Frits Haverkate lecture

Universitair Medisch Centrum Utrecht

The pathophysiology of lupus anticoagulant and the consequences for laboratory diagnosis

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Disclosures

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Honoraria	**No relevant conflicts of interest to declare**
Scientific Advisory Board	**No relevant conflicts of interest to declare**

Lupus anticoagulant

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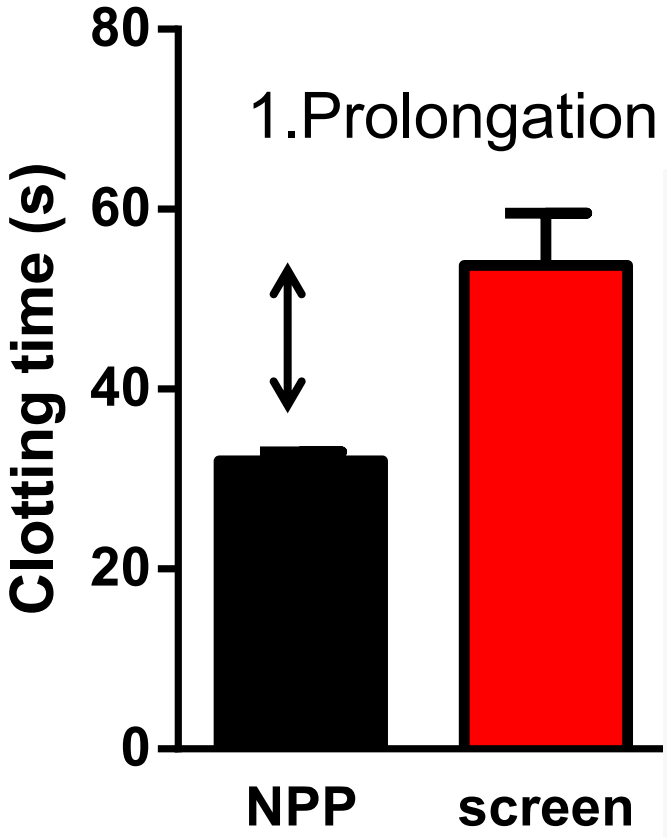
LA-ratio: $\frac{\text{Screen}_{patient}/\text{Screen}_{normal}}{\text{Confirm}_{patient}/\text{confirm}_{normal}}$ **>99th percentile of normal**



1.Prolongation

2. Correction by addition of excess phospholipids

Lupus anticoagulant

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- Use plasma with a platelet count < 10^{10} platelets/L
- Prolongation of an APTT or a dRVVT
- Evidence of inhibitory activity: no correction of the prolonged clotting time by mixing normal pooled plasma with patient plasma
- Evidence that inhibitory activity is dependent on PL by adding extra phospholipids

SSC guidelines. Pengo et al. J Thromb. Haemost. 2009; 7: 1737-40

1952

First publication describing two patients with APS

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- 2 patients with SLE
- Peculiar hemorrhagic disorder
- Prolongation of clotting times
- No correction after mixing
- No inhibition of thrombin time
- Stable at 65 °C
- Unstable at 80 °C
- Not dialyzable
- False positive syphilis test

➢ Autoimmune disease

➢ Lupus anticoagulant

➢ Antibody

➢ Anti-Cardiolipin Antibodies

A Hemorrhagic Disorder Caused by Circulating Anticoagulant in Patients with Disseminated Lupus Erythematosus. C. Lockard Conley * and Robert C. Hartmann, Baltimore, Maryland.

1963

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The first study in a larger populations showing the correlation between thrombosis and prolongation of clotting assays

(8 patients with circulating anticoagulant, of these 4 had thrombosis)

Thrombosis in systemic lupus erythematosus despite circulating anticoagulants

E. J. WALTER BOWIE, JOHN H. THOMPSON, JR., CHRIS A. PASCUZZI, and CHARLES A. OWEN, JR. *Rochester, Minn.*

J. Lab. Clin. Med 62 (1963) 416-430

Classification criteria for APS

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

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A patient with:

1. thrombosis

   recurrent pregnancy loss

   &

2. lupus anticoagulant

   anti-cardiolipin antibodies

   anti-β_2-glycoprotein I antibodies

diagnosis

ANTI-PHOSPHOLIPID SYNDROME

The serological markers should be positive in two samples, collected at least 12 weeks apart

Thrombosis in APS

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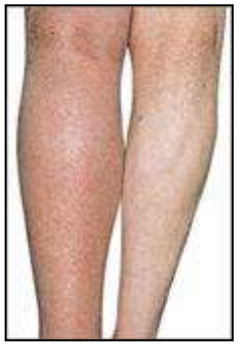
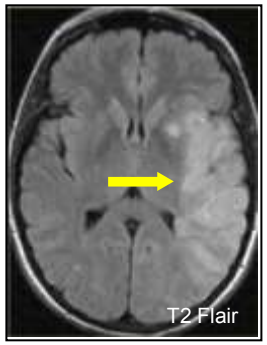
May occur in any vessel

Most frequently afflicted vessels:

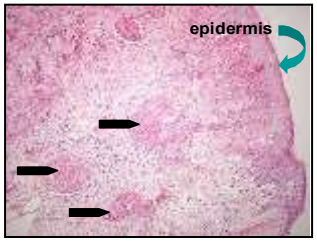
- deep venous thrombosis, pulmonary emboli
- cerebral vasculature (TIA, stroke)



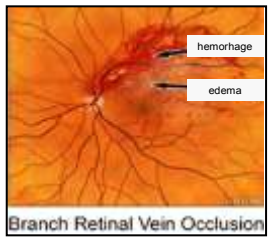
DVT



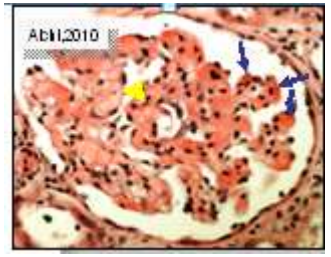
Cerebral infarct



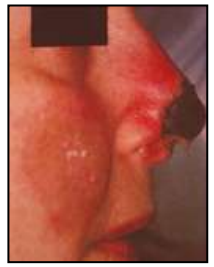
Skin



Eye



Kidney



Nose

Pregnancy complications in APS

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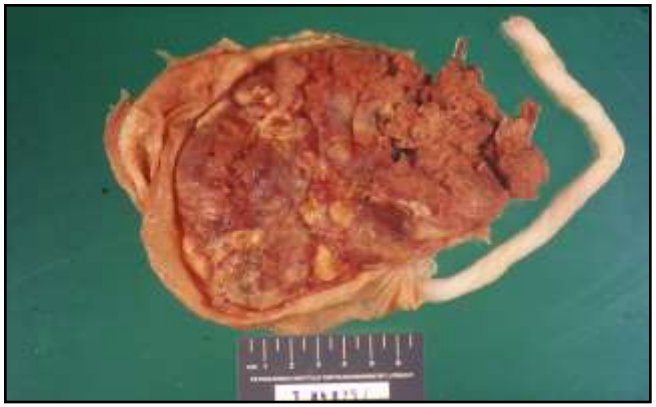
Thrombotic



Non-thrombotic

Impairment of throphoblast migration and invasion?

Sebire et al. Hum.Reprod 2002; 17: 1067-71

Serology

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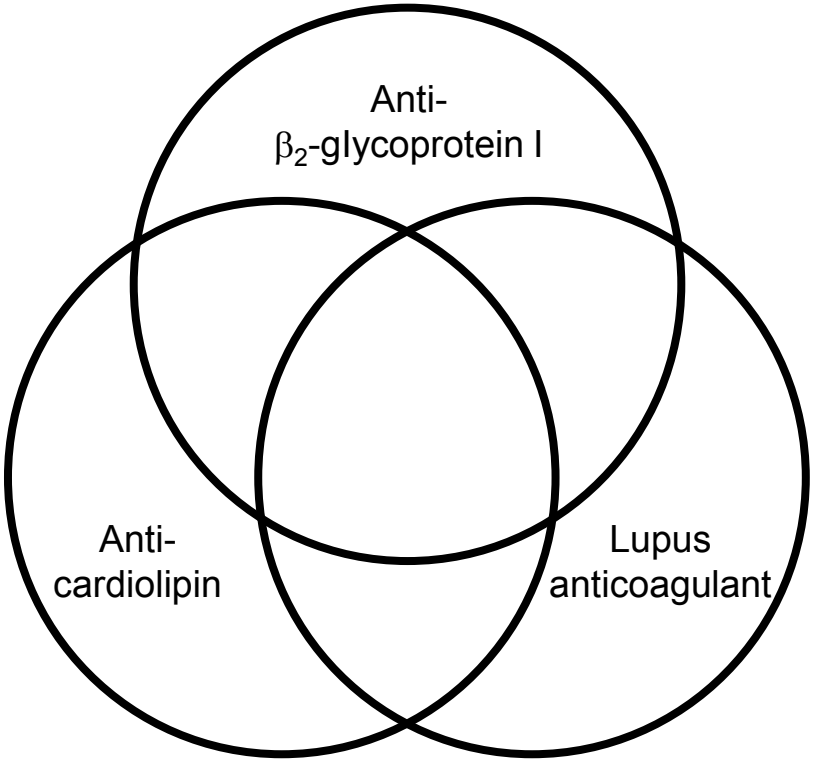
- Persistently present antibodies, one of three different subsets:
  - Anticardiolipin antibodies
  - Anti-β_2-glycoprotein I antibodies
  - Phospholipid dependent coagulation inhibitor known as lupus anticoagulant

Relevance of antibodies



LA, anti-cardiolipin antibodies and anti-$\beta_2$glycoprotein I antibodies are antibodies with overlapping specificity but they are not identical antibodies.

Clinical significant antibodies

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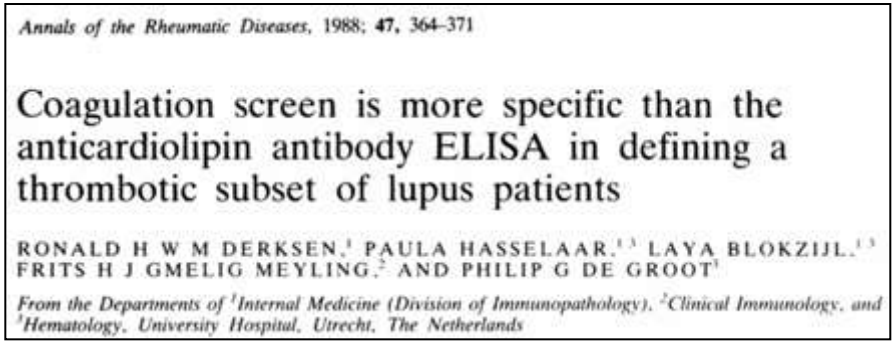

Annals of the Rheumatic Diseases, 1988; **47**, 364–371

Coagulation screen is more specific than the anticardiolipin antibody ELISA in defining a thrombotic subset of lupus patients

RONALD H W M DERKSEN,[1] PAULA HASSELAAR,[1,3] LAYA BLOKZIJL,[1,3] FRITS H J GMELIG MEYLING,[2] AND PHILIP G DE GROOT[1]

From the Departments of [1]Internal Medicine (Division of Immunopathology), [2]Clinical Immunology, and [3]Hematology, University Hospital, Utrecht, The Netherlands

blood

2003 101: 1827-1832
Prepublished online October 3, 2002;
doi:10.1182/blood-2002-02-0441

Lupus anticoagulants are stronger risk factors for thrombosis than anticardiolipin antibodies in the antiphospholipid syndrome: a systematic review of the literature

Monica Galli, Davide Luciani, Guido Bertolini and Tiziano Barbui

- **Medline searches of retrospective studies have shown that lupus anticoagulant is the assay of choice**
- **Additional studies have confirmed these publications**
- **How about prospective studies?**

Antiphospholipid antibody profile thrombotic risk

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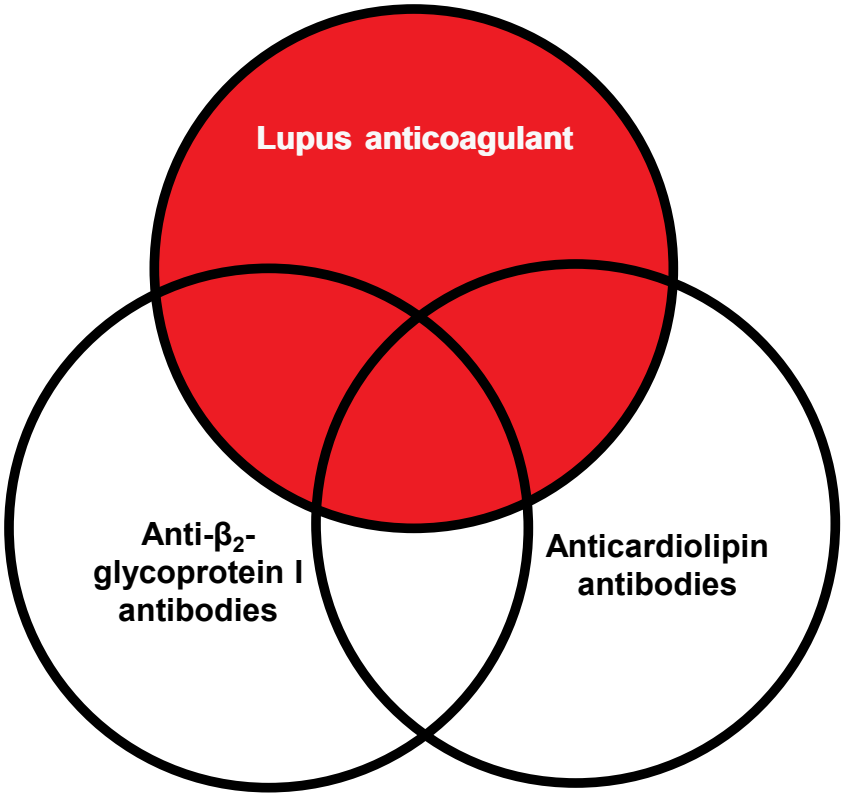

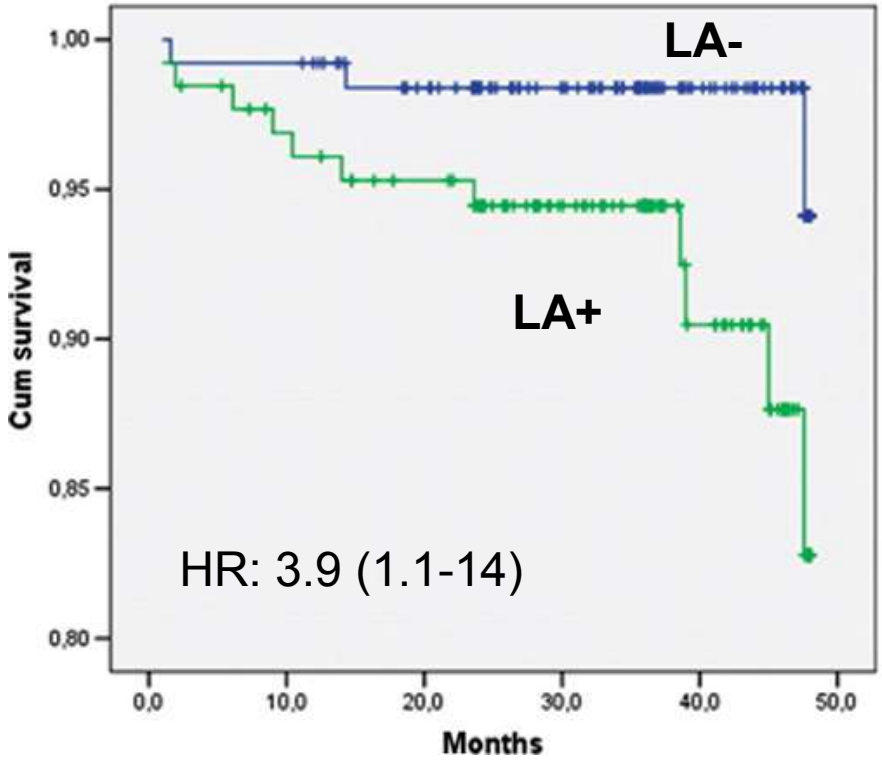

Ruffati et al. Ann Rheum Dis 2011

Antiphospholipid antibody profile adverse pregnancy outcome

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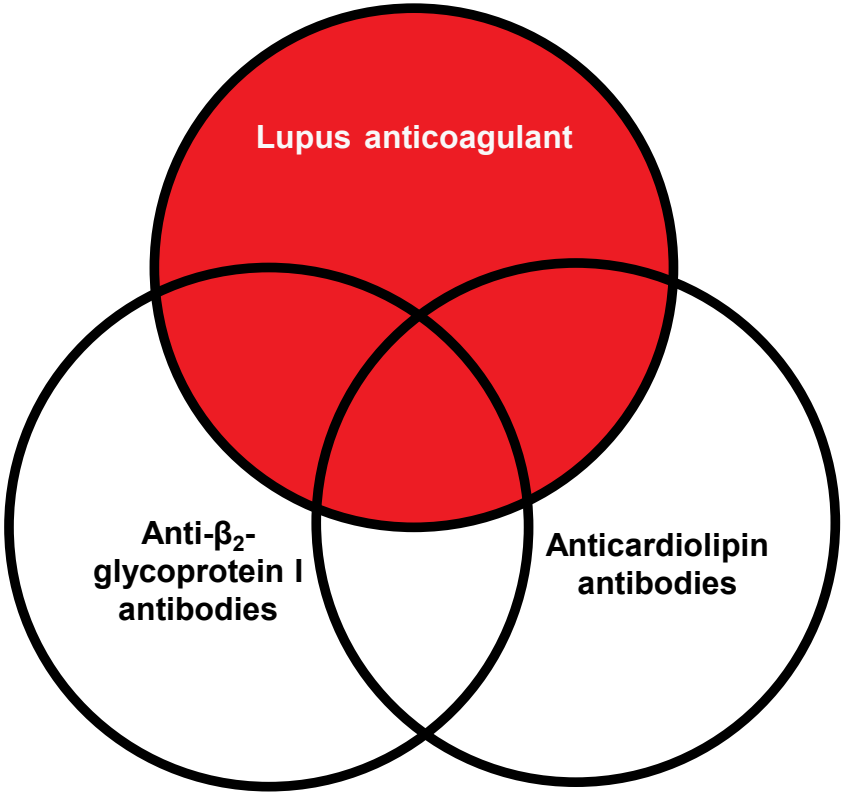

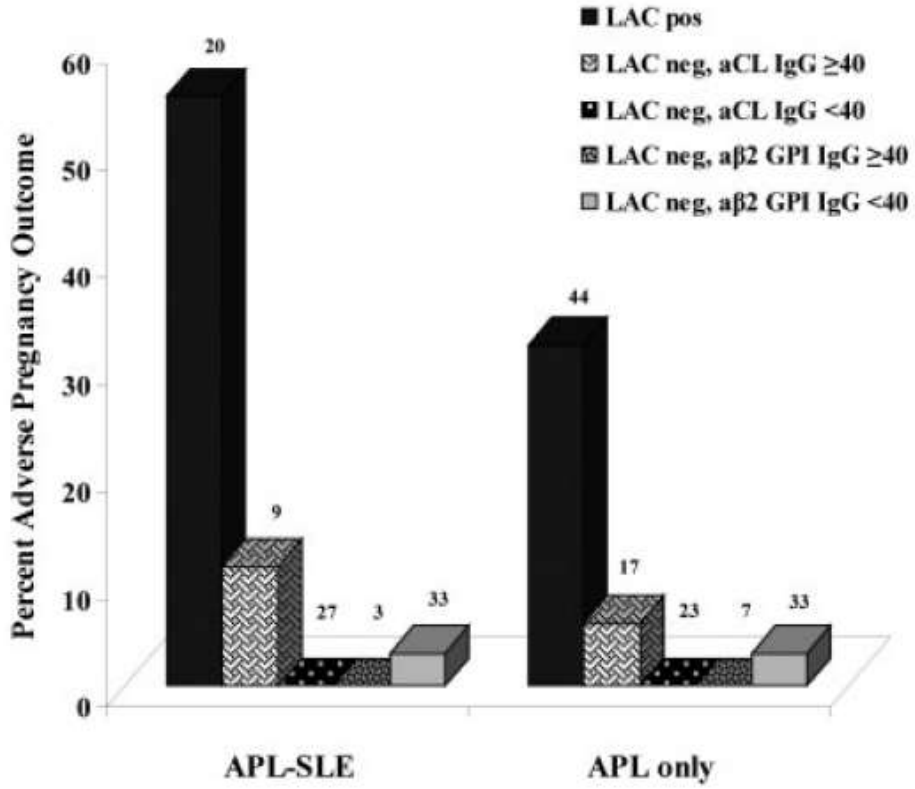

Lockshin et al. Arthritis Rheum 2012

Lupus anticoagulant

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- Retrospective and prospective studies agreed that lupus anticoagulant correlates best with the clinical manifestations.
- The highest correlation is found when all three assays are positive.
- Single positivity for anti-cardiolipin antibodies (as measured with the current assays) does not correlate with the clinical manifestations.
- Titer is important.
- Higher risk in combination with other risk factors.
  - Erkan et al. Arthritis Rheum 2007; 56: 2382

Conclusion

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Lupus anticoagulant is the assay of choice

Why are the other assays inferior to detect patients at risk?

- The lack of standardization of the assays →
  Large differences in sample exchange programs.
- The ELISAs are designed to pick up irrelevant low affinity antibodies →
  Assays often positive in healthy individuals.
- The ELISAs measure a heterogeneous population of antibodies →
  Not all auto-antibodies are risk factors.

Irrelevant low affinity antibodies

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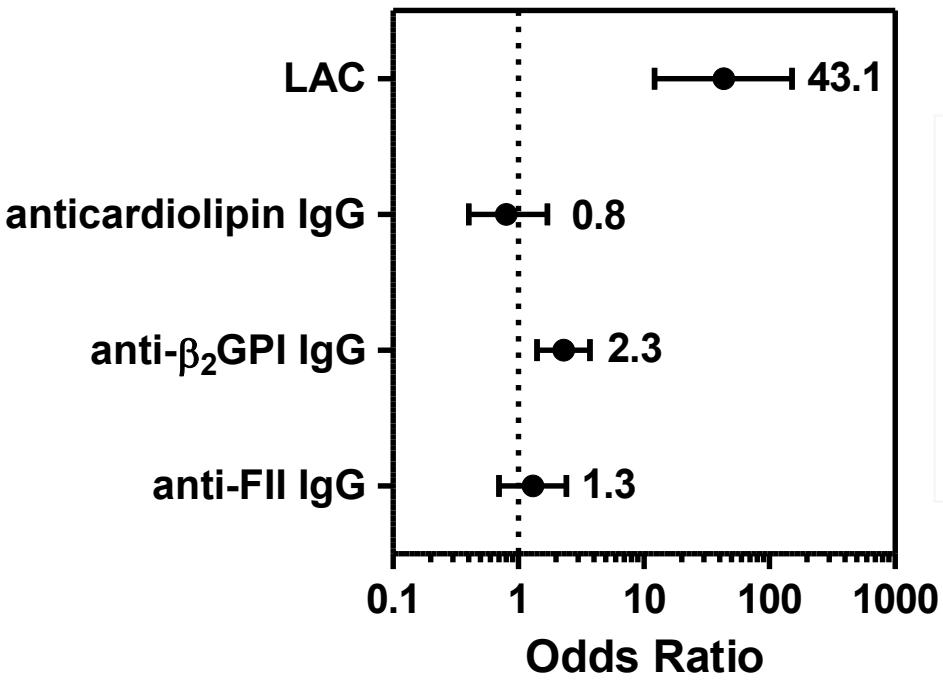
RATIO study: Ischemic stroke in young women (<50 years)



	Controls	Cases
LAC -	623	145
+	4	**30**
Anti-β_2GPI -	566	136
+	62	**39**

Only lupus anticoagulant correlates strongly with stoke

Urbanus et al. Lancet Neurol. 2009; 8: 998

Irrelevant low affinity antibodies

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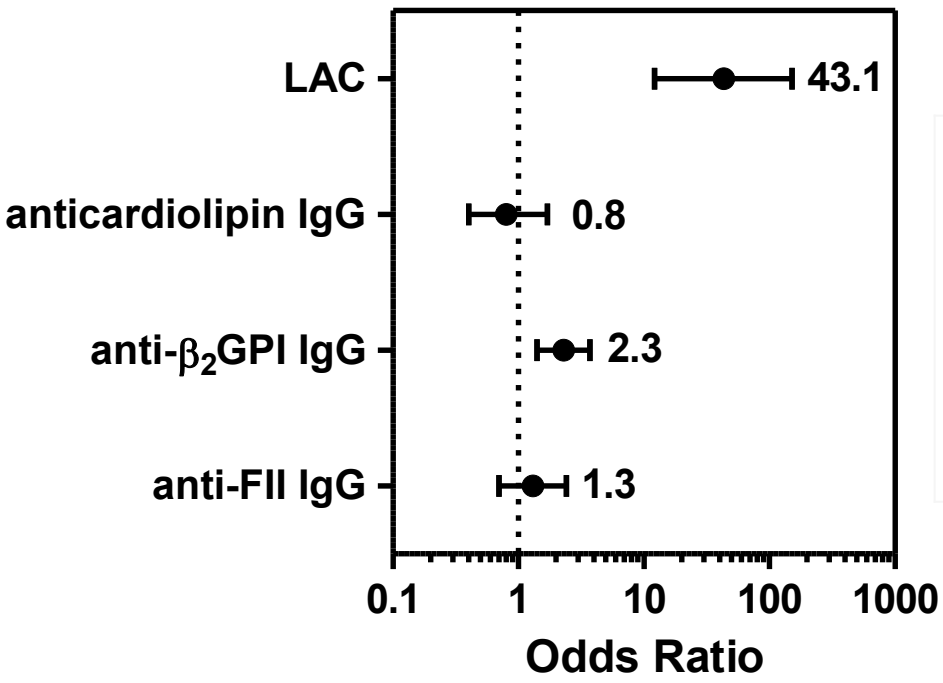
RATIO study: Ischemic stroke in young women (<50 years)



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Only lupus anticoagulant correlates strongly with stoke

Urbanus et al. Lancet Neurol. 2009; 8: 998

Antiphospholipid antibodies ↔ thrombosis

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One of the many challenges:

Lupus anticoagulant correlates strongly with thrombosis.

Lupus anticoagulant is caused by antibodies directed against β_2-glycoprotein I or prothrombin.

Antibodies against β_2-glycoprotein I or prothrombin hardly correlate with thrombotic complications.

Are anti-β_2-glycoprotein I antibodies a consequence of another disease process, such as tissue damage, and simply represent a 'footprint' that was left behind or are they directly responsible for the observed clinical complications?

Anti-β_2Glycoprotein I antibodies and thrombosis

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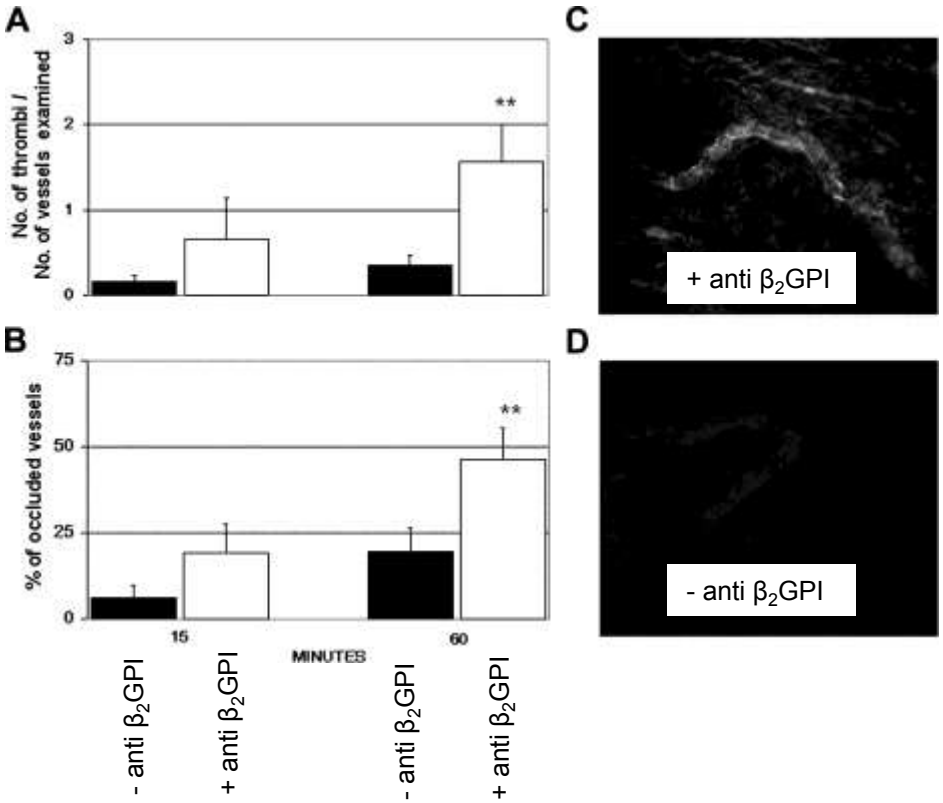
blood

2005 106: 2340-2346
Prepublished online June 14, 2005;
doi:10.1182/blood-2005-03-1319

Thrombus formation induced by antibodies to β2-glycoprotein I is complement dependent and requires a priming factor

Fabio Fischetti, Paolo Durigutto, Valentina Pellis, Alessandra Debeus, Paolo Macor, Roberta Bulla, Fleur Bossi, Federica Ziller, Daniele Sblattero, Pierluigi Meroni and Francesco Tedesco



Anti-β_2Glycoprotein I antibodies and thrombosis

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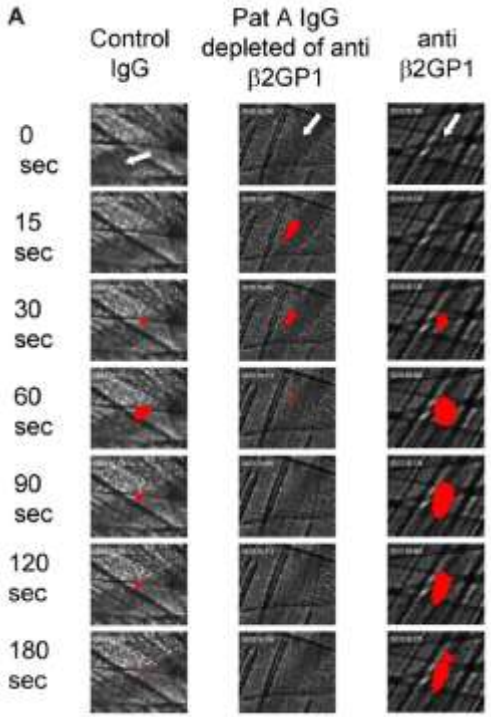
blood

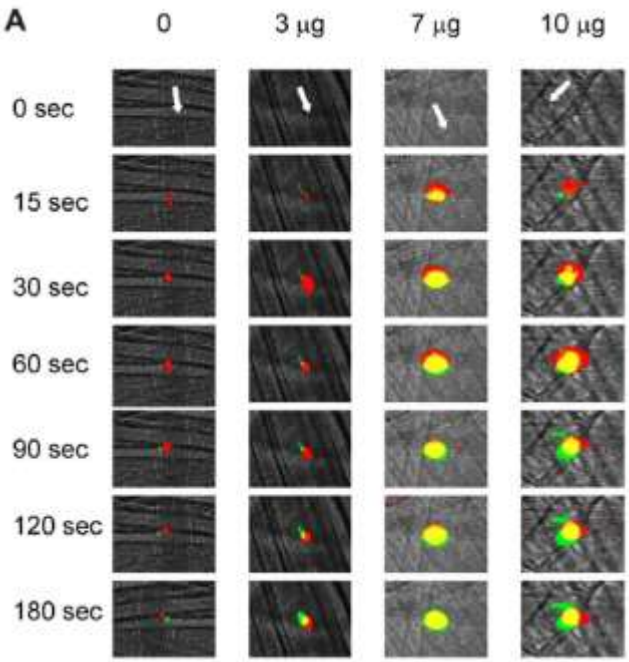
2011 117: 3453-3459
Prepublished online January 18, 2011;
doi:10.1182/blood-2010-08-300715

β_2-glycoprotein-1 autoantibodies from patients with antiphospholipid syndrome are sufficient to potentiate arterial thrombus formation in a mouse model

Ariela Arad, Valerie Proulle, Richard A. Furie, Barbara C. Furie and Bruce Furie



Patient-derived auto-antibodies specific for β_2-glycoprotein I enhanced dose-dependently a thrombotic response in a mouse model of APS



Domain I of β_2-Glycoprotein I

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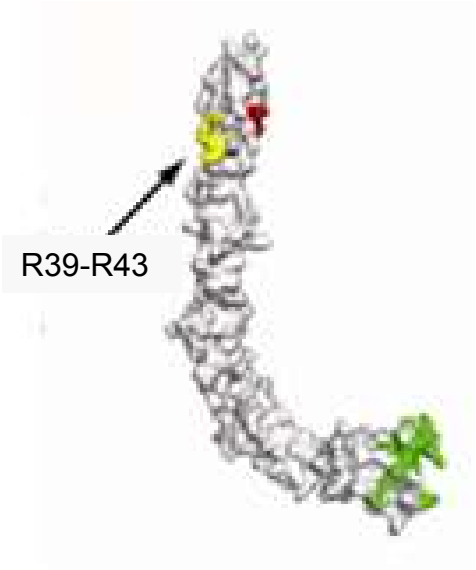
Blood. 2005 Feb 15;105(4):1540-5. Epub 2004 Oct 26.

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

de Laat B, Derksen RH, Urbanus RT, de Groot PG.



Anti-domain I antibodies: a high specificity but a low sensitivity

Pathological antibodies against first domain of β_2Glycoprotein I

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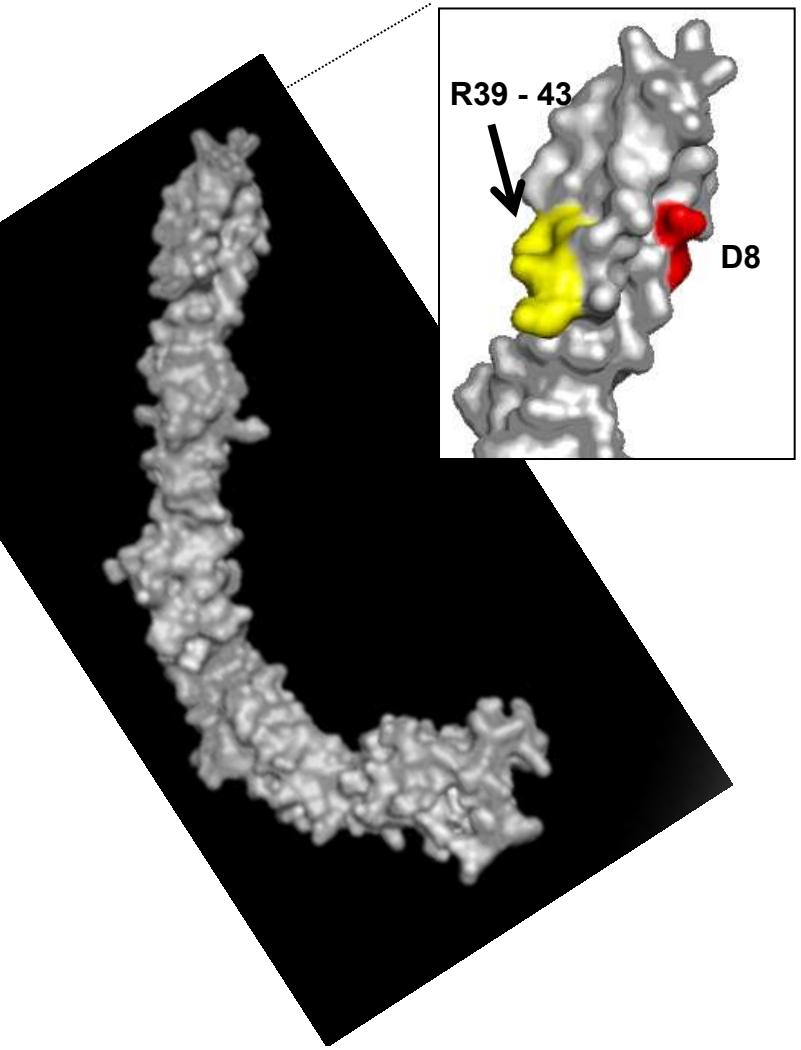

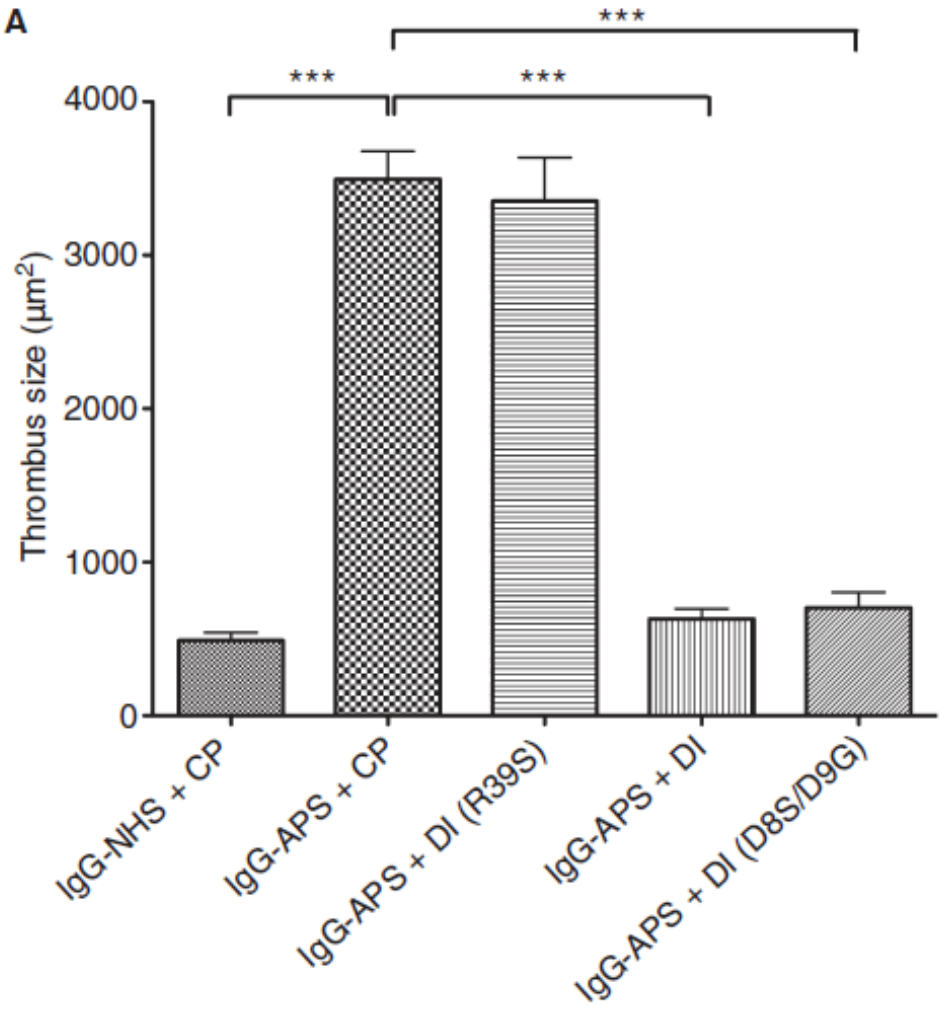

Ioannou et al. J Thromb Haemost. 2009

Proof-of-concept

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Rheumatology Advance Access published September 30, 2014

RHEUMATOLOGY 264, 267

Concise report doi:10.1093/rheumatology/keu360

Proof-of-concept study demonstrating the pathogenicity of affinity-purified IgG antibodies directed to domain I of β_2-glycoprotein I in a mouse model of anti-phospholipid antibody-induced thrombosis

Charis Pericleous[1], Patricia Ruiz-Limón[2], Zurina Romay-Penabad[2], Ana Carrera Marín[2], Acely Garza-Garcia[3], Lucy Murfitt[3], Paul C. Driscoll[3], David S. Latchman[1], David A. Isenberg[1], Ian Giles[1], Yiannis Ioannou[1,4], Anisur Rahman[1] and Silvia S. Pierangeli[2,*]

Conclusion. These data directly demonstrate that the ability to cause thrombosis *in vivo* is concentrated in the aDI fraction of aPL.

Domain I antibodies ↔ lupus anticoagulant

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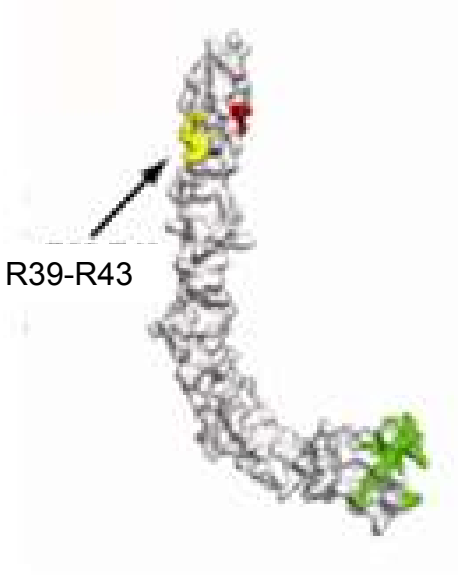
Blood. 2005 Feb 15;105(4):1540-5. Epub 2004 Oct 26.

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

de Laat B, Derksen RH, Urbanus RT, de Groot PG.



		β_2GPI-dependent LAC	
		+	-
Domain I ELISA	+	23	7
	-	2	167

SLE-patients

Anti-domain I antibodies express LA activity

Conclusion

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Auto-antibodies directed against domain I of β_2-glycoprotein I can induce a pro-thrombotic phenotype in mice.

Domain I auto-antibodies induce Lupus Anticoagulant activity when added to normal plasma.

SSC ↔ CSLI

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Guidelines for the performance of lupus anticoagulant assay

ISTH (2009)	CSLI (2014)
Cut-off: 99%	Cut-off: + 2SD
dRVVT first, then aPTT	Both dRVVT and APTT screen
APTT activator: silica	APTT activator: no restriction
Only dRVVT and aPTT	Does not restrict supplemental test
Screen-mix-confirmatory	Screen-confirmatory-mix
Ratio: relative to mean normal pool	Ratio: relative to mean reference interval

Order of assays

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Screen – Mix – Confirm ↔ Screen – Confirm – (Mix)

What is more important, exclusion of a factor deficiency or demonstration of a phospholipid dependent inhibitor?

Prioritize the demonstration of phospholipid dependence of the antibody over showing an possible deficiency of clotting factors.

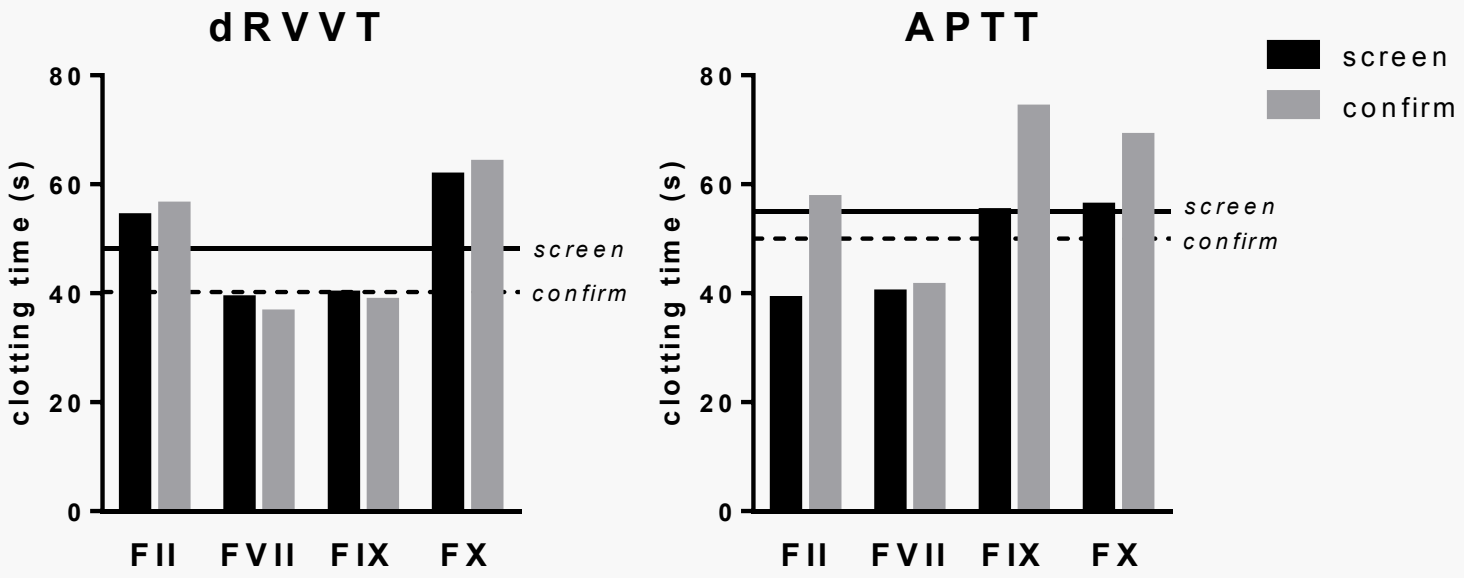
Screen –Confirm- (Mix)

Thromb Haemost. 2014 Jul 10;112(4). [Epub ahead of print]

Optimisation of lupus anticoagulant tests: should test samples always be mixed with normal plasma?

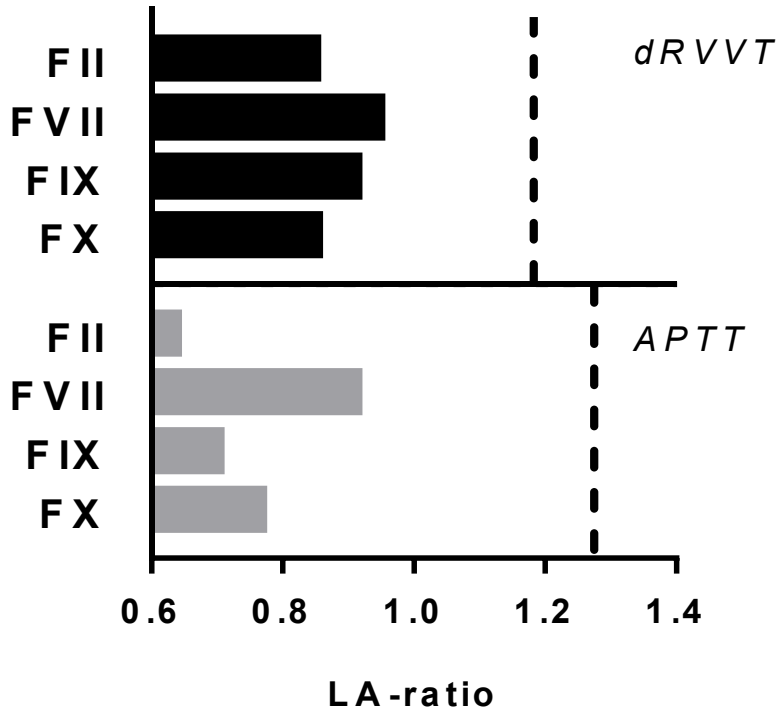
Pennings MT, De Groot PG, Meijers JC, Huisman A, Derksen RH, Urbanus RT[1].

Is mixing necessary?



10% of the indicated coagulation factor

Effect of deficiency of vitamin K dependent factors on dRVVT and APTT



LA-ratio far below threshold for LA positivity

$$\text{LA-ratio} = \frac{Screen_{patient}/Screen_{mean\ normal}}{Confirm_{patient}/Confirm_{mean\ normal}}$$

Oral anticoagulants and LA assessment

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LA detection in patients on long-term vitamin K antagonists (VKA)

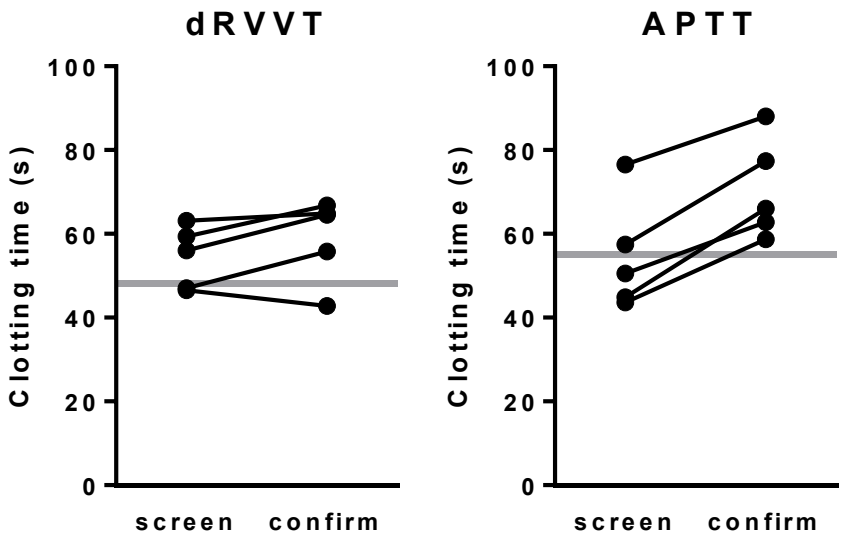
1 The interpretation of results is difficult because of the prolonged basal clotting time. To avoid misinterpretation, it is recommended to perform laboratory procedures 1 to 2 weeks after discontinuation of treatment or when the international normalized ratio (INR) is less than 1.5. Bridging VKA discontinuation with LMWH is recommended with the last dose of LMWH administered more than 12 h before the blood is drawn for LA testing.

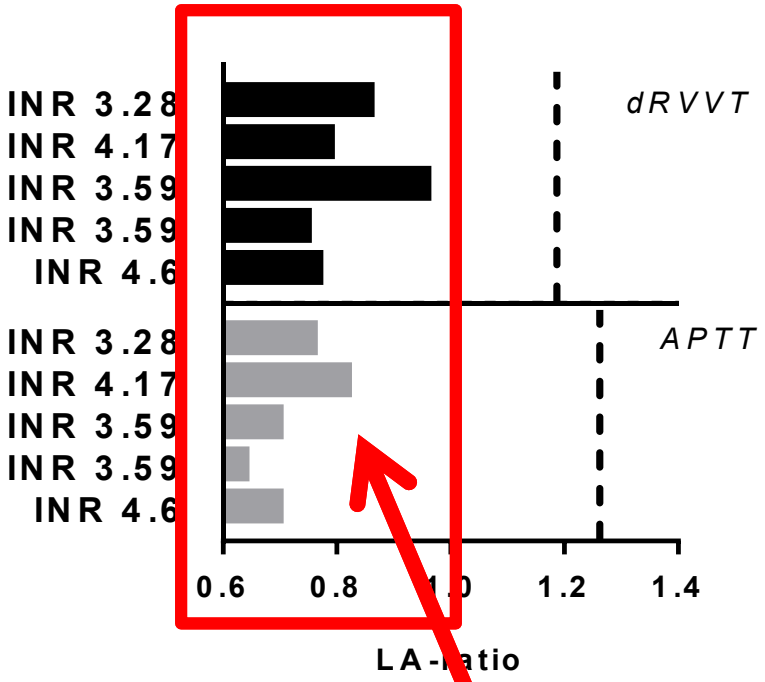
Unwanted situation

Pengo et al. Update of the guidelines for lupus anticoagulant detection. J Thromb Haemost 2009; 7: 1737-40

Do VKA interfere with LA-detection?

LA-assessment in LA-negative patients on high intensity VKA

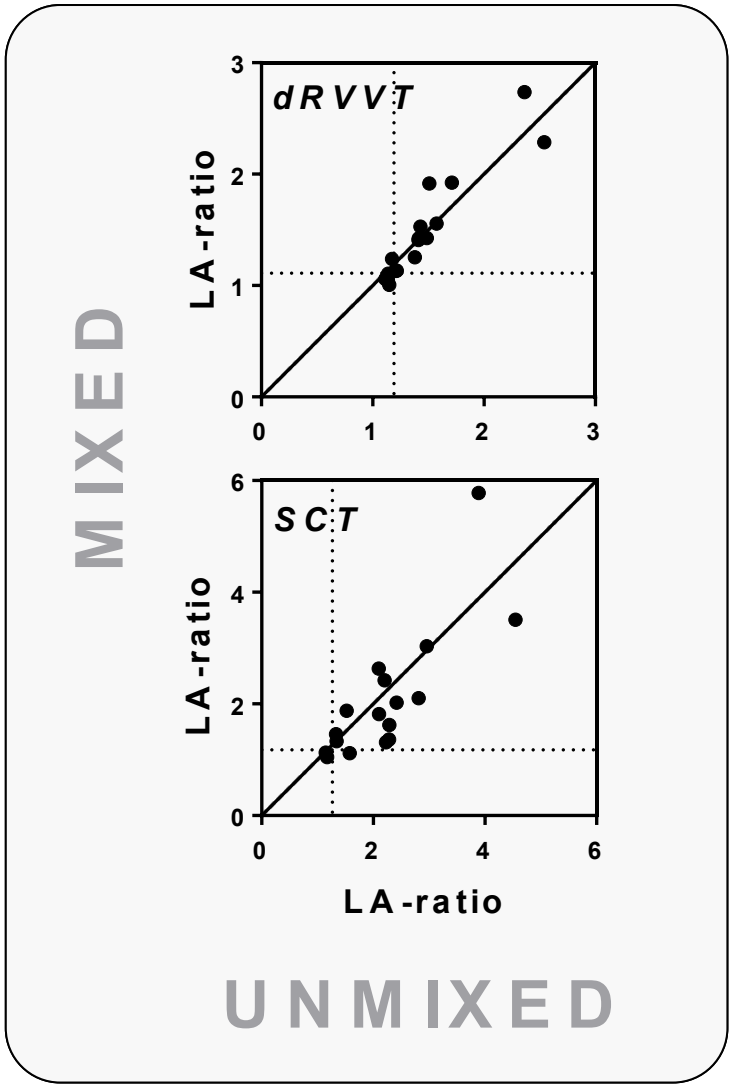




VKA do not cause false positive LA

False negative LA?

Performance of mixing tests in LA-positive patients



Effects of mixing on LA classification are small.

Two categories:

- ***Cofactor effect***: sample becomes (more) positive after mixing
- ***Dilution effect***: lower LA-ratio after mixing

Can be a problem when LA is weak

Pennings et al. Thromb Haemost 2014;112:736-42

Effect of mixing on LA assessment in 11 LA-positive patients with INR > 2.5

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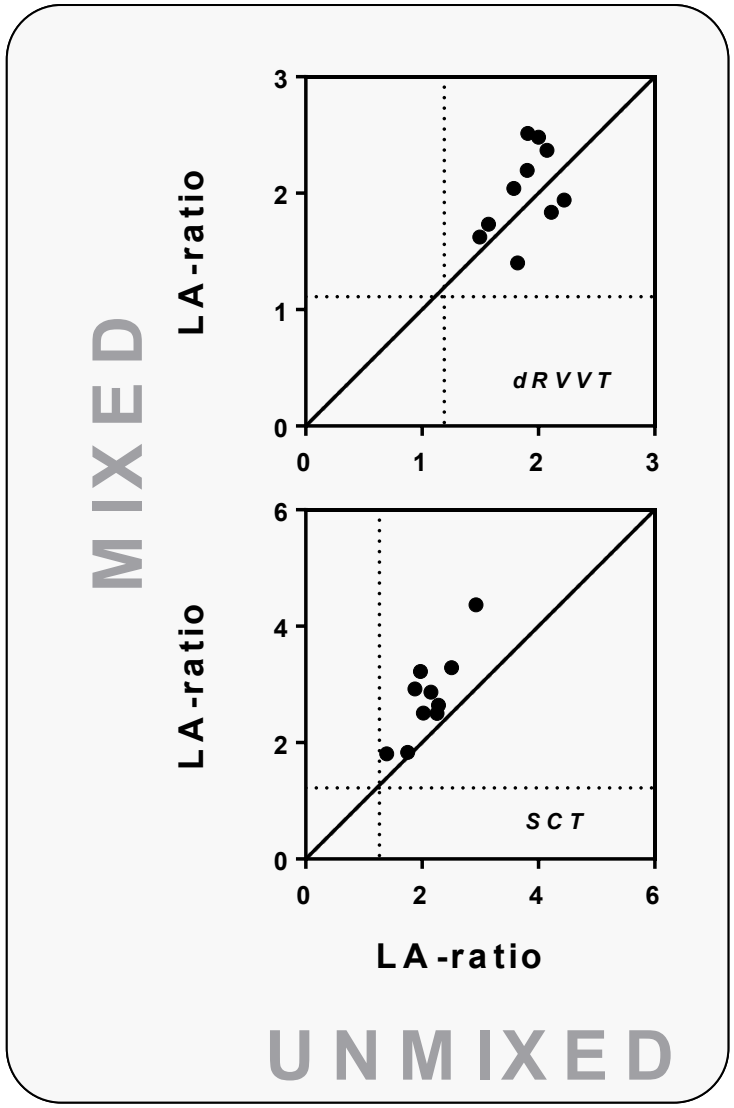

- *Mixing has no effect on dRVVT LA-ratio*
- *Mixing enhances strength of LA determined with SCT*

No misclassification of LA

Pennings et al. Thromb Haemost 2014; 112:736-42

Hemophilia A and FVIII inhibitors

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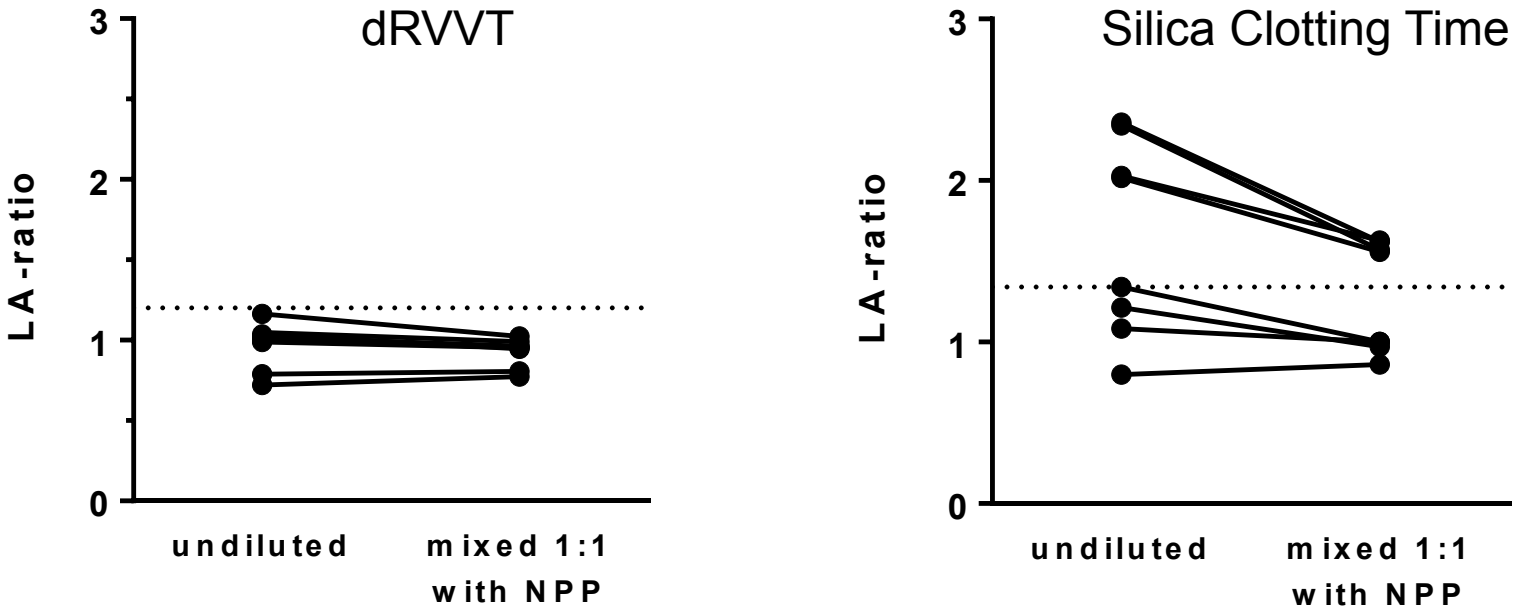
LA frequently observed in Hemophilia A

Blanco et al. Thromb Haemost. 1997, Tripodi et al. Clin Chem. 2005



Mixing test does not discriminate between FVIII inhibitors and true LA – use dRVVT instead

Mixing

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VKA do not cause false positive LA test results

Mixing does not influence dRVVT test results in patients with INR>2.5

Mixing leads to stronger LA using SCT reagents

No misclassification of LA positive samples with INR>2.5 using either dRVVT or SCT

VKA might lead to underestimation of LA, especially in weakly positive samples.

Mixing might lead to misclassification of weakly positive samples

Mixing might be useful in haemophilia A samples

LA can be reliably assessed in plasma with INR>2.5. Mixing tests are only necessary in rare cases

Antithrombotic treatment?

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- Platelet function inhibitors
  - No problem
- Heparin
  - Heparin neutralizer? No problem <0.8U.mL
- LMWH
  - No problem.
- Vitamin K antagonist
  - No problem, if doubts, mix 1:1 with normal plasma
- Direct Xa inhibitors
  - Taipan clotting time / Ecarin clotting time
- Direct thrombin inhibitors
  - No LA testing possible

Lupus anticoagulant
A pseudo biomarker

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Lupus anticoagulant might have the highest correlation with a risk of thrombosis or pregnancy morbidity, however, it teaches us nothing about the pathophysiology of the syndrome.

Prolongation of clotting assays is normally correlated with a bleeding tendency

How is that possible?

Lupus anticoagulant

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Why does the presence of a lupus anticoagulant not induce a bleeding tendency?

Strange observations

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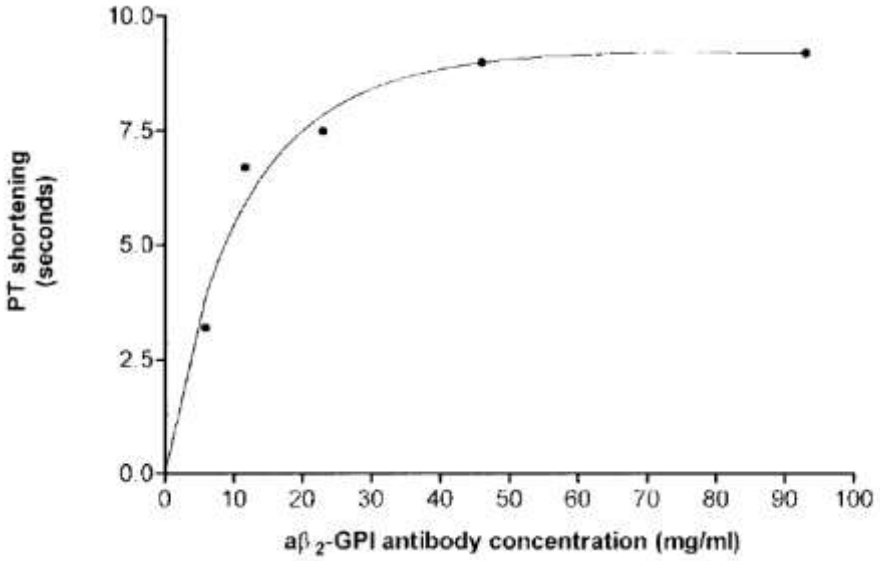
blood 1999 94: 3814-3819

Procoagulant Effect of Anti–β2-Glycoprotein I Antibodies With Lupus Anticoagulant Activity

V. Pengo, T. Brocco, A. Biasiolo, P. Rampazzo, P. Carraro and R. Zamarchi



- LA only expresses its anticoagulant effect when the incubation takes place in the absence of Ca^{2+}
- In the presence of Ca^{2+}, purified patient antibodies prolong the PT when added to normal plasma.

Strange observations

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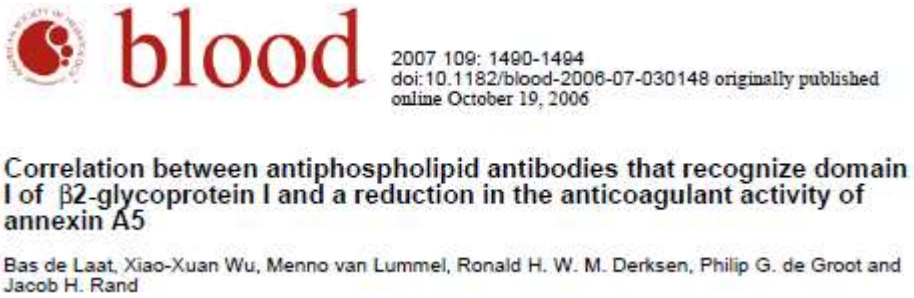

blood

2007 109: 1490-1494
doi:10.1182/blood-2006-07-030148 originally published online October 19, 2006

Correlation between antiphospholipid antibodies that recognize domain I of β2-glycoprotein I and a reduction in the anticoagulant activity of annexin A5

Bas de Laat, Xiao-Xuan Wu, Menno van Lummel, Ronald H. W. M. Derksen, Philip G. de Groot and Jacob H. Rand

Domain I antibodies ↔ β_2GPI-dependent LA ↔ annexin V resistance ↔ shortening PT

The shortening of a PT identifies patients with domain I antibodies.

Binding of β_2GPI to anionic phospholipids

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Biochemistry **1996,** *35,* 13833−13842

Role of Divalency in the High-Affinity Binding of Anticardiolipin Antibody−β_2-Glycoprotein I Complexes to Lipid Membranes

George M. Willems,*,‡ Marie P. Janssen,‡ Maurice M. A. L. Pelsers,‡ Paul Comfurius,‡ Monica Galli,§ Robert F. A. Zwaal,‡ and Edouard M. Bevers‡

Table 2: Effect of NaCl and $CaCl_2$ Concentration on the Binding Affinity of β_2GPI

membrane composition	[NaCl] (mM)	[$CaCl_2$] (mM)	K_d (μM)	Γ_{max} ($\mu g \cdot cm^{-2}$)
PS/PC (20/80)	60	0	0.032	0.18
PS/PC (20/80)	120	0	0.17	0.17
PS/PC (20/80)	120	1	0.63	0.16
PS/PC (20/80)	120	3	3.9	0.18
PS/PC (10/90)	120	0	3.7	0.16
PS/PC (10/90)	120	3	14.0	0.17[a]

β_2GPI hardly binds to anionic phospholipids under physiological Ca^{2+} concentrations

Lupus anticoagulant

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The activity of anti-phospholipid antibodies on in-vitro coagulation are two-fold:

At low Ca^{2+} concentration the antibodies can compete with clotting factors for the available anionic phospholipids.

At physiological Ca^{2+} concentrations there seems to be a phospholipid independent stimulation of fibrin formation.

lupus anticoagulant is an in-vitro artefact

If a patient with lupus anticoagulant bleeds, check prothrombin levels

confirmation

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The confirmation assay is the essential step for the detection of a lupus anticoagulant.

- Role of β_2-Glycoprotein I.
- Effect of composition and amount of phospholipids.
- Alternative assays
  - Thrombin generation
  - Purified clotting factors

Lupus anticoagulant
confirmation = competition

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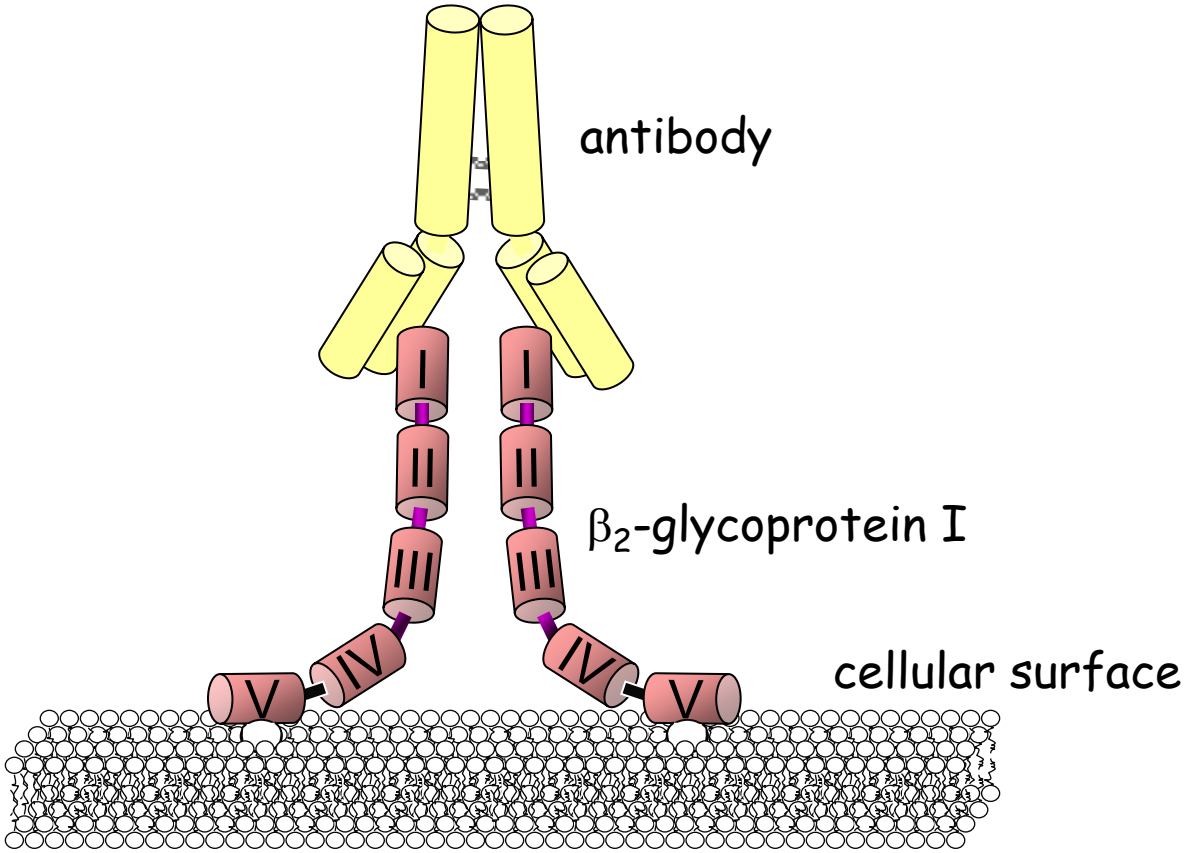

Dimerisation of β_2-glycoprotein I increases its affinity for anionic phospholipids → competition with clotting factors

β_2-Glycoprotein I

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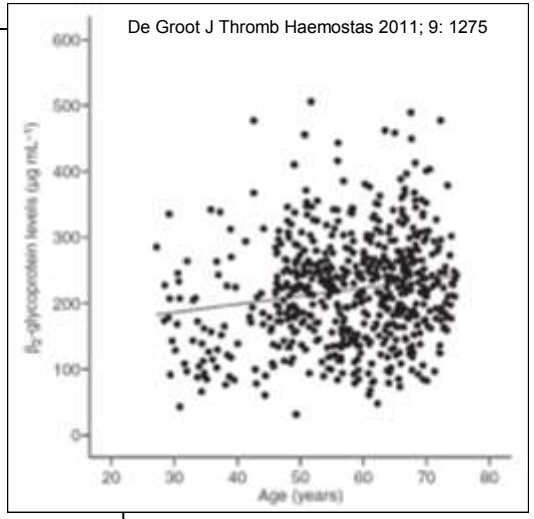
- phospholipid binding protein
- complement control protein family
- 326 amino acids in 5 domains
- strong evolutionary conservation
- plasma levels increase with age (figure)
- function largely unknown
  - in absence: no clinical phenotype in man
- probable role in innate immunity
  - scavenges lipopolysaccharide
  - clears microparticles from the circulation
- function is conformation-dependent



β_2-Glycoprotein I: two conformations

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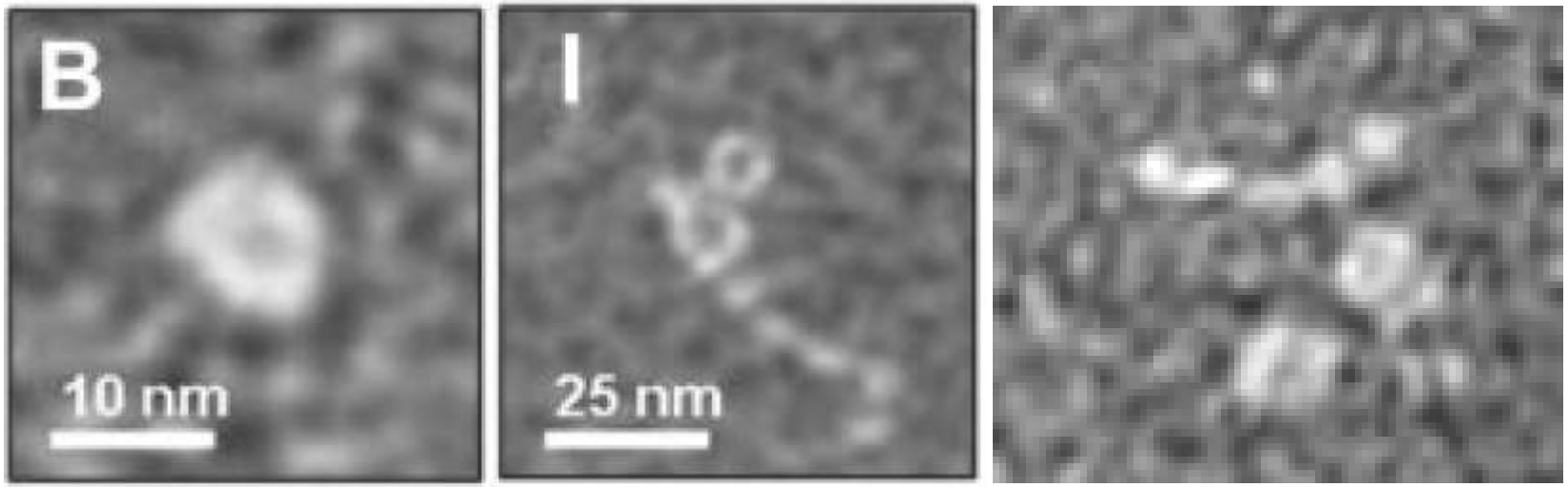
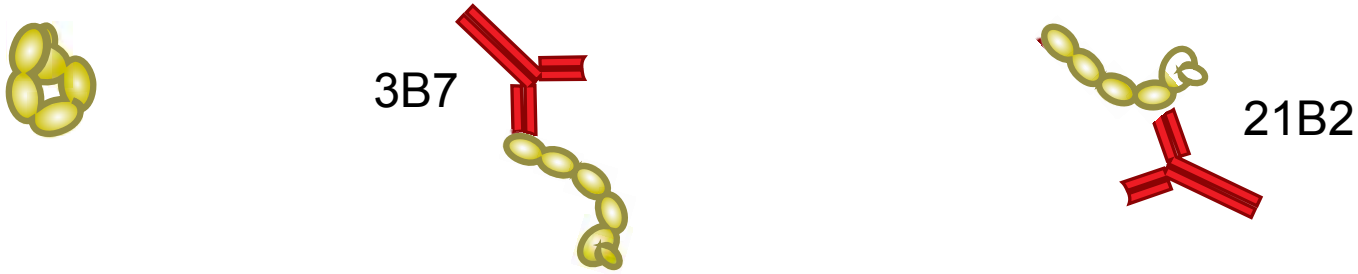
Plasma β_2GPI

+ antibodies

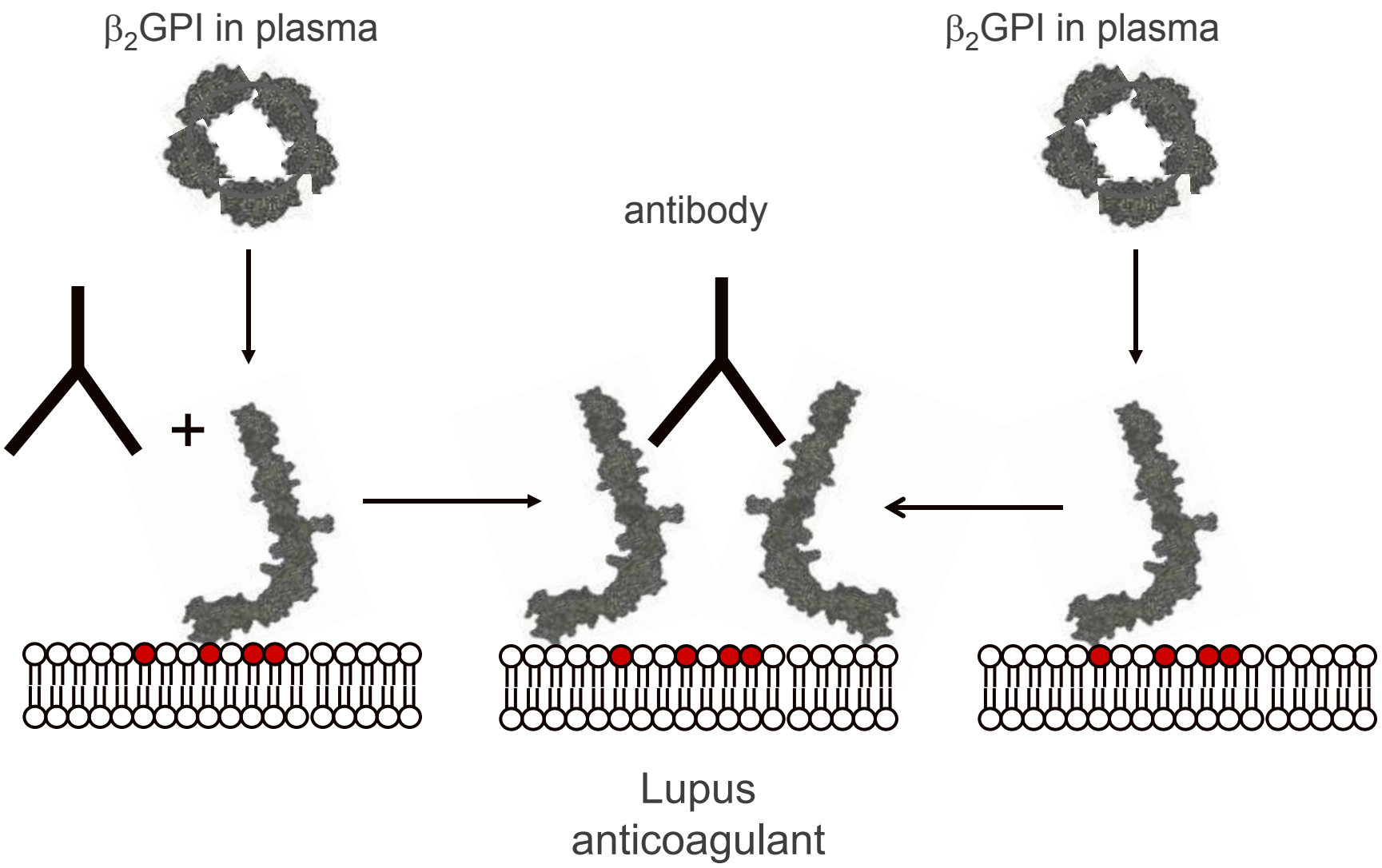




Monoclonal antibodies with specificity for different domains of β_2-glycoprotein I can induce a major conformational change.

Agar et al. Blood 2010

Mode of action



Dimerisation or conformational change?

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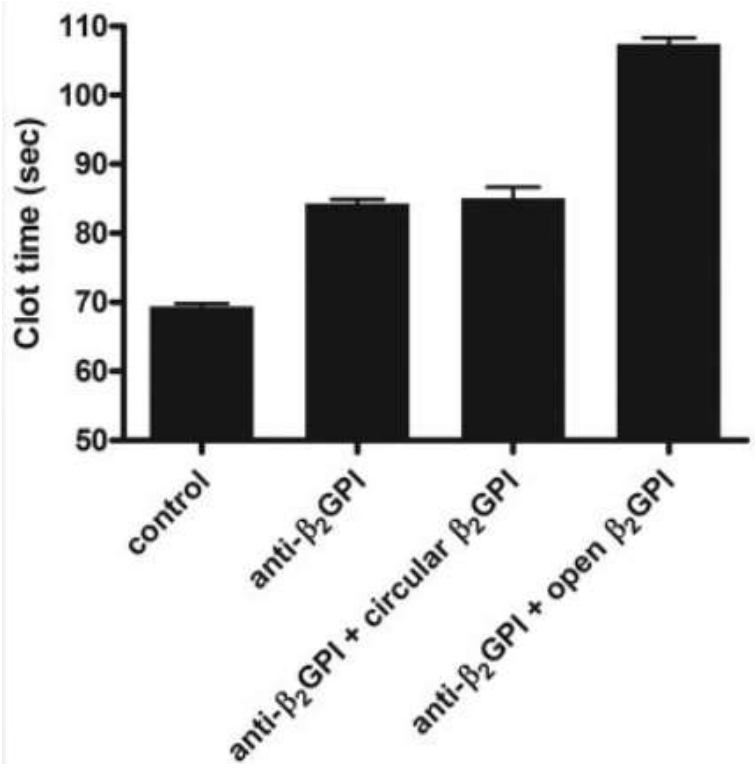

Both opening of β_2-glycoprotein I and dimerisation by antibodies is important

confirmation

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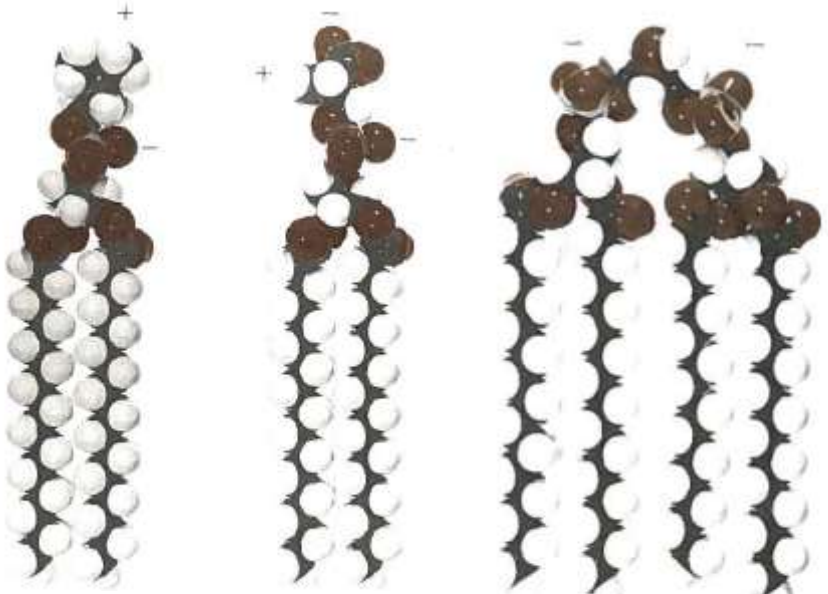
The phospholipids within the confirmation reagents are undefined.

Could we improve the assay by using defined phospholipid preparations?

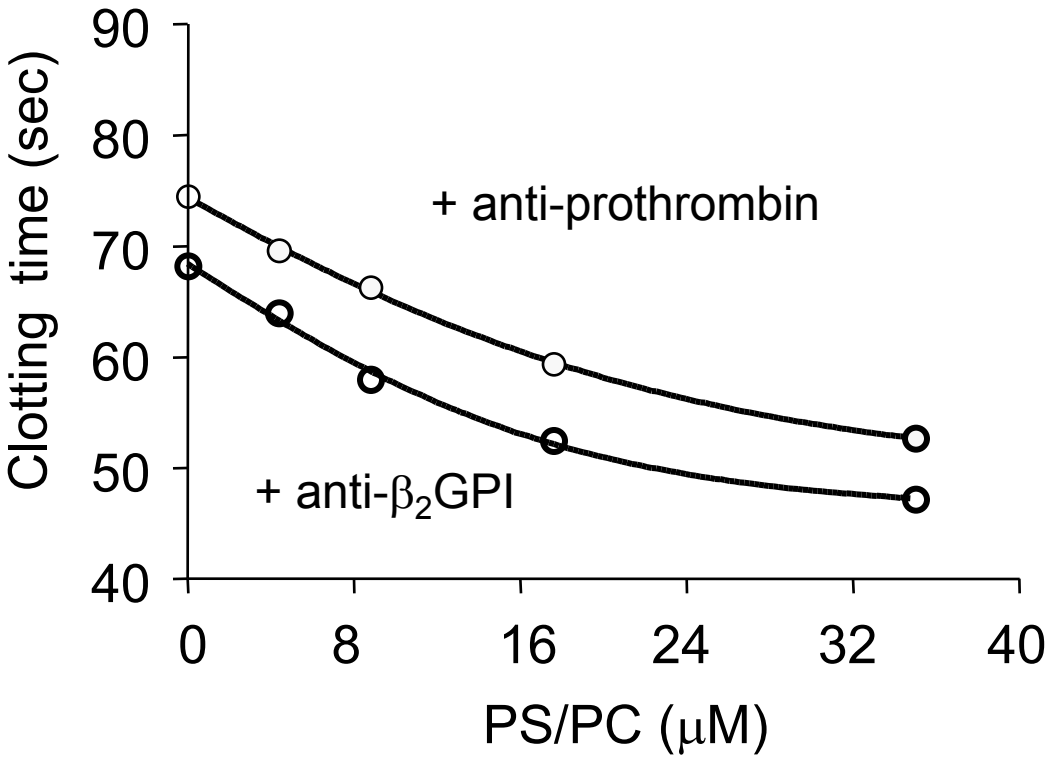


Phosphatidyl choline

Phosphatidyl serine

cardiolipin

Effect of different phospholipids



Effect of different phospholipids

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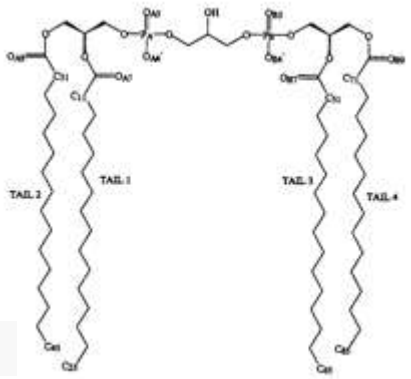
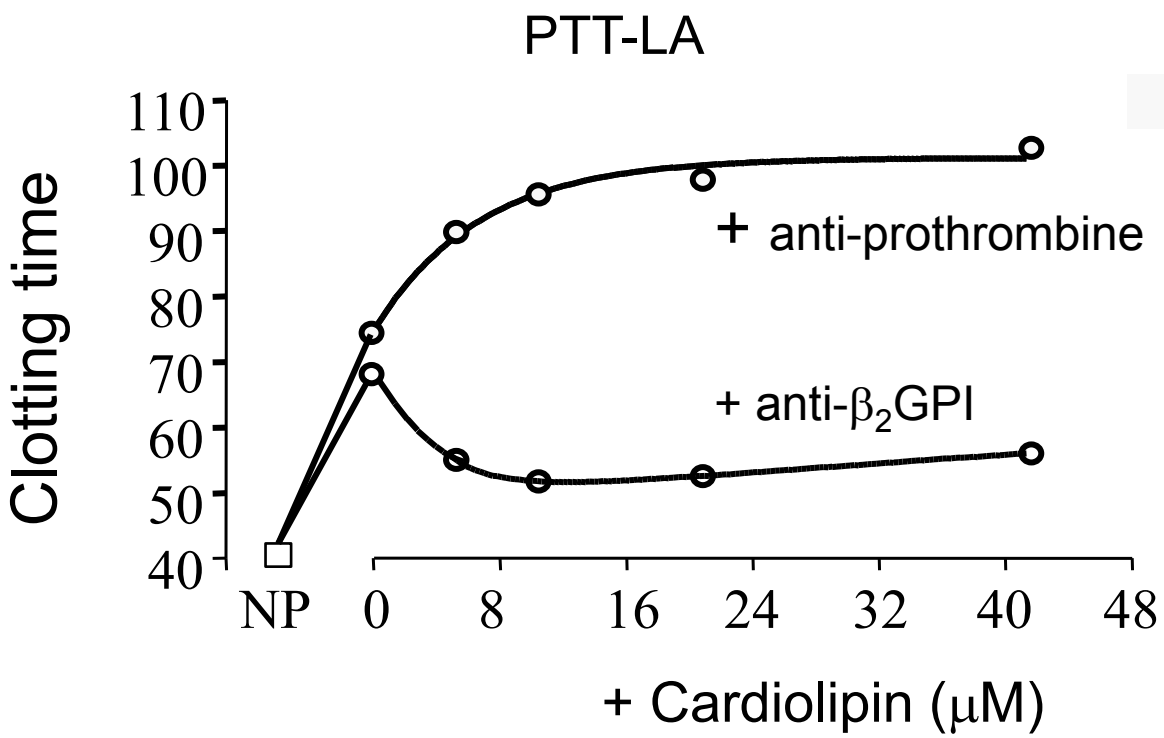
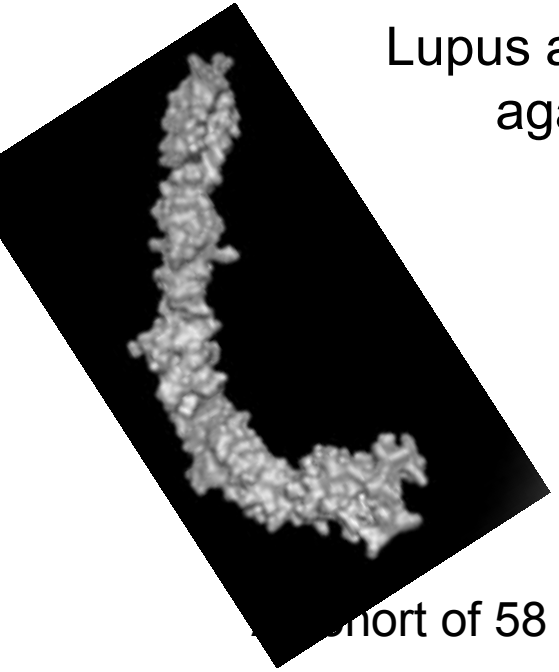


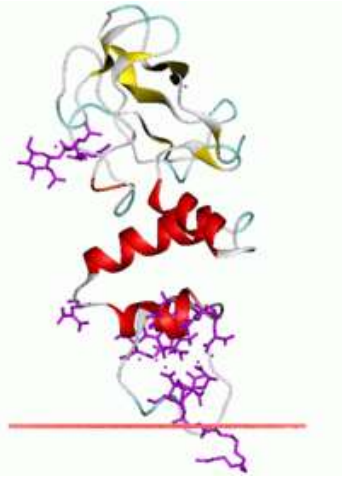


Simmelink et al. JTH 2003; 1: 740-747

Lupus anticoagulant



Lupus anticoagulant can be caused by antibodies against β_2-glycoprotein I or prothrombin.



A cohort of 58 patients positive for Lupus anticoagulant.

25 patients had a β_2-glycoprotein I dependent LA of which 23 had a history of thrombosis.
33 patients had a prothrombin dependent LA of which 13 had a history of thrombosis.

De Laat et al.2004; 104: 3598-3602

confirmation

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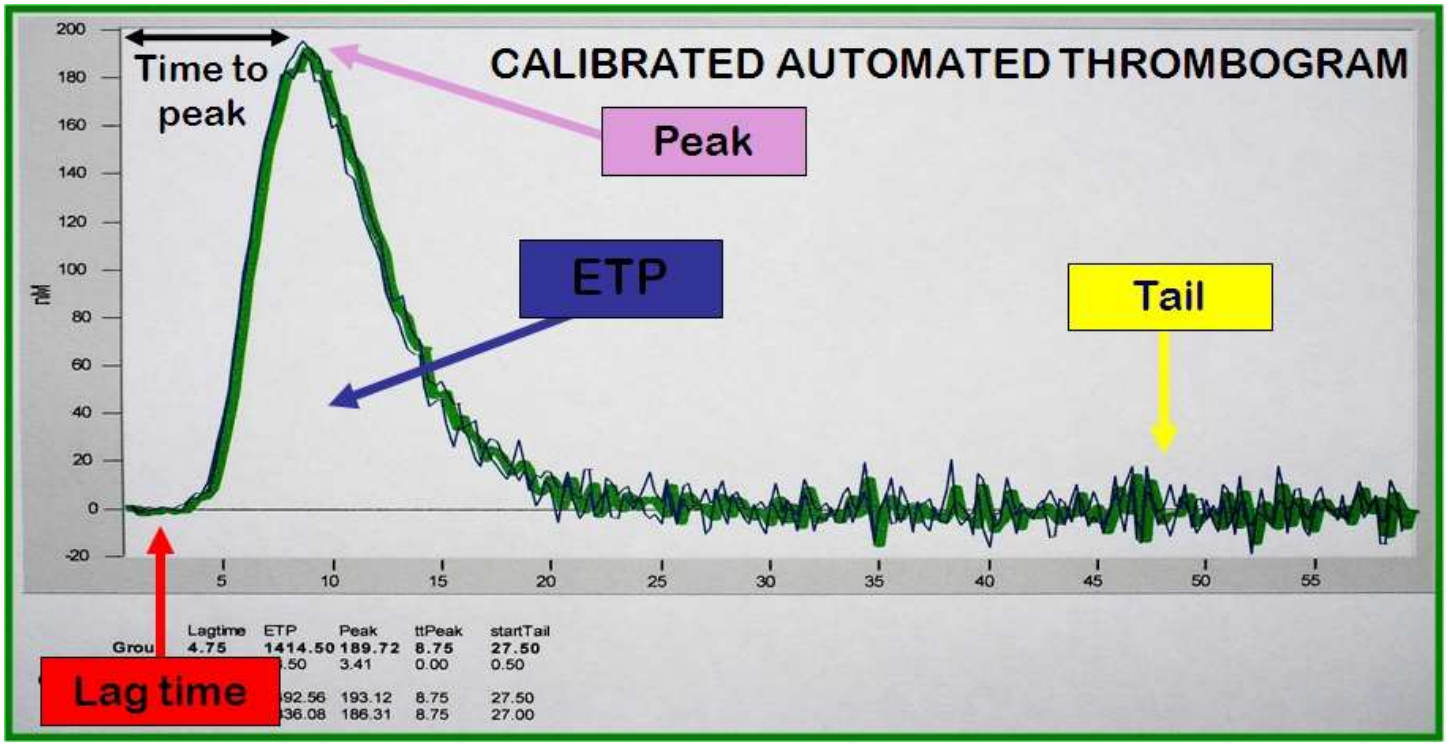
Conclusion:

- β_2-Glycoprotein I dependent LA correlates better with APS-related clinical manifestations that a prothrombin-dependent LA

- Phospholipid composition of the confirm reagent has a significant effect on the results of the assay

- The phospholipid reagent is not robust enough to improve the LA assay

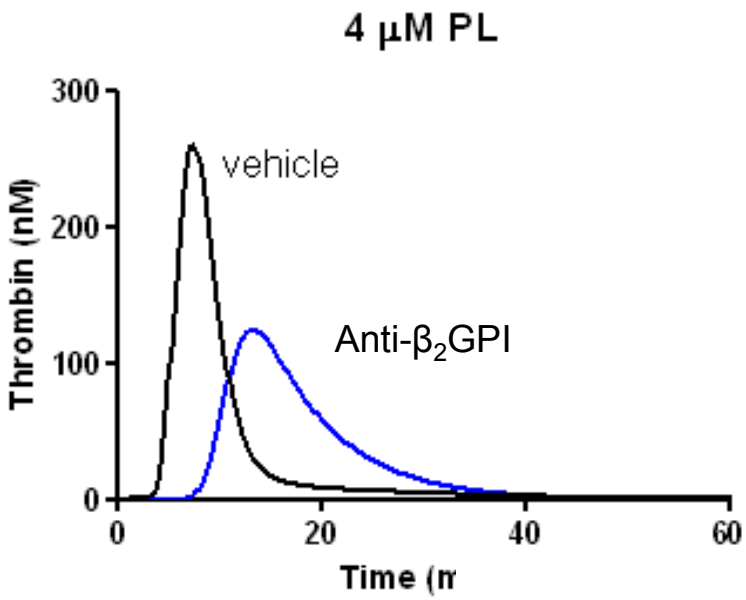
Thrombin generation

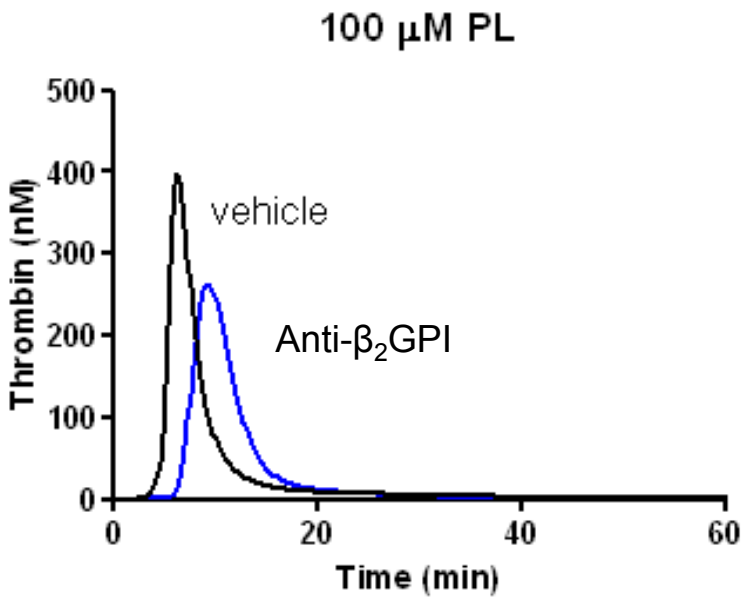


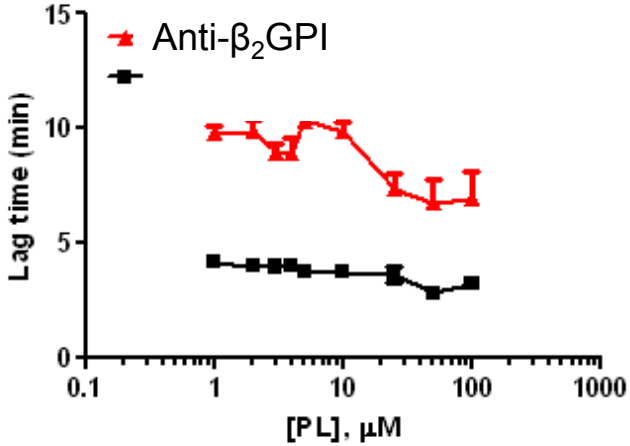
Plasma clots when about 1% of the prothrombin is converted to thrombin

The lag-time represent fibrin formation → Lag-time represents LA

Thrombin generation







Provisional conclusion

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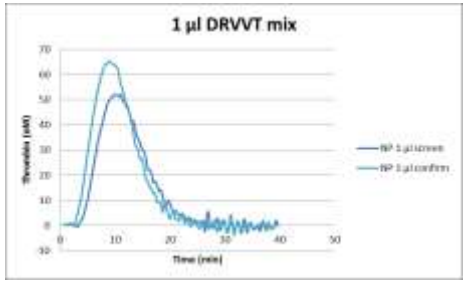
- A lupus anticoagulant measured with thrombin generation is not neutralized by purified anionic phospholipids.

- When thrombin generation is measured with commercial dRVVT reagents, lupus anticoagulant is neutralized



The effects of lupus anticoagulant could not be explained fully by assuming that the antibodies complete with clotting factors for anionic phospholipids.

➢ What is the mechanism by which coagulation is inhibited by these antibodies?

Enzyme kinetics

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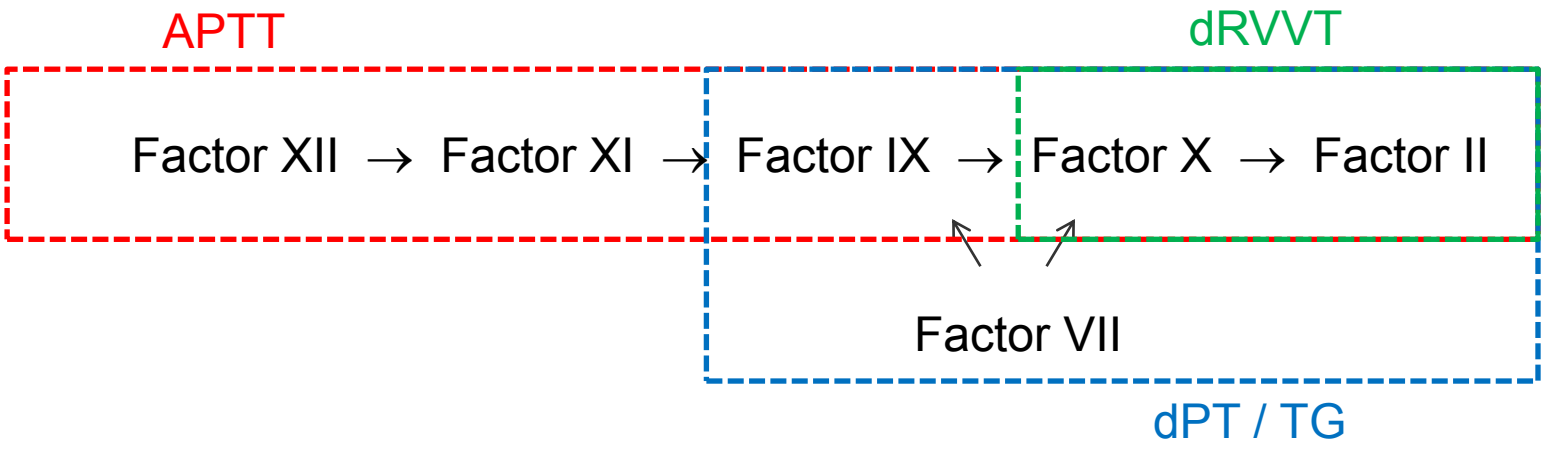
Vmax: mainly infuenced by co-factor activity (FVa and FVIIIa)

Km: mainly effected by surface (e.g. phospholipids)

Nesheim *et al.* 1979, Rosing *et al.* 1980

Coagulation cascade



Can we mimic the effects of anti-β_2-glycoprotein I antibodies with assays using purified clotting factors?

Tenase complex	Factors IXa, VIIIa & X +/- β_2GPI + antibody
Prothrombinse complex	Factors Xa, Va & II +/- β_2GPI + antibody

Tenase complex + antibody

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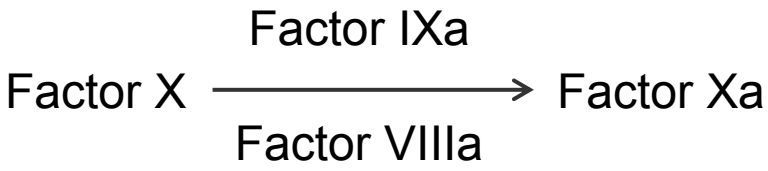

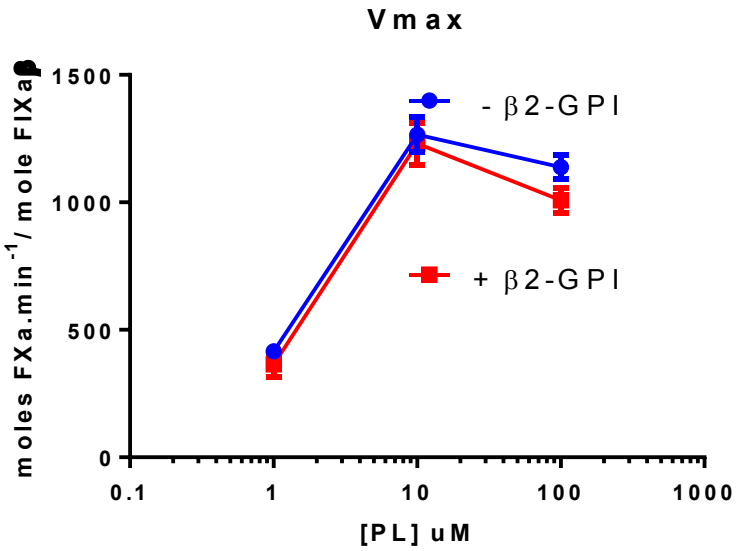

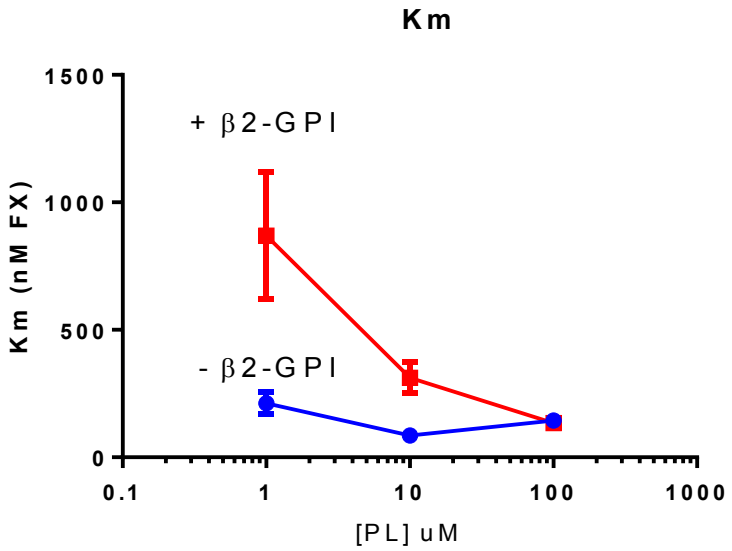

"Cofactor"

"Phospholipids"

The effects of the auto-antibodies on tenase complex can be explained completely by competition between β_2GPI-antibody complexes and clotting factors for anionic phospholipids

Prothrombinase complex + antibody

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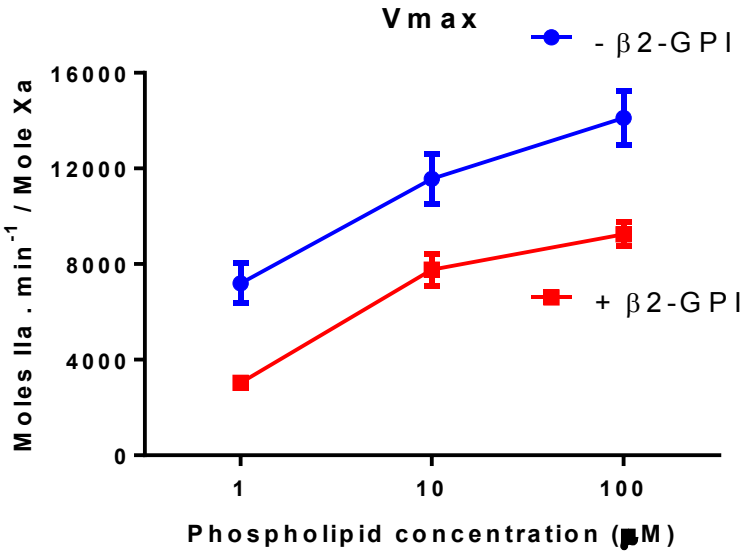
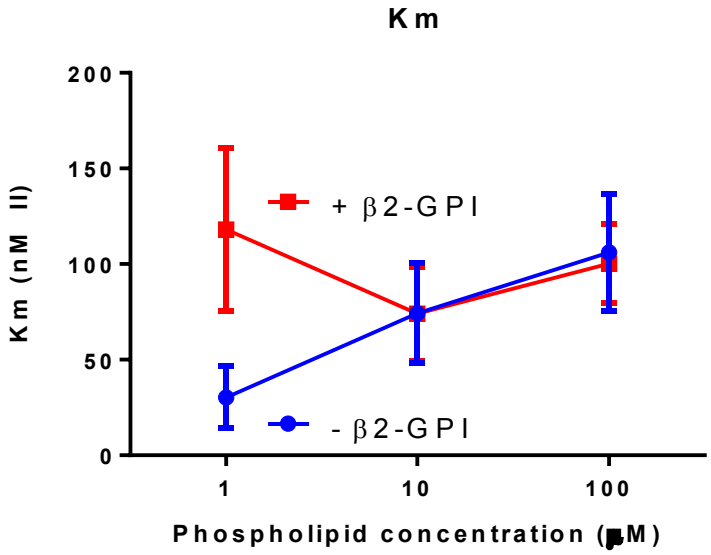
Factor II —(Factor Xa / Factor Va)→ factor IIa (thrombin)



"Cofactor"



"Phospholipids"

The effects of the auto-antibodies on prothrombinase complex can be explained only partly by competition between β_2GPI-antibody complexes and clotting factors for anionic phospholipids

Our challenge

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A direct effect of auto-antibodies / β_2-Glycoprotein I has been described for:

- Factor XII — regulation of contact activation
- Factor XI — regulation of activation by thrombin
- Thrombin — inhibition by heparin cofactor II
- Factor V — interference with inactivation
- TFPI — suppress TFPI activity
- Protein S — decreased activity
- Protein Z — inhibition of factor Xa

- Protein C — inhibition of activity

A personal hypothesis

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If we understand lupus anticoagulant, we understand the pathophysiology of the anti-phospholipid syndrome

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