The antiphospholipid syndrome: an update

Vittorio Pengo M.D.

Clinical Cardiology, Thrombosis Center,

University of Padua, Italy

SYDNEY, 2005

A preconference workshop, preceding the Eleventh International Congress on antiphospholipid antibodies (aPL), Sydney consensus conference established the update classification criteria for APS

One clinical criteria (thrombosis or pregnancy loss)

+

One laboratory criteria: anticardiolipin antibodies (no longer required the aCL ELISA to be β2GPI –dependent), Lupus Anticoagulant AND anti β2-GPI antibodies.
[Positive 12 week apart]

Miyakis S et al. J Thromb Haemost 2006; 4: 295–306

Clinician's topics in antiphospholipid syndrome (APS)

- In whom and when checking for the presence of antiphospholipid antibodies
- How to read the results
- How definite is the diagnosis of APS
- How to treat APS

Checking for aPL: In whom?

- Young subjects (less than 50 yrs of age)
- Idiopathic VTE and CTPH
- VTE in uncommon sites
- If present an associated autoimmune diseases
- Cryptogenic stroke in general and when:
  - Other concomitant conditions are present (i.e. dementia, livedo reticularis, epilepsy, valvular heart disease) in the absence of overt atherosclerosis
- In case of unexplained recurrence
- In women with pregnancy loss (especially in case of fetal death)
- Unexpected a PTT prolongation in otherwise healthy subjects

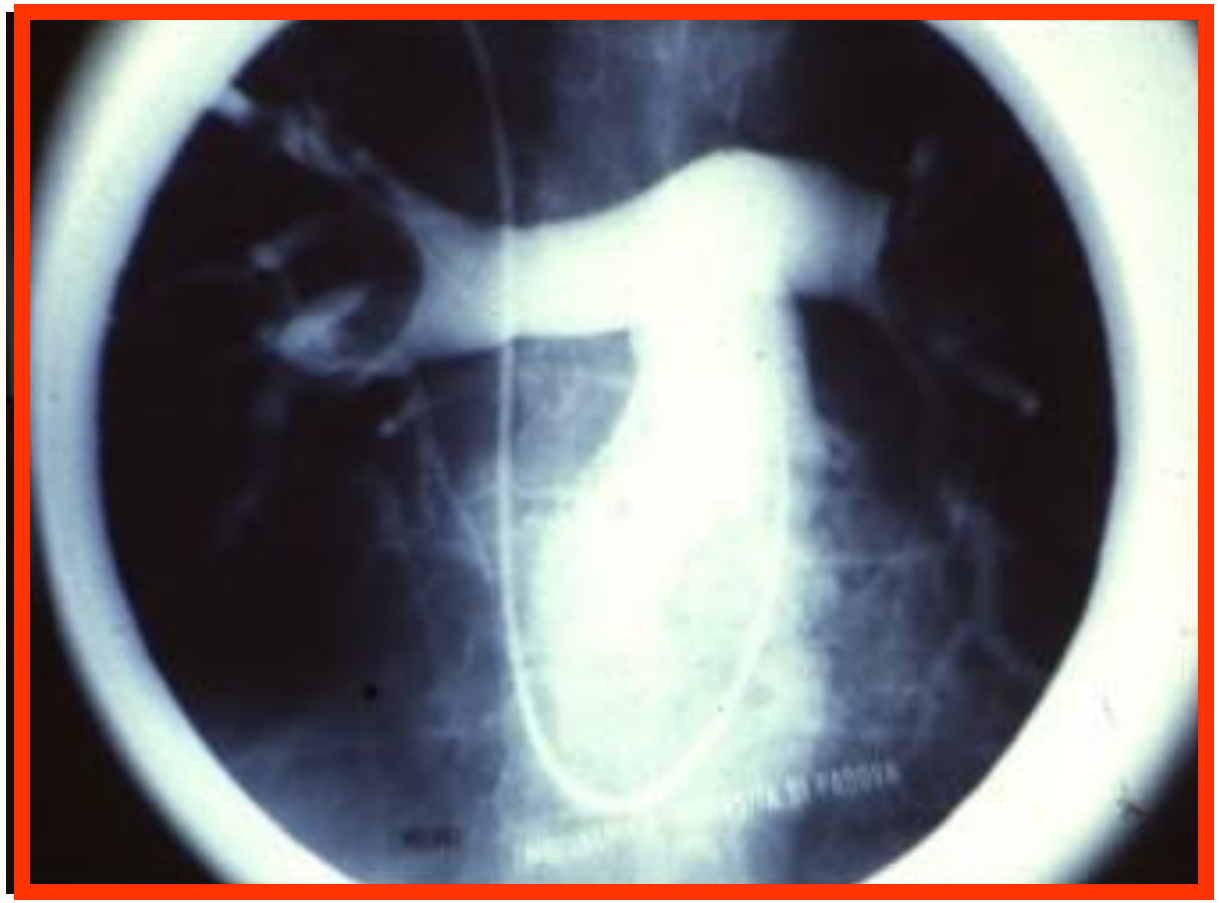
MASSIVE POLMONARY EMBOLISM

MC/ Male

18 yrs of age

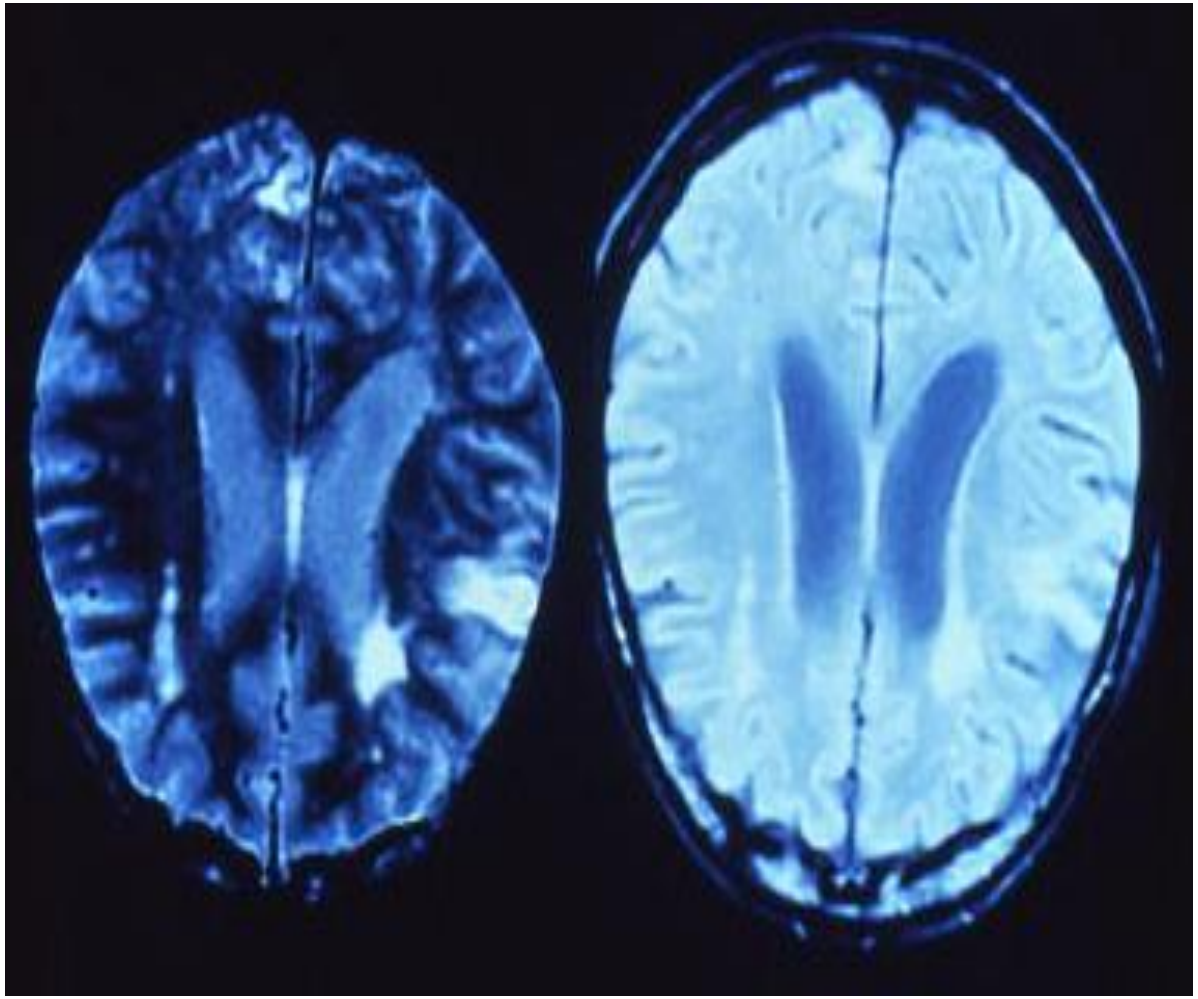
Unprovoked

Proximal DVT/PE



Clinical Cardiology, Padua

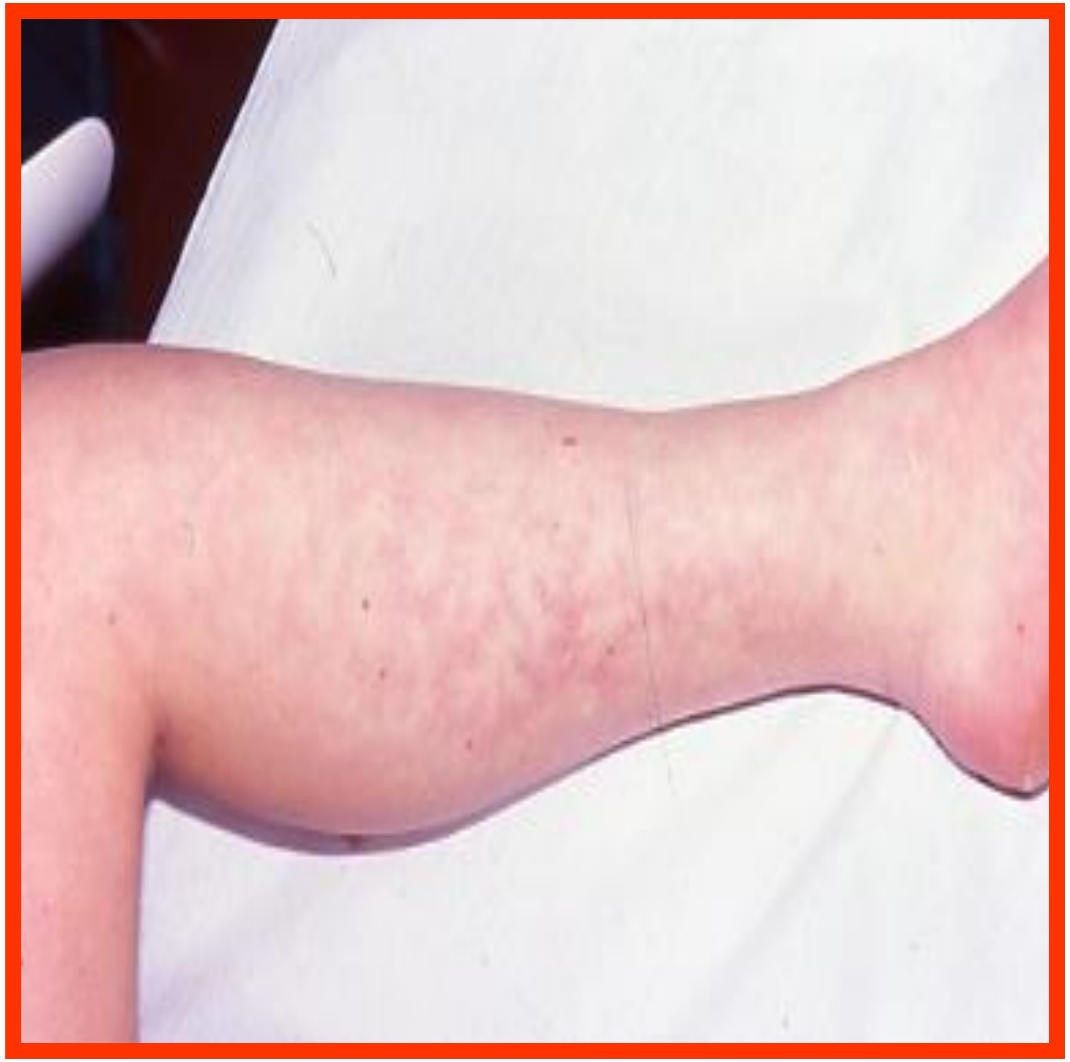
Multiple cerebral infarctions in 48 years old female (N. C.) with hemiparesis and epilepsy



Courtesy of Clinical Reumatology, Padua

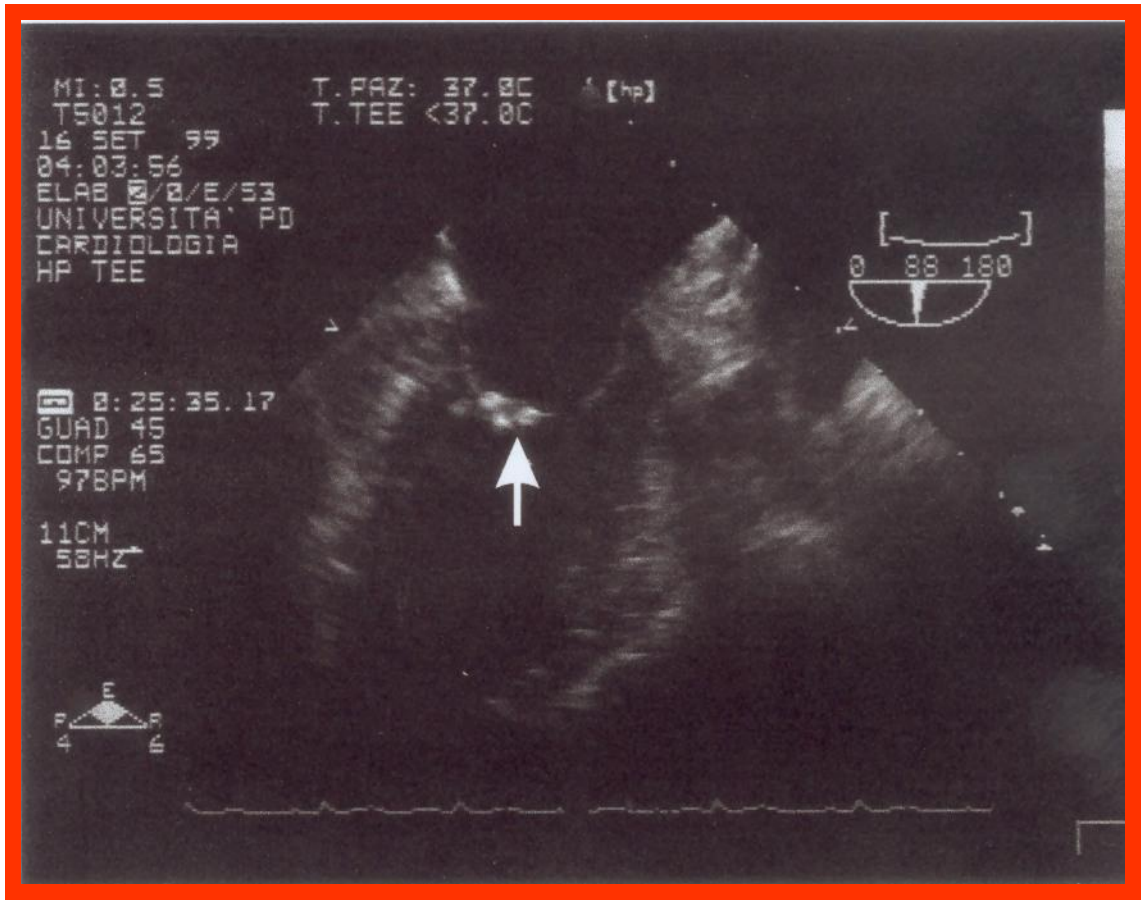
LIVEDO RETICULARIS

Cerebral ischemia + livedo reticularis: Sneddon's syndrome



Courtesy of Clinical Reumatology, Padua

Minor stroke and multiple mitral valve thickening in 20 year of age young women



Clinical Cardiology, Padua

Checking for aPL: when?

- In patients with venous thromboembolism (VTE):
  - ❖Before the initiation of anticoagulant treatment (difficult)
  - ❖When deciding to prolong or discontinue anticoagulant treatment

- In patients with arterial thromboembolism (ATE):
  - ❖Initially, to decide the use of antiplatelet or anticoagulant drugs or both

- In women with pregnancy losses:
  - ❖Initially, to establish an appropriate treatment during pregnancy

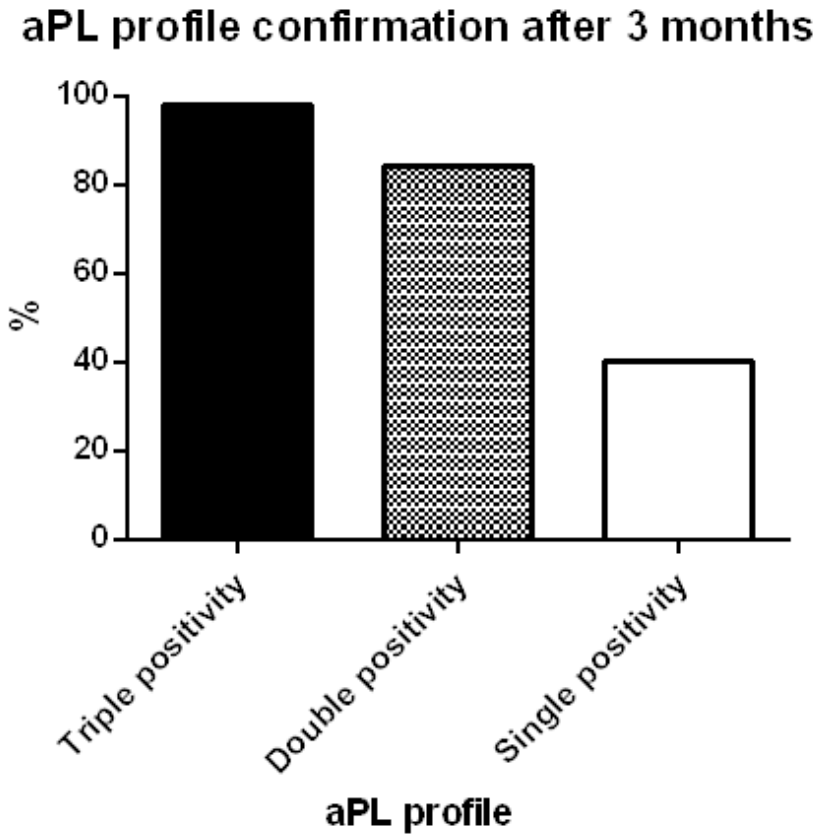
CONFIRM DATA AFTER 12 WEEKS TO EXCLUDE TRANSIENT ANTIBODIES

- Consecutive patients referred to our Center initially positive to one or more tests exploring the presence of aPL were tested after 3 months.

- During a four-years period 225 patients were initially positive to one or more test and 161 were available for confirmation after 3 months.

- Patients were classified as triple positive (n=54: LAC+, aCL+, aβ2GPI+, same isotype), double positive (n=50: LAC-, aCL+, aβ2GPI+, same isotype) and single positive (n=53: LAC or aCL or aβ2GPI antibodies as the sole positive test).

Pengo V et al. JTH 2013



Pengo V et al. JTH 2013

How to read the results:
Are they Associated with thromboembolic events?

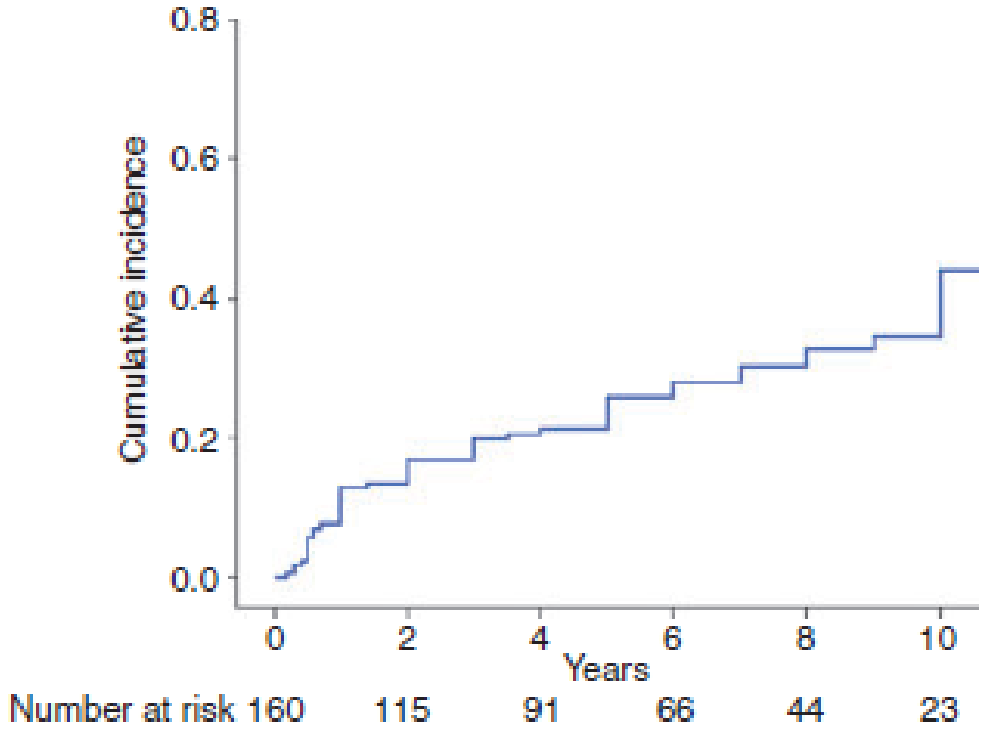
Association between antiphospholipid profiles and thrombosis

Lupus anticoagulant/ Anti-cardiolipin antibodies/ Anti-β2-glycoprotein I antibodies	Thrombosis (N=340) no.(%)	No thrombosis (N=278) no.(%)	Odds Ratio			
			univariate	95% CI	Multivariate ◦	95% CI
→ **LA+/aCL+/ab2+**	**34 (10)**	**2 (1)**	**14.9**	**3.5-62.7**	**33.3**	**7.0-157.6**
X LA+/aCL-/ab2-	0 (0)	5 (2)	NA	-	NA	-
→ LA-/aCL+/ab2+	18 (5)	13 (5)	1.2	0.6-2.5	2.2	1.0-5.2
X LA-/aCL+*/ab2-	7 (2)	13 (5)	0.5	0.2-1.2	0.8	0.3-2.1
X LA-/aCL-/ab2+	4 (1)	4 (1)	0.9	0.2-3.5	1.3	0.3-5.7

* > 40 GPL/MPL

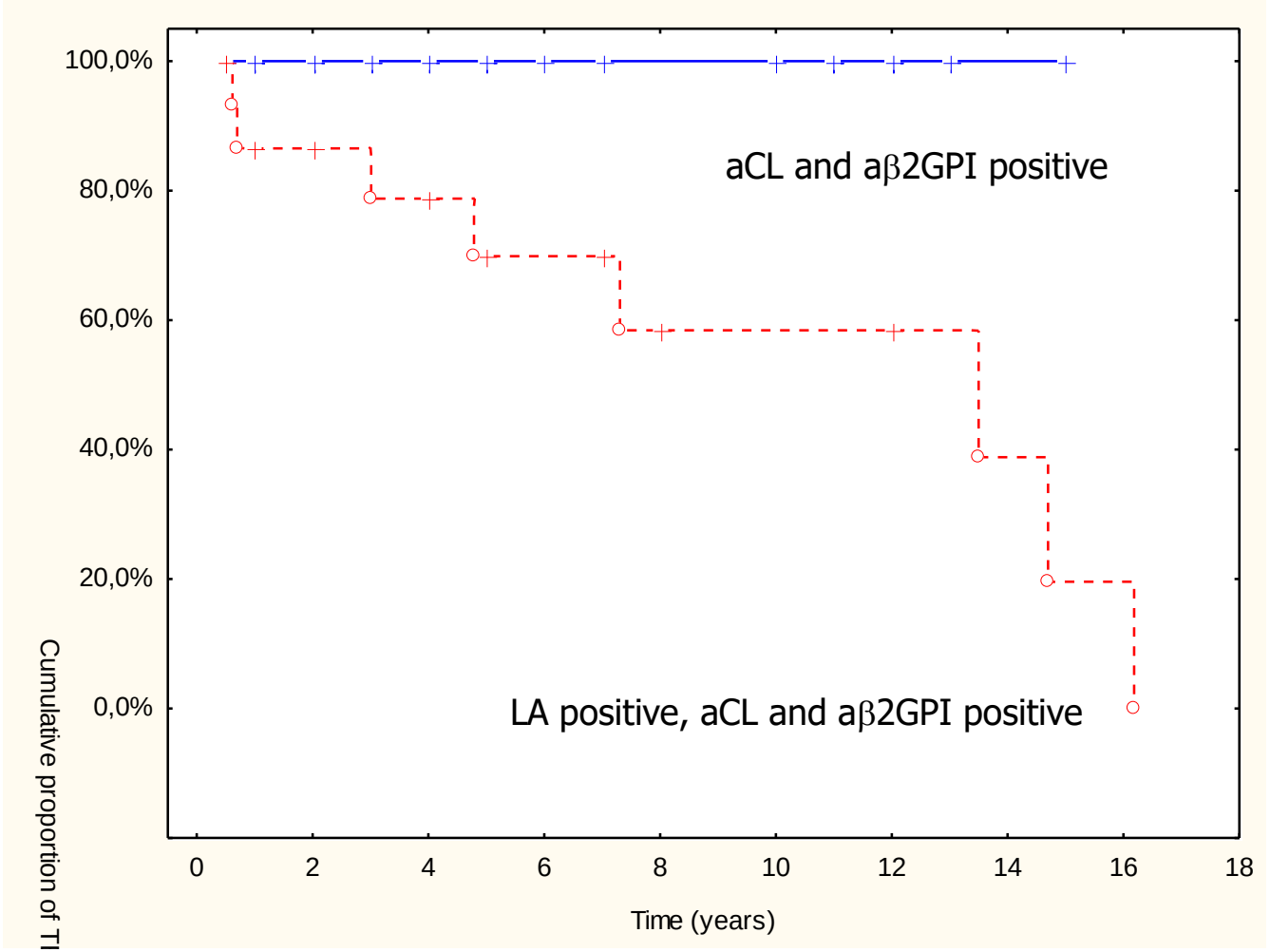
V Pengo et al, 2005

Cumulative incidence of thromboembolic events in high risk triple positive APS patients (n=160)



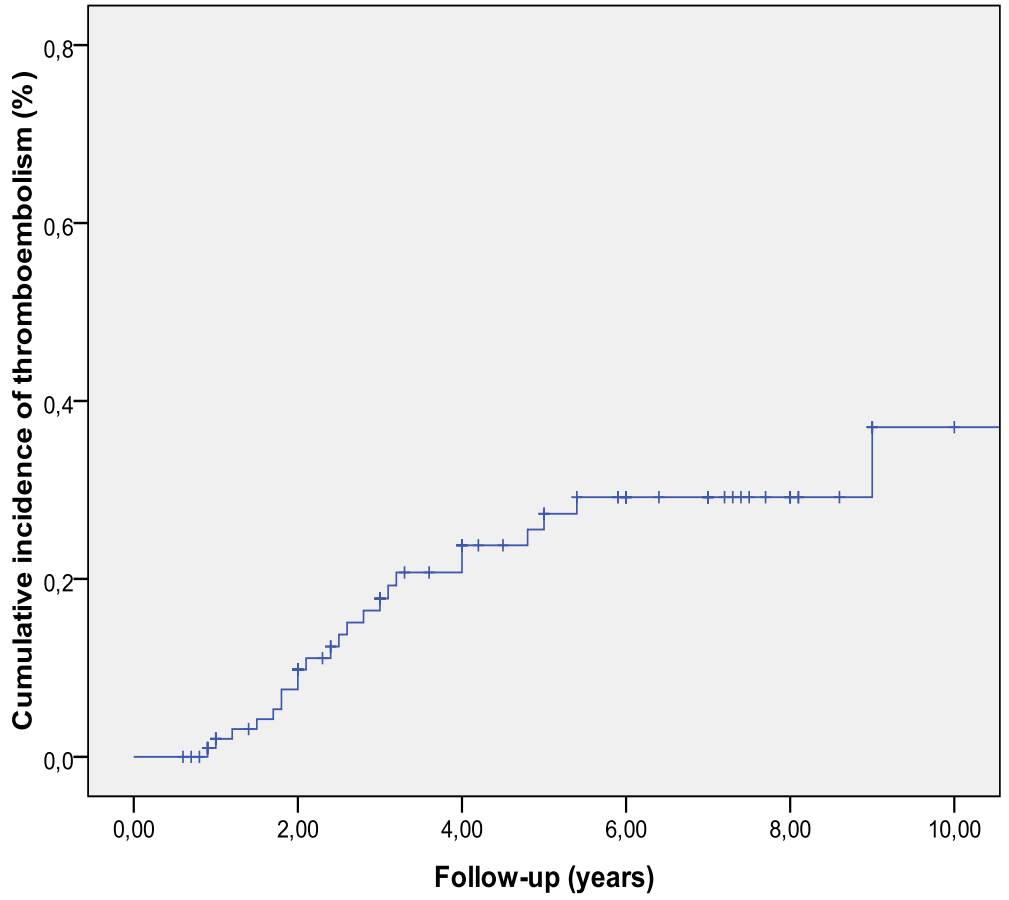
Pengo V, JTH 2010

Antiphospholipid profile and subsequent TE in obstetric APS



Ruffatti A, Pengo V et al. 2006

Cumulative incidence of thromboembolic events in the follow up period of 104 carriers of triple positivity for antiphospholipid antibody tests.



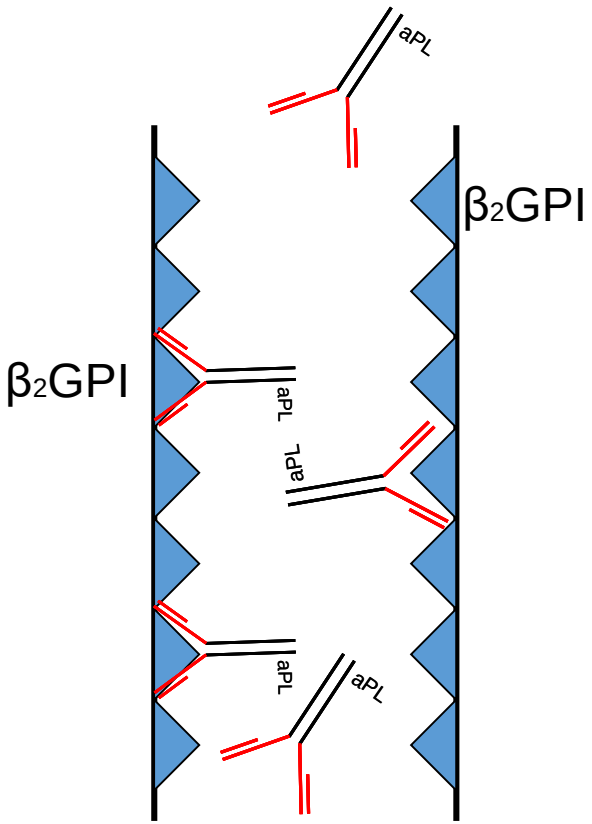
37.1% (95% CI, 19.9-54,3) after 10 years

Pengo V et al. Blood 2011

Why triple positivity is unique?

Answer: In contrast to single test positivity, triple positivity arises from the presence of a single (possible pathogenic) antibody

Triple positive plasma passed through a beta2GPI affinity column



Affinity purified abeta2GPI
Spiked into normal plasma

aβ2GPI +
aCL +
LAC +

V.Pengo et al. Thromb Haemost 1999

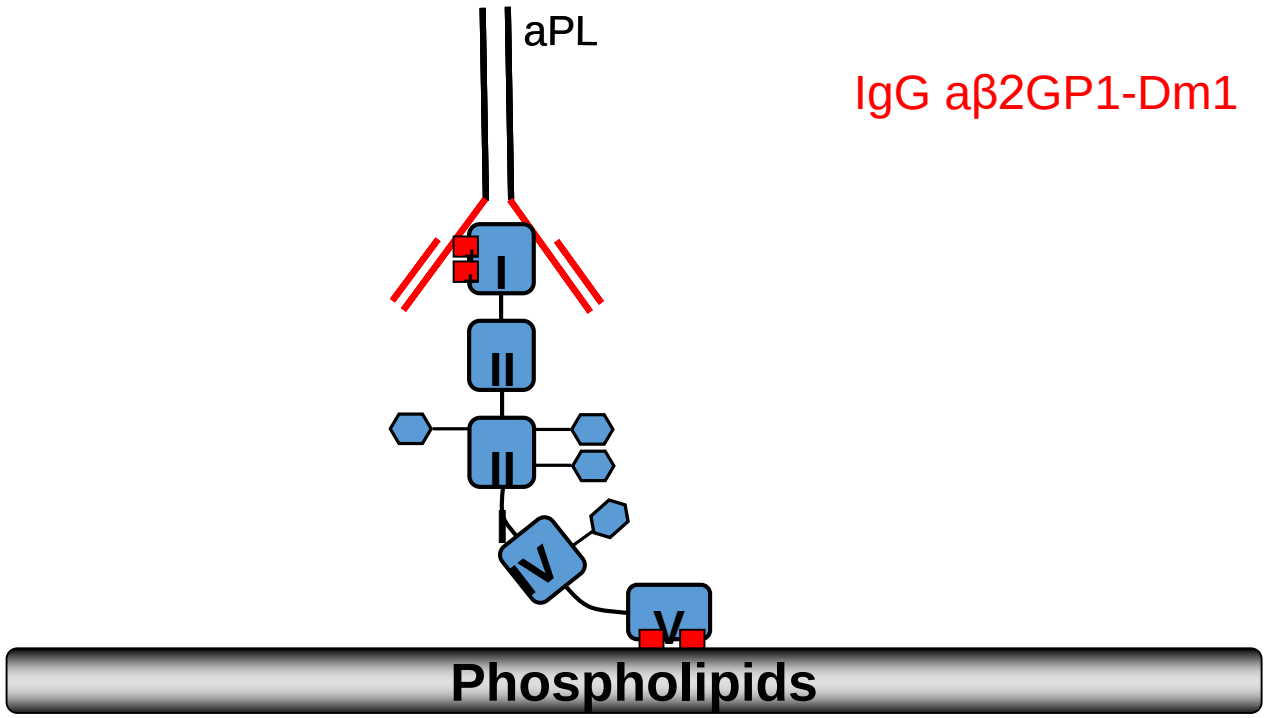
aCL ELISA and LAC activity of affinity-purified anti human ß2-GPI autoantibodies from triple positive patients

	Affinity purified anti β2-glycoprotein I antibody preparations					
	Control IgG	1	2	3	4	5
Protein [µg/ml]	75	61	39	49	68	34
β2GPI ELISA	0.015	2.378	2.658	2.297	2.242	2.255
aCL ELISA	**0.005**	**2.081**	**2.037**	**1.645**	**1.806**	**1.648**
dRVVT ratio	**0.95**	**1.6**	**1.3**	**1.6**	**1.4**	**1.5**

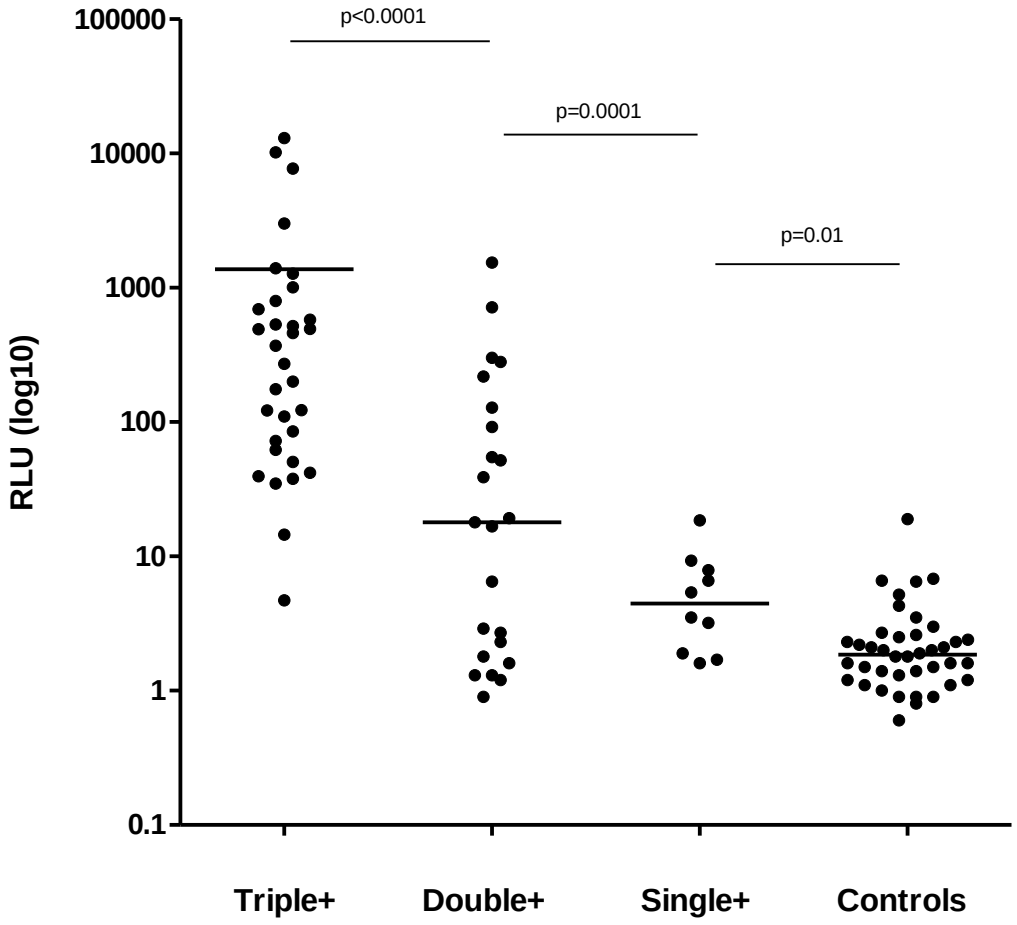
V.Pengo et al. Thromb Haemost 1999

IgG antibodies that recognize epitope Gly40-Arg43 in domain I of 2-glycoprotein I cause LAC and their presence correlates strongly with thrombosis

Bas de Laat et al., Blood 2004

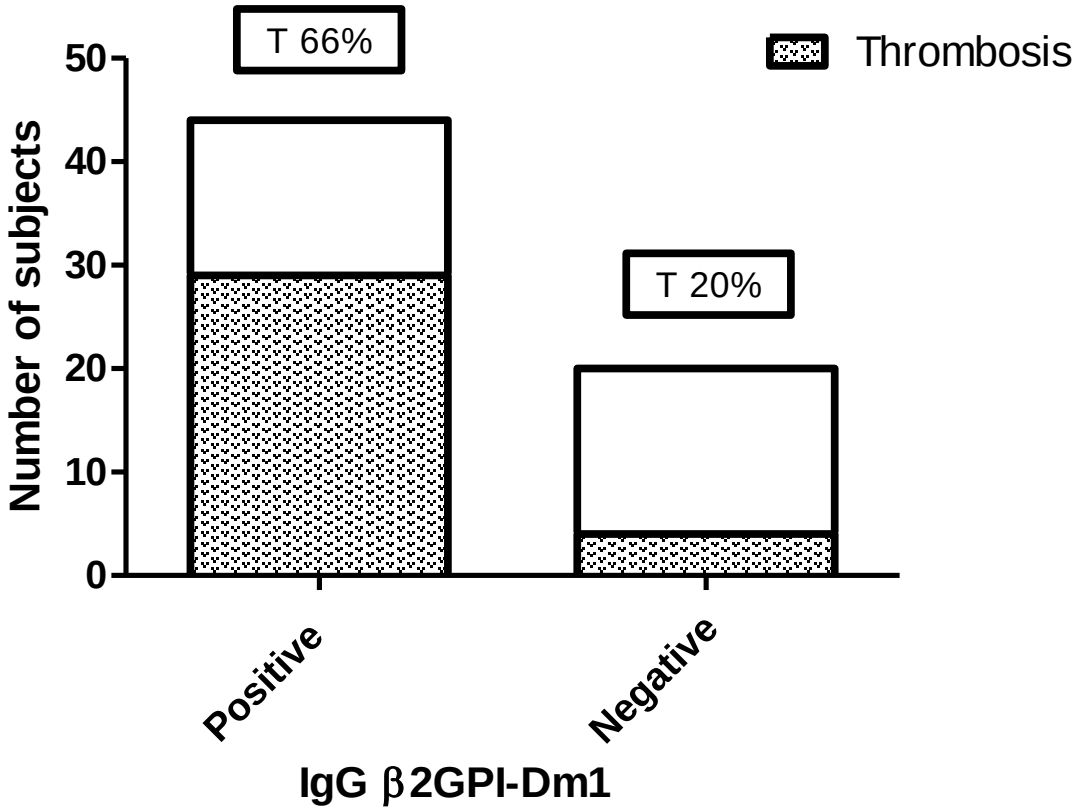


IgG aβ2GP1-Dm1 and risk categories



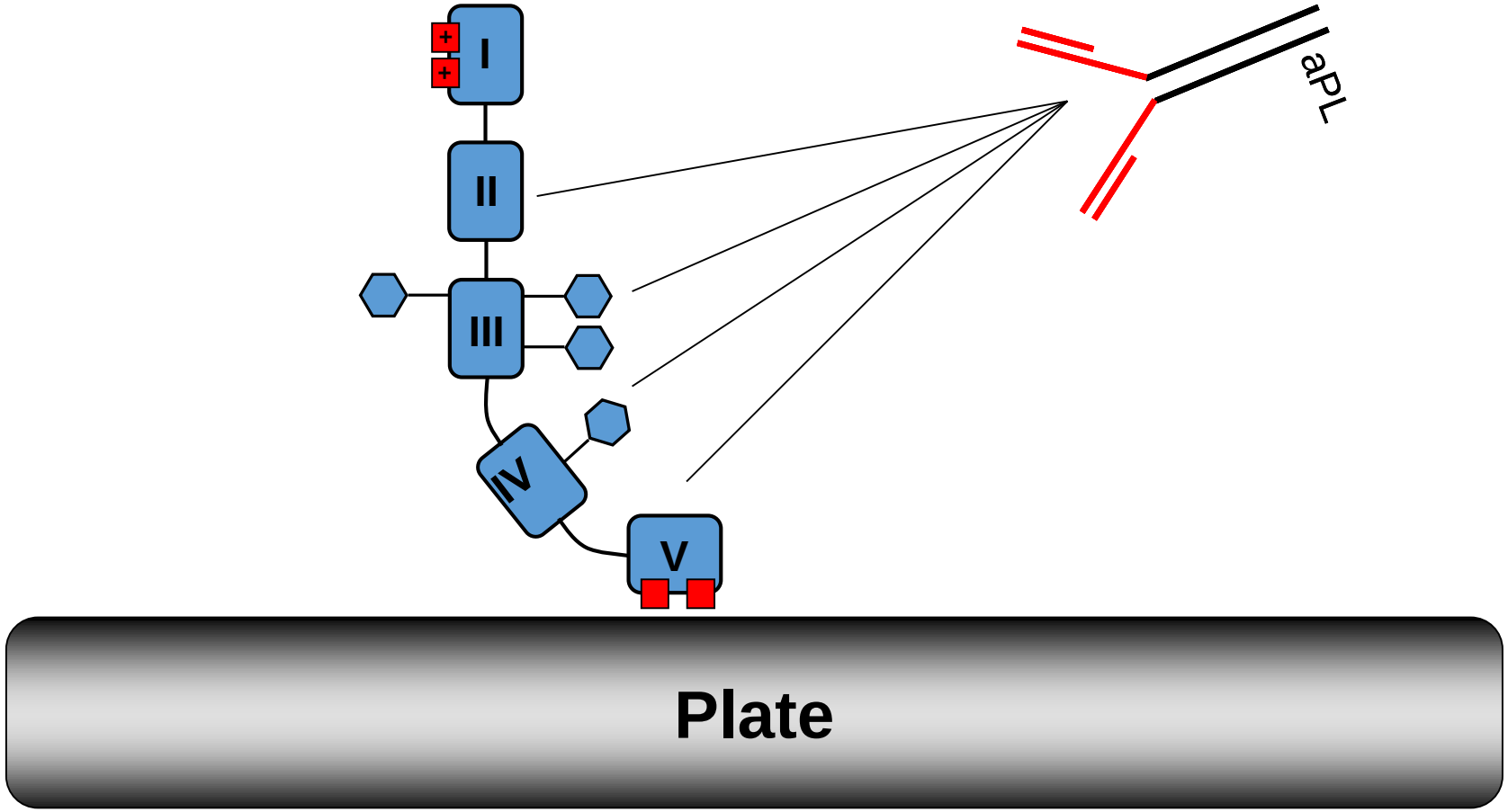
Pengo V et al. (JTH 2015)

Association of positive IgG aβ2GP1-Dm1 with thrombosis



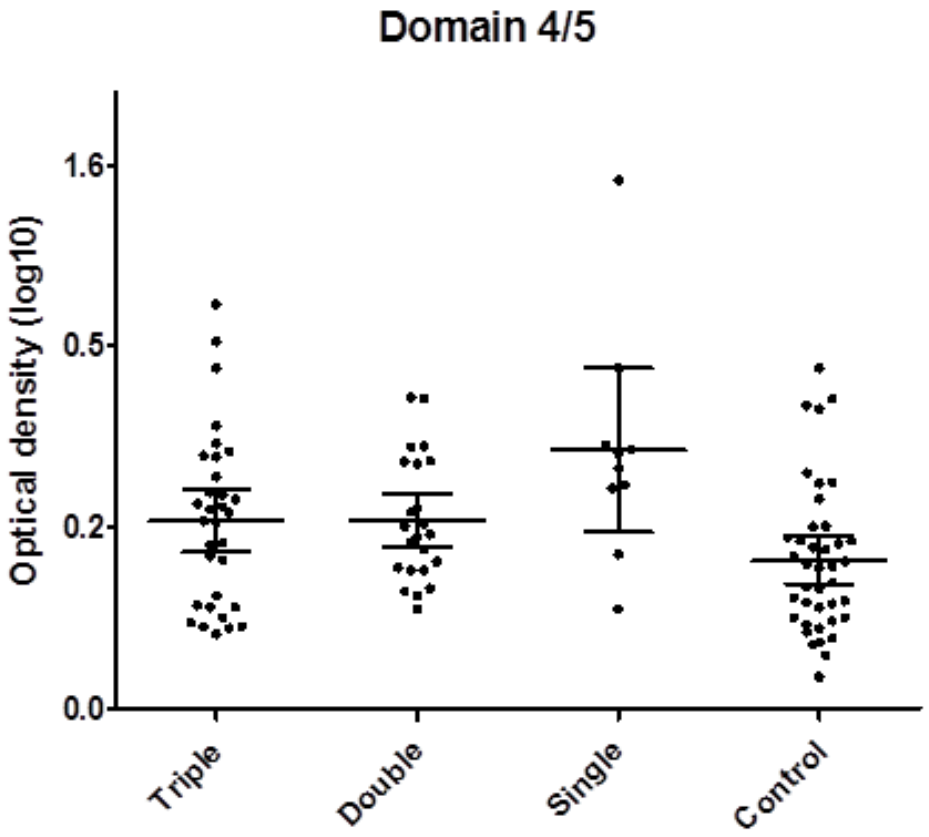
Pengo V et al. (JTH 2015)

Anti-Domain 4/5 antibodies have been detected in non-thrombotic conditions, like atherosclerosis, leprosy and in children with atopic dermatitis or those born to mothers with systemic autoimmune diseases.



LAC - aCL - abeta2 +

Domain 4/5



Pengo V et al. Thromb Res 2015

APS treatment

- VKAs
- Intensity (INR 2.0-3.0) (Crowther NEJM 2003, Finazzi JTH 2005)
- NOACS ? (A few case series)
- Duration of treatment ?

A prospective, randomized clinical trial comparing rivaroxaban vs warfarin in high risk patients with antiphospholipid syndrome (TRAPS)

Objective:

In persistently triple aPL-positive APS patients with or without other systemic autoimmune diseases, to determine the efficacy and safety of rivaroxaban 20 mg qd as compared to warfarin (INR 2.0-3.0) in thrombosis prevention of persistently triple aPL-positive APS patients.

Type of study:

Non inferiority trial

End point:

Cumulative: Venous or arterial thromboembolism, major bleeding, total mortality.

Sample size:

536 subjects (268 in the reference group and 268 in the treatment group)

Starts: 2015 **Ends:** 2018/9

Duration of VKA treatment

Long term in all high risk patients

VKA plus Aspirin in patients with Cerebral ischemia or myocardial infarction

Possible short term in VTE APS if:

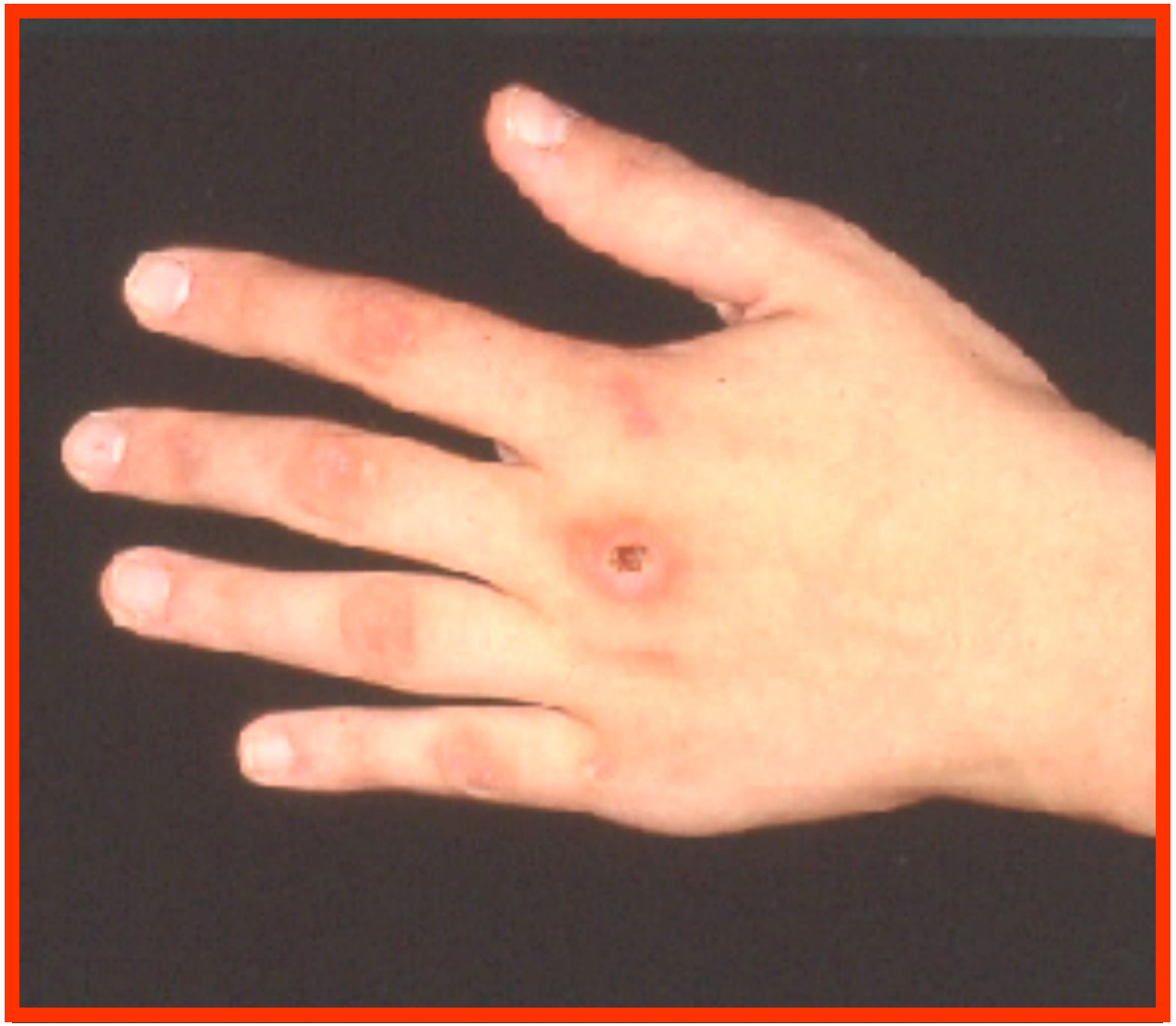
- VTE was provoked
- aPL profile: single positivity
- Other thrombophilias are absent
- No associated autoimmune disease

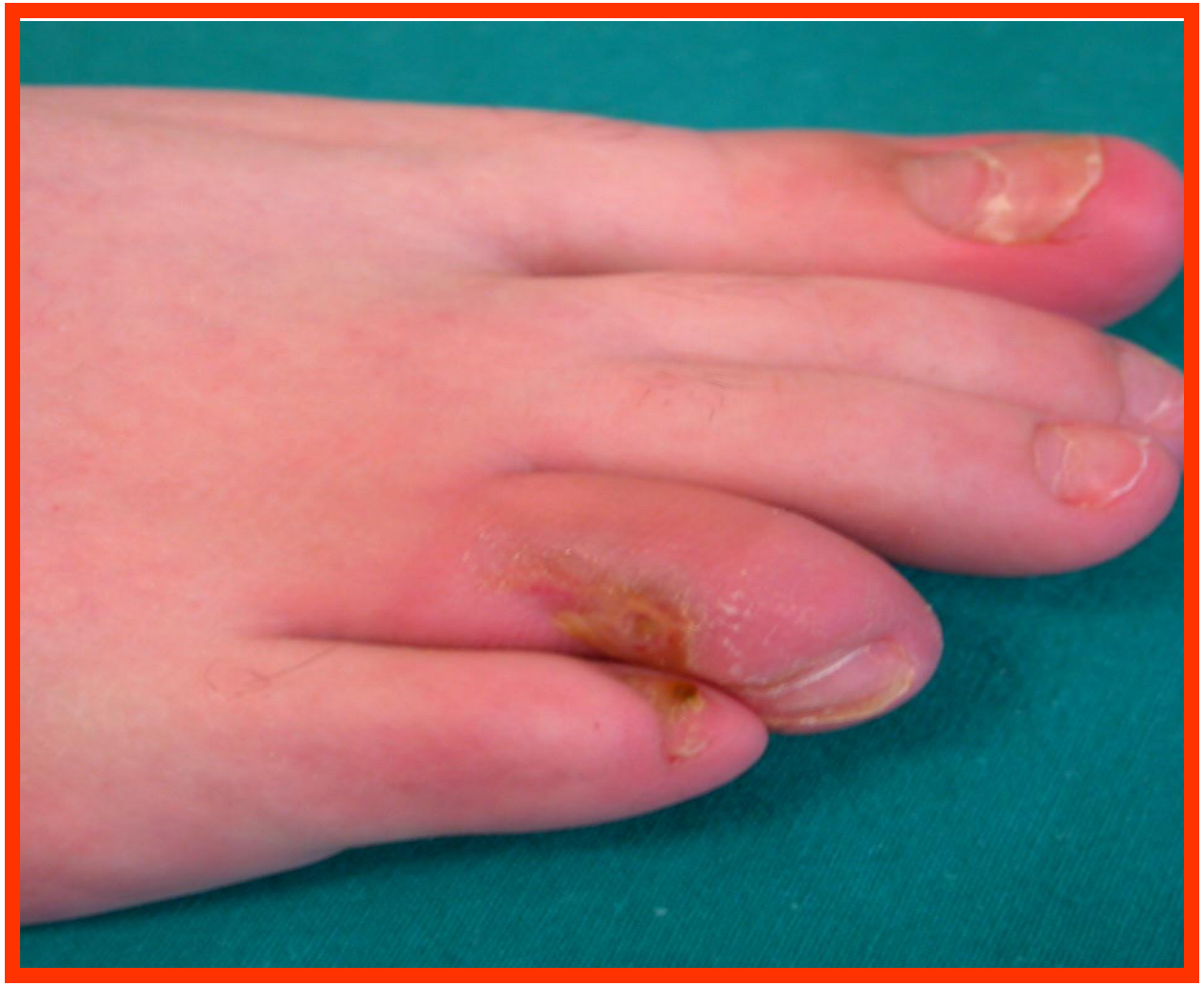
CATASTROPHIC APS

- Term proposed in 1992
- Accelerated form of APS with multiorgan thrombotic failure
- Around 50% mortality, it may show up ‘ex novo’
- Trigger: infection in many cases
- 1% prevalence in APS

Case 1. M.S. 20 years of age

- First manifestation: Cutaneous necrosis
- Adrenal ischemia-hemorrhage
- Renal infarction
- Evans syndrome (hemolitic anemia +thrombocytopenia)
- DVT/PE





Treatment

Anticoagulation with intravenous heparin

Corticosteroids
- Metylprednisolone (1000mg/die) ev for 3-5 days
- Metylprednisolone 1-2/mg/kg/die

Intavenous immunoglobulin 0.4g/kg/die for 4-5 days

Plasmaexchange in order to remove:
- Antiphospholipid antibodies
- Cytokines, TNF-alfa and complement products
- Coagulant factors

OUR EXPERIENCE

Contents lists available at ScienceDirect

Autoimmunity Reviews

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

Recovery from catastrophic antiphospholipid syndrome by a plasma exchange procedure: report of four cases and review of the literature

Maria Bortolati [a,*], Piero Marson [b], Fabrizio Fabris [c], Vittorio Pengo [d], Myriam Facchinetti [a], Giustina De Silvestro [b], Amelia Ruffatti [a]

[a] Rheumatology Unit, Department of Clinical and Experimental Medicine, University of Padua, Padua, Italy
[b] Apheresis Unit, Blood Transfusion Service, University Hospital of Padua, Padua, Italy
[c] Internal Medicine, Department of Medical and Surgical Sciences, University of Padua, Padua, Italy
[d] Clinical Cardiology, Thrombosis Center, Department of Cardio-Thoracic and Vascular Sciences, University of Padua, Padua, Italy

Other treatments

Cyclophosphamide (if SLE) 0.5-1g/m^2 Pay attention to infection

Rituximab anti-CD20

Eculizumab anti C5a

Summary: Definite thrombotic APS

- Triple positive patients (LAC positive, IgG or IgM aCL> 99th percentile, IgG or IgM ab2GPI> 99th percentile) and proven venous/arterial thrombosis.

Definite thrombotic APS

Remarks

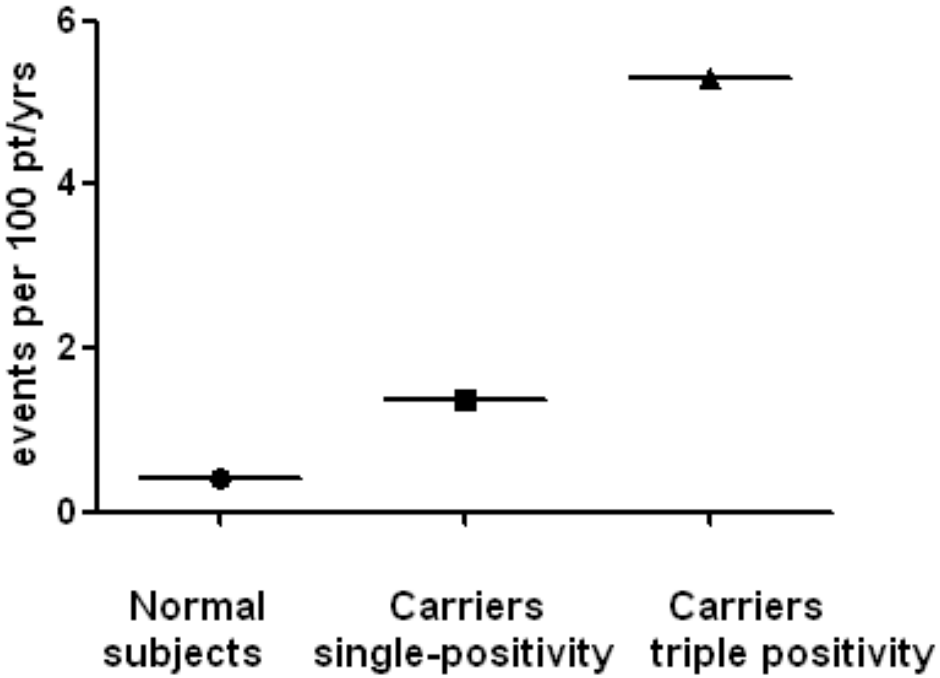
All the following reinforce the diagnosis of definite APS

- Young age (less than 50 years),
- unprovoked VTE or VTE in unusual site or in microcirculation, cryptogenic stroke
- IgG isotype,
- High titre of antibodies and strong LAC.
- Positive anti-β2GP1-Domain 1

How to read the results:
Incidence of recurrent thromboembolic events

How to read the results:
Incidence of a first thromboembolic event in aPL

Risk for thrombosis in antiphospholipid antibody carriers



Average annual rates of first cardiovascular events (including VTE) in caucasian normal population (●); in single aPL positive carriers (■);
and that shown in triple positive carriers in this study (▲).

Pengo V, Blood 2011

Which test (possibly in the same plasma sample)

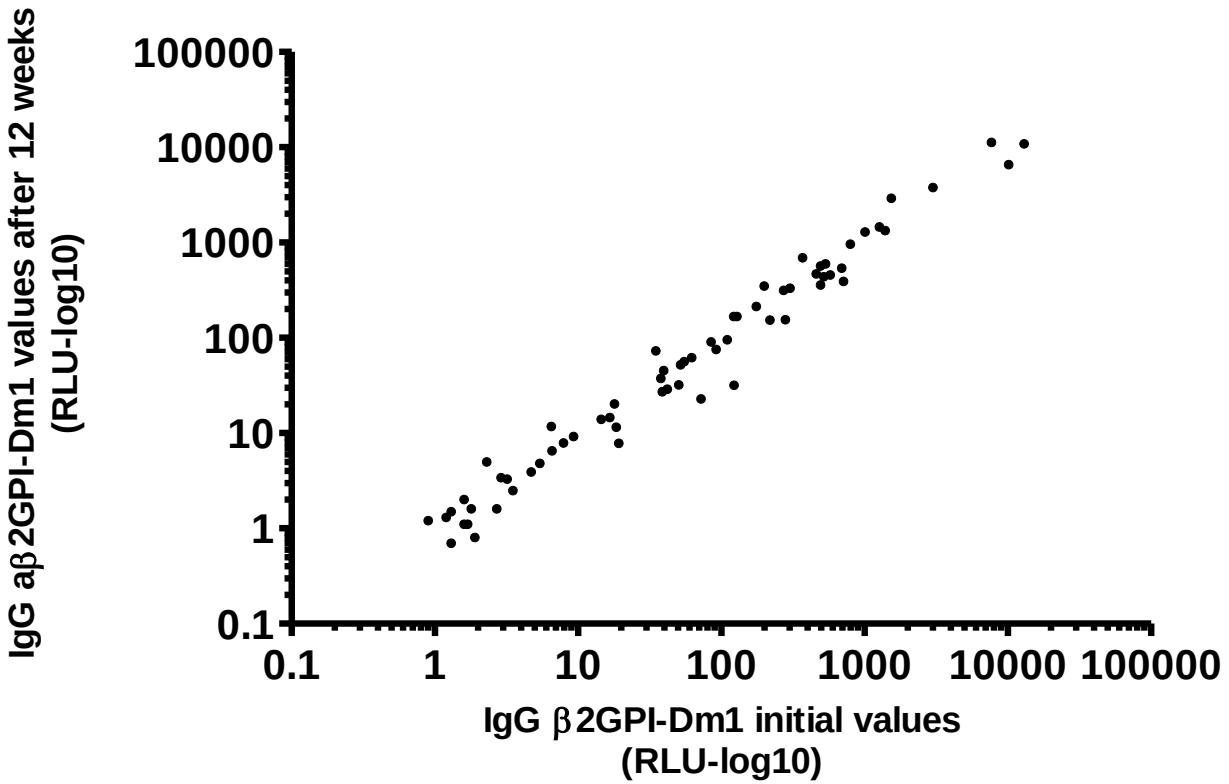
- Lupus anticoagulant (dRVVT and an aPTT-based test)
- IgG and IgM anti-cardiolipin (aCL) antibodies
- IgG and IgM anti-β2GPI (aβ2GPI) antibodies

- *IgA aCL and IgA anti-β2GPI: insufficient data*
- *IgG and IgM anti PS/PT: promising but undetermined significance*
- *Anti-β2GPI-Domain I and anti-β2GPI-Domain 4/5 could be useful*

Table 2: Association between aPL and thrombosis

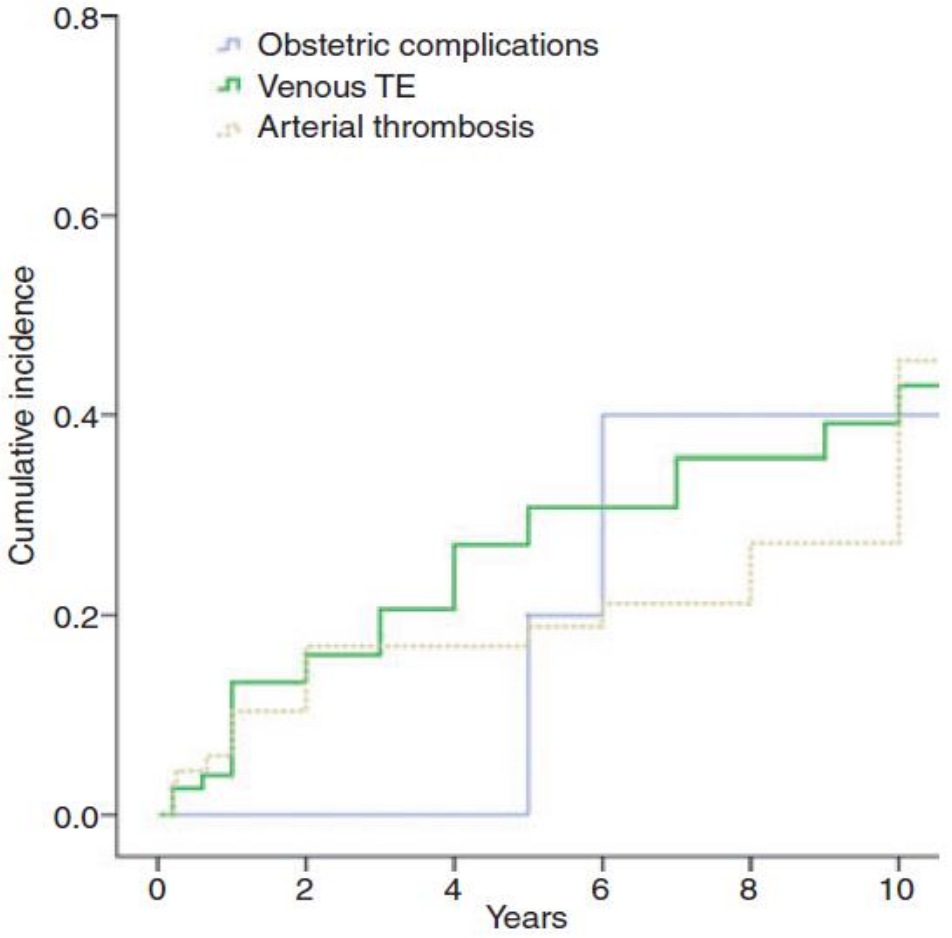
	Odds ratio (95% confidence interval)
Anti-domain I IgG	**3.5** *(2.3-5.4)**
Non-domain I Anti-beta2GPI IgG	0.4 *(0.3-0.6)*
Anti-beta2GPI IgM	0.9 *(0.6-1.3)*
LAC	**1.8** *(1.1-3.1)**
aCL	1.1 *(0.6-2.1)*

De Laat B, JTH 2009

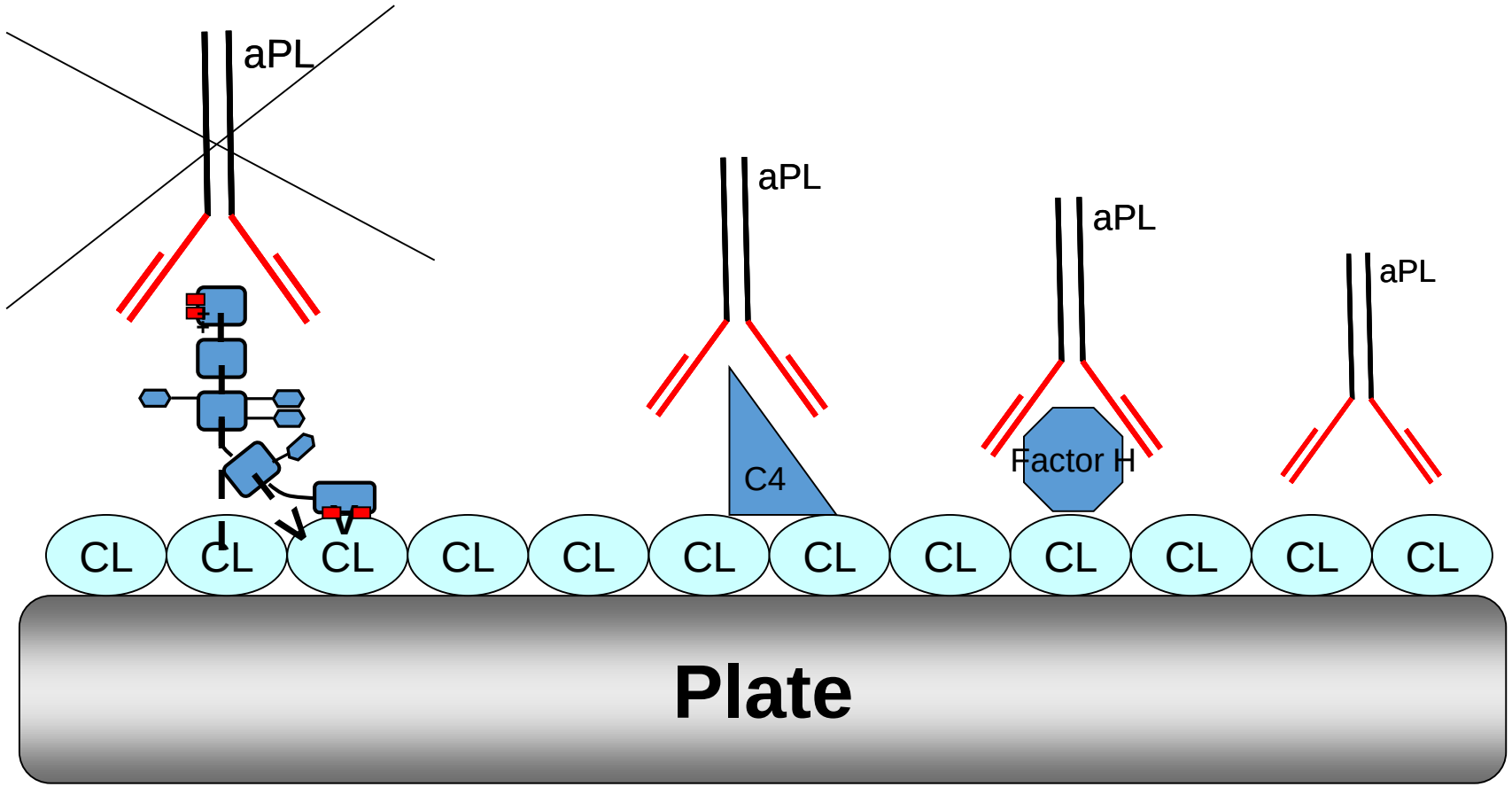

IgG aβ2GPI-Dm1 values after 12 weeks
(RLU-log10)
100000
10000
1000
100
10
1
0.1
0.1
1
10
100
1000
10000
100000
IgG β2GPI-Dm1 initial values
(RLU-log10)

Cumulative incidence of thromboembolic events in triple positive APS patients (n=160) according to the clinical features at diagnosis

Patients mean age:
41,1 yrs
VTE n.76
ATE n. 69
Obstetric n.11
Catastrophic n.4



Pengo V, JTH 2010

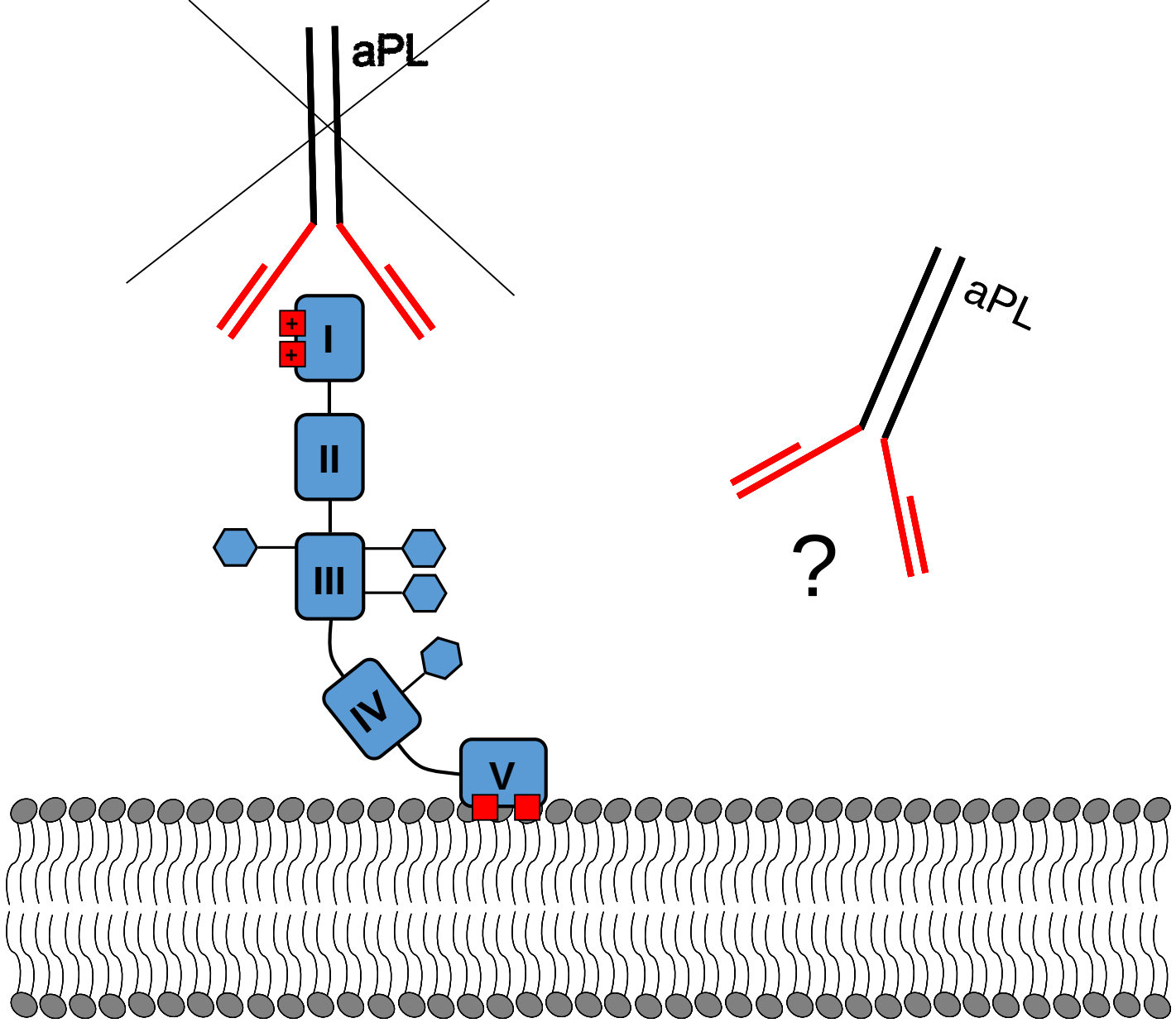


LAC - aCL + abeta2 -

Sole aCL positivity (negative LA and aβ2GPI)

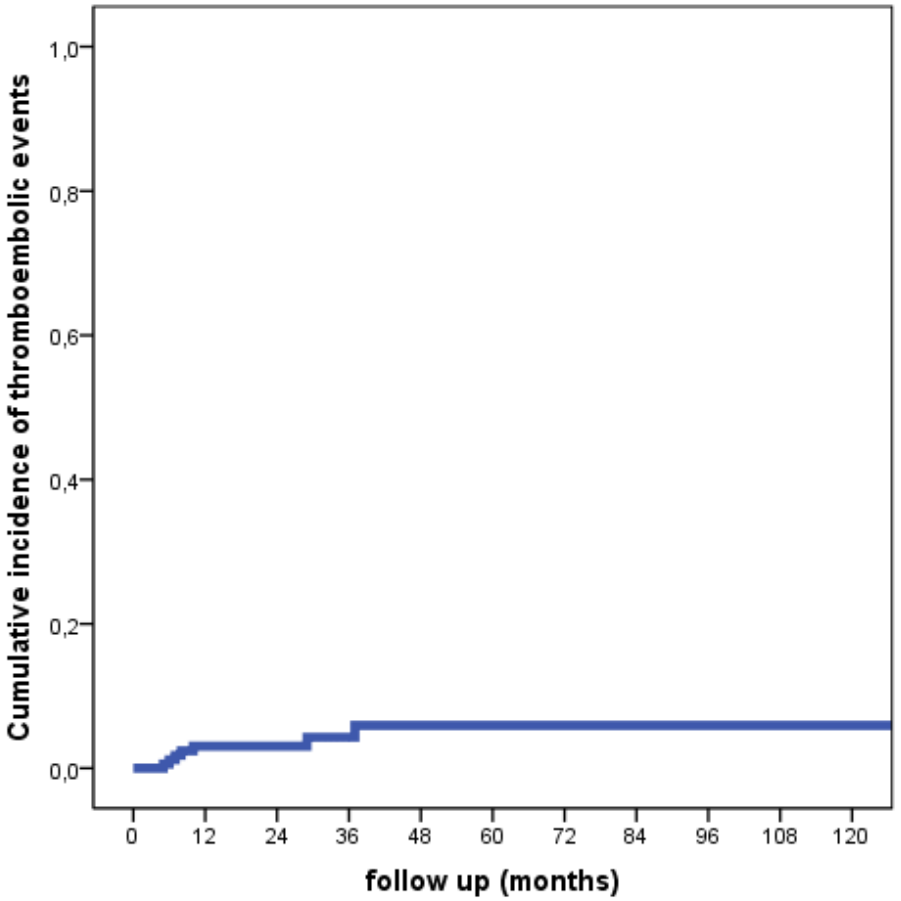
No association with thrombosis

Ruffatti A J Thromb Haemost 2008; 6: 1693–6.
Runchey SS Br J Haematol 2002;119:1005–10.
Proven A Mayo Clin Proc 2004;79:467–75.



LAC + **aCL -** **abeta2 -**

Carriers of sole LA positivity



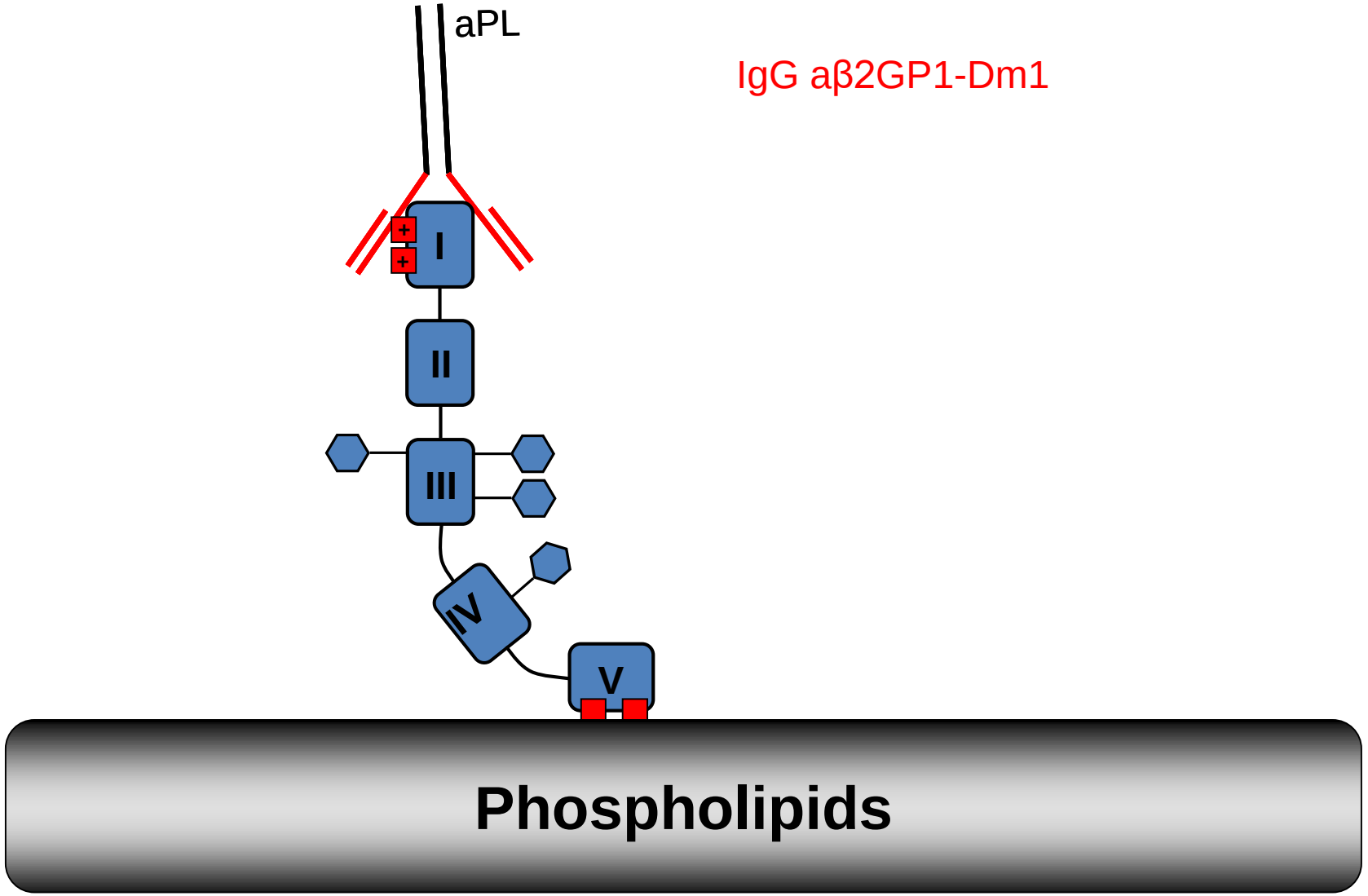
5.9% (95% CI 1.2-10.6)
after 10 years

Pengo V et al. Thromb Res 2015

Characteristics at initial testing

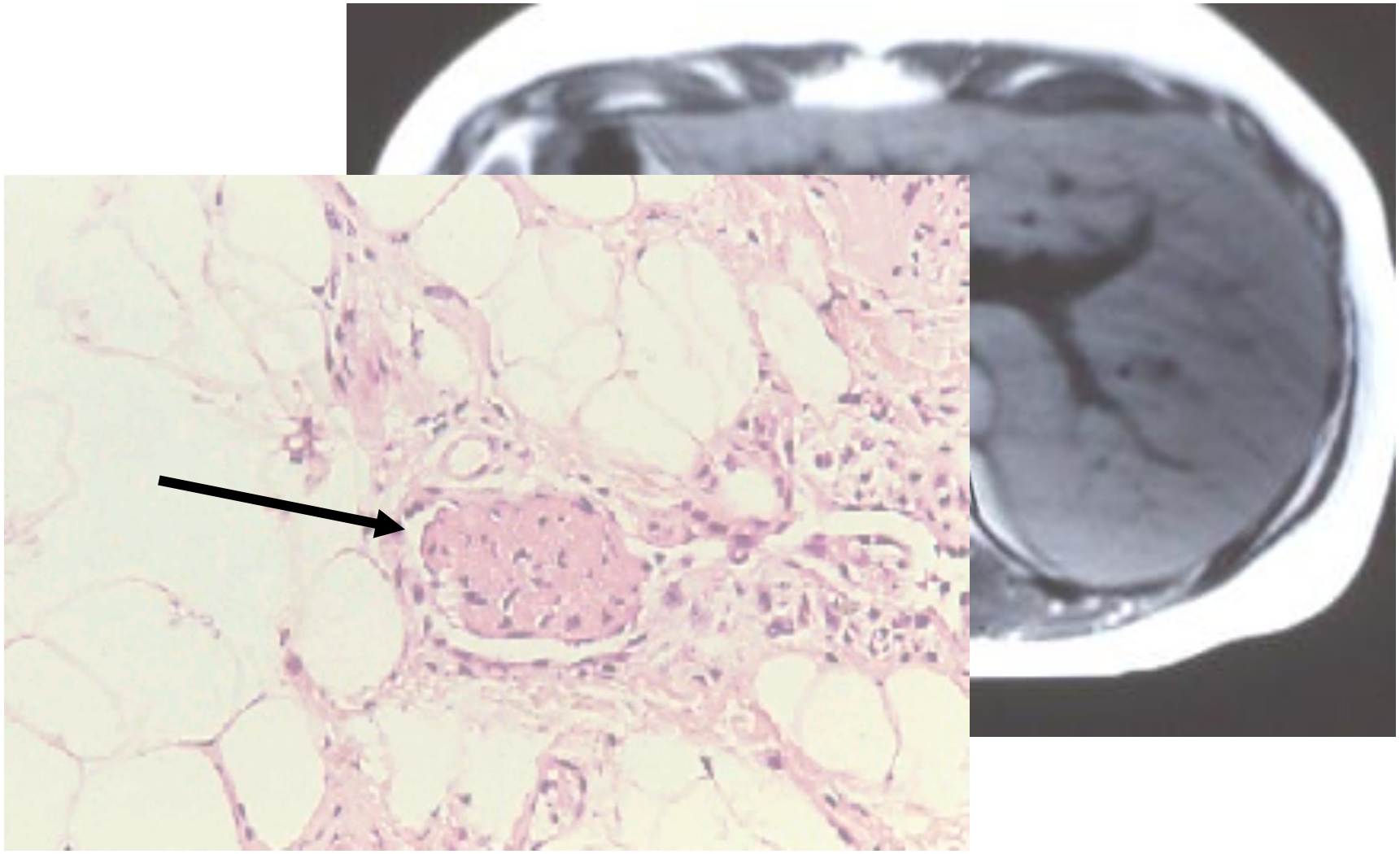
	Triple positive n=54	Double positive n=50	Single positive* n=53	P value
Age –yrs (mean±SD)	42±14	45±13	38±12	0.02
Female—no.(%)	**42 (78)**	**48 (96)**	**49 (92)**	**<0.01**
Predominant IgG isotype—no.(%)	**42 (78)**	**23 (46)**	**NA**	**0.001**
Autoimmune disorders—no.(%)	6 (11)	12 (24)	16 (30)	0.0504
Venous or Arterial Thrombosis—no.(%)	**42 (78)**	**15 (30)**	**4 (7)**	**<0.0001**
Pregnancy loss—no.(%)	**7 (13)**	**28 (56)**	**7 (13)**	**<0.0001**

Pengo V et al. JTH 2013



IgG aβ2GP1-Dm1

Scansione TC: infarto surrenalico sinistro (freccia) della paziente n°2



Cerebral ischemia:secondary prevention

For patients with noncardioembolic stroke or TIA, we recommend antiplatelet agents over oral anticoagulation (Grade 1A).

Remark: Some experts recommend oral anticoagulants for specific patient populations with noncardioembolic stroke, including patients with cervical artery dissection (see above), severe carotid stenosis prior to endarterectomy, **antiphospholipid antibody syndrome**, symptomatic intracranial large-artery stenosis, and coagulation factor deficiencies. Whether anticoagulants are superior to antiplatelet agents for these indications is unknown.

ACCP 2008

SYDNEY, 2005

Investigators are strongly advised to classify APS patients in studies into one of the following categories

I: More than one Laboratory criteria present (any combination)

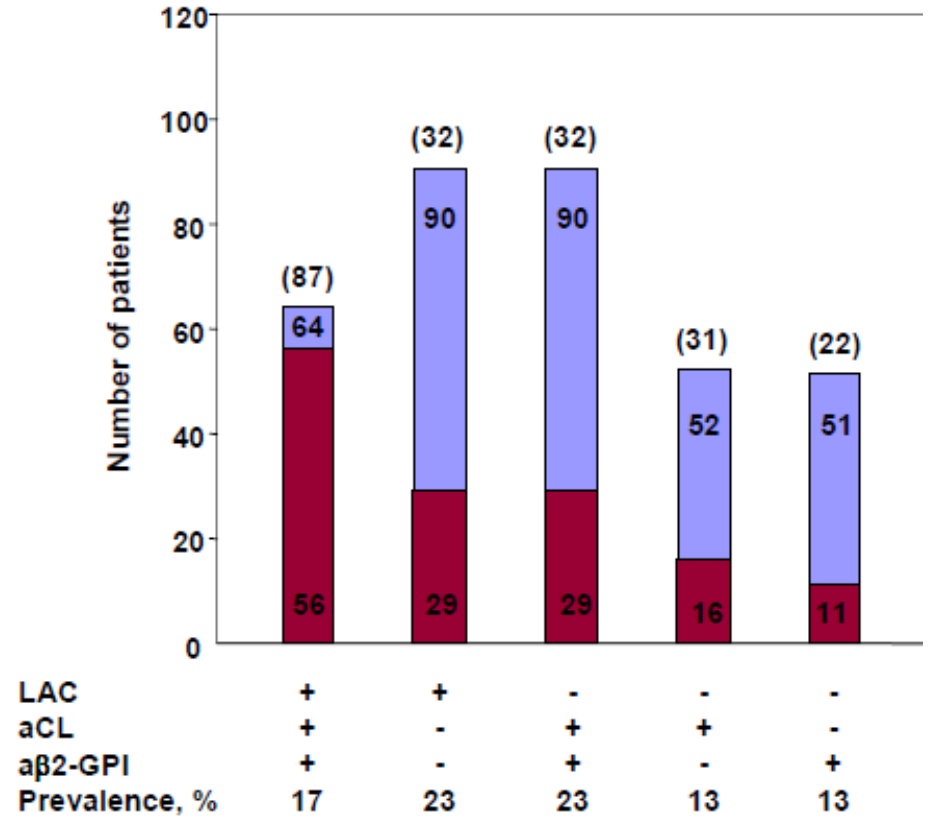
IIa: Lupus Anticoagulant present alone

IIb: Anti-cardiolipin antibody present alone

IIc: Anti-β2 glycoprotein-I antibody present alone

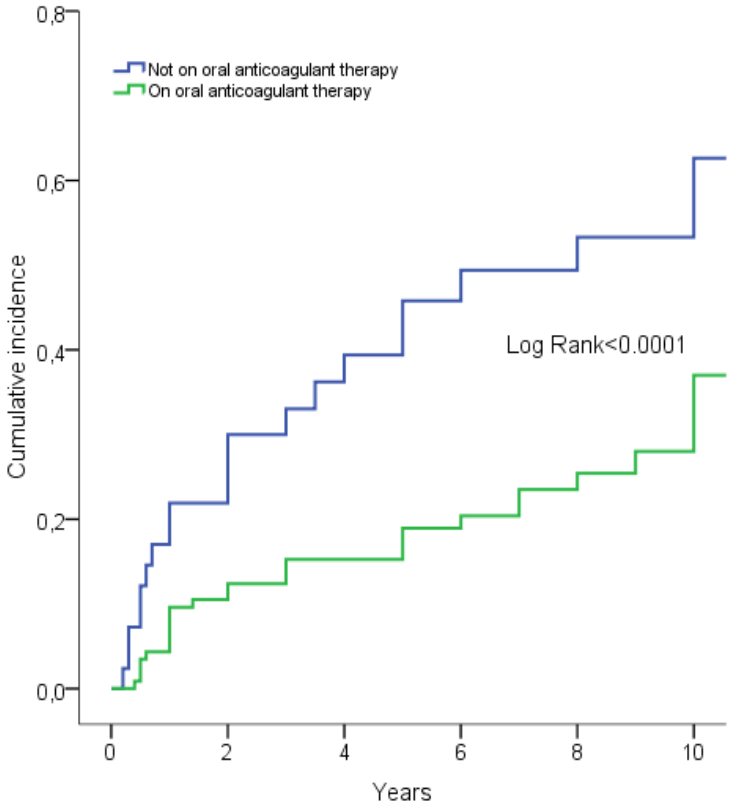
Miyakis S et al. J Thromb Haemost 2006; 4: 295–306

Cumulative analysis of the prevalence and association with thrombosis of aPL profiles in 385 patients (3 studies)



Modified from Galli M. JTH 2010 (commentary)

Cerebral ischemia:secondary prevention: VKAs plus aspirin 100mg qd



Cumulative incidence of thromboembolic events in high risk triple positive APS patients (n=160) according to treatment

Pengo V, JTH 2010

Clinical and laboratory features of CAPS patients

Case number	1	2	3	4
Age	13	23	33	34
Diagnosis	CAPS+SLE	CAPS+SLE	CAPS+lupoid hepatitis	CAPS
Trigger	Gastroenteritis	Unknown	Puerperium	Oral contraceptives
Antiphospholipid antibodies	LA, high level IgG aCL[a]	LA, high level IgG and IgM aCL[a]	LA, high level IgG aCL and IgG aβ_2GPI	LA, high level IgG aCL and IgG aβ_2GPI
Thrombotic events	Kidney, brain, mesenteric artery	Skin, adrenal gland, kidney, venous thromboembolism	Multiorgan failure	Skin, liver, brain, kidney
Number of TPE[b] sessions / time	86 / 18 months	33 / 5 months	6 / 10 days	11 / 30 days
Treatments other than TPE[b]	Prednisone, cyclophosphamide, anticoagulation	Methylprednisolone, anticoagulation	Anticoagulation	Prednisone, anticoagulation
Follow up	22 years	18 years	10 years	2 years

[a] antiβ_2GPI not determined;
[b] TPE: therapeutic plasma exchange.