULAR recommendations for the management of antiphospholipid syndrome in adults

Maria G Tektonidou,[1] Laura Andreoli,[2] Marteen Limper,[3] Angela Tincani,[2] Michael M Ward[4]

High-risk antiphospholipid antibody (aPL) profile

Lupus anticoagulant (x2 occasions 12 weeks apart, according to ISTH guidelines), or

Double aPL positivity, or

Triple aPL positivity, or

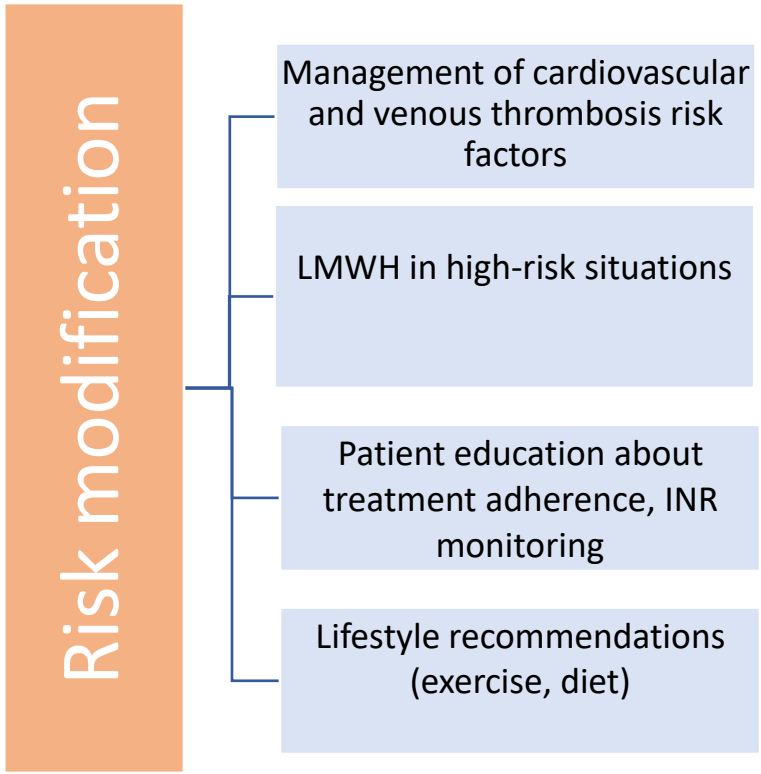
Persistently high aPL titres

Low-risk aPL profile

Isolated aCL or antibeta2glycoprotein I antibodies at low-medium titres

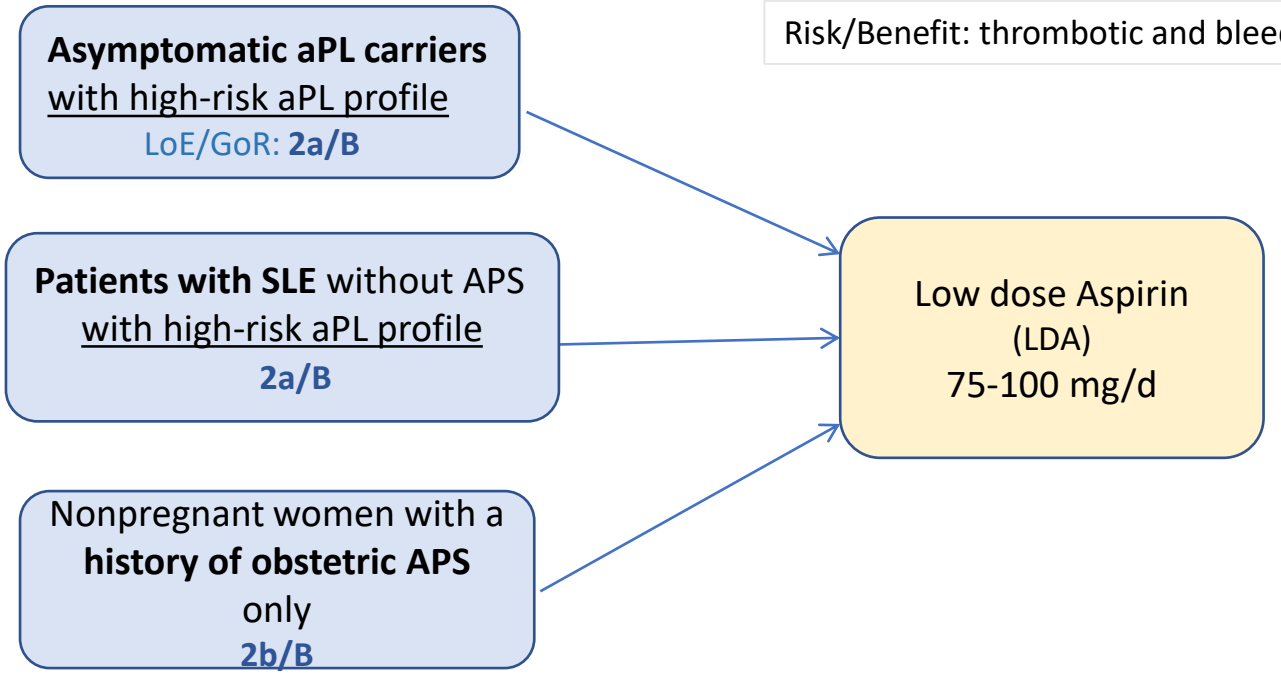
particularly if transiently positive

Primary and secondary thrombosis prevention



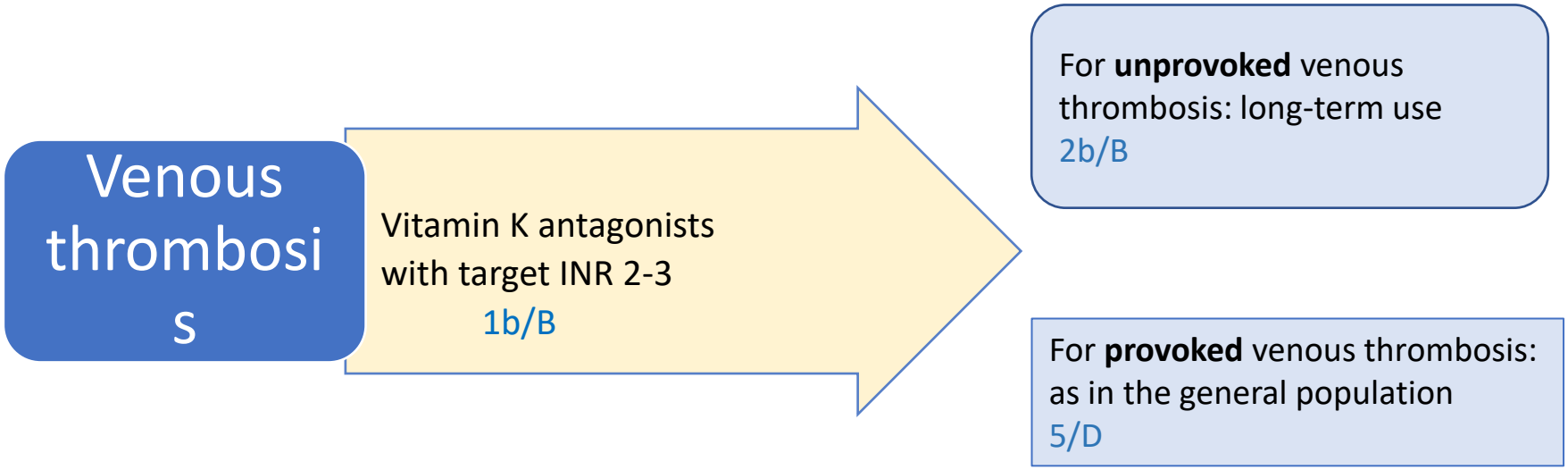
Recommendations

Primary thromboprophylaxis in aPL subjects



Risk/Benefit: thrombotic and bleeding risk factors

Secondary Thromboprophylaxis



Secondary Thromboprophylaxis

Arterial thrombosis

- Vitamin K antagonists over LDA alone **2b/C**
- INR 2-3 or 3-4 (bleeding/thrombosis risk) **1b/B**
- INR 2–3 plus LDA **4/C**

Rivaroxaban
should not be used in APS patients
with **triple aPL positivity**
(based on TRAPS trial data)
1b/B

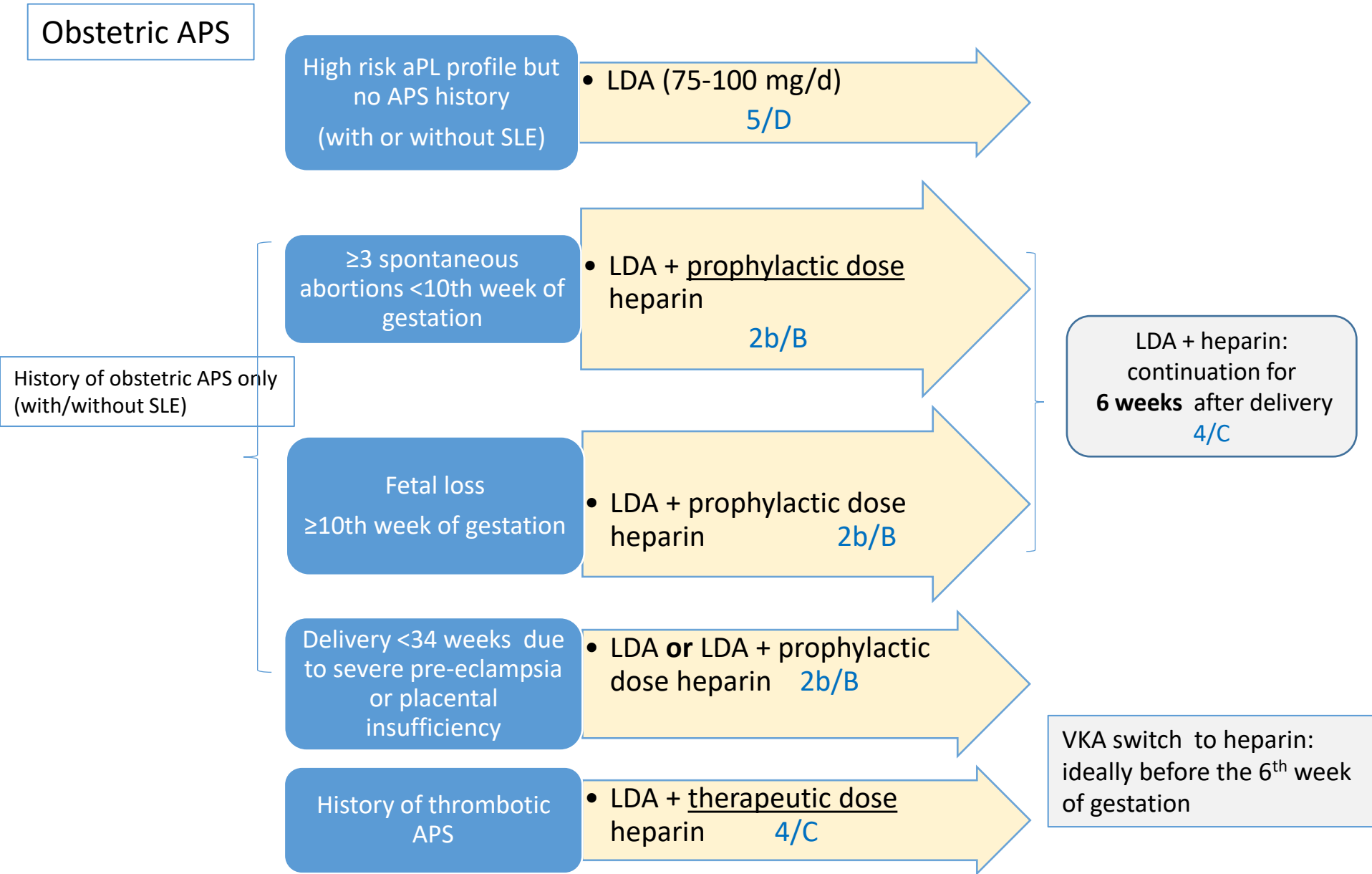
Secondary Thromboprophylaxis

Recurrent venous or arterial thrombosis *despite adequate treatment*

Rule-out other potential causes

- increase of INR target to 3-4, or
- addition of LDA, or
- switch to LMWH

4-5/D


Obstetric APS
High risk aPL profile but no APS history
(with or without SLE)
• LDA (75-100 mg/d)
5/D
History of obstetric APS only (with/without SLE)
≥3 spontaneous abortions <10th week of gestation
• LDA + prophylactic dose heparin
2b/B
Fetal loss
≥10th week of gestation
• LDA + prophylactic dose heparin 2b/B
LDA + heparin: continuation for 6 weeks after delivery
4/C
Delivery <34 weeks due to severe pre-eclampsia or placental insufficiency
• LDA or LDA + prophylactic dose heparin 2b/B
History of thrombotic APS
• LDA + therapeutic dose heparin 4/C
VKA switch to heparin: ideally before the 6th week of gestation

Obstetric APS

Recurrent pregnancy complications

despite LDA + prophylactic heparin treatment

- increase heparin to therapeutic dose (5/D)
  or
- addition of hydroxychloroquine (4/D)
  or
- addition of low-dose prednisolone in the 1st trimester (4/D)

- IVIG *only in highly selected cases* (5/D)

Catastrophic APS

Prevention

- Prompt treatment of infections
- Minimization of anticoagulation interruption/ low INR levels

4/D

1st line treatment

- glucocorticoids
- heparin
- plasma exchange or
- IV immunoglobulins

Refractory CAPS

- B-cell depletion or complement inhibition *may be considered*

4/D

Adjunctive treatments

Old drugs, new roles

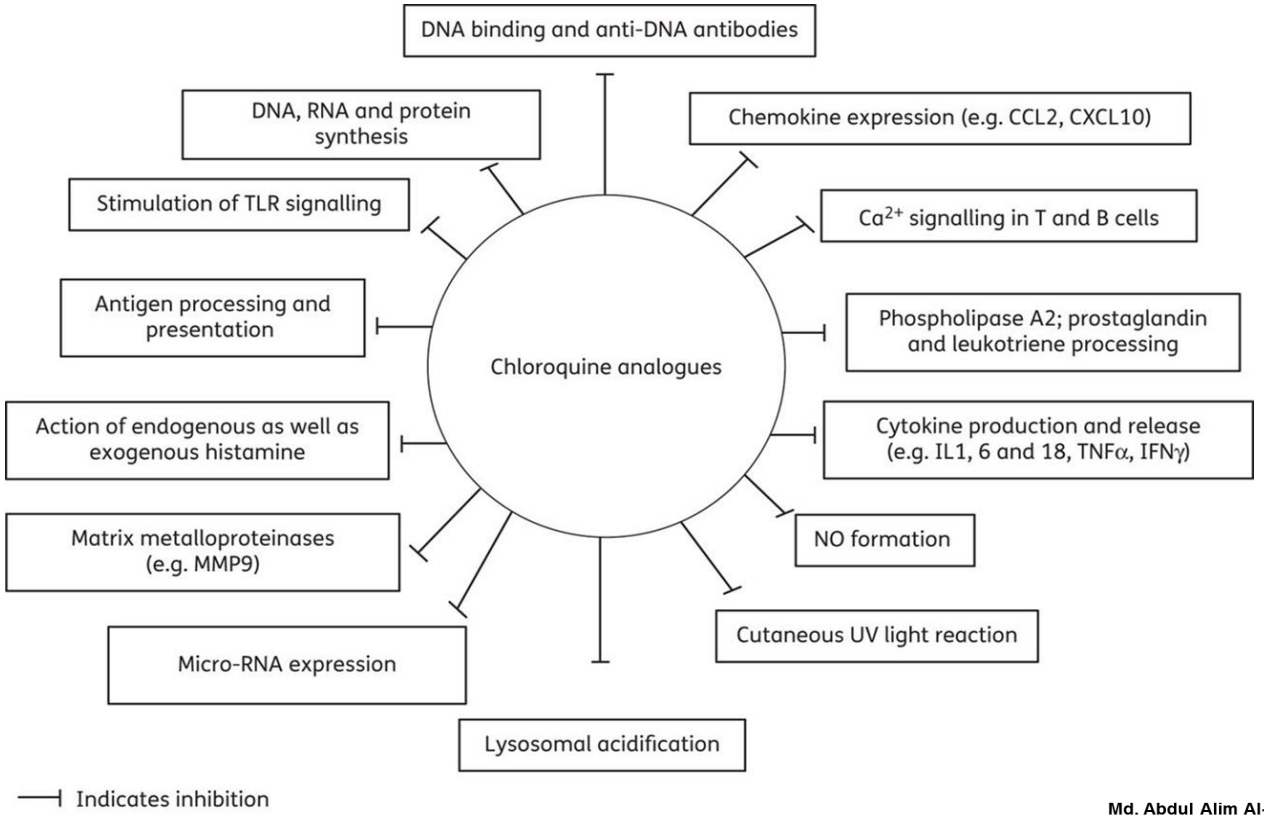
- Hydroxychloroquine
- Statins

Potential treatments for aPL/ APS patients

- in vitro and/or animal studies
- clinical studies

Hydroxychloroquine

Major anti-inflammatory and immunomodulatory effects of chloroquine analogues.



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Schrezenmeier E, Thomas Dörner T.
Nature Reviews Rheumatology 2020

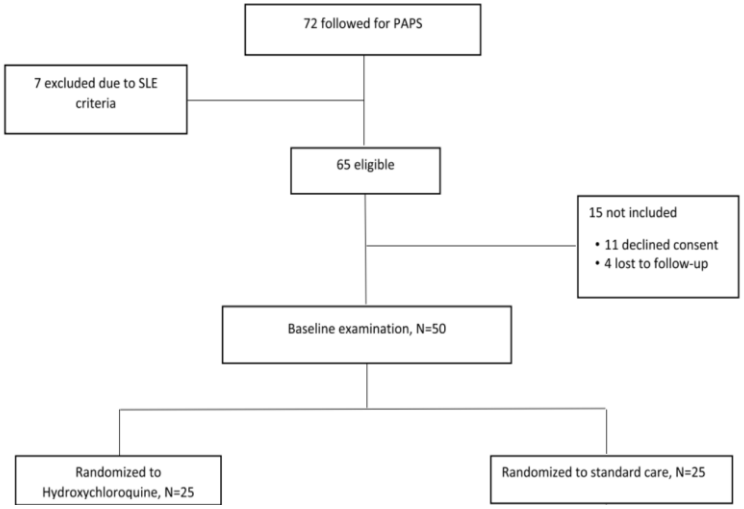
The effect of hydroxychloroquine on thrombosis prevention and antiphospholipid antibody levels in primary antiphospholipid syndrome: A pilot open label randomized prospective study

Evrydiki Kravvariti[a], Alexandra Koutsogianni[a], Evangelia Samoli[b], Petros P. Sfikakis[a], Maria G. Tektonidou[a,*]

Randomized Controlled Trial

doi: 10.1016/j.autrev.2020.102491.

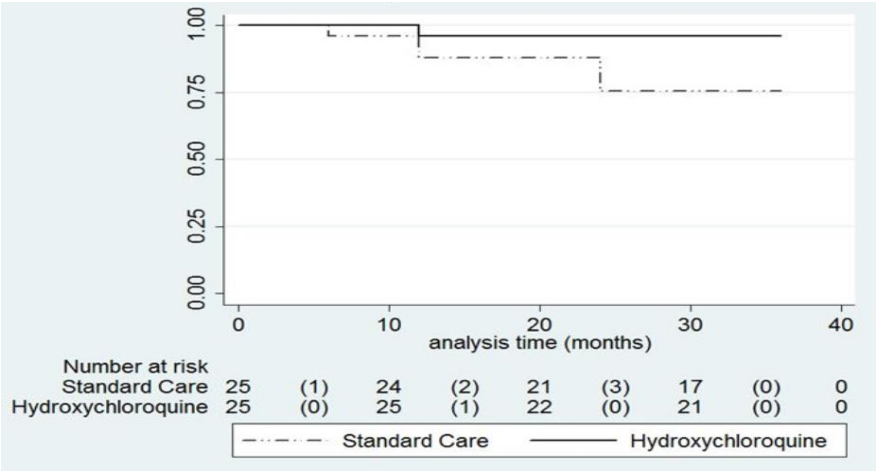
Autoimmun Rev. 2020 Apr;19(4):102491.



- Open-label pilot RCT, 3yr follow-up
- HCQ efficacy on 1. thrombosis prevention in 50 PAPS patients

2. aPL titers of 50 PAPS patients and 15 asymptomatic aPL carriers

Probability of thrombosis-free survival in PAPS patients on HCQ vs standard care alone



Lower incidence rate of thrombosis in HCQ + standard care vs standard care alone (0.001 vs. 0.007, log-rank p =0.048)

The effect of hydroxychloroquine on thrombosis prevention and antiphospholipid antibody levels in primary antiphospholipid syndrome: A pilot open label randomized prospective study

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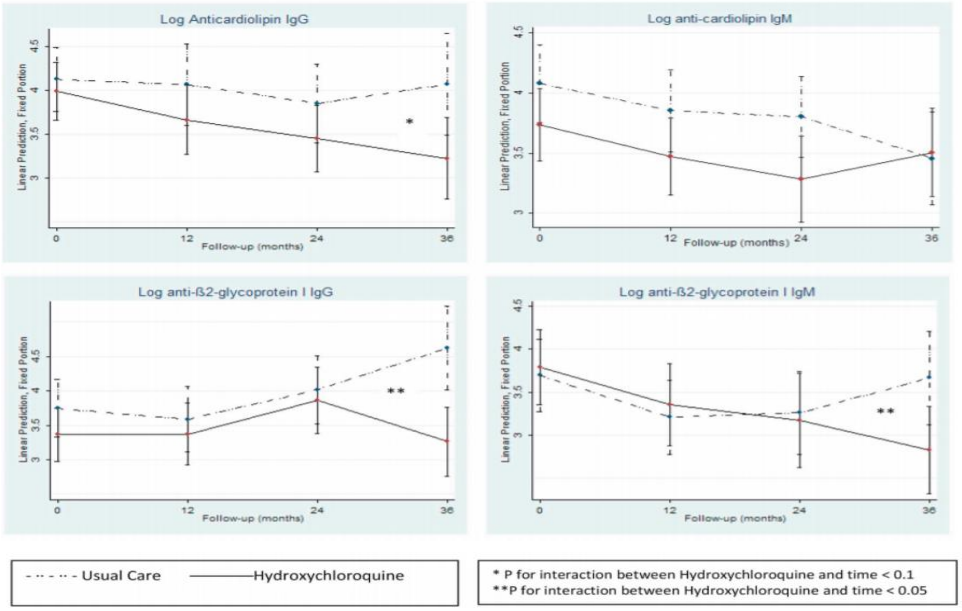
Multivariate analysis and longitudinal antibody titers

- HCQ use and a history of recurrent thrombotic episodes were the most significant determinants of thrombotic risk
- aCL titers tended to decrease overtime in both patient groups ; **aβ2GPi titers tended to decrease in HCQ users**

Stratified multivariate cox regression for the effect of hydroxychloroquine on thrombotic risk in patients with PAPS[a]

	Hazard ratio	95% CI	*P* value
Hydroxychloroquine	0.09	0.01–1.26	0.074
Age (per year)	0.98	0.90–1.06	0.571
Female sex	1.39	0.25–7.56	0.705
≥ 2 traditional cardiovascular risk factors at baseline	5.65	0.68–46.72	0.108
Recurrent thrombotic episodes at baseline	6.31	0.90–44.03	0.063
Quality of anticoagulation during follow-up	0.90	0.12–6.63	0.915



16th International Congress on Antiphospholipid Antibodies
Task Force Report on APS Treatment Trends

Cohen H , Cuadrado MJ, Erkan D, Duarte-Garcia A , Isenberg D, Knight J, Ortel T, Rahman A, Salmon J, Tektonidou MG, Williams D, Willis R, Woller S, Andrade D.

Lupus 2020, 29(12): 1571–1593

Task force recommendations

The addition of HCQ may be considered as adjunctive to antithrombotic treatment for anticoagulant-refractory thrombotic APS

Statins

In vitro/animal studies

- Inhibit aPL-induced endothelial cell activation
- Inhibit up-regulation of tissue factor
- Prevent expression of cellular adhesion molecules and IL-6
- Reduce thrombogenic effects of aPL in aPL-injected mice

Meroni 2001, Ferrara 2004, Ferrara 2003, Redecha 2007, Martinez 2007, Redecha 2008

Statins

Clinical studies in aPL positive patients

- Fluvastatin 20 mg for 1 month:

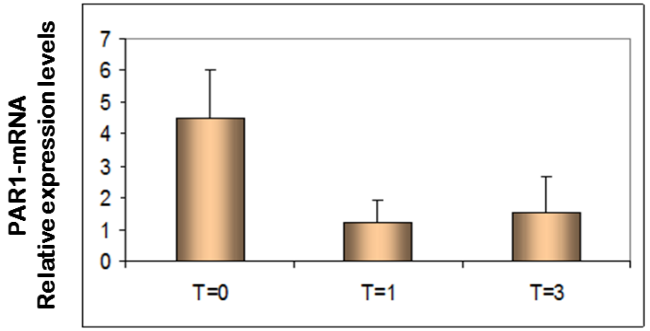
  decreased expression of TF, Protein activator receptor 1 and 2, Vascular endothelial factor, Annexin II

López-Pedrera 2011

- Fluvastatin 40 mg for 3 months:

  reduced levels of 6/12 proinflammatory and prothrombotic biomarkers (IL1β -IFNα -IL6 -IL8 -IP10 -TNFα -sCD40L -sTF -VCAM1 -ICAM1 -E-selectin)

Erkan D 2013



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Task force recommendations

Based on available data, statins cannot be recommended in patients with aPL/APS in the absence of hyperlipidaemia, in accordance with general population guidelines

Statins may be considered as adjunctive to antithrombotic treatment in anticoagulant-refractory thrombotic APS patients

Current Rheumatology Reports (2020) 22:51
https://doi.org/10.1007/s11926-020-00935-2

ANTIPHOSPHOLIPID SYNDROME (S ZUILY, SECTION EDITOR)

Management of Non-criteria Manifestations in Antiphospholipid Syndrome

Eleni Xourgia[1] · Maria G. Tektonidou[2]

Immunosupressives in APS?

Table 2 Potential treatment approaches and the source of available evidence

	Valvular heart disease	Diffuse alveolar hemorrhage	Severe thrombocytopenia	Hemolytic anemia	Antiphospholipid syndrome nephropathy	Livedoid vasculopathy	Skin ulceration	Cognitive dysfunction	Epilepsy
Antiplatelets	+ As prophylactic treatment*	– Not be used in the acute phase	– Not be used in severe thrombocytopenia (can be used in mild thrombocytopenia)		+*	+ *	+*	+*	+ post-stroke, as indicated#§
Anticoagulants	+In valve vegetation* + In valve vegetation with arterial embolization *§	– Not be used in the acute phase	– Not be used in severe thrombocytopenia		+ in thrombotic APS*, **, §	+*	+*	+*	+ post-stroke, as indicated#§
Corticosteroids	+* (Long-term use potential harmful)	+*	+ High iv doses as induction treatment */**/#	+ High iv doses as induction treatment */**/#	+ in co-existing lupus nephritis§§	+*			
Traditional immunomodulatory agents (CYC, MMF, AZA)		+ CYC, MMF*	+ *	+ 1st or 2nd line*/**/#	+ * or in co-existing lupus nephritis§	+*	+*	+*	
Rituximab	No effect***	+ 2nd line* or in CAPS* or in refractory CAPS§	+ In refractory severe thrombocytopenia, or in CAPS*/***/# or in refractory CAPS§	+2nd line*/#	+ */*** or in CAPS *§		+***	+***	
Eculizumab		+ In refractory CAPS*	+ In CAPS*		+*				
Plasmapheresis		+2nd line* or in CAPS§	+ In CAPS§		+ 2nd line*		+*		
Intravenous immunoglobulin	+ 2nd line*	+ 2nd line* or in CAPS*§	+ 1st and 2nd line* or in CAPS*§	+*		+ *	+*		
Belimumab		+*					+*		
Sirolimus					+*/**				
Other	Replacement valve surgery in severe valvulopathy*		Splenectomy (2nd line)*#	Splenectomy (2nd line in autoimmune hemolytic anemia)*#	Renin-angiotensin inhibitors for hypertension and proteinuria control*	Sildenafil, dipyridamole, pentoxyfiline, hyperbaric oxygen *	Sildenafil, recombinant tissue plasminogen activator*		Anticonvulsants when ≥2 unprovoked seizures occur 24 h apart or epileptogenic foci appear on MRI**, #

+potential beneficial effect, –harmful effect

Targeted treatments in APS

Contents lists available at ScienceDirect
International Immunopharmacology
journal homepage: www.elsevier.com/locate/intimp

Immunotherapy in antiphospholipid syndrome

Ch. Lopez-Pedrera [a,*], M.A. Aguirre [a], P. Ruiz-Limon [a], C. Pérez-Sánchez [a], Y. Jimenez-Gomez [a], N. Barbarroja [a], M.J. Cuadrado [b]

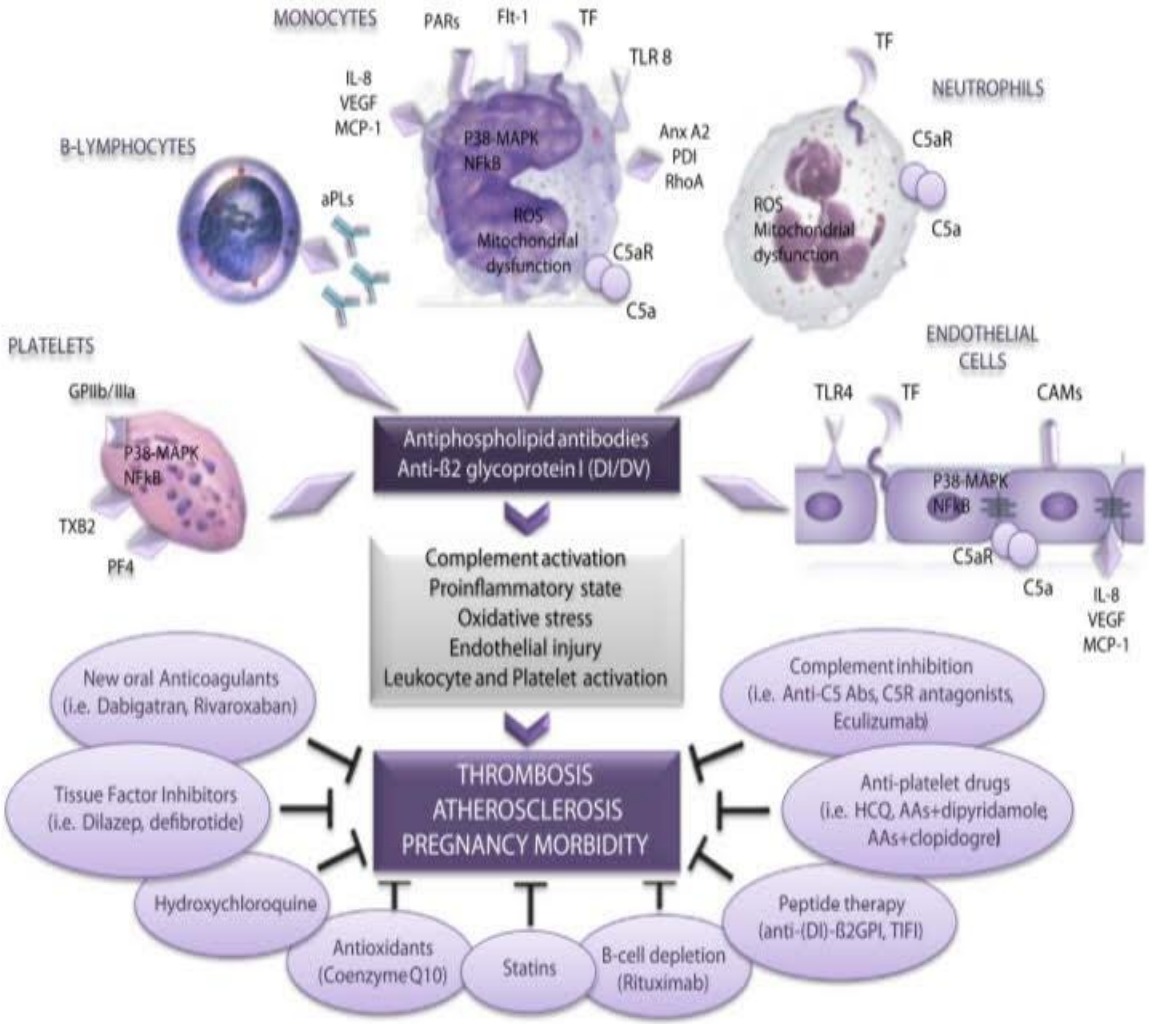

Fig. 1. Mechanisms involved in the aPL-mediated pathogenesis of antiphospholipid syndrome and new therapeutic approaches. Antiphospholipid antibodies (including anti-β2GPI–β2GPI