Thrombotic APS pathophysiology: consequences for laboratory diagnosis

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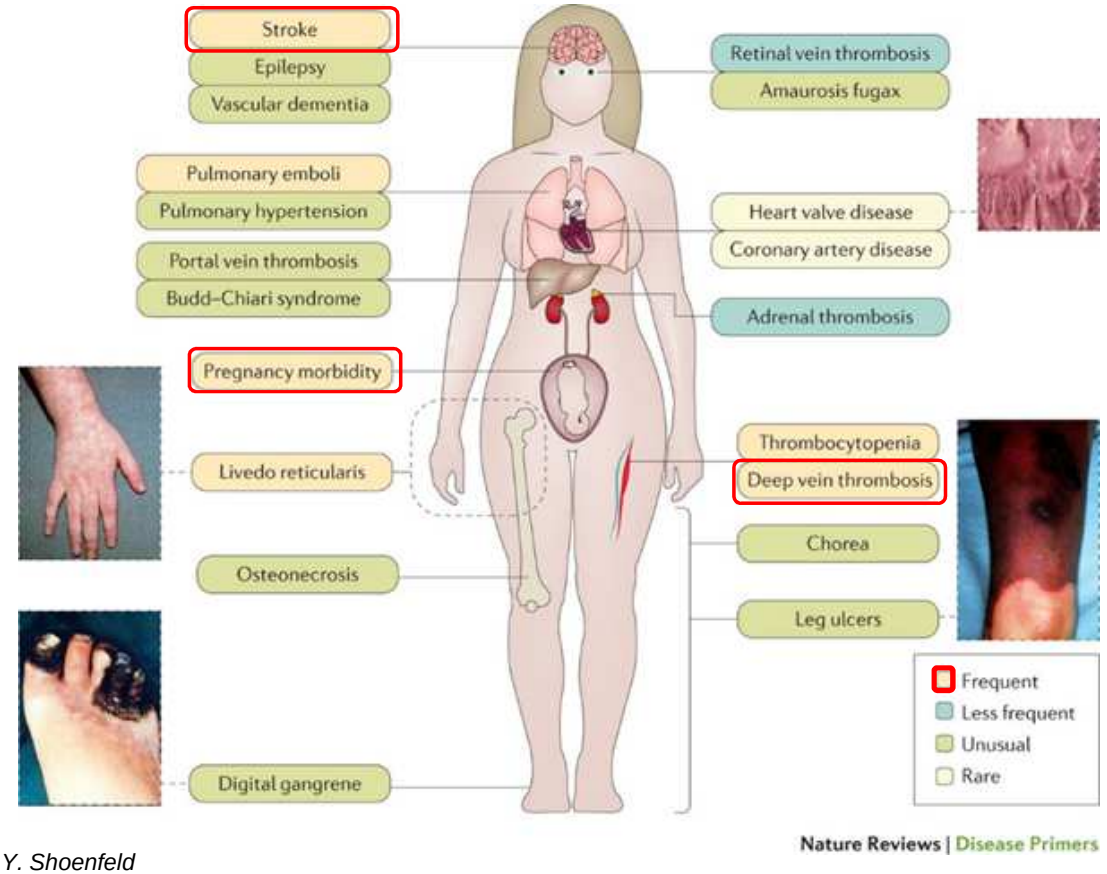
ECAT FOUNDATION

Antiphospholipid syndrome (APS)

Clinical manifestations



Images courtesy of Y. Shoenfeld

SCHREIBER, K. ET AL. (2018) ANTIPHOSPHOLIPID SYNDROME
NATURE REVIEWS DISEASE PRIMERS 4, 2018, JAN 11;4: 17103. DOI: 10.1038/NRDP.2017.103.

Antiphospholipid syndrome (APS)

Clinical manifestation

Thrombosis
Pregancy complications

Sydney classification criteria

MIYAKIS ET AL, J THROMB HAEMOST 2006; 4: 295-306

Other non-criteria:

-Hematological
- thrombocytopenia

-Skin
- livedo reticularis
- leg ulcers

-Cardiopulmonary
- hart valve disease
- pulmonary hypertension

-Central Nerve System
- chorea

-Kidney
- nephropathy

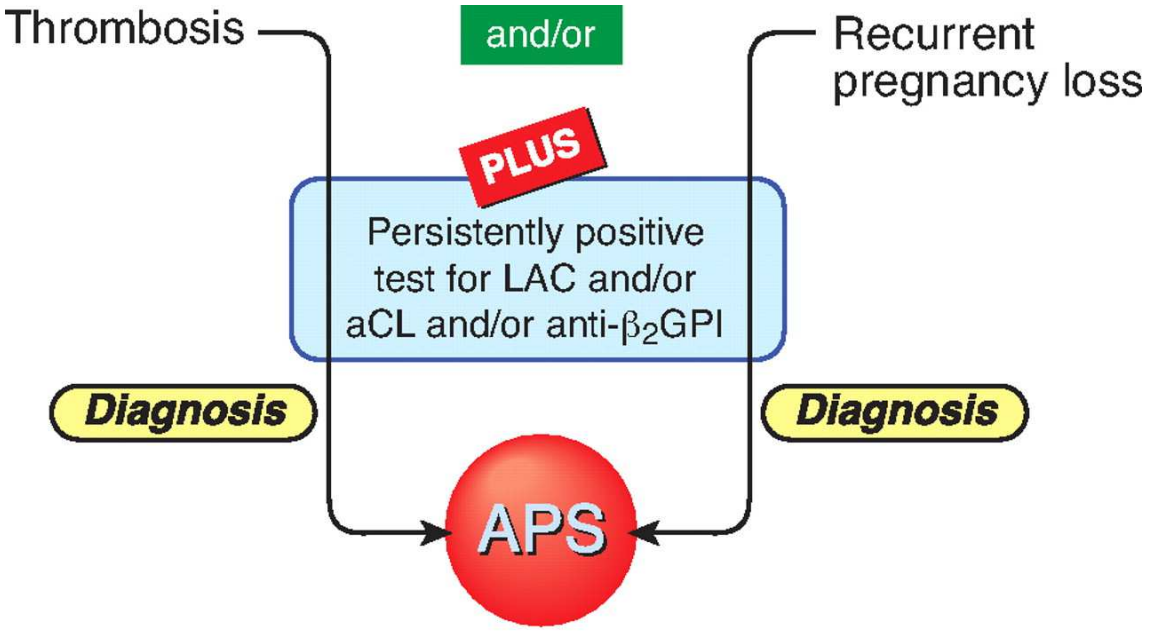
Non-thrombotic

No other hypercoagulable states associated with these symptoms

Unique pathophysiology!

Antiphospholipid syndrome (APS)

- autoimmune disease
- antiphospholipid antibodies (aPL)

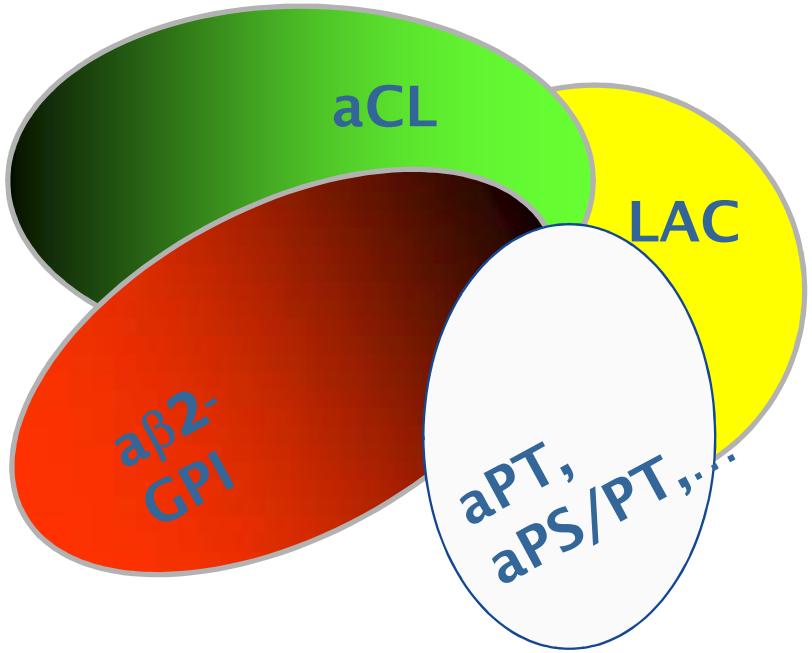


GIANNAKOPOULOS B ET AL. BLOOD 2009;113:985-994;
MIYAKIS ET AL, J THROMB HAEMOST 2006; 4: 295-306

Antiphospholipid syndrome (APS)

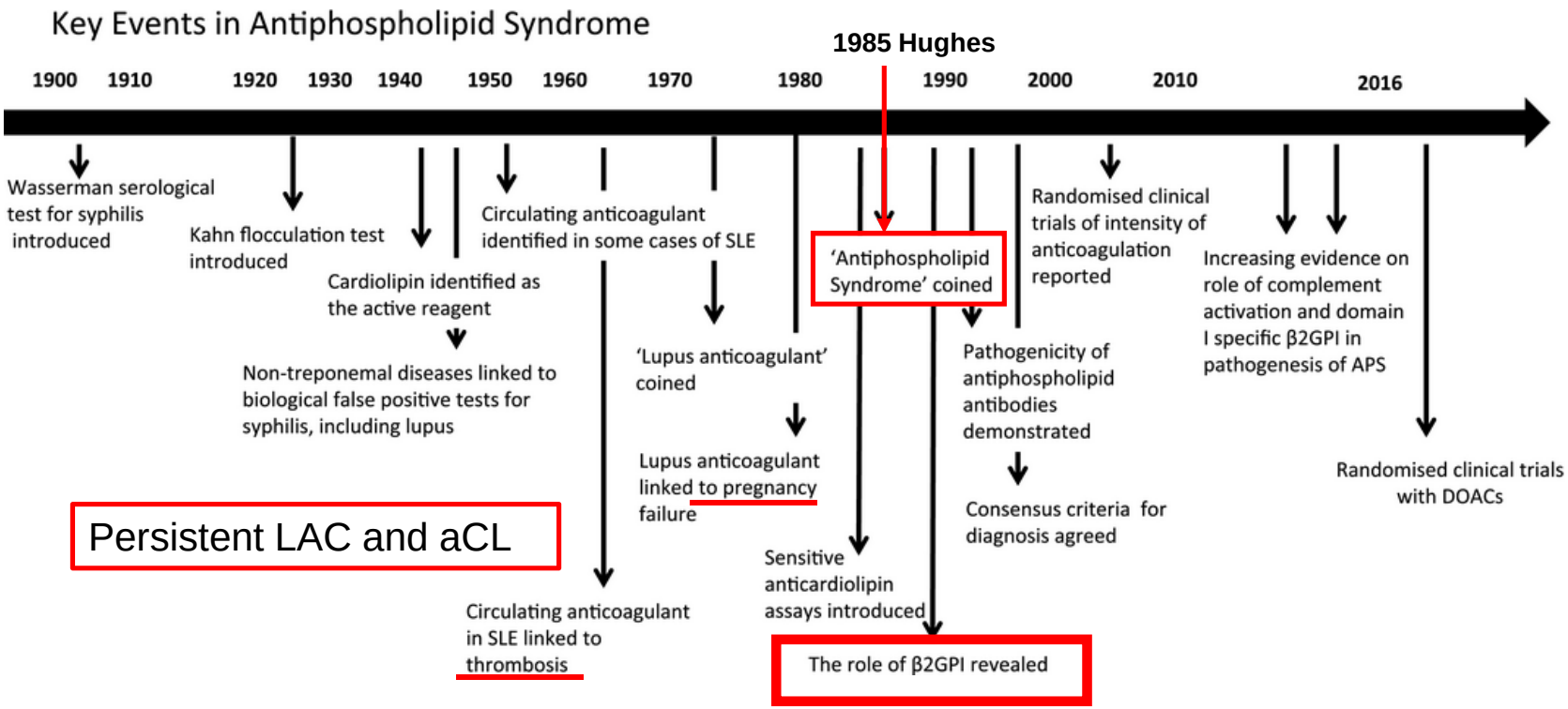
Antiphospholipid antibodies (aPL)

- Lupus anticoagulants (LAC)
- Anticardiolipin antibodies (aCL)
- β2-glycoprotein I antibodies (aß2GPI)
- Antiprothrombin, antiphosphatidyl serine/prothrombin



MIYAKIS ET AL, SYDNEY CRITERIA 2006

Antiphospholipid syndrome (APS)



Adapted from figure originally drawn by Prof. Mike Greaves

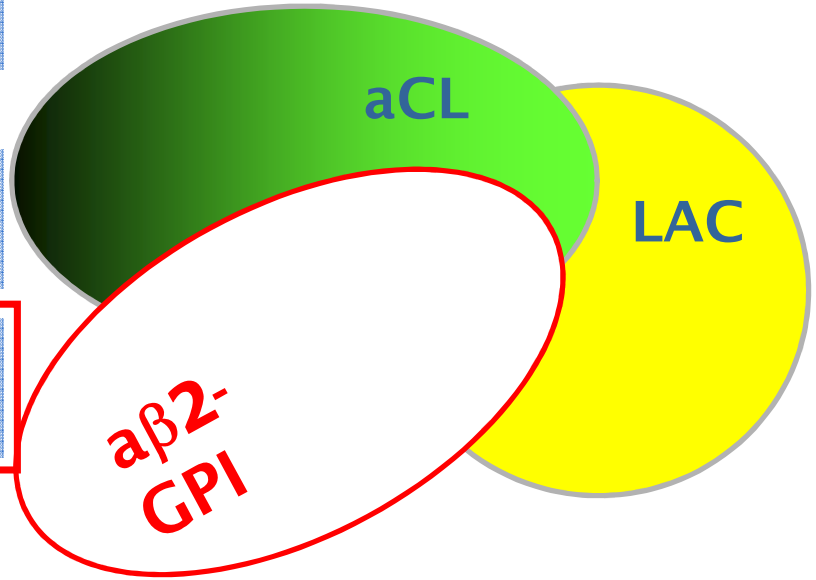
ARACHCHILLAGE ET AL BRITISH JOURNAL OF HAEMATOLOGY
VOLUME 178, ISSUE 2, PAGES 181-195, 24 MAR 2017

Antiphospholipid syndrome (APS)

Lupus anticoagulants (LAC)

Anticardiolipin antibodies (aCL)

β2-glycoprotein I antibodies (aß2GPI)

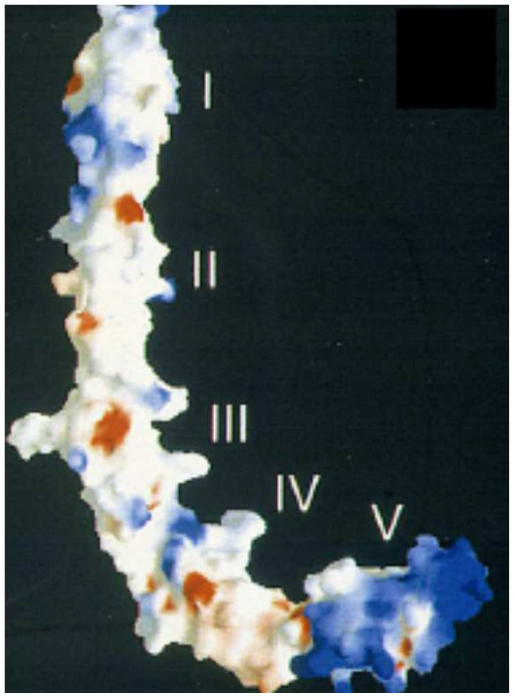


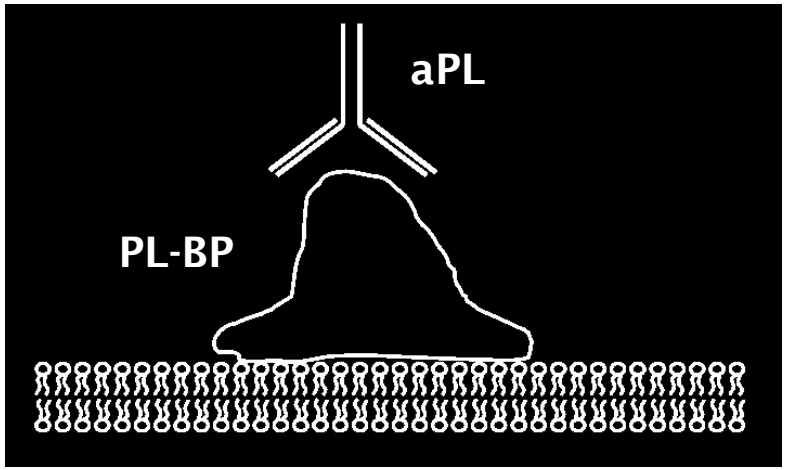
Third lab criterion

SYDNEY CRITERIA: MIYAKIS ET AL, J THROMB HAEMOST. 2006, 4: 295-306
SAPPORO CRITERIA: WILSON ET AL. ARTHRITIS RHEUM. 1999, 42: 1309-11

Antiphospholipid antibodies (aPL)

“APS”= wrong name





$ß_2$- glycoprotein I (ß2GPI)

-described in 1966

-deficiency not associated with symptoms

GALLI ET AL, MC NEILL ET AL, MATSUURA ET AL, 1990

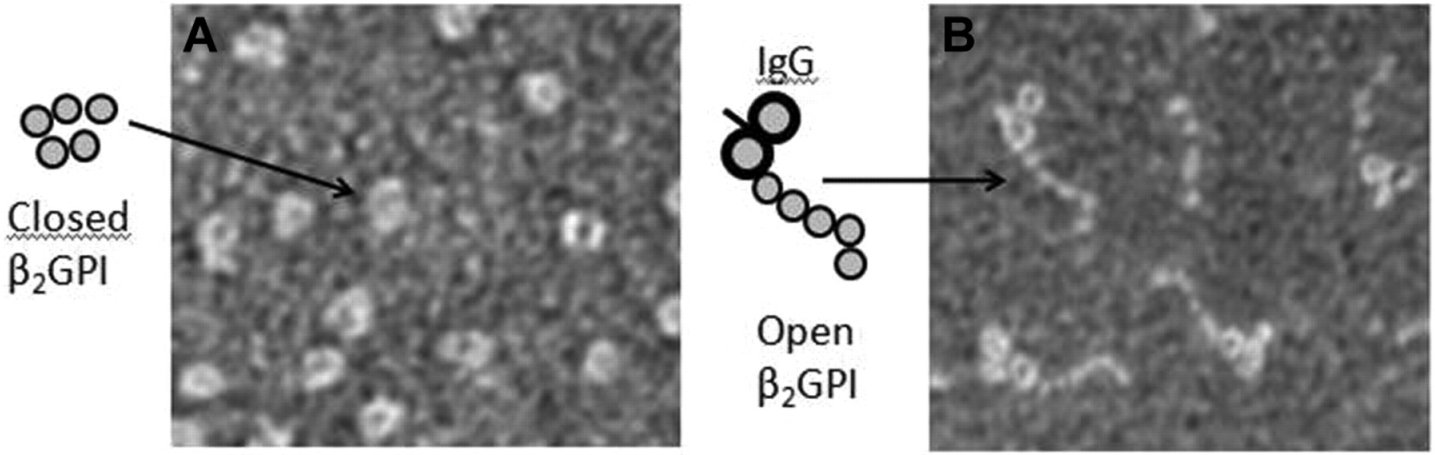
ß2- glycoprotein I (ß2GPI)

- No circulating ß2GPI-antibodies complexes in APS patients
- Levels of ß2GPI are similar in APS patients and controls
- Epitope on ß2GPI that is recognized by pathogenic antibodies is cryptic

AGAR ET AL. BLOOD 2010; 116: 1336-1343
KUWANA ET AL. BLOOD 2005; 105: 1552-1557
PHILIP G. DE GROOT AND ROLF T. URBANUS. BLOOD 2012;120:266-274

ß2- glycoprotein I (ß2GPI)

ß2-glycoprotein I changes conformation on antibody binding.

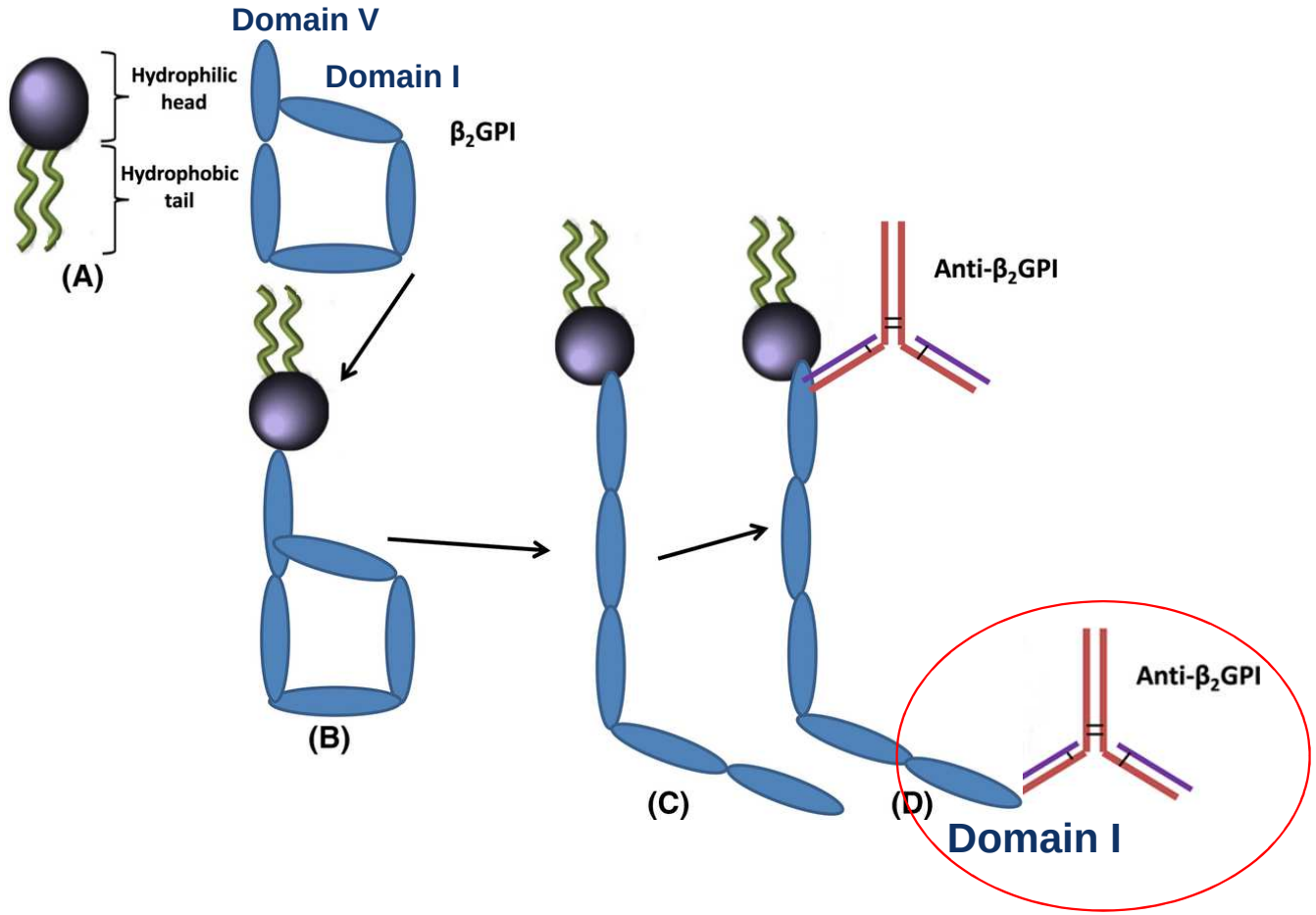


ß2GPI in plasma

ß2GPI in plasma +
anti-domain I antibodies

DE GROOT AND URBANUS BLOOD 2012; 120:266-274
AGAR ET AL. BLOOD 2010; 116: 1336-1343
KUWANA ET AL. BLOOD 2005; 150: 1552-1557

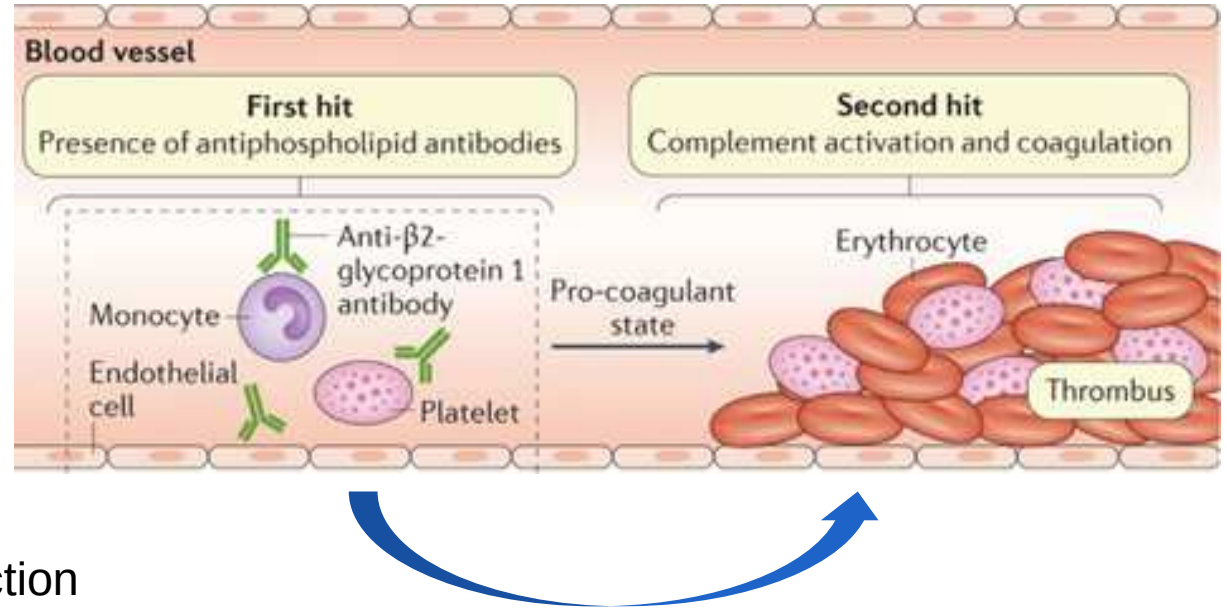
ß2- glycoprotein I (ß2GPI)



ARACHCHILLAGE ET AL. BR J OF HAEMATOL 2017; 178: 181-195

VAN OS ET AL. J THROMB HAEMOST 2011; 9: 2447-2456

Why thrombosis?

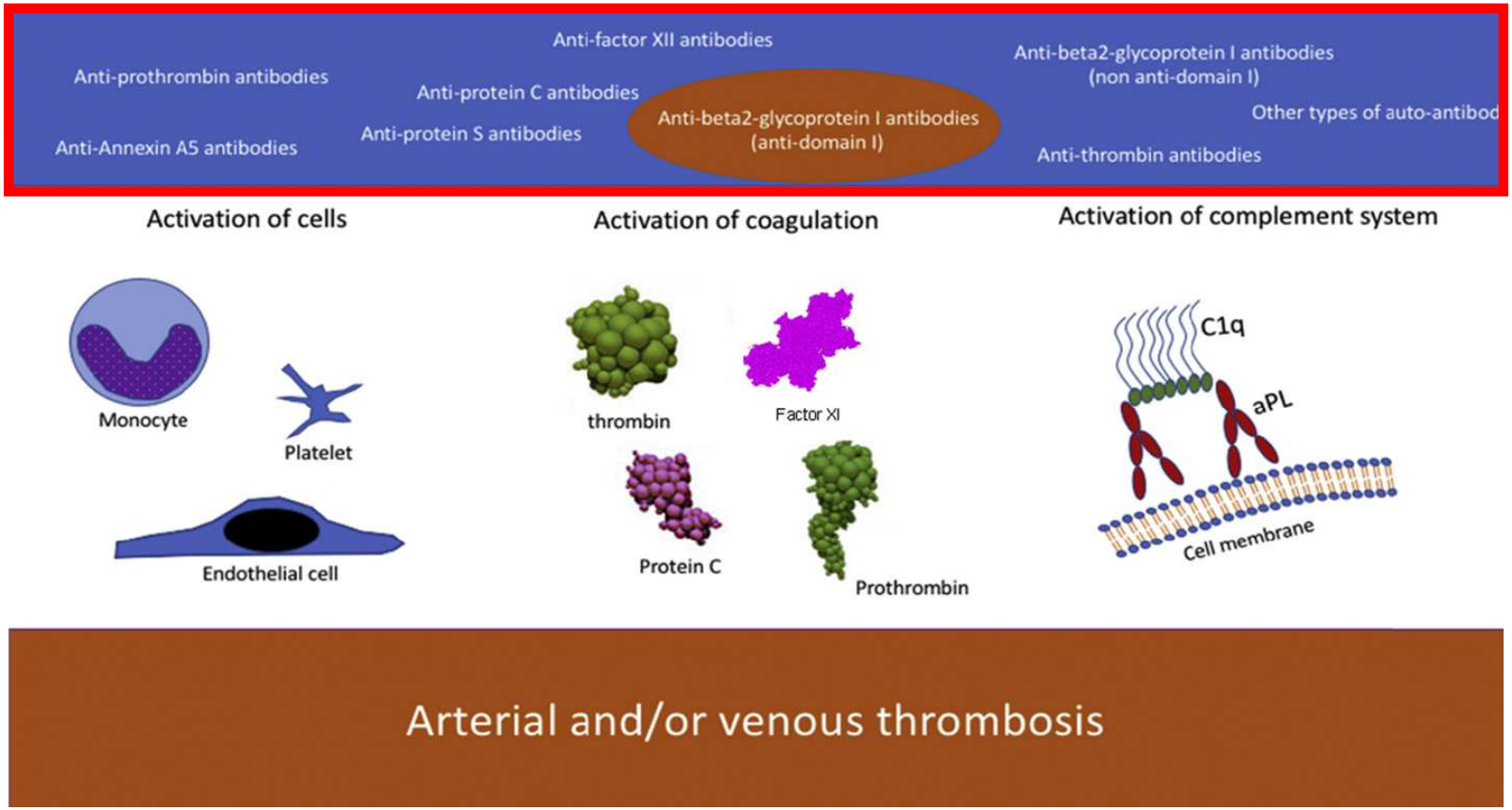


-Infection
-Inflammatory factors (e.g. concomitant connective tissue diseases)
-Non-immunological procoagulant factors (e.g.oestrogen-containing contraceptives, surgery, immobility)
-Minor vascular injury
-Genetic constitution

HLA-DR4, HLA-DRw53, IRF5, STAT4

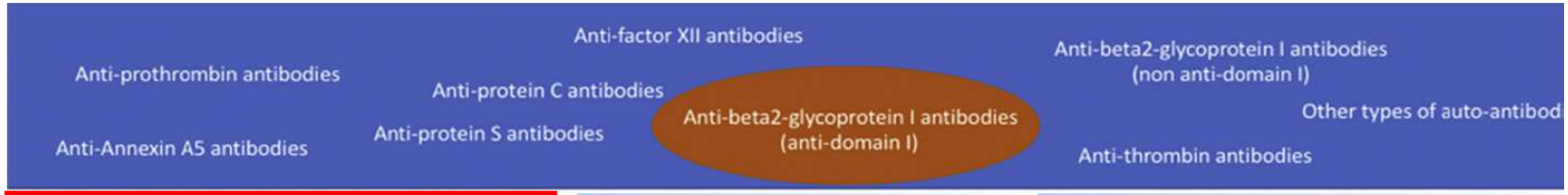
SCHREIBER, K. ET AL. NAT. REV. DIS. PRIMERS 2018 DOI:10.1038/NRDP.2017.103

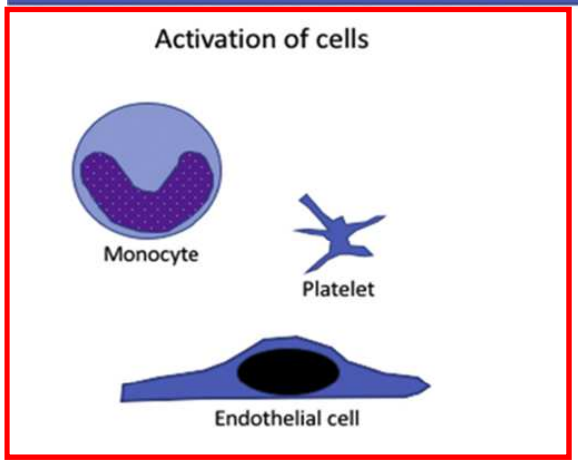
Different players in APS pathophysiology



DE GROOT AND DE LAAT, BEST PRACTICE AND RES CLIN RHEUMATOL 2017; 31: 334-341

Different players in APS pathophysiology



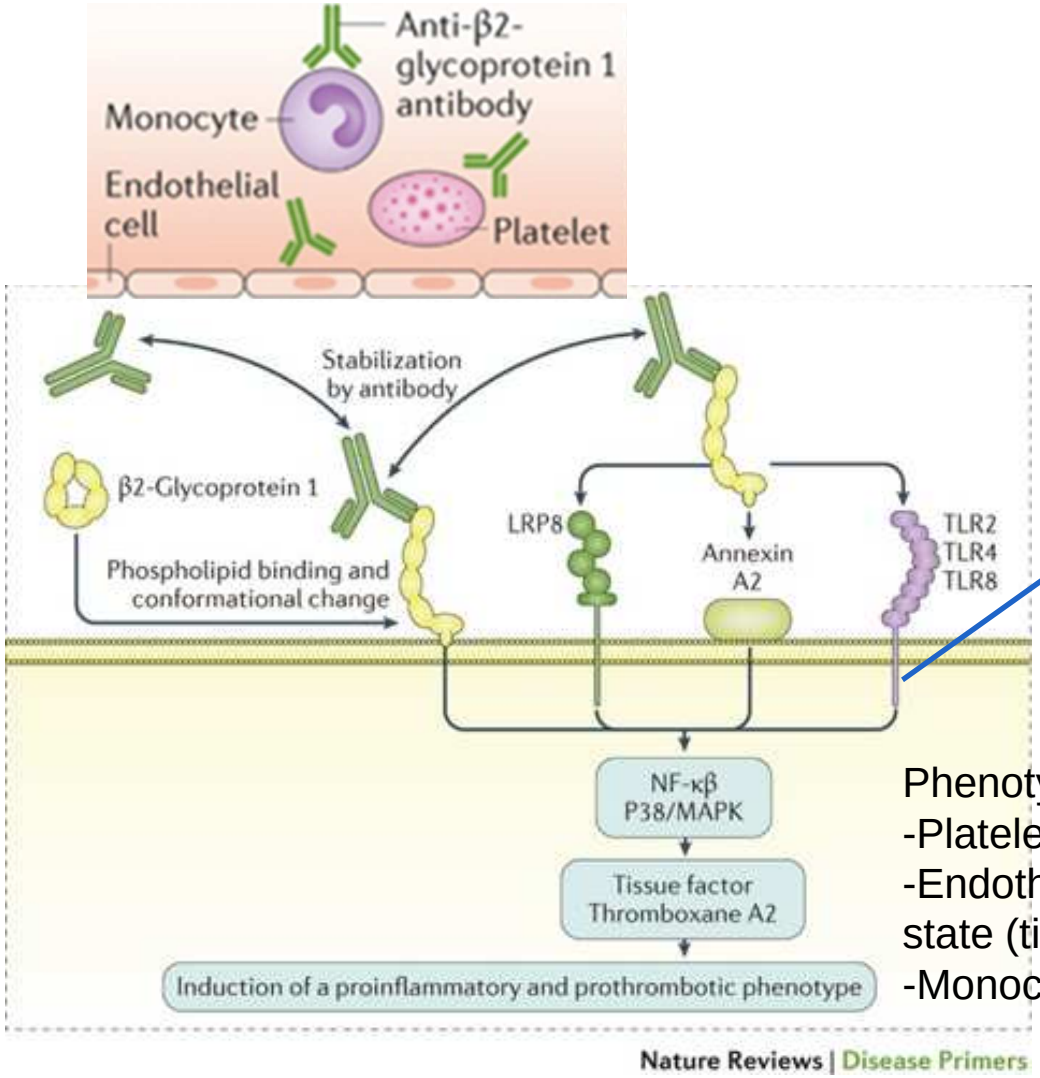


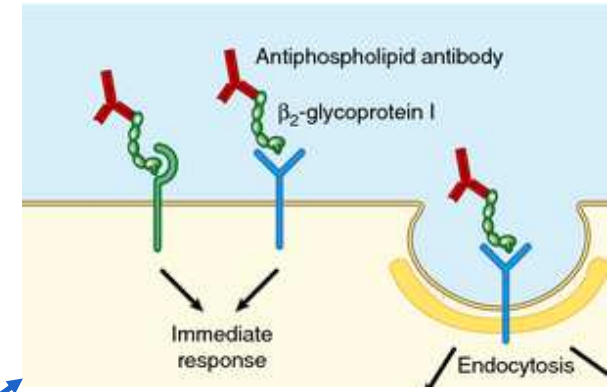
-which cell is the key player in vivo
-Which receptors are involved
-What are the phenotypic changes of the cells
-How is the extracellular signal transduced to the nucleus of the cell

Arterial and/or venous thrombosis

DE GROOT AND DE LAAT, BEST PRACTICE AND RES CLIN RHEUMATOL 2017; 31: 334-341

Mechanism of aß2GPI in cell activation

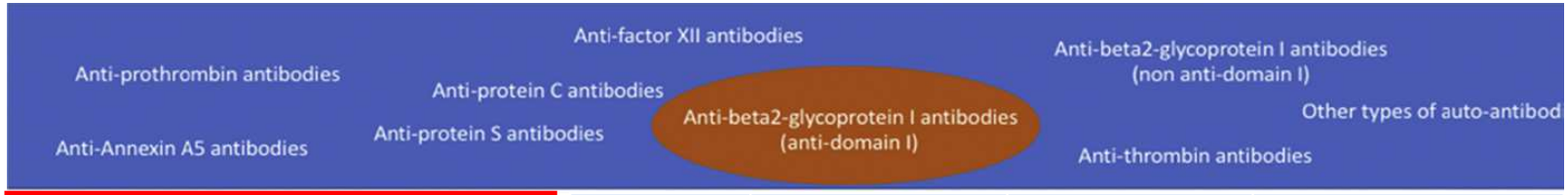


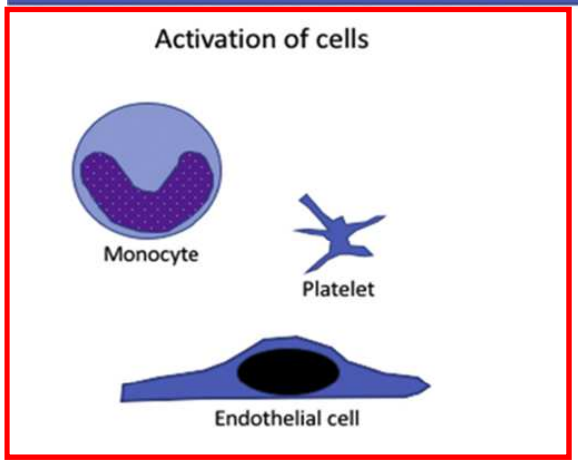


Phenotypic changes in
-Platelets: aggregation
-Endothelial cells: proinflammatory state (tissue factor)
-Monocytes: tissue factor

SCHREIBER, K. ET AL. NAT. REV. DIS. PRIMERS 2018 DOI:10.1038/NRDP.2017.103

Different players in APS pathophysiology



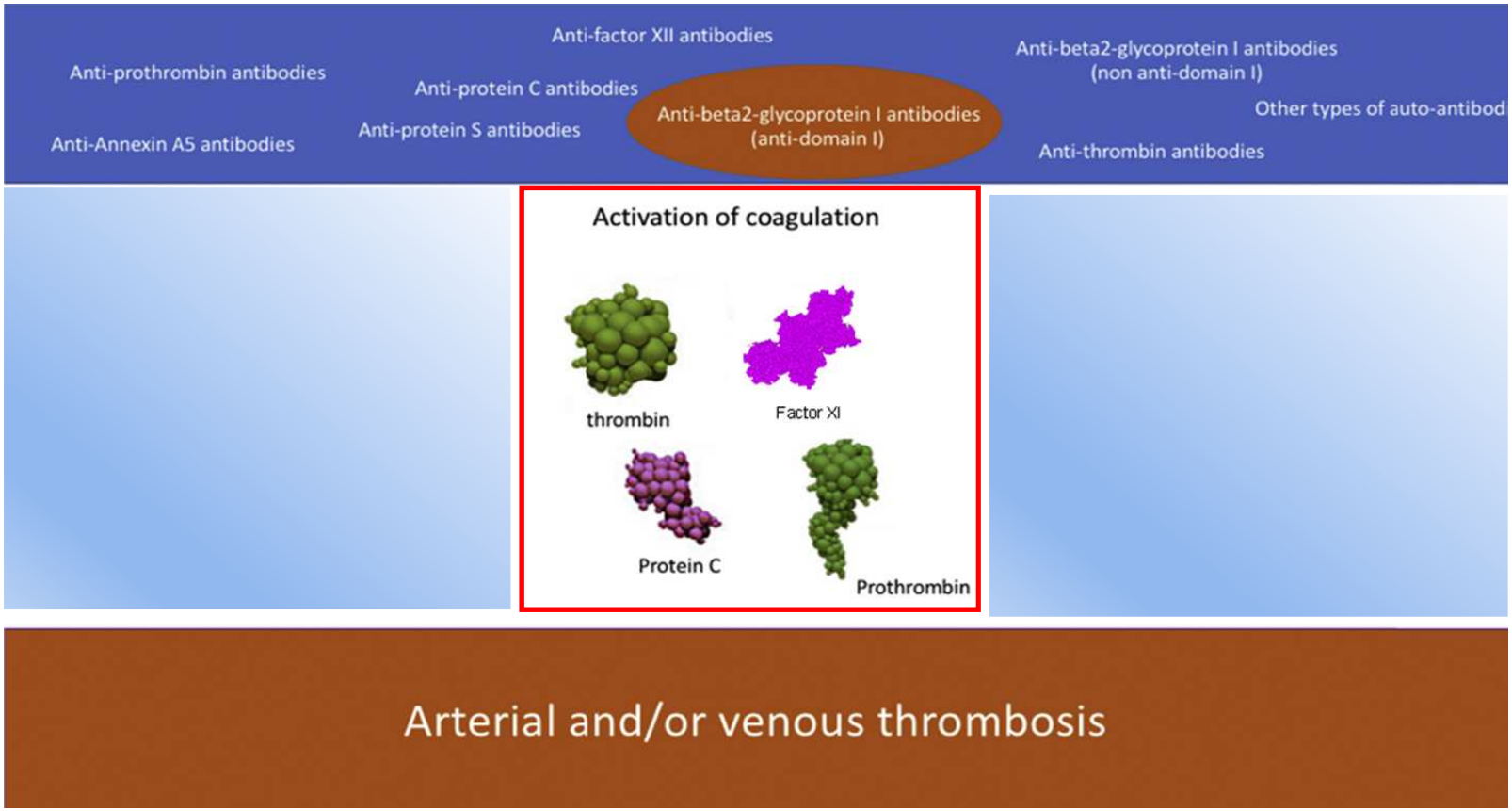


Pathway	Antibody specificity	Cell types activated	Involved in pathogenesis in vivo
ANXA2	β2GPI	M, EC	Thrombosis
ANXA5	β2GPI, aCL suggested	EC, T	nd
TLR2	β2GPI suggested	M, EC	nd
TLR4	β2GPI suggested	M, EC	Thrombosis
LRP8	β2GPI	P, M, EC	Thrombosis, fetal resorption
Endo-NOX2	aCL	M, N, pDC, EC	Thrombosis

Arterial and/or venous thrombosis

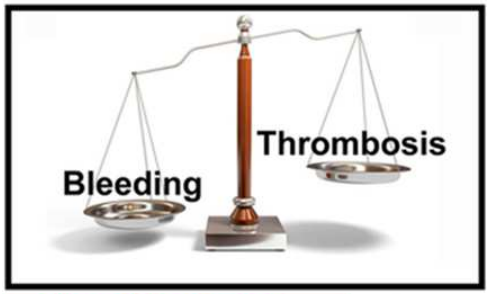
DE GROOT AND DE LAAT, BEST PRACTICE AND RES CLIN RHEUMATOL 2017; 31: 334-341
MÜLLER-CALLEJA AND LACKNER. SEMIN THROMB HEMOST 2017. DOI: 10.1055/S-0036-1597290

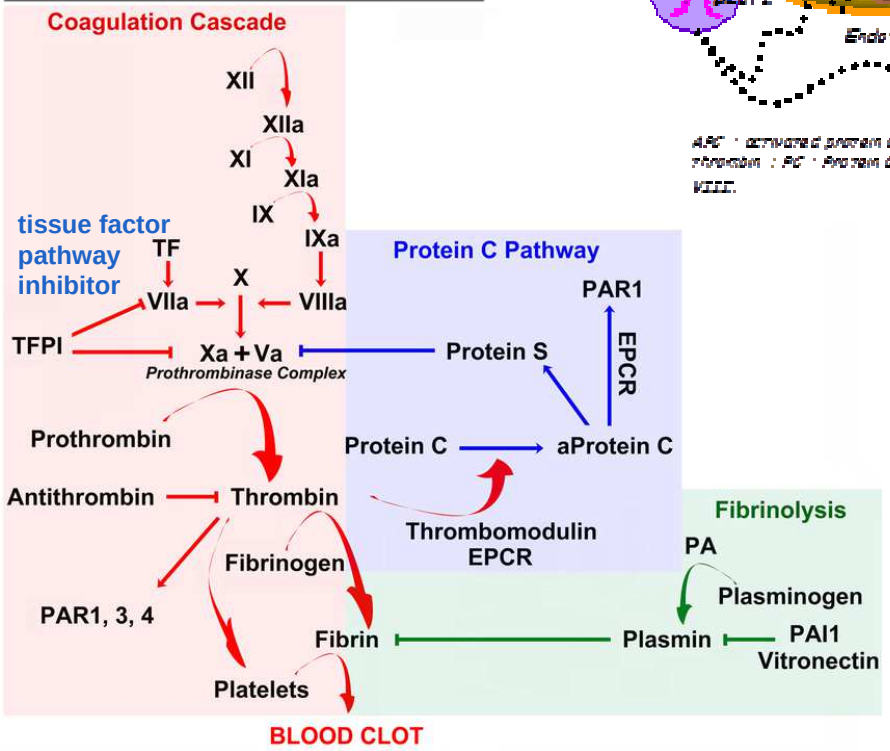
Different players in APS pathophysiology

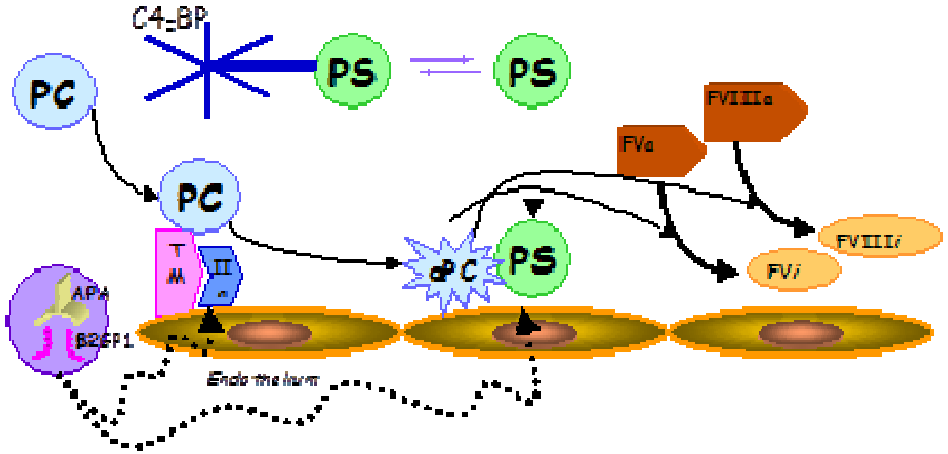


DE GROOT AND DE LAAT, BEST PRACTICE AND RES CLIN RHEUMATOL 2017; 31: 334-341

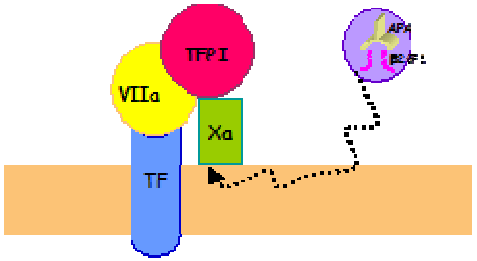
Interaction of aPL with coagulation regulation





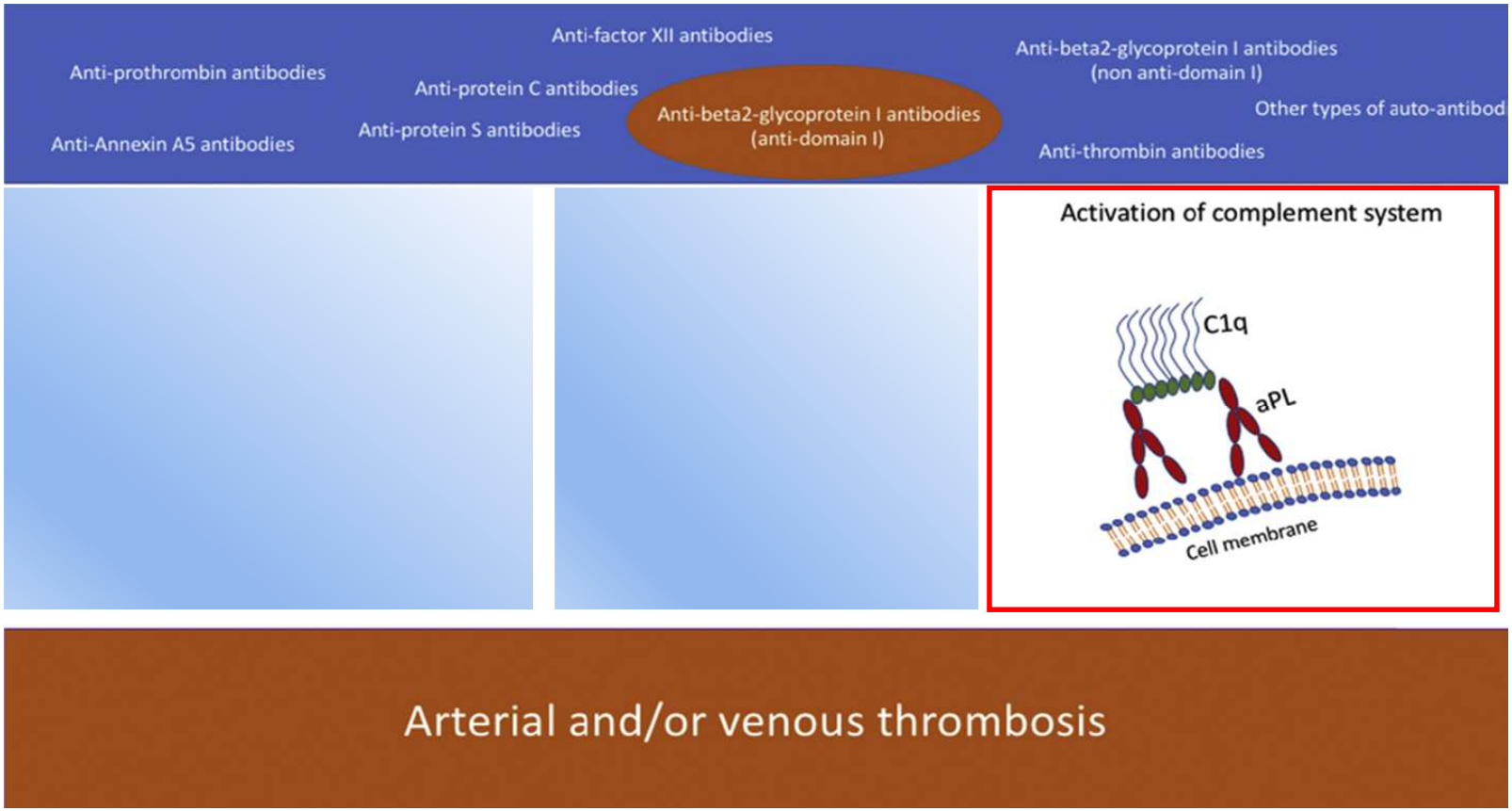


APC : activated protein C ; TM : thrombomodulin ; PS : protein S ; C4BP : C4b binding protein ; IIa : thrombin ; PC : Protein C ; Va & VIIIa : activated Factor V & VIII ; Vi & VIIIi : inactivated Factor V & VIII.



TF : Tissue Factor, TFPI : Tissue Factor Pathway Inhibition, Xa : Factor Xa, VIIa : Factor VIIa

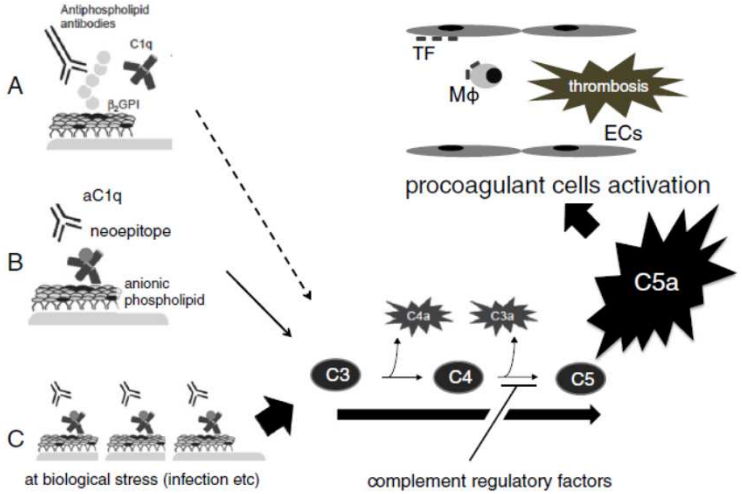
Different players in APS pathophysiology

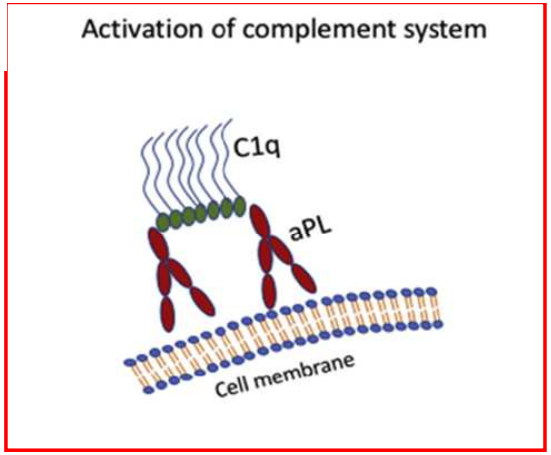


DE GROOT AND DE LAAT, BEST PRACTICE AND RES CLIN RHEUMATOL 2017; 31: 334-341

Role of complement in APS pathophysiology

- C3, C4, C5 deficient mice injected with aPL combined with a vascular challenge showed a reduced thrombotic response
- Patients with primary APS show hypocomplementemia (consumption, activation)
- Anti C1q in APS patients, induce complement activation





DE GROOT AND DE LAAT, BEST PRACTICE AND RES CLIN RHEUMATOL 2017; 31: 334-34
PIERANGELI ET AL. ANN NY ACAD SCI 2005; 1051: 413-420
OKU ET AL. AUT. REVIEWS 2016; 15: 1001-1004

Pathogenicity of aPL

- Mouse models:
  - purified aβ2GPI IgG from APS patients injected to mice with injured blood vessels potentiates thrombus formation

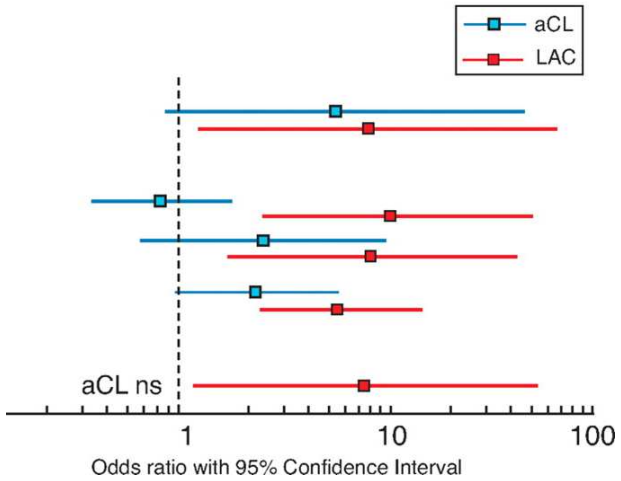
- Cell cultures: activation of monocytes, endothelial cells, platelets by aPL results in expression of adhesion molecules, vascular cell adhesion molecules, E-selectin or tissue factor

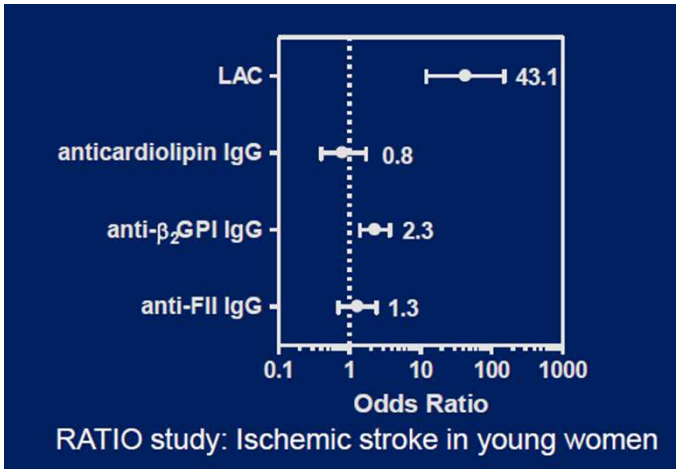
- Thrombotic risk in APS patients
  - Serological and clinical factors
  - Type and level of aPL
  - Coexistence of predisposing thrombotic risk factors
  - Association with underlying autoimmune diseases (SLE)
  - The laboratory parameters in risk stratification for thrombotic complications in APS

ARAD ET AL., BLOOD 2011; 117: 3453-3459; PIERANGELI ET AL, SEM THROMB HAEMOST 2008; 34: 236-250
ARACHCHILLAGE ET AL. BR J HAEMATOL 2017, 176; 181-195;
DEVREESE. THROMB RES 2012, 130 SUPPL 1:S37-40

Pathogenicity of aPL

- LAC
  - stronger risk factor for thrombosis than aCL
  - risk factor for venous and arterial thrombosis
  - discrepancies in reported risk:
    - OR VTE: 3.6-9.4
    - OR Ischemic stroke: 1.8-43.1

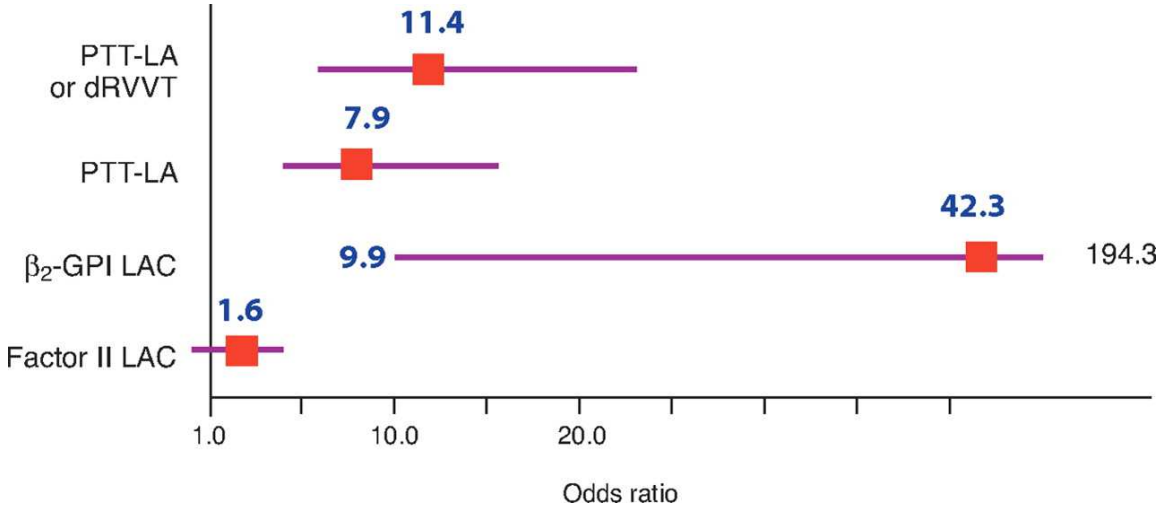




DEVREESE. THROMB RES. 2012 OCT;130 SUPPL 1:S37-40
GALLI ET AL, BLOOD 2003; 101: 1827-1832
URBANUS ET AL, LANCET NEUROLOGY, 2009, 8: 998-1005
DE GROOT ET AL, JTH 2005; GINSBERG ET AL, BLOOD 1995, BREY ET AL STROKE 2002

Pathogenecity of aPL

- LAC: functional antibodies by coagulation assays, “all” aPL independent of cofactor
  - β2GPI-dependent LAC strongly associates with thrombosis, compared with factor II (prothrombin)-dependent LAC



GIANNAKOPOULOS B ET AL. BLOOD 2009;113:985-994, DE LAAT ET AL, BLOOD 2004; 104: 3598-3602, PENGO ET AL 2015

Pathogenecity of aPL

- ß2GPI-dependent LAC
  - ***Simmelink et al, 2003***
    - Adding cardiolipin vesicels shortens the coagulation time (aPTT) in ß2GPI-dependent LAC
      Stronger relation (odd ratio 42.3) with thrombosis than LAC (10.2) and than ELISA anti-ß2GPI (6.8)
  - ***Pengo et al, 2004***
    - In low conc. $CaCl_2$ more prolonged clotting times (dRVVT and dPT) in patients positive for ß2GPI-antibodies
  - ***Devreese, 2007***
    - More prolonged clotting times in LAC positive patients with ß2GPI-antibodies in aPTT screening test (PTT-LA), also in routine CaCl2 concentrations (8.3mM)
  - ***de Laat et al, 2011***
    - aPTT based ß2GPI-dependent LAC assay in multicenter study correlated better with thrombosis compared to classic LAC assay, but sensitive to sodium citrate concentration (109 M vs 129 M)

Complicated, not commercially available, not robust

Pathogenicity of aPL

- Isolated positivity for LAC
  - In absence of clinical symptoms
  - In elderly patients
  - On a first occasion, not confirmed after 12 weeks
  - not ß2GPI-dependent
  - Clinical studies: low risk of thrombosis

Leiden Thrombophilia Study 472 controls, 473 patients	**OR**	**OR 95% CI**
LAC	3,6	1,2-10,9
aβ2GPI IgG	2,4	1,3-4,2
aPT IgG	1,4	1,0-2,1
LAC + aβ2GPI or aPT	10,1	1,3-79,8

PENGO ET AL J THROMB HAEMOST 2007, 2015;

DE GROOT ET AL , J THROMB HAEMOST 2005, 3: 1993-7

Pathogenicity of aPL

aCL IgG

- OR ELISA
  - not consistent
  - VTE: 4.7-5.5
  - Arterial thrombosis: 1.4-15

- OR automated chemiluminescent techniques
  - VTE: 11,7 [5,8-23,7]
  - VTE: 55,7 [24,9-124,6]

- Isolated positivity: no association with thrombosis, except in SLE

GALLI ET AL, BLOOD 2003; URBANUS ET AL, LANCET NEUR 2009; AHMED ET AL STROKE 2000; BREY ET STROKE 2000; NAESS ET AL JTH 2006; SANMARCO ET AL, 2007; GINSBURG ET AL,1992; WU ET AL, 1992; SAIDI ET AL, 2009; DE MOERLOOSE ET AL, JTH 2010; DE CRAEMER ET AL, JTH 2016; PENGO ET AL 2005; RUFFATI ET AL 2008; RUNCHEY ET AL 2002; PROVEN ET AL 2004; LES ET AL, SEMIN THROMB HEMOST 2009

aß2GPI IgG

- modest risk: OR
  - VTE: 1.6-2.4
  - MI: 2.5
  - Stroke: 2.3

- ELISA
  - OR 4 -15.4
  - OR 7.6-11.7

- OR automated chemiluminescent techniques
  - VTE: 6,2 [3,4-11,3]
  - VTE: 7,9 [3,9-16,1] and 139,0 [41,8-463,0]

- Isolated positivity: no association with thrombosis

PETRI ET AL 2010; DE GROOT ET AL, 2005; MERONI ET AL, 2007; URBANUS ET AL, 2009; DEVREESE ET AL, BLOOD 2010; VAN HOECKE AND DEVREESE, INT J LAB HEMATOL, 2012; DE MOERLOOSE ET AL, JTH 2010) ; DE CRAEMER ET AL, JTH 2016; PENGO ET AL 2005; URBANUS ET AL 2009

aCL and aβ2GPI testing

- Isotype

  - discussion about the role of IgM: thrombosis/pregnancy
  - aCL/aß2GPI same isotype (IgG/IgM)= high risk for thrombosis

  - IgA: further investigations

  - Systematic review on the role of IgM included studies 2001-2014

    -More significant correlations with thrombosis for the IgG

    -Significant associations for IgM also found with corresponding IgG

    -How many APS patients missed upon omission of IgM?

DEVREESE ET AL, ISTH-SSC RECOMMENDATIONS, J THROMB HAEMOST 2014; 12: 792-5

DEVREESE ET AL, J THROMB HAEMOST 2018; 16: 809–13
LABORATORY CRITERIA FOR ANTIPHOSPHOLIPID SYNDROME: COMMUNICATION FROM THE SSC OF THE ISTH.

KELCHTERMANS H, PELKMANS L, DE LAAT B, DEVREESE K. IGG/IGM ANTIPHOSPHOLIPID ANTIBODIES PRESENT IN THE CLASSIFICATION CRITERIA OF THE ANTIPHOSPHOLIPID SYNDROME: A CRITICAL REVIEW OF THEIR ASSOCIATION WITH THROMBOSIS. J THROMB HAEMOST 2016, 14:1530-48

aCL and aβ2GPI testing

- ß2GPI dependent aCL and aβ2GPI IgG and IgM

-comparable sensitivity/ specificity for aCL and aβ2GPI

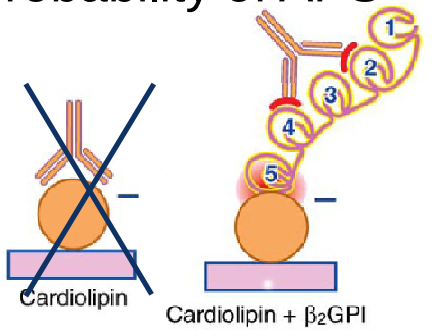
-good correlation between aCL and aβ2GPI

-aCL assays with human β2GPI in the reagent increase assay specificity

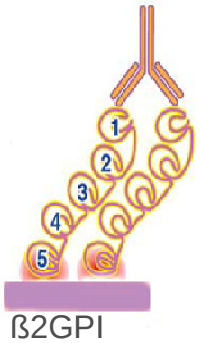
-aCL and aβ2GPI of same isotype reinforces probability of APS

-high titer: > 99th percentile

aCL



aβ2GPI



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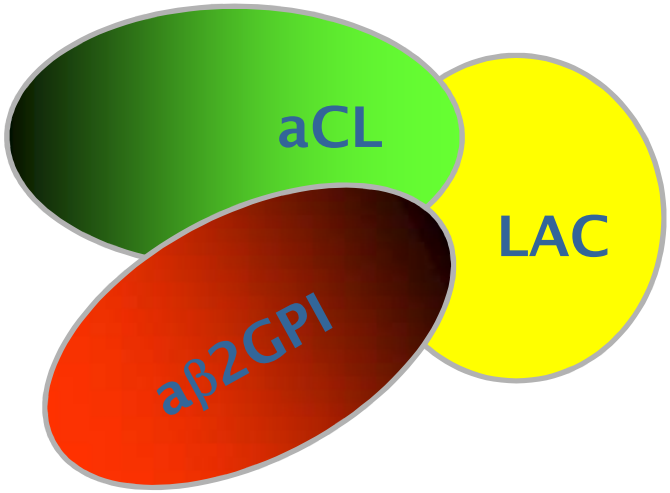
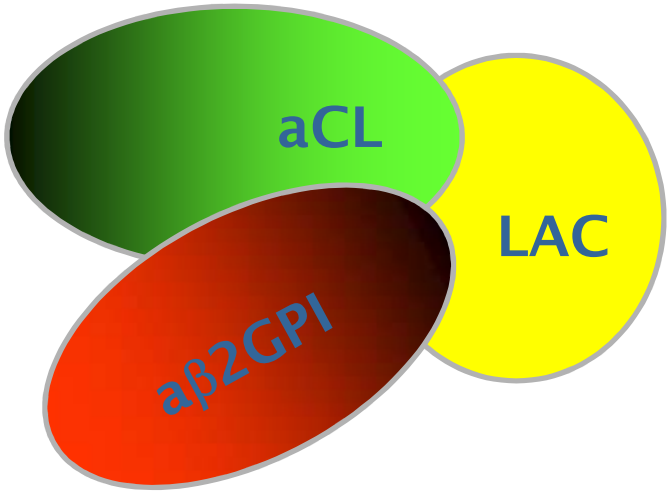
Pathogenicity of aPL



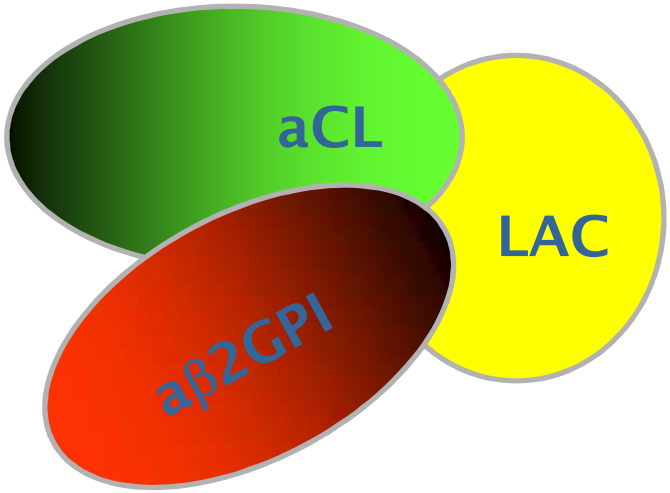
Pathogenicity of aPL



Antibody profiles:
Triple positivity

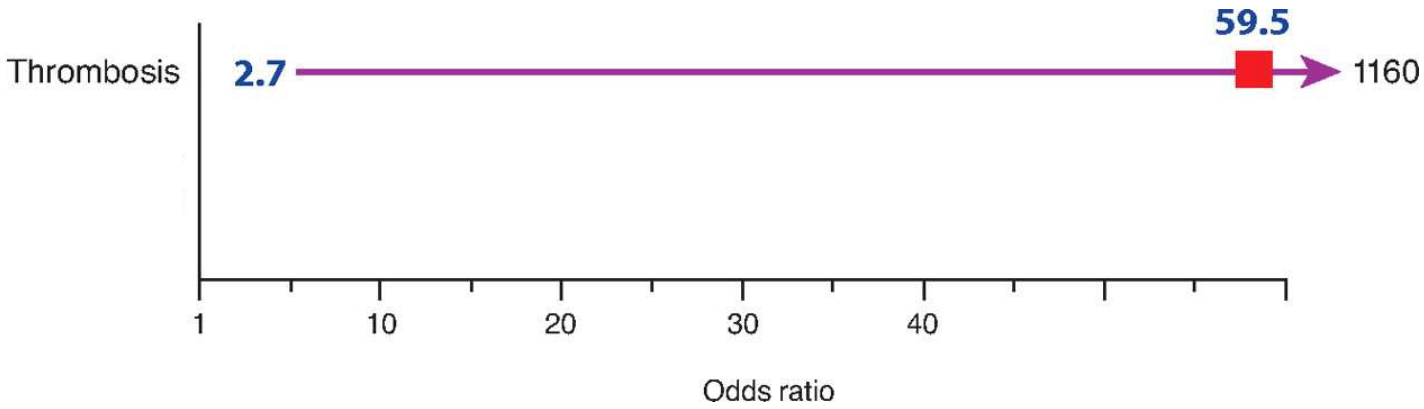
Positivity on multiple assays (LAC/aCL/aβ2GPI) is associated with an increased risk of thrombosis

Pathogenicity of aPL



Antibody profiles:
Triple positivity

Positivity on multiple assays (LAC/aCL/aβ2GPI) is associated with an increased risk of thrombosis



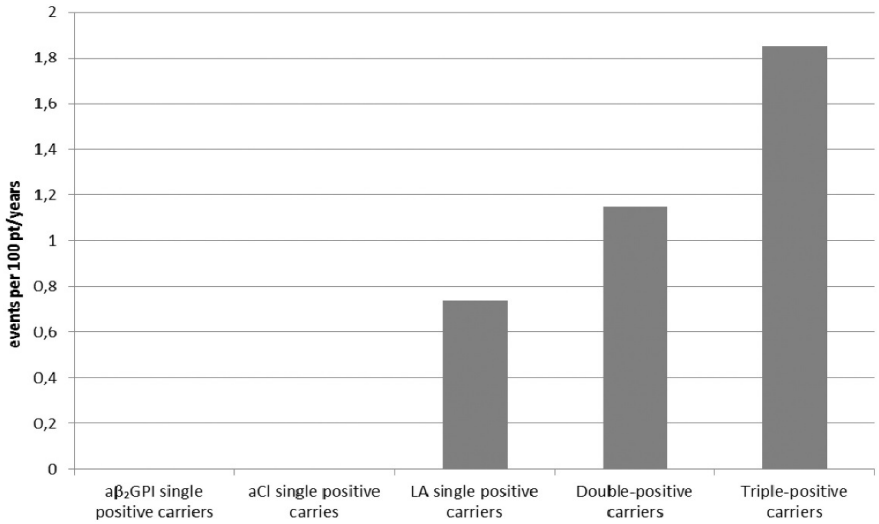
GIANNAKOPOULOS B ET AL. BLOOD 2009;113:985-994;RUFFATTI ET AL, THROMB HAEMOST 2006; 96: 337-341; PENGO ET AL JTH 2010; PENGO ET AL, LUPUS 2012;PENGO ET AL. JTH 2005; PENGO ET AL JTH 2010; RUFFATTI ET AL.THROMB HAEMOST 2006; RUFFATTI ET AL JTH 2008; LEE ET AL THROM RES 2003; PENGO ET AL BLOOD 2011; P MUSTONEN ET AL. LUPUS 2014; 23, 1468-1476.

Pathogenicity of aPL

Antibody profiles

Double or triple positivity for aPL = risk factor for future thrombotic events
- Especially in individuals with an underlying autoimmune disease

- single positivity does not seem to carry an elevated risk



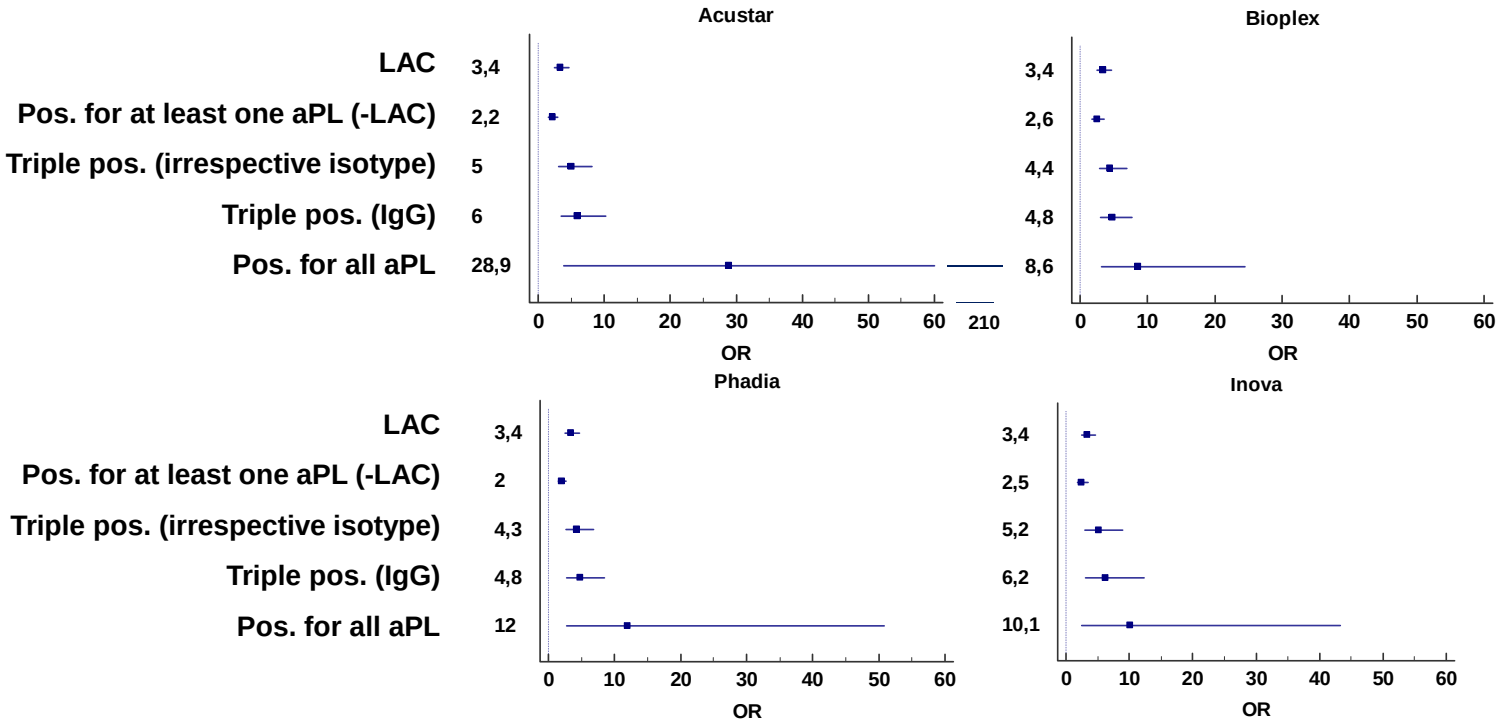
Average annual rates of first thrombotic events in single aPL-positive, double and triple aPL-positive carriers in a Finnish aPL **carrier cohort**.

P MUSTONEN; K V LEHTONEN; K JAVELA; M PUURUNEN; LUPUS 2014; 23, 1468-1476.

Pathogenicity of aPL

Antibody profiles

Multicenter solid phase assay study
APS thrombosis n=259
Non-APS thrombosis n=204
+ AID+HC: n=390



- Clinical association was globally concordant between solid phase test systems considering antibody profiles
- Considering all aPL, OR differ, measuring the four aPL with one test system

CHAYOUA ET AL, J THROMB HAEMOST. 2018; DOI - 10.1111/JTH.14261

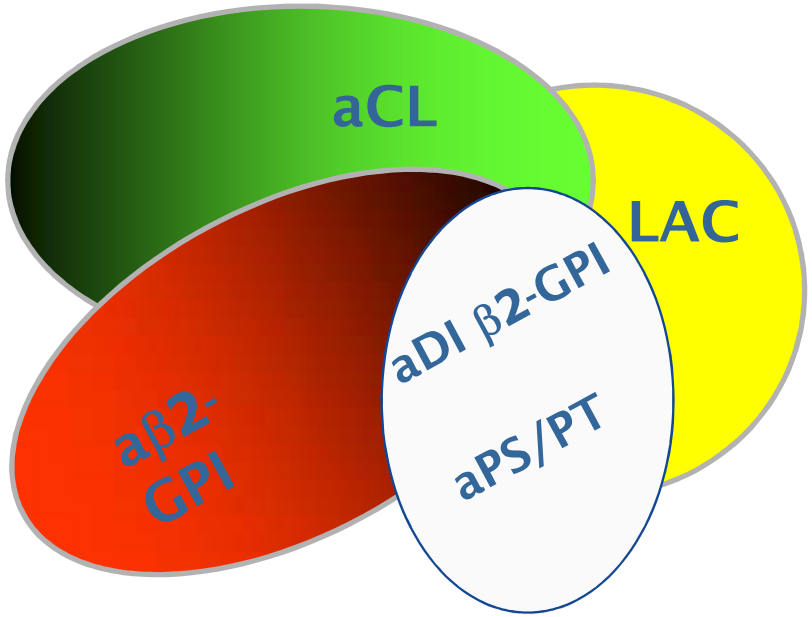
Antiphospholipid antibodies (aPL)

Lupus anticoagulants (LAC)

Anticardiolipin antibodies (aCL)

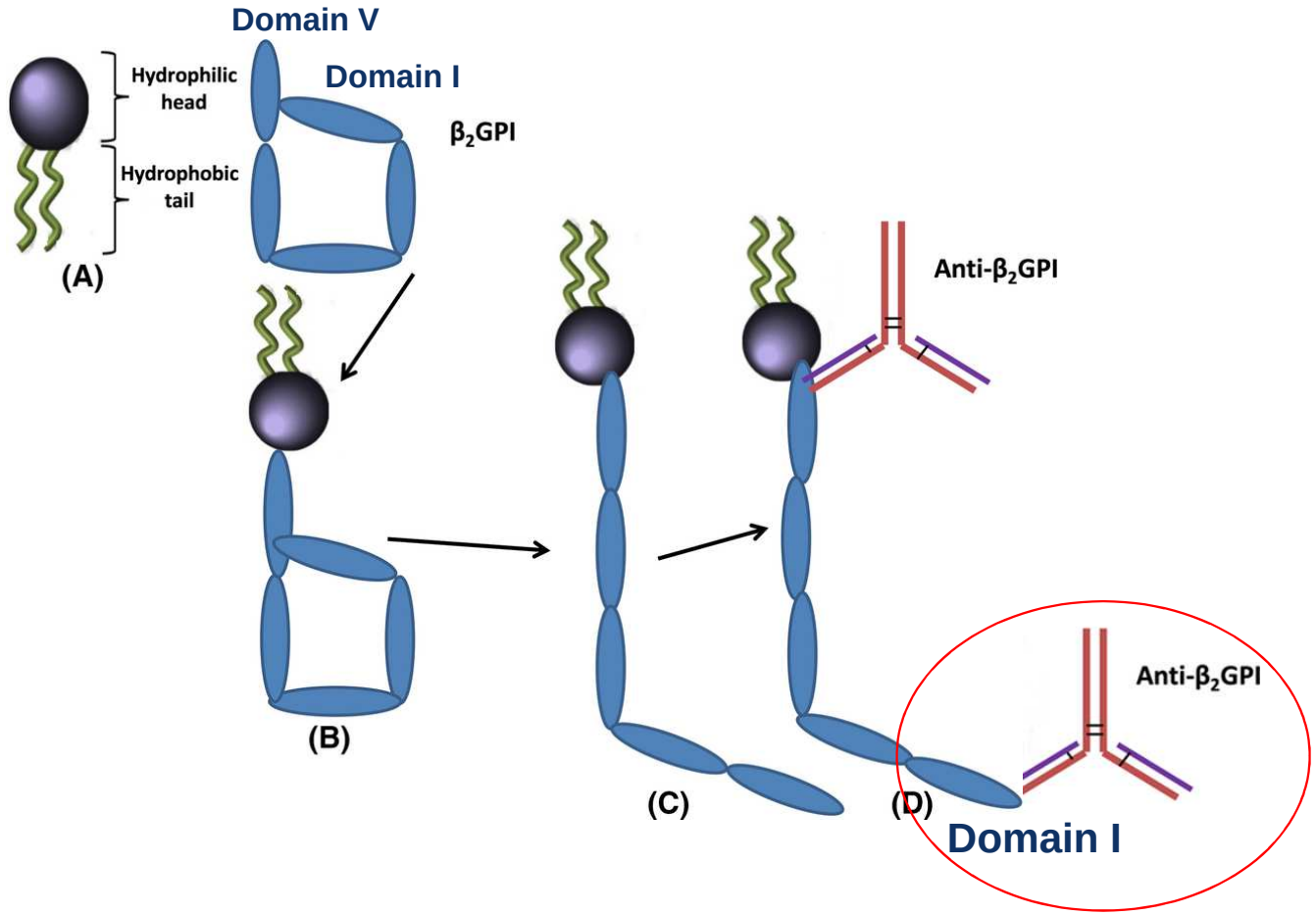
β2-glycoprotein I antibodies (aß2GPI)

Other aPL



"Non-criteria aPL"

Non-criteria aPL: subgroup of aß2GPI



ARACHCHILLAGE ET AL. BR J OF HAEMATOL 2017; 178: 181-195

VAN OS ET AL. J THROMB HAEMOST 2011; 9: 2447-2456

Pathogenecity of aPL

- anti-domain I aβ2GPI
  - increased association with thrombosis

    OR 18.9 *(DE LAAT ET AL, BLOOD 2005; 105:1540-5)*

    OR 3.5 *(DE LAAT ET AL, J THROMB HAEMOST. 2009;7:1767-73)*

Table 2 Association between aPL and thrombosis

	Odds ratio (95% confidence interval)
Anti-domain I IgG	**3.5 (2.3–5.4)***
Non-domain I Anti-beta2GPI IgG	0.4 (0.3–0.6)
Anti-beta2GPI IgM	0.9 (0.6–1.3)
LAC	**1.8 (1.1–3.1)***
aCL	1.1 (0.6–2.1)

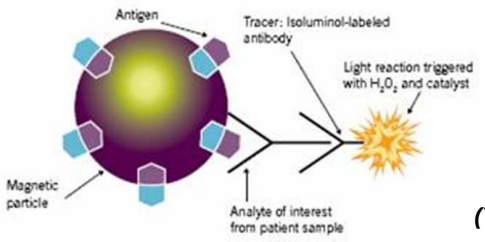
Non-criteria aPL: anti-domain I β2GPI

- First in-house ELISA
  - increased association with thrombosis
    - OR 18.9 *(DE LAAT ET AL, BLOOD 2005; 105:1540-5)*
    - OR 3.5 *(DE LAAT ET AL, J THROMB HAEMOST. 2009;7:1767-73)*

- Two other types of in-house ELISA
  - A direct aDI ELISA *(COUSINS ET AL. ANN RHEUM DIS 2015; 74: 317-319; PERICLEOUS ET AL. PLOS ONE 2016; 11: E0156407)*
  - A competitive inhibition ELISA *(POZZI ET AL, PROTEIN SCI 2010; 19:1065-1078; BANZATO ET AL. THROMB RES 2011; 128:583-586)*

- Commercial ELISA (INOVA) *(ANDREOLI ET AL, ANN RHEUM DIS 2011; 70: 380-383; ANDREOLI ETVAL, ARTHRITIS RHEUMATOL 2015; 67: 2196-2204; AKHTER ET AL. J RHEUMATOL 2013; 40: 282-286)*

- Chemiluminescense assay QUANTA Flash® assay (BioFlash/ Acustar, Werfen)
  - Since 2014
  - 17 published studies



(YIN ET AL, AUTOIMMUNITY REVIEWS, 2018, IN PRESS)

Non-criteria aPL: anti-domain I β2GPI

- Commercial QUANTA Flash® assay

  BioFlash/ Acustar (Werfen): chemiluminescence immunoassay

Meneghel L et al. Detection of IgG anti-Domain I beta2 Glycoprotein I antibodies by chemiluminescence immunoassay in primary antiphospholipid syndrome. Clin Chim Acta. 2015;446:201-5.

Mondejar R et al. Role of antiphospholipid score and anti-b2-glycoprotein I Domain I autoantibodies in the diagnosis of antiphospholipid syndrome. Clin Chim Acta. 2014;431:174-8.

Pengo V et al. Antiphospholipid syndrome: antibodies to Domain 1 of b2-glycoprotein 1 correctly classify patients at risk. J Thromb Haemost. 2015;13:782-7.

Mahler M et al. Autoantibodies to domain I of beta2GPI determined using a novel chemiluminescence immunoassay demonstrate association with thrombosis in patients with APS. Lupus 2016; 25:911-916.

A.S. De Craemer, J.Musial, K. Devreese. Role of anti-domain 1-b2glycoprotein I antibodies in the diagnosis and risk stratification of antiphospholipid syndrome. J Thromb Haemost 2016, 14:1779-87

Non-criteria aPL: anti-domain I β2GPI

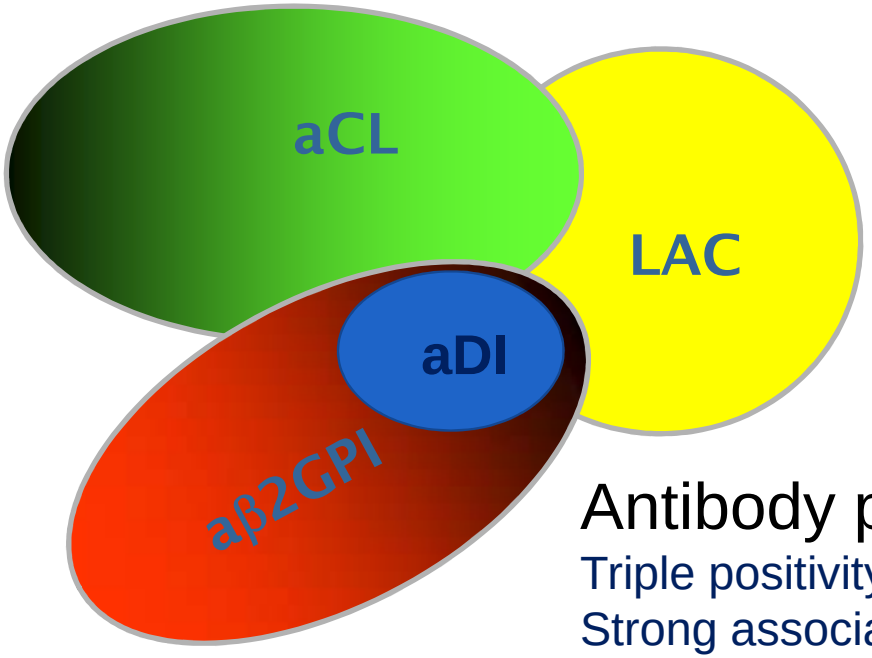
	aβ2GPI (20 CU)	aβ2GPI (164 CU)	β2GPI-aD1 (20 CU)	β2GPI-aD1 (190 CU)
Sensitivity %			34.9	
Specificity %			99.5	
OR	2.3	4.1	4.0	8.7

MAHLER ET AL, LUPUS 2016, 25:911-916

	aβ2GPI (20 CU)	aβ2GPI (60 CU)	β2GPI-aD1 (20 CU)	β2GPI-aD1 (44 CU)
sensitivity		56.4	53.5	48.5
specificity		99.1	97.8	99.1
OR		139	52.2	101

DE CRAEMER ET AL, J THROMB HAEMOST 2016, 14:1779-87

Non-criteria aPL: anti-domain I β2GPI



Antibody profiles:

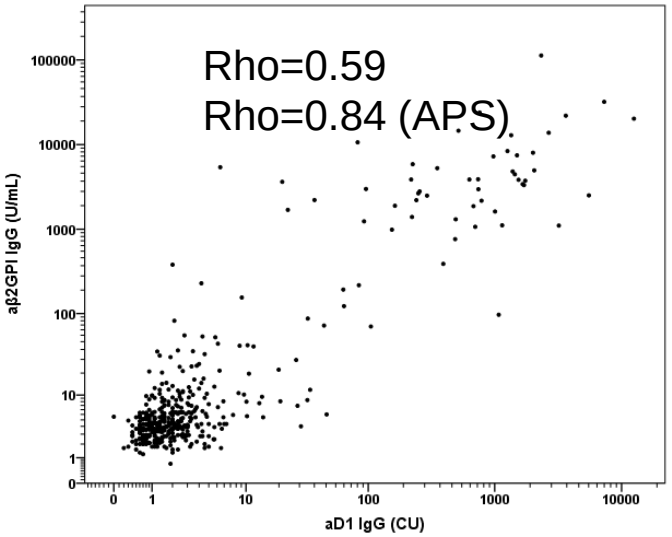
Triple positivity = patients at risk

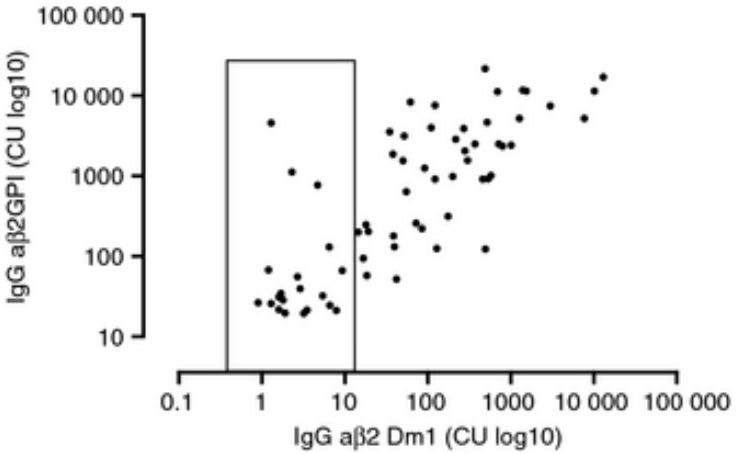
Strong association with anti-domain I β2GPI (aDI)

MENEGHEL ET AL. CLIN CHIM ACTA. 2015;446:201-5;
MONDEJAR ET AL. CLIN CHIM ACTA. 2014;431:174-8;
PENGO ET AL.. J THROMB HAEMOST. 2015;13:782-7;
MAHLER M ET AL. LUPUS 2016; 25:911-916;
DE CRAEMER ET AL. J THROMB HAEMOST 2016, 14:1779-87

Non-criteria aPL: anti-domain I β2GPI

- good correlation for anti-domain I and aβ2GPI for commercial assay QUANTA Flash® assay





qualitative agreement aDI /aβ2GPI	
de Laat, 2009	*positive agreement 55%*
Pengo, 2015	positive agreement 69%
Mondejar, 2014	overall agreement 91%
Meneghel, 2015	overall agreement 91%
Devreese, 2016	positive agreement 92%

DE CRAEMER ET AL, J THROMB HAEMOST 2016, 14:1779-87 *PENGO ET AL, J THROMB HAEMOST 2015, 14:1779-87*

Non-criteria aPL: anti-domain I β2GPI

- Added value of the commercial aDI assay compared to criteria aPL: inconsistency in results

- Yes: *Lee et al, Clin Chem Lab Med 2017; 55: 882-889; Pericleous et al, PLoS One 2016; 11: e0156407; Nakamura et al, Arthritis Care & Research 2017: 1-46; Nojima et al, Thromb Res 2017; 153: 83-84*
- No: *Iwaniec et al, Thromb Res 2017; 153: 90-94; De Craemer et al, J Thromb Haemost 2016; 14: 1779-1787; Marchetti et al, J Thromb Haemost 2016; 14: 675-684*

Covariates		AUC predicted probability
LAC + aCL IgG/IgM	+ aβ2GPI IgG	0.77
LAC + aCL IgG/IgM	+ aD1 IgG	0,76
LAC + aCL IgG/IgM + aβ2GPI IgG	+ aD1 IgG	0,77

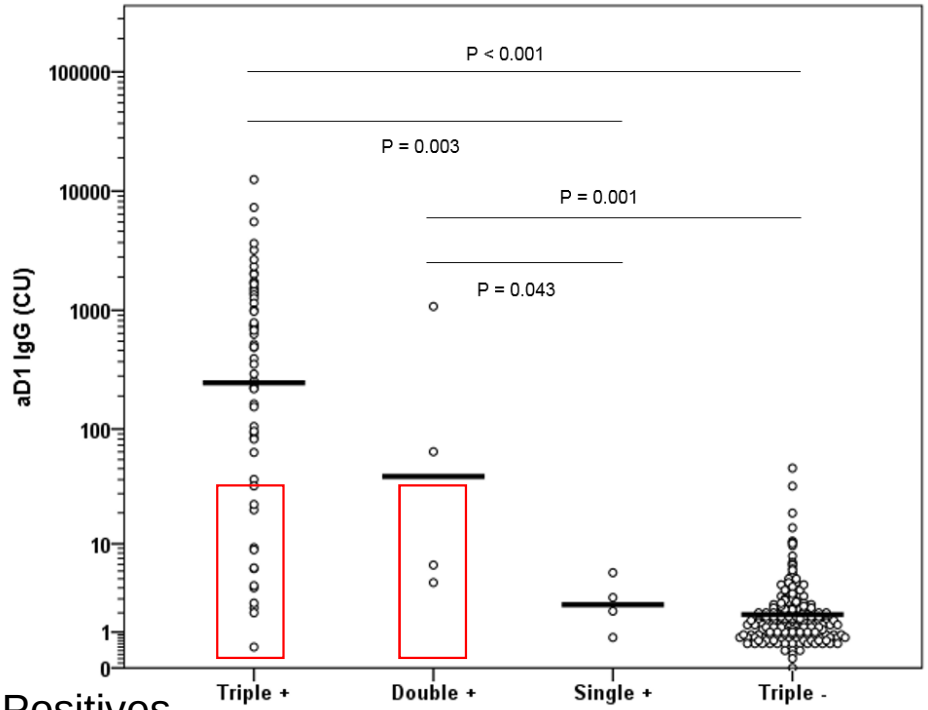
De Craemer et al, J Thromb Haemost 2016, 14:1779-87

		AUC
LAC		0.872
LAC	+ aD1	0.755
aβ2GPI IgG		0.770
aβ2GPI IgG	+ aD1	0.728
Triple pos		0.829
Triple pos	+aD1	0.755

Iwaniec et al, Throm Res 2017, 153: 90-94

Non-criteria aPL: anti-domain I β2GPI

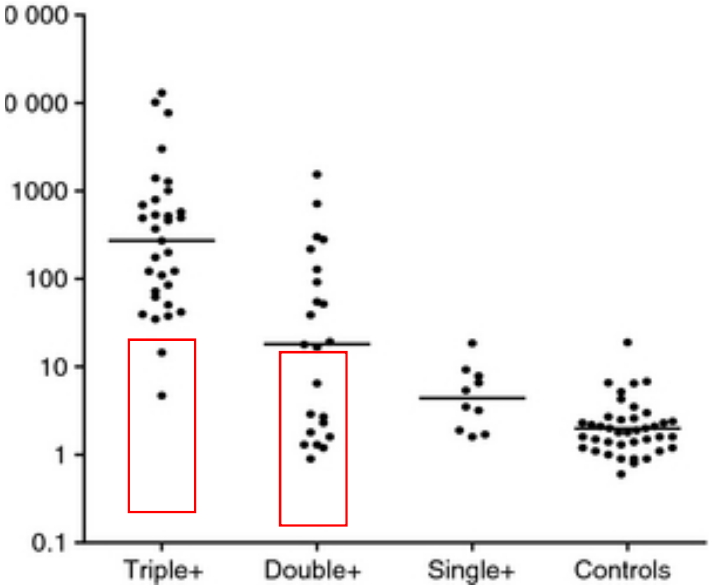
292/ 426 patient samples (APS, AID, DC, HC), positive for IgG aβ2GP1



Positives /group 52/62 2/4 0/4 2/222

DE CRAEMER ET AL, J THROMB HAEMOST 2016, 14:1779-87

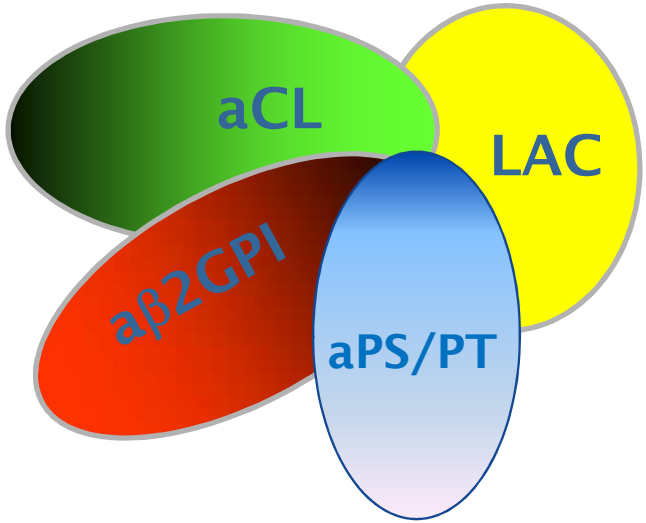
65 individuals over the three groups, all positive for IgG aβ2GP1



PENGO ET AL, J THROMB HAEMOST 2015, 14:1779-87

Non-criteria aPL: Anti-phosphatidyl serine/prothrombin

- Promising results
- Often associated with LAC
- Few studies in animal models
- Unknown epitope on prothrombin
  to which antibodies are directed
- Further studies



SCIASCIA, S. ET AL.. THROMB. HAEMOST. 2014; 111, 354–364
VEGA-OSTERTAG M, ET AL. BR J HAEMATOL 2006;135:214-209
HAJ-YAHIA S ET AL. LUPUS 2003;12:364-369

Conclusion: pathophysiology

- Different cell populations are activated by anti-beta2GPI antibodies
- A combination of mechanisms or dependent of the specificty of the antibodies
- Haemostasis and complement activation play a part in the induction of thrombosis by aPL

- Antibodies against domain I of ß2GPI are pathogenic
- Are anti-domain I of ß2GPI the only pathogenic antibodies?
- Other pathogenic antibodies? Other cofactors?
- Antibodies against the complex of prothrombin and phosphatidyl serine
- Are co-factor independent aPL irrelevant in the pathogenesis of APS?

DE GROOT AND DE LAAT. BEST PRACTICE AND RES CLIN RHEUMATOL 2017; 31: 334-341;
LACKNER ET AL. J THROMB HAEMOST 2016; 14: 1117-20;
MANUKYAN ET AL. J THROMB HAEMOST 2016; 14: 1011-1020;
LACKNER ET AL. HÄEMOSTASEOLOGIE 2017; 37: 202-207

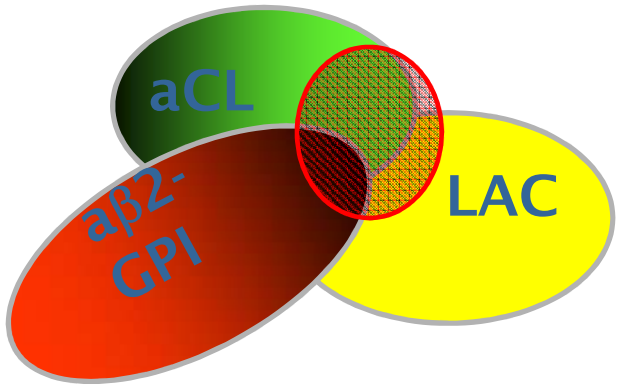
Conclusions: Laboratory diagnosis of APS

RECOMMENDATIONS AND GUIDELINES J THROMB HAEMOST 2018; 16: 809–13

Laboratory criteria for antiphospholipid syndrome: communication from the SSC of the ISTH

K. M. J. DEVREESE,* T. L. ORTEL,† V. PENGO‡ and B. DE LAAT§¶FOR THE SUBCOMMITTEE ON LUPUS ANTICOAGULANT/ANTIPHOSPHOLIPID ANTIBODIES

- Perform all three assays **LAC, aCL, aß2GPI IgG/M** to increase diagnostic utility, integrated interpretation of LAC, aCL and aβ2GPI
- Other aPL are not recommended yet



THANK YOU FOR YOUR ATTENTION