

New developments in the classification of the APS

PL Meroni

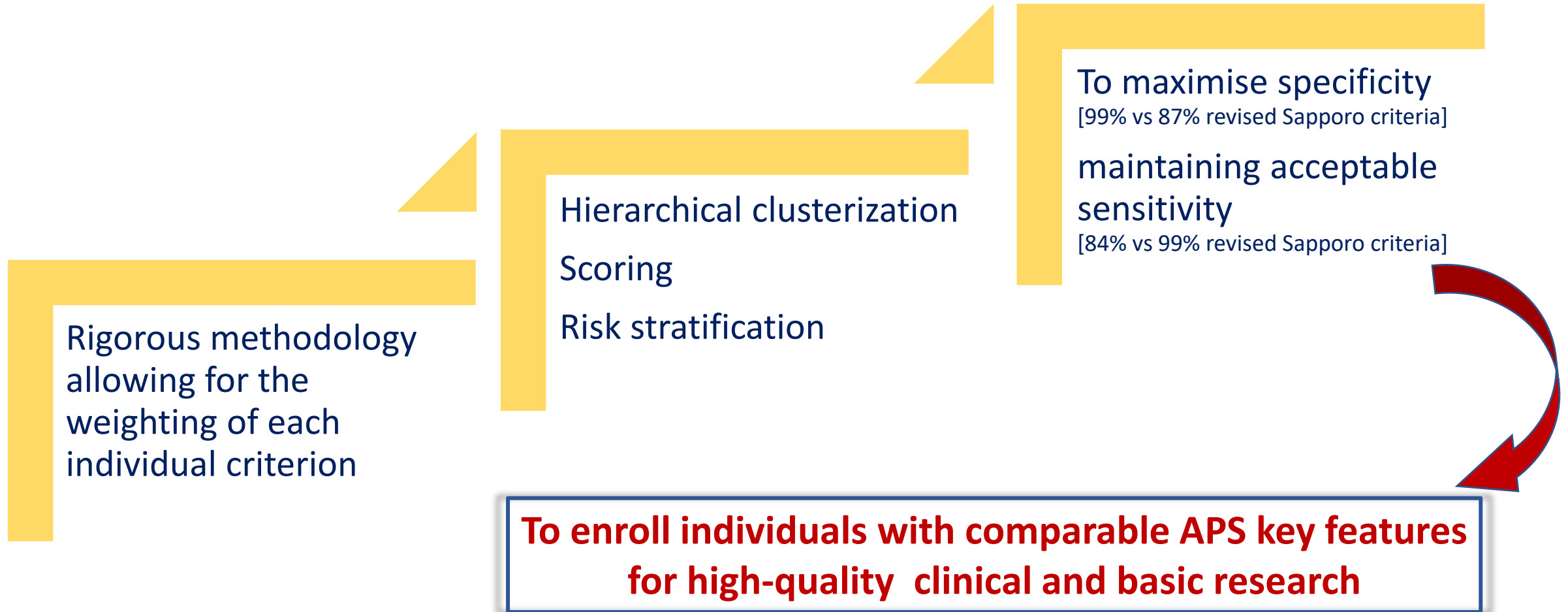
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Outline of presentation

- New classification criteria for APS
- Lab criteria issues:
 - Harmonization of criteria
- The possible algorithms in the clinical setting

Clinical domains and criteria	Weight		Weight
D1. Macrovascular (Venous Thromboembolism [VTE])		D2. Macrovascular (Arterial Thrombosis [AT])	
VTE with a high-risk VTE profile ^(c)	1	AT with a high-risk CVD profile ^(c)	2
VTE without a high-risk VTE profile ^(c)	3	AT without a high-risk CVD profile ^(c)	4
D3. Microvascular		D4. Obstetric	
Suspected (one or more of the following)	2	≥3 Consecutive pre-fetal (<10w) and/or early fetal (10w 0d -15w 6d) deaths	1
Livedo racemosa (exam)			
Livedoid vasculopathy lesions (exam)			
Acute/chronic aPL-nephropathy (exam or lab)		Fetal death (16w 0d – 33w 6d) in the absence of pre-eclampsia (PEC) with severe features or placental insufficiency (PI) with severe features	1
Pulmonary hemorrhage (symptoms and imaging)			
Established (one of more of the following)	5	PEC with severe features (<34w 0d) <u>or</u> PI with severe features (<34w 0d) with/without fetal death	3
Livedoid vasculopathy (pathology ^(d))		PEC with severe features (<34w 0d) <u>and</u> PI with severe features (<34w 0d) with/without fetal death	4
Acute/chronic aPL-nephropathy (pathology ^(d))			
Pulmonary hemorrhage (BAL or pathology ^(d))			
Myocardial disease (imaging or pathology)			
Adrenal hemorrhage (imaging or pathology)			
D5. Cardiac Valve		D6. Hematology	
Thickening	2	Thrombocytopenia (lowest 20-130x10 ⁹ /L)	2
Vegetation	4		

2023 APS classification criteria: goals



APS vasculopathy

Classical APS

Medium-Large vessels

Microcirculation Involvement

(APS nephropathy, skin, myocardiopathy, CNS etc)

CAPS

TTP, HUS, HELLP

Microcirculation

Laboratory (aPL) domains and criteria ³	Weight		Weight
D7. aPL test by coagulation-based functional assay (lupus anticoagulant test [LAC])		D8. aPL test by solid phase assay (anti-cardiolipin antibody [aCL] ELISA and/or anti-β_2-glycoprotein-I antibody [aβ_2GPI] ELISA [persistent])	
Positive LAC (single – one time)	1	Moderate-high positive (IgM) (aCL and/or a β_2 GPI)	1
Positive LAC (persistent)	5	Moderate positive (IgG) (aCL and/or a β_2 GPI)	4
		High positive (IgG) (aCL <u>or</u> a β_2 GPI)	5
		High positive (IgG) (aCL <u>and</u> a β_2 GPI)	7

- aPL assay is an example of a laboratory test that moved from dichotomous to quantitative/semiquantitative results consistent with the idea that aPL titer offers more diagnostic/prognostic information.
- Although the new laboratory criteria have been validated for classification and not for APS diagnosis, the weight given to the individual criteria can also provide an idea of their diagnostic value.

Laboratory classification criteria D8: aPL test by solid phase assay

Critical points

➤ aCL and a β_2 GPI IgG/IgM moderate/high levels

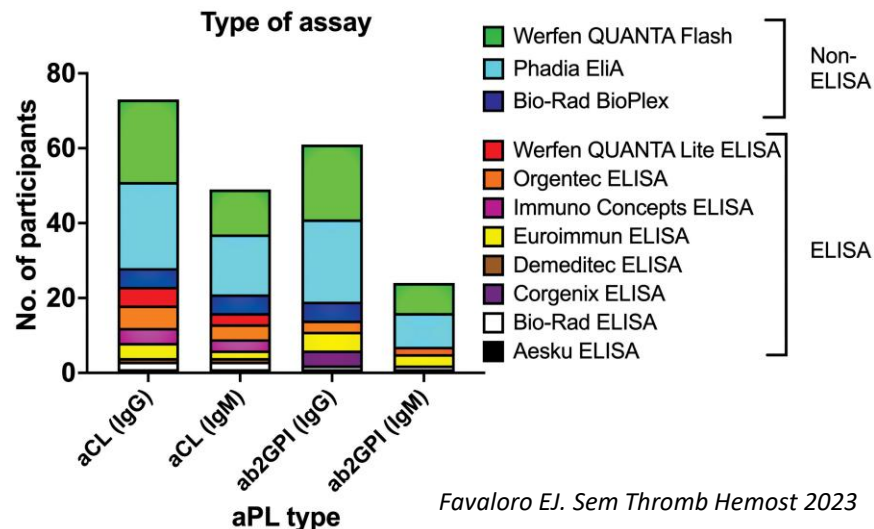
➤ Fixed thresholds

- moderate 40-79 U
- high ≥ 80 U

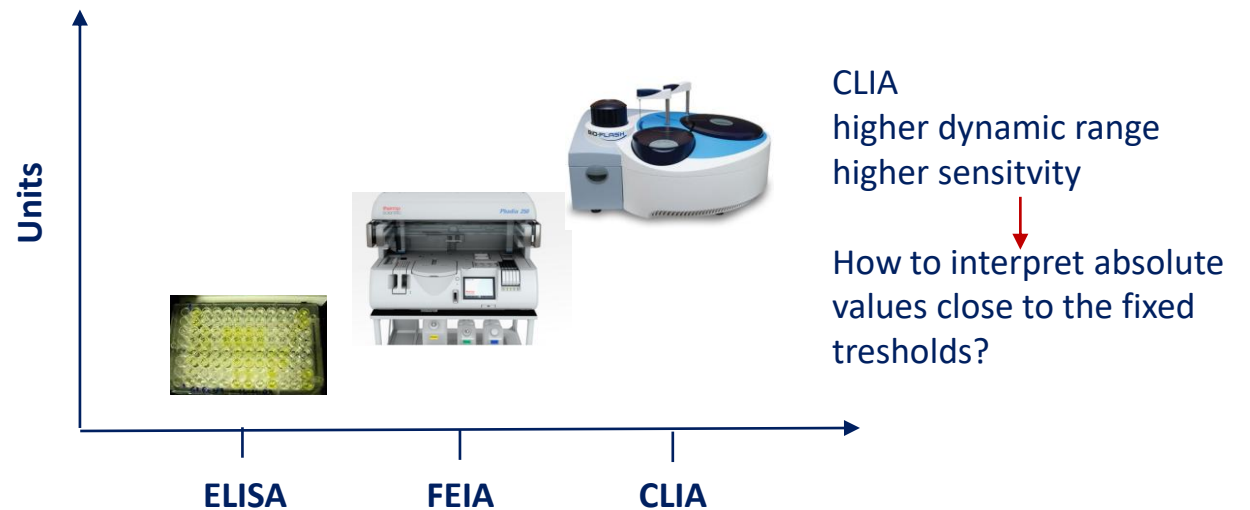
standardized ELISA
not other testing modalities

Issues

- Highly increased use of non-ELISA assays



- aCL/a β_2 GPI levels are not equivalent between assays



Entry Criteria¹

At least one documented clinical criterion listed below (domains 1-6)

plus

A positive antiphospholipid antibody (aPL) test
(a lupus anticoagulant test, or moderate-to-high titers of anticardiolipin or anti- β_2 -glycoprotein-I antibodies [IgG or IgM])
within three years* of the clinical criterion



If absent, do not attempt to classify as APS - If present, apply additive criteria



TOTAL SCORE

Classify as Antiphospholipid Syndrome for research purposes if there are
at least 3 points from clinical domains AND at least 3 points from laboratory domains

APS Classification versus Diagnosis

- **Classification criteria** are intended for use in research settings. Ensuring a uniform study population in terms of the condition under investigation for the validity and reliability of the research findings.
- **Diagnosis**, *in contrast*, is a healthcare provider's clinical decision to identify a specific disease or condition in a patient. In the clinical context, diagnosing APS should involve a comprehensive assessment of the patient.
- *Although classification criteria can inform the diagnostic process, they should not replace it. However, the better-defined clinical manifestations are helpful for diagnosis.*

aCL/aβ₂GPI harmonization: how to reach the goal?

Aim

To make aCL/aβ₂GPI results interpretation comparable between different assays

Method

Classify positive results into the semiquantitative categories low-medium-high by determining method-specific

Semiquantitative thresholds

- vary between platforms
- are different for aCL and aβ₂GPI
- depend on the isotype
- differ for thrombotic APS and obstetric APS
- differ for monoclonal and polyclonal reference materials

clinical significance

Reference materials

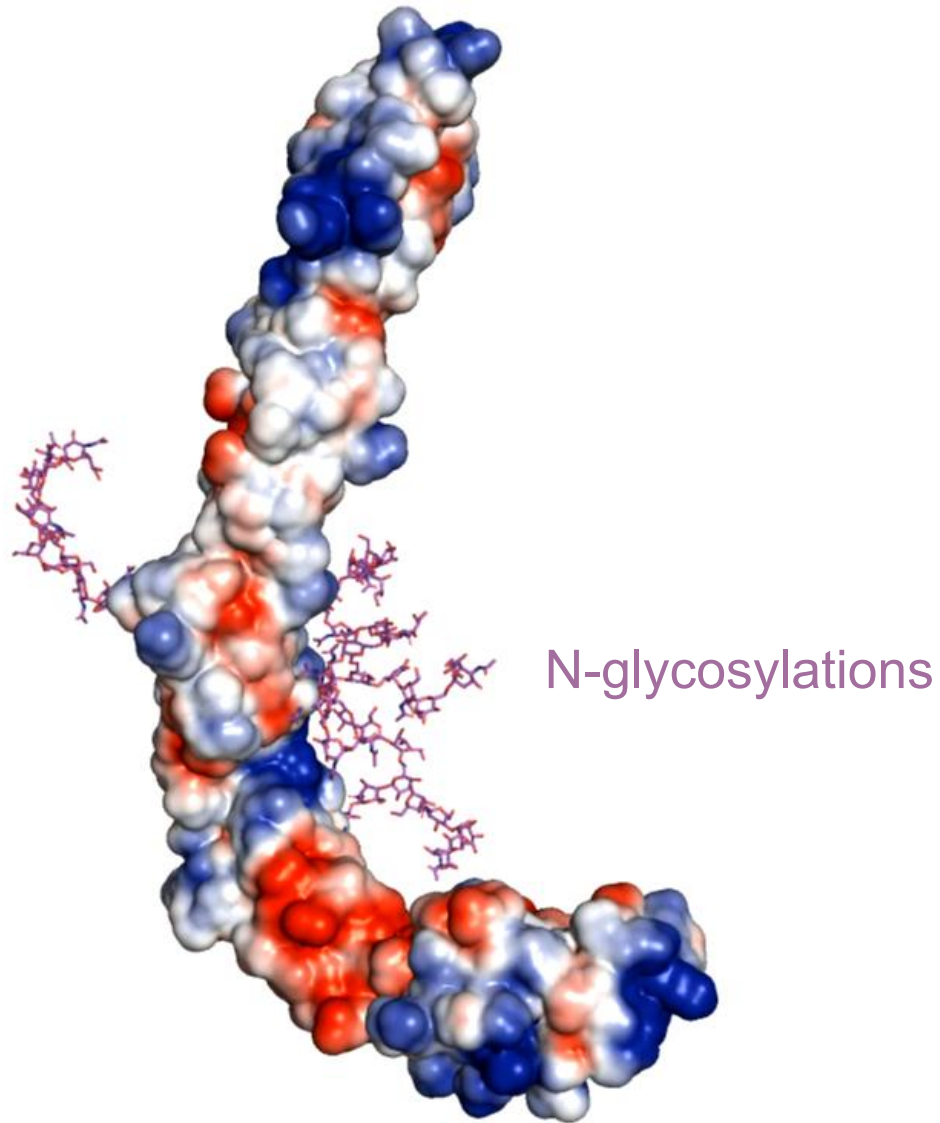
- | | |
|---|--|
| <ul style="list-style-type: none">• Monoclonal reference materials (e.g. Sapporo standards HCAL/EY2C9)• Polyclonal reference materials (e.g. Harris standards) | } Serial dilutions, handled as patient samples
Linear regression to determine semiquantitative thresholds |
|---|--|

aCL/a β 2GPI harmonization: caveats

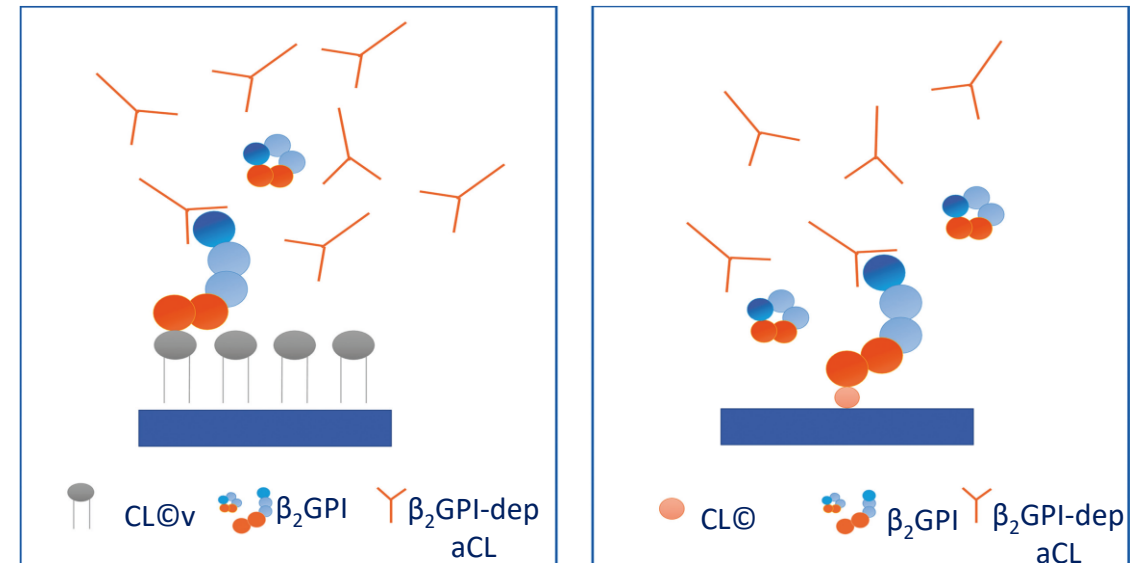
Reference materials

- Monoclonal anti- β 2GPI antibody
 - HCA
 - Polyclonal anti- β 2GPI antibody
- To improve harmonization of aCL/a β 2GPI results interpretation between ELISA and non-ELISA platforms*
- ✓ an international collaborative effort between Antiphospholipid Syndrome Alliance for Clinical Trials and International Networking (APS ACTION) and the ISTH Scientific and Standardization Committee Subcommittee on LA/aPL is ongoing to evaluate different approaches and include larger study cohorts
 - ✓ the use of internationally validated reference materials could provide added value
- error the
ents'

Structure of β_2 -glycoprotein I

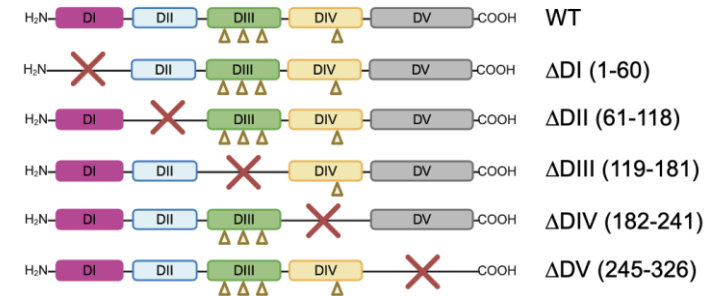
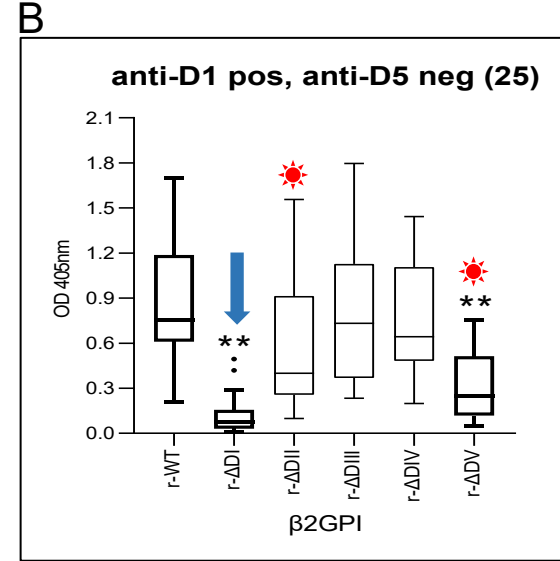
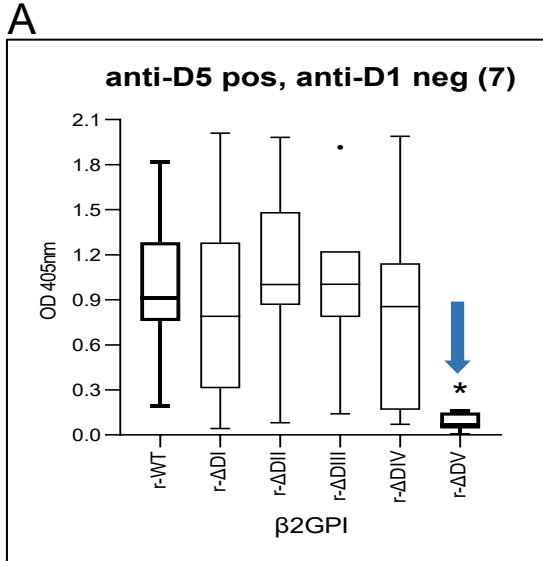


aCL and a β_2 GPI detection by ELISA
 β_2 GPI is the assay key target antigen



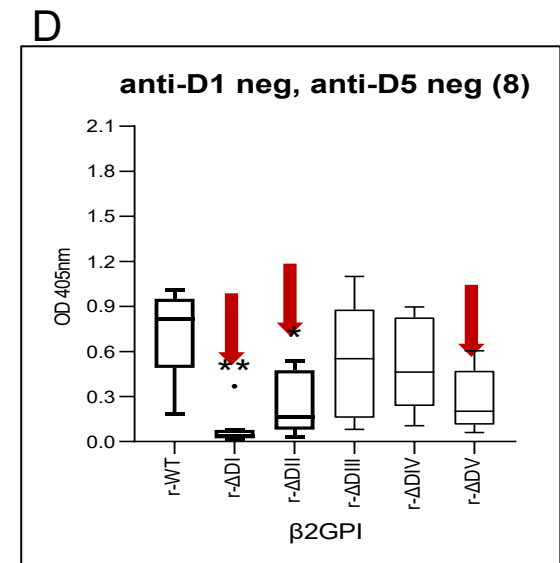
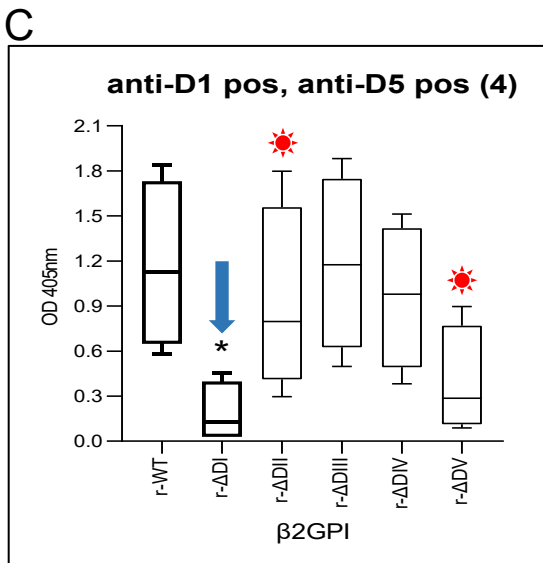
Positive charge
Negative charge

Beyond the 2023 APS lab classification criteria: the complexity of β 2GPI-dependent serology



Anti-D5 monospecific samples lost their reactivity towards r-ΔDV almost completely, without displaying any dependency on D1 (A)

A statistically significant D1-dependent reduction of reactivity was evidenced in anti-D1 positive sera (B,C)



Anti-D1 pos samples displayed a considerable reduction of their binding to r-ΔDV and also showed a partially reduced binding to r-ΔII

APS patients showed a decreased reactivity against r-ΔII higher than aPL carriers

Anti-D1/D5 double negative samples displayed a significant decrease of reactivity against r-ΔI and r-ΔV, together with a decreased binding to r-ΔII (D)

Subjects not fulfilling the APS classification criteria displayed a higher D5-dependency as compared to APS patients

Claudia Grossi*, Liesbet Deprez, Caterina Bodio, Maria Orietta Borghi, Suresh Kumar, Nicola Pozzi, Paolo Macor, Silvia Piantoni, Angela Tincani, Massimo Radin, Savino Sciascia, Gustavo Martos, Evanthia Monogioudi, Ingrid Zegers, Joanna Sheldon, Rohan Willis and Pier Luigi Meroni

Antiphospholipid IgG Certified Reference Material ERM[®]-DA477/IFCC: a tool for aPL harmonization?

Objectives: The Certified Reference Material (CRM) ERM[®]-DA477/IFCC is a new polyclonal IgG anti-beta2-glycoprotein I (anti- β 2GPI) material for the harmonization of the laboratory diagnosis of antiphospholipid syndrome (APS). We evaluated CRM's ability to represent the heterogeneity of APS patient anti- β 2GPI antibodies and to calibrate IgG anti- β 2GPI methods.

Background:

Polyclonal a β 2GPI pooled patient serum sample standard

[Willis R. et al. Lupus 2014]

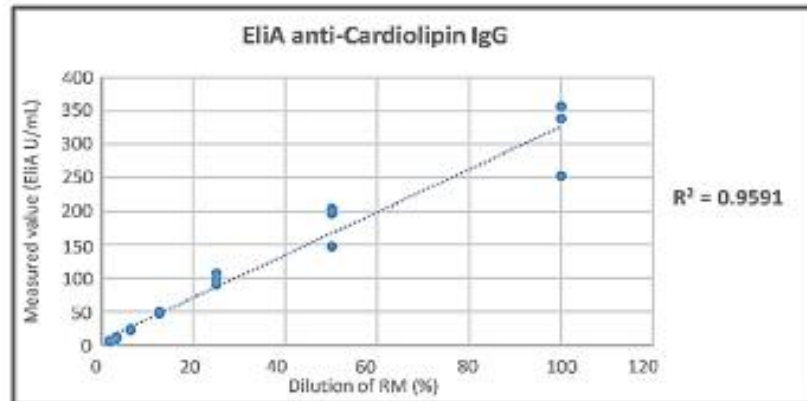
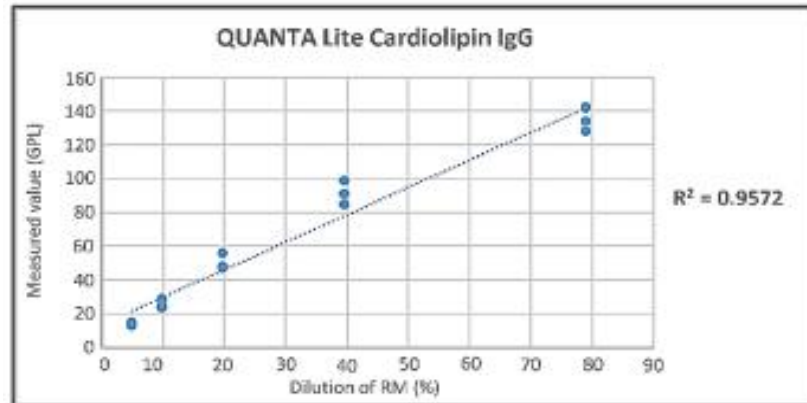
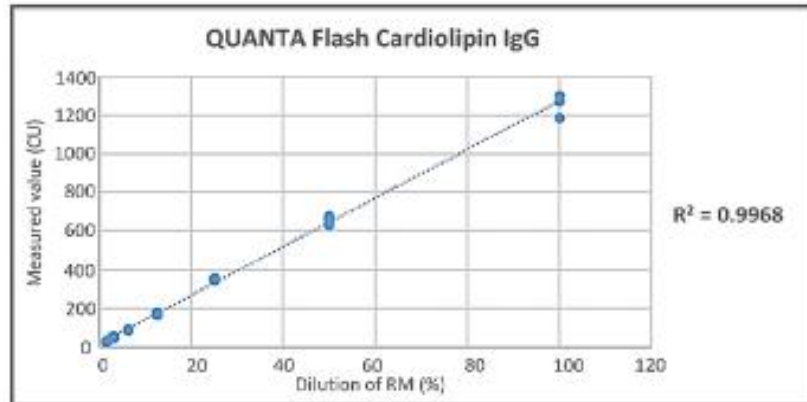
Assigned arbitrary value in International Units (IU)

[Monogioudi E. et al. Luxembourg: EUR 31090 EN, Publications Office of the European Union; 2022]

Stable, homogeneous and commutable between different ELISA

[Monogioudi E. et al. Clin Chem Lab Med. 2020]

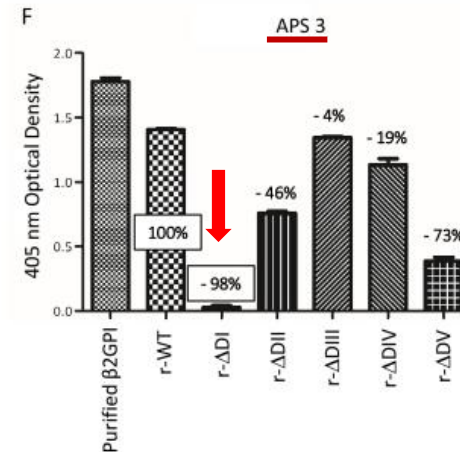
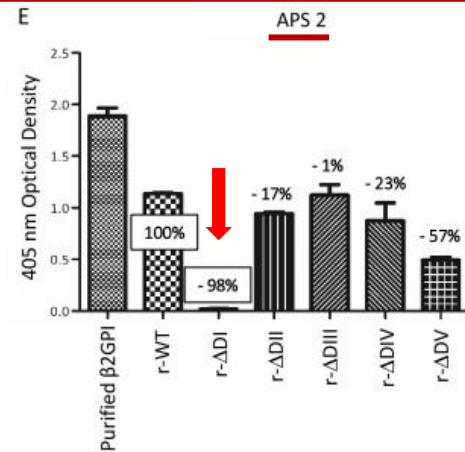
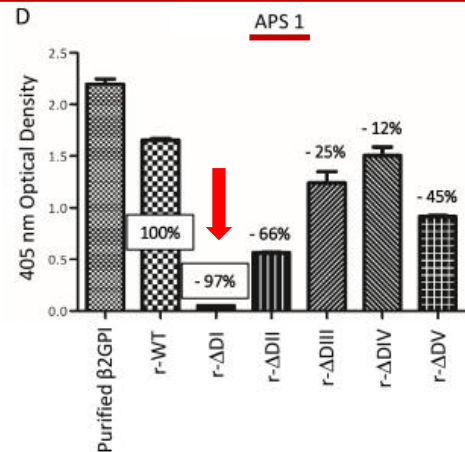
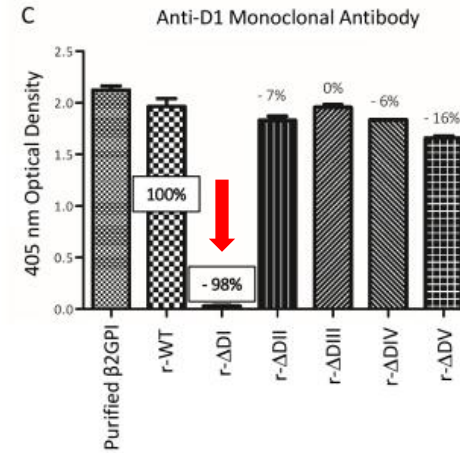
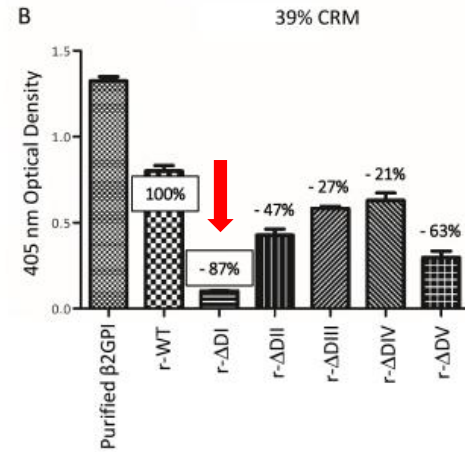
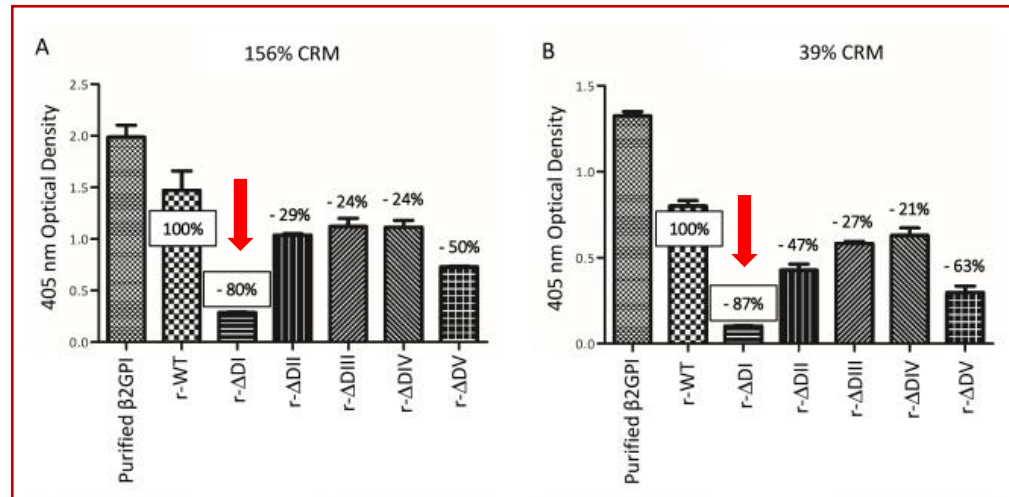
CRM aPL profile characterization: aCL reactivity



CRM reacts with CL in a dilution-dependent manner when tested by CLIA, ELISA or FEIA

CRM aPL profile characterization: β_2 GPI domain-specific reactivity

In-house ELISA employing recombinant β_2 GPI and single domain-deleted β_2 GPI variants



Significantly reduced CRM binding to D1-deleted β_2 GPI variant

Trend towards reduced binding to D5- and D2-deleted molecule

Comparable results obtained with 3 PAPS serum samples

Anti-D1 main representative of anti- β_2 GPI antibodies in the CRM

CRM may mirror serological profile of APS patients

CRM as calibrator of different anti- β 2GPI IgG assays?

Relationship between CRM IU/ml concentrations and the units of anti- β 2GPI IgG using 4 assays

Linear relation good for CLIA, sub-optimal for FEIA and commercial ELISA, poor at the high range for the in-house ELISA

Calibration of the 4 methods with CRM

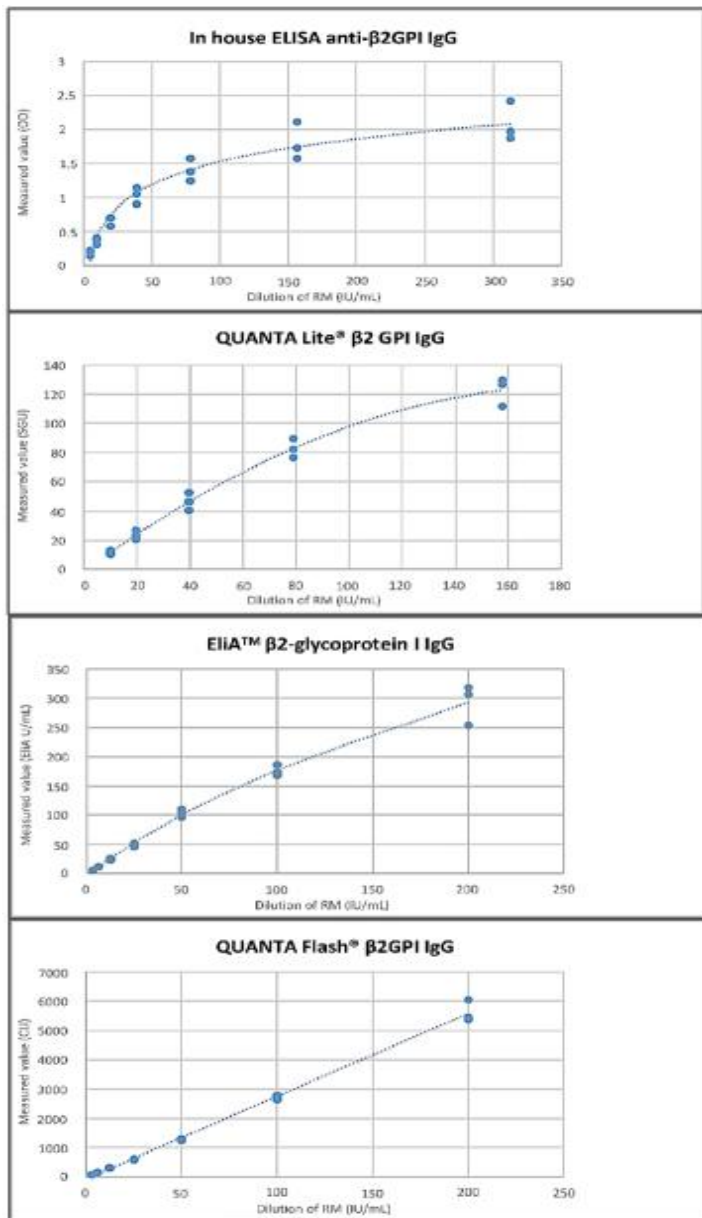
Study cohort: 133 aPL-positive samples and 99 aPL-negative controls (24 SLE, 75 HC)

CRM as calibrator improved comparability of the quantitative results for commercial ELISA and CLIA only

New cut-off (99th percentile) calculated in IU/ml for each assay improved quantitative agreement between in-house ELISA, FEIA, and CLIA leading to 85% concordance compared to 66% concordance with assay-specific calibration

CRM should improve anti- β 2GPI IgG assay harmonization

The level of harmonization is affected by different assay selectivity (e.g. β 2GPI epitope/domain exposure, specific assay chemistry)



CRM as a tool for aPL detection harmonization

- ❑ The CRM ERM-DA477/IFCC is representative of the heterogeneity of anti- β_2 GPI/CL IgG antibodies in APS patient
- ❑ It substantially contributes towards the improvement of agreement among anti- β_2 GPI IgG detecting assays
- ❑ The recalibration of the assays by the CRM is not sufficient to reach a complete harmonization owing to assay-specific features
- ❑ Main point is to evaluate if the harmonization level achievable with the CRM may fulfill the clinical requirements for the assays



Some advice to avoid traps

- **Do not trust “isolated aPL positivities”**

Isolated LA:

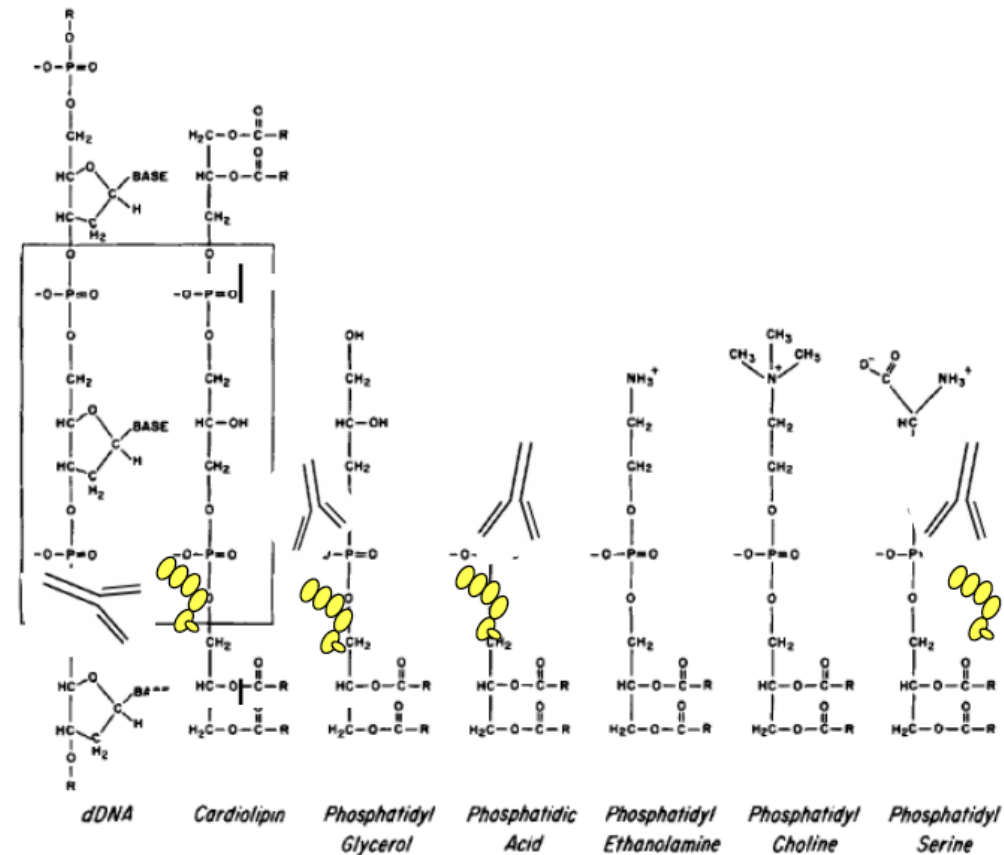
- VKA or DOAC therapy
- high CRP levels
- perform 2nd level assays if possible
- > aPS/PT ?

• Do not trust “isolated aPL positivities”

Isolated aCL:

- β 2GPI dependent aPL display the most diagnostic/prognostic value

The search for another anionic PL (e.g. aPS, aPhosphatidic acid, aPG) does not make sense since the true Ag is β 2GPI.



• Do not trust “isolated aPL positivities”

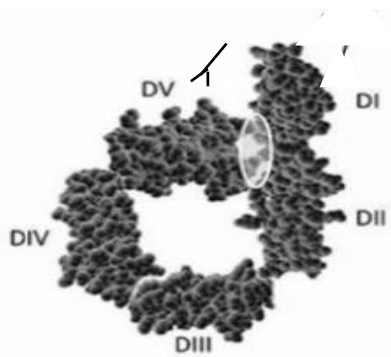
Isolated anti- β 2GPI Abs:

anti-D4,5 IgG interact with β 2GPI in the fluid phase or bound randomly to the plate

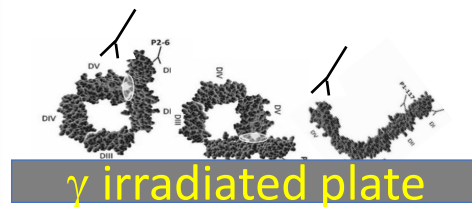
anti-D4,5 IgG do not recognize β 2GPI bound to CL

Anti-D4,5 β 2GPI Abs:

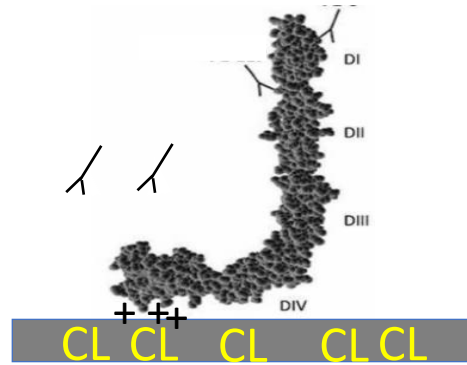
- NOT associated with APS
- detectable in infectious diseases
- Not thrombogenic in animals



circulating blood

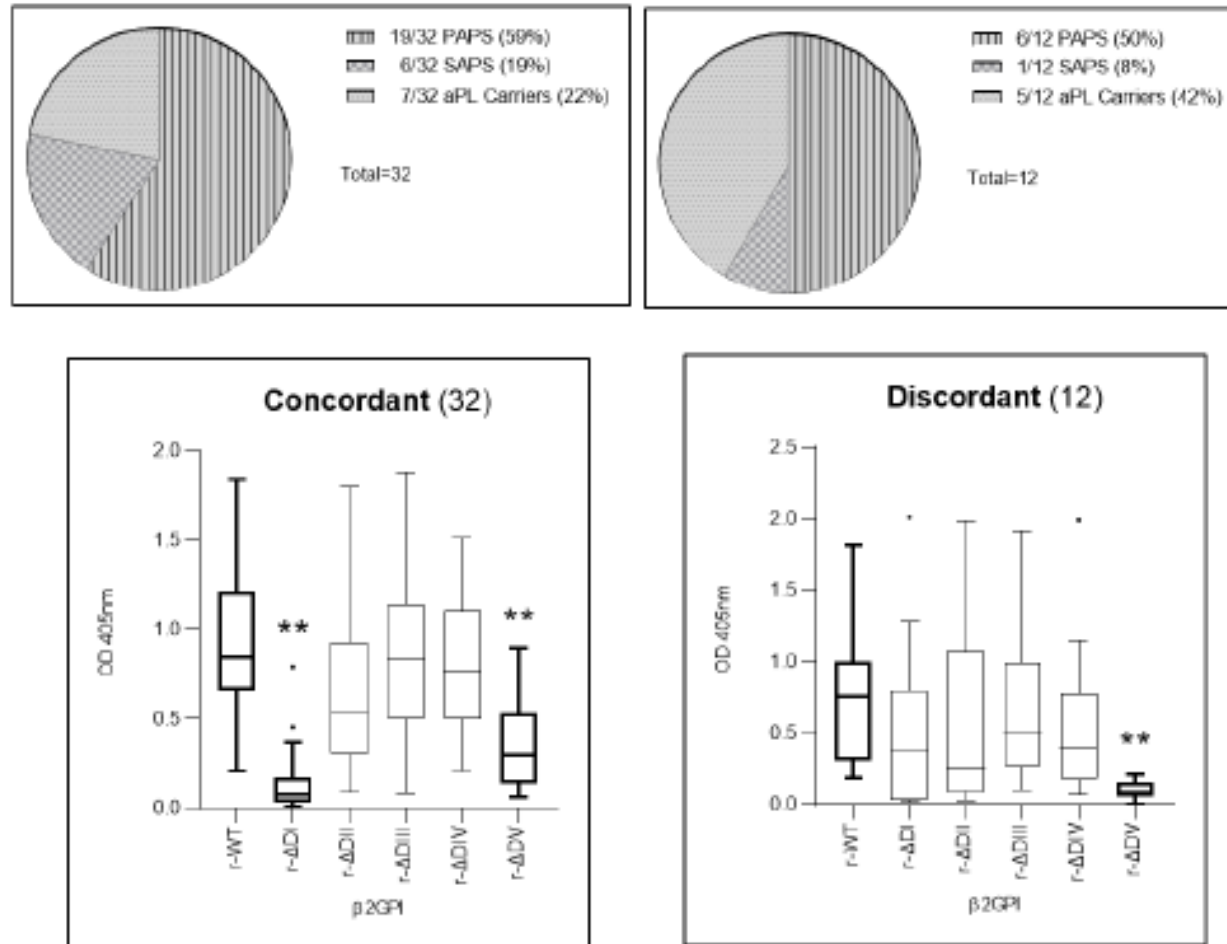


anti- β 2GPI assay



- aCL assays -

When tested in different anti- β 2GPI IgG diagnostic platforms (ELISA, FEIA, CLIA), concordant samples displayed significant D1-dependent reactivity, followed by significant D5 dependency, whereas discordant samples had a strongly significant D5-dependent reduction only.



- While there is poor quantitative agreement in aCL or a β 2GPI analytes between ELISA and automated platforms, there is, fortunately, categorical (positive/negative) clinically relevant concordance between the different platforms when considering the results of the four aPL assays together, and when the sample displays medium-to-high aPL titers.
- Despite this, low/borderline values represent the problem.
- The issue of the c.off values.
- Moreover, “moderate” or “high” aCL/a β 2GPI levels in the new platforms have not been widely established.

Sample F996

IgM

1,63

n.v. <0.27 C

Cognome e Nome:

Richiesta 102641983 del 29 gen 2024 09:11
Provenienza: S LUCA RICERCA IMMUNOLOGIA

CLIA

PI

aCL

IgG

IgM

IgG

383

62

74

v.n< 20 AU

To avoid this risk, physicians should consider the technique used to detect aPL, mainly when aPL results are at low titers

Sample F996

IgM

0.226

n.v. <0.27 C

Ab Anti Beta-2-Glicoproteina IgG
Materiale: Siero
Metodo: CLIA

19.80

Ab Anti Beta-2-Glicoproteina IgM
Materiale: Siero
Metodo: CLIA

61.10

Ab Anti Cardiolipina IgG
Materiale: Siero
Metodo: CLIA

19.70

Ab Anti Cardiolipina IgM
Materiale: Siero
Metodo: CLIA

69.40

CU	Negativo	< 20
	Dubbio	21 - 50
	Positivo debole	51 - 100
	Positivo	> 100
CU	Negativo	< 20
	Dubbio	21 - 50
	Positivo debole	51 - 100
	Positivo	> 100
CU	Negativo	< 20
	Dubbio	21 - 50
	Positivo debole	51 - 100
	Positivo	> 100
CU	Negativo	< 20
	Dubbio	21 - 50
	Positivo debole	51 - 100
	Positivo	> 100

CLIA

PI

aCL

IgG

IgM

IgG

30.4

1.00

44.40

v.n< 20 AU

Take home messages

- The restriction of classification criteria to ELISA assays for aCL and a β 2GPI might not reflect the routine practice of most diagnostic laboratories that efficiently employ different platforms.
- While there is poor quantitative agreement in aCL or a β 2GPI analytes between ELISA and automated platforms, there is, fortunately, categorical clinically relevant concordance between the different platforms when considering the results of the four aPL assays together.
- Laboratory restriction to aPL detection by only ELISA is needed for APS classification only.
- Waiting for ad hoc studies to harmonize the different techniques.

Acknowledgements

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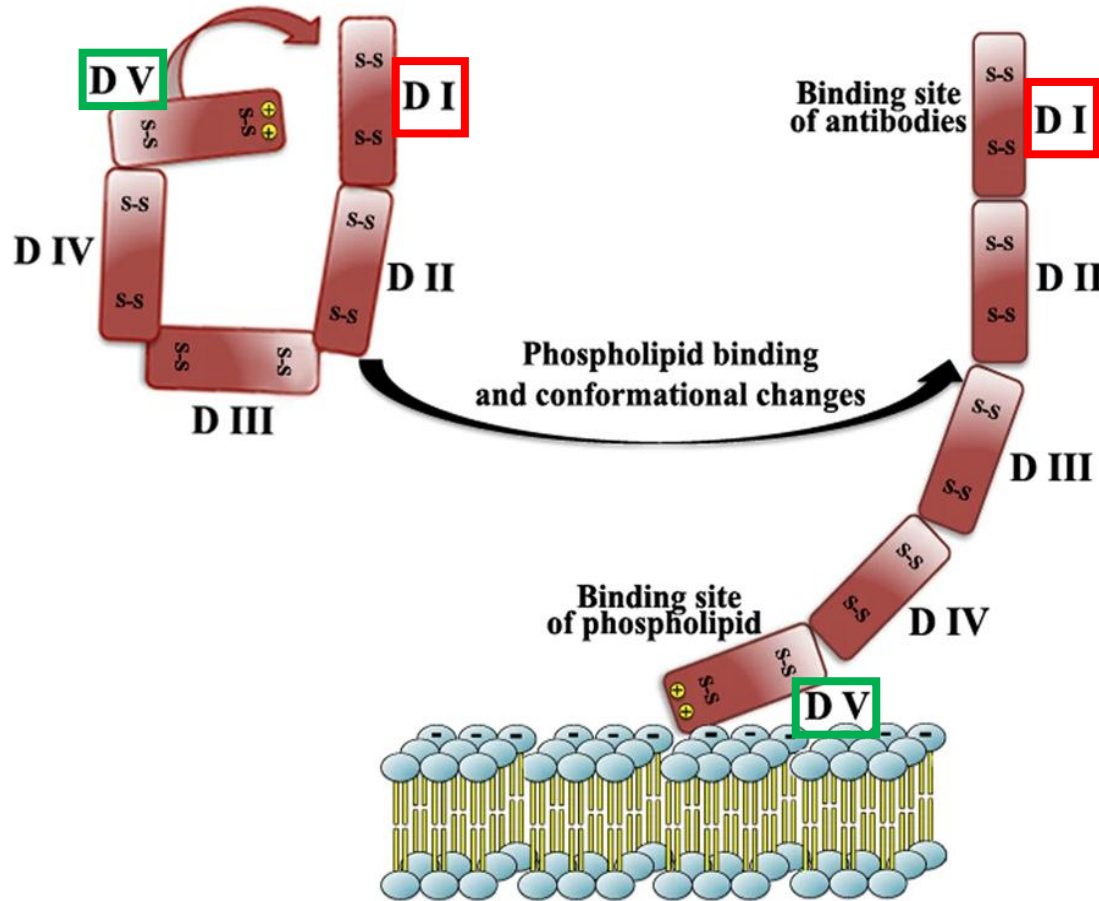
Savino Sciascia

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Galveston, Texas

Rohan Willis

CRM characterization

Beta 2-glycoprotein I



What's known

β₂GPI key autoantigen in APS

[Barbhaiya M et al. *Ann Rheum Dis.* 2023; McDonnell T et al. *Blood Rev* 2020]

Anti-β₂GPI Domain I recognized pathogenic/diagnostic role

[Raschi E. et al. *Rheumatology* 2024]

Monospecific anti-β₂GPI Domain 4-5 detected mainly in aPL-carriers

[Andreoli L. et al. *Arthritis Rheumatol.* 2015]

Anti-β₂GPI D5 not thrombogenic in a rat model and less pathogenic in patients

[Durigutto P. et al. *Haematologica* 2019]



Evaluation of anti-β₂GPI D5 reactivity may improve APS patients profiling

What's to be investigated

CRM as mirror of the heterogeneity of β₂GPI-dependent aPL

CRM as assay calibrator to improve harmonization

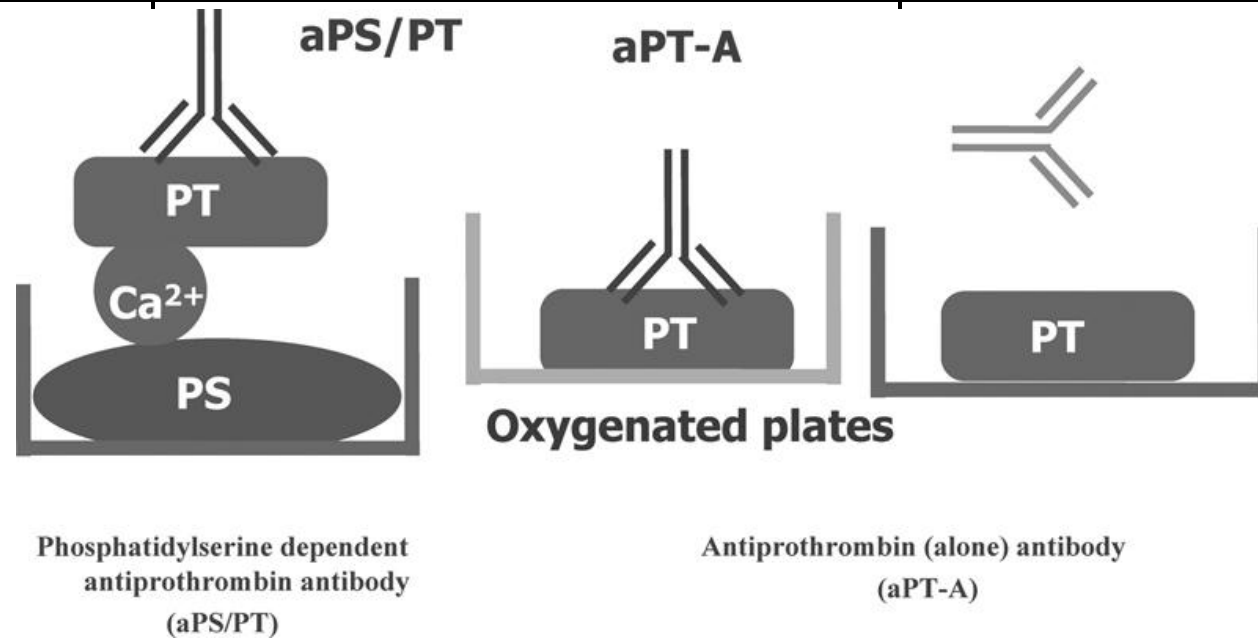
Real life scenario

- ❑ Heterogeneity of the β_2 GPI-dependent profile in aPL-positive patients
- ❑ Polyreactivity of anti- β_2 GPI IgG antibodies
- ❑ Confirmed prevalent D1-dependency in APS and D5-dependency in subjects not fulfilling APS classification criteria
- ❑ Reactivity against other domains, particularly D2
- ❑ Possible impact on assays performance

Non classification aPL assays

Immunodominant D1 β 2GPI epitope	Human β 2GPI Domain I/Domain I peptide	Anti-DI β 2GPI antibodies ELISA/CLIA [§]
Human PT	human PS/PT complex (ELISA/CLIA)	Anti-PS/PT complex antibodies ELISA
Protein C, Protein S and C4b-binding protein, Activated Protein C, Thrombomodulin	Anionic PL	Mostly anti- β 2GPI antibodies
Annexin V	Annexin V γ -irradiated plates	Anti-Annexin V antibodies ELISA, LIA
High molecular weight kininogen	Neutral PL (phosphatidylethanolamine - PE)	Anti-PE antibodies ELISA, LIA

Human PT	human PS/PT complex (ELISA/CLIA)	Anti-PS/PT complex antibodies ELISA
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Anti-PS/PT are not yet included in the lab classification criteria.
 There is preliminary evidence that may display a diagnostic/prognostic value.
 LA “surrogate” ??

Additional suggestions

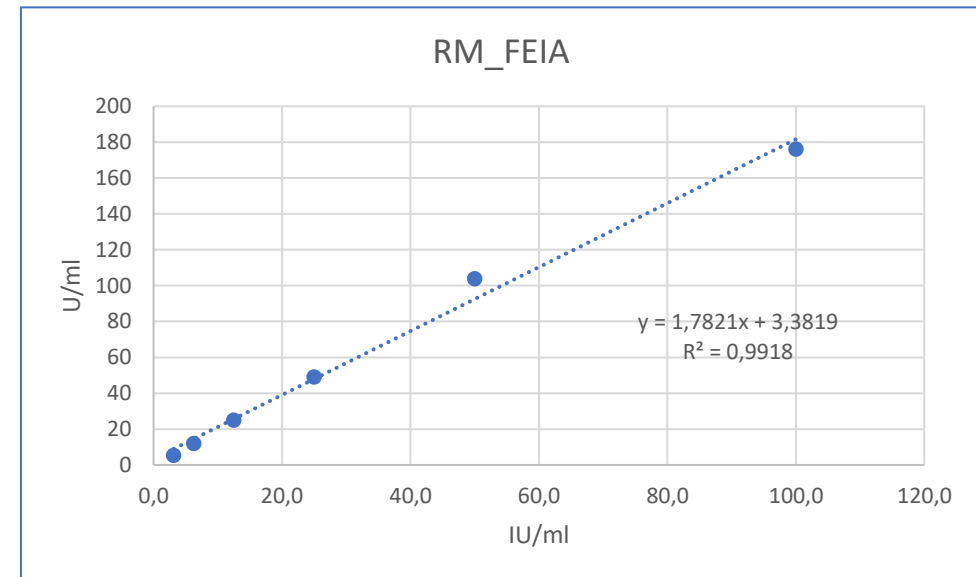
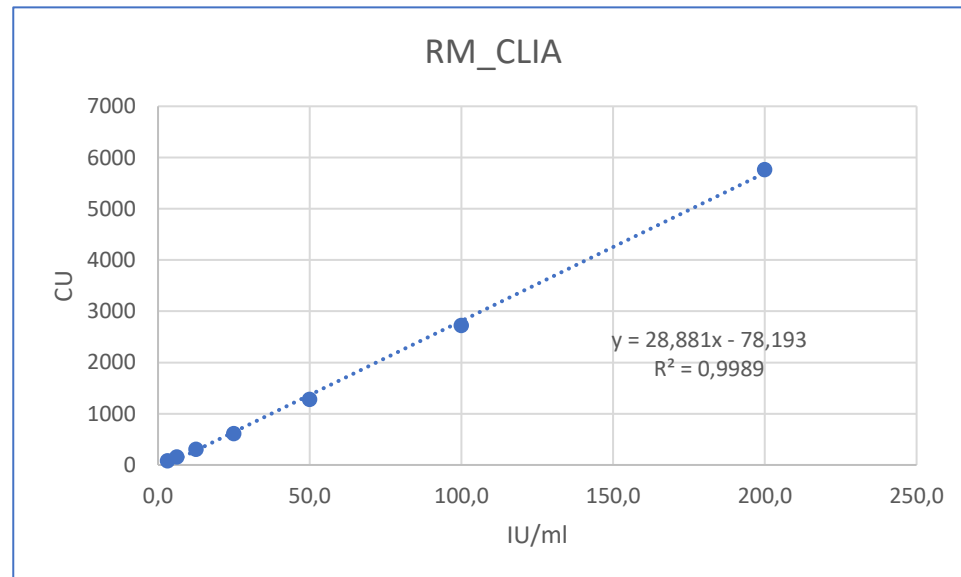
- In case of uncertainty (e.g., low or fluctuating titers), employing more than one assay to confirm aPL positivity can be beneficial.
- There are polyclonal reference materials potentially helpful in setting the assays.

CLIA vs FEIA

WHO Ref Mat (RM) for anti-β2GPI IgG

RM_CLIA	
IU/ml	CU Means of 3 Assay Means
200.0	5764
100.0	2719
50.0	1281
25.0	613
12.5	306
6.3	153
3.1	78

RM_FEIA	
IU/ml	U/ml Means of 3 Assay Means
200.0	278 Excluded
100.0	176
50.0	104
25.0	49
12.5	25
6.3	12
3.1	5



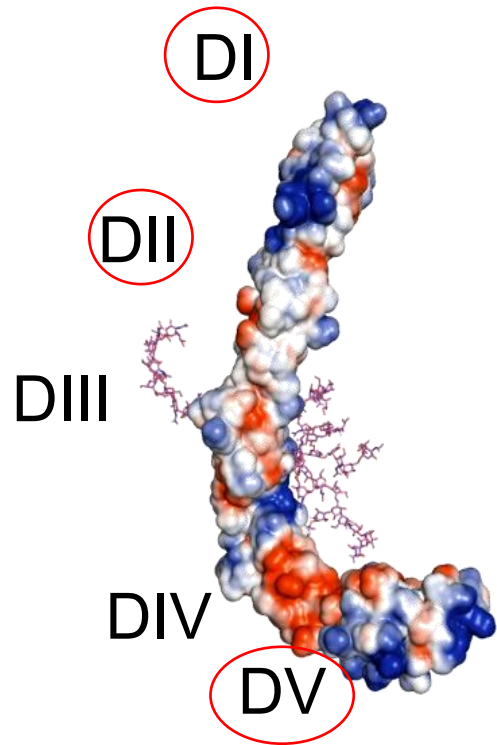
APS ACTION – ISTH collaboration to harmonize enzyme-linked and non-enzyme-linked immunosorbent assays for aCL and anti- β 2GPI antibody measurement: Communication from the ISTH SSC Subcommittee on APS.

Vandeveldel et al submitted

- aCL and a β 2GPI levels vary between ELISA and non-ELISA platforms.
- Semiquantitative interpretation (low-moderate-high levels) improves harmonization
- Sensitivity-based thresholds are platform- and parameter-dependent.
- Sensitivity-based thresholds are robust and clinically relevant.

- Given the above, an international collaborative effort between the International Society on Thrombosis and Hemostasis LA/aPL Subcommittee and the Antiphospholipid Syndrome Alliance for Clinical Trials and International Working (APS ACTION) has been initiated.
- The objectives of the working group are to describe:
 - a) how the chosen laboratory solid-phase assays for APS classification criteria impact routine clinical practice and
 - b) describe efforts to improve harmonization between ELISA and non-ELISA solid phase aPL assays.

APS displays a polyclonal anti-β2GPI IgG response



APS-Action
n.191

	aPL carriers (42)	Thrombotic APS (115)	Obstetric APS (15)	Thrombotic & obstetric APS (19)
Single pos aD5	2/42(5%)	4/115 (3%)	0/15 (0%)	0/19 (0%)
Single pos aD1	25/42 (60%)	86/115 (75%)	8/15 (53%)	15/19 (79%)
Double pos aD5, aD1	4/42 (10%)	7/115 (6%)	1/15 (7%)	1/19 (5%)
Double neg aD5, aD1	11/42 (26%)	18/115 (16%)	6/15 (40%)	3/19 (16%)

Validation Cohort
n. 105

	aPL carriers (24)	Thrombotic APS (52)	Obstetrical APS (12)	Thrombotic & obstetrical APS (17)
Single pos aD5	4/24(17%)	2/52 (4%)	2/12 (17%)	1/17 (6%)
Single pos aD1	12/24(50)	30/52 (58%)	7/12 (58%)	10/17 (59%)
Double pos aD5, aD1	0/24 (0%)	5/52 (10%)	1/12 (8%)	2/17 (12%)
Double neg aD5, aD1	8/24(33%)	15/52 (29%)	2/12 (17%)	4/17 (23%)

Background

- The ideal reference material would be a polyclonal Ig preparation representative of the autoAb subpopulations spontaneously occurring in patients; the use of pooled patient serum samples is a good strategy for this

Domain specificity
aCL IgG assay calibration
Anti- β 2GPI IgG assay calibration

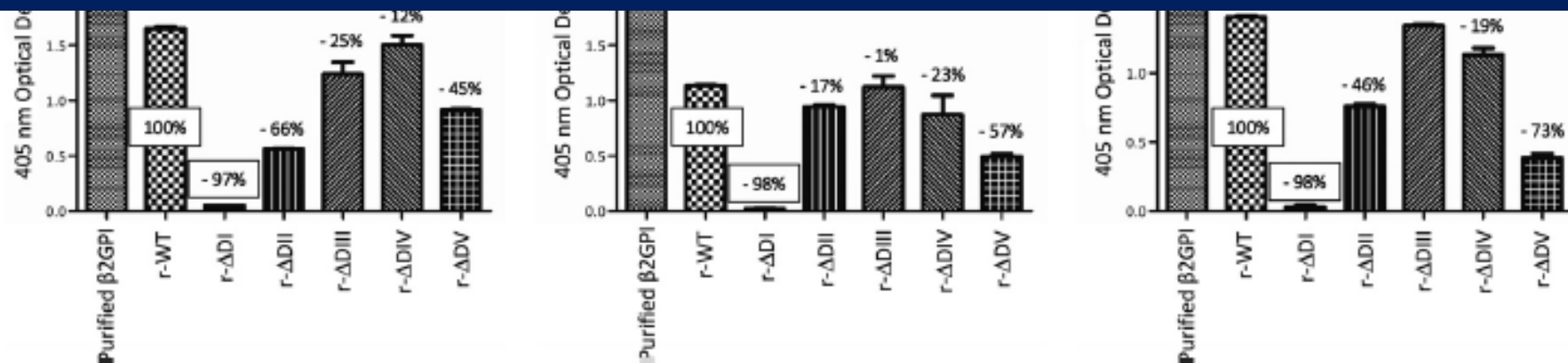
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CRM β 2GPI domain specificity



Direct reactivity against DI (CLIA Inova) and DIV-V (in house ELISA) was found.

The reactivity profile towards the β 2GPI domains reproduces the one most frequently seen in patients' sera

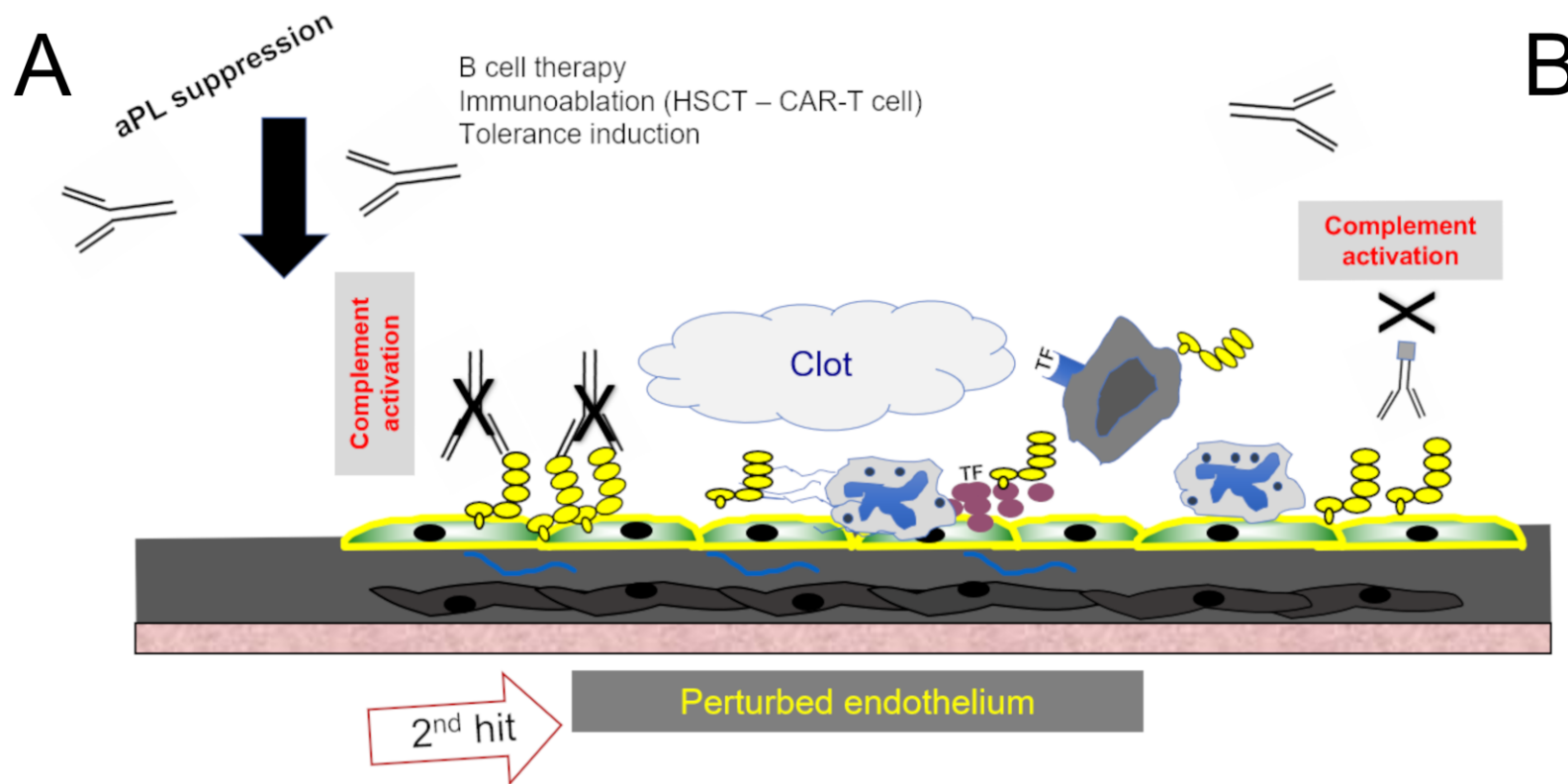


Target Ag	Plates coated with/ biological material used	Technical characteristics of the assay and type of detectable antibodies
Bovine β_2 GPI	Anionic PL	aCL solid phase assay
Human β_2 GPI	γ -irradiated plates	anti- β_2 GPI solid phase assay
Human β_2 GPI/ Domain I/Domain I peptide	Hydrophobic/hydrophilic or γ - irradiated plates	Anti-DI β_2 GPI solid phase assay
Human PT	Anionic PL (PS)	Anti-PT / anti-PS/PT solid phase assay
Protein C, Protein S and C4b-binding protein Activated Protein C Thrombomodulin	Anionic PL	Mostly anti- β_2 GPI antibodies
Annexin V	Anionic PL	Mostly anti- β_2 GPI antibodies
High molecular weight kininogen	Neutral PL (PE)	anti-PE solid phase assay
Human β_2 GPI / PT	Human plasma	LAC: functional PL dep. coagulation assay

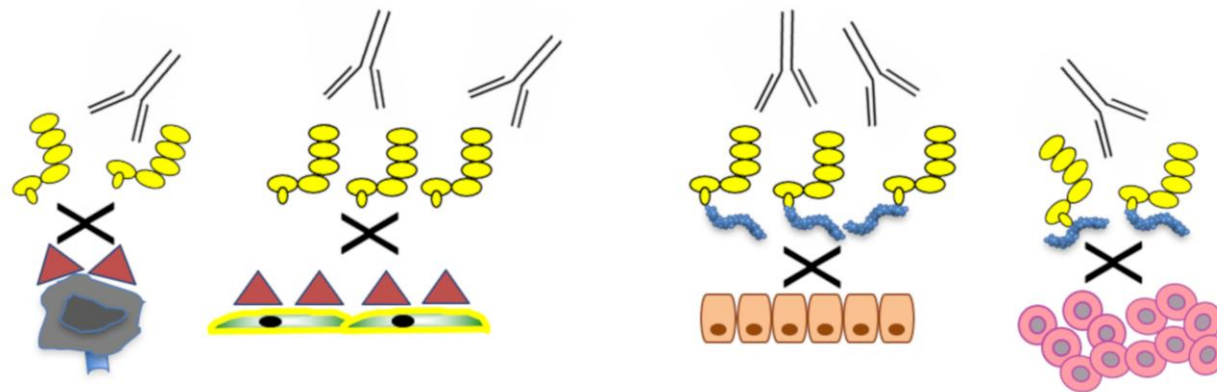
The obstetric risk and the effect of treatment in women with low titer anti-phospholipid antibodies

- ✓ Persistent low titre aPL increases the probability to have an obstetric complication (*high β 2GPI tissue expression*)
- ✓ The risk increases in case of double aPL positivity
- ✓ High response to treatment

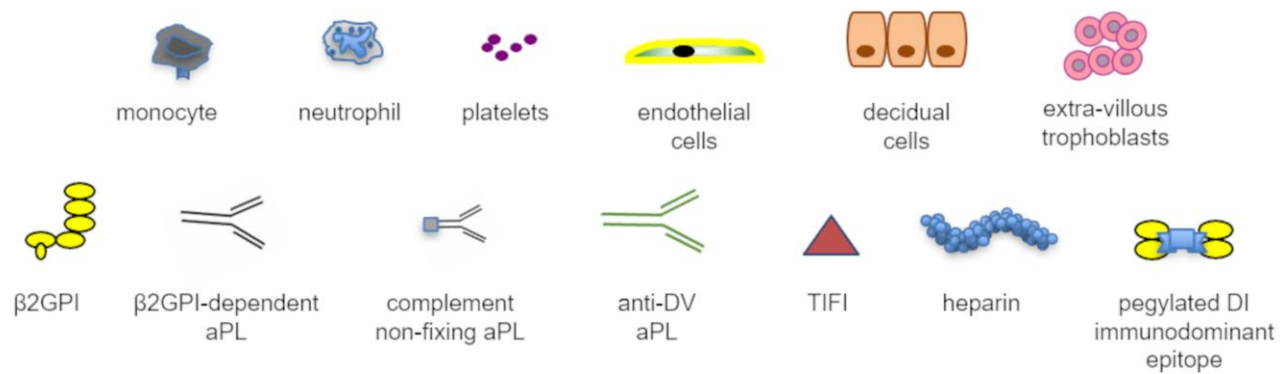
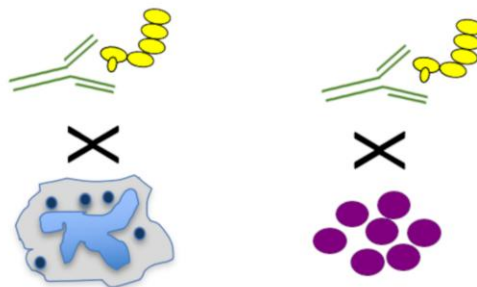
→ Time to reconsider the current classification criteria for obstetric APS?



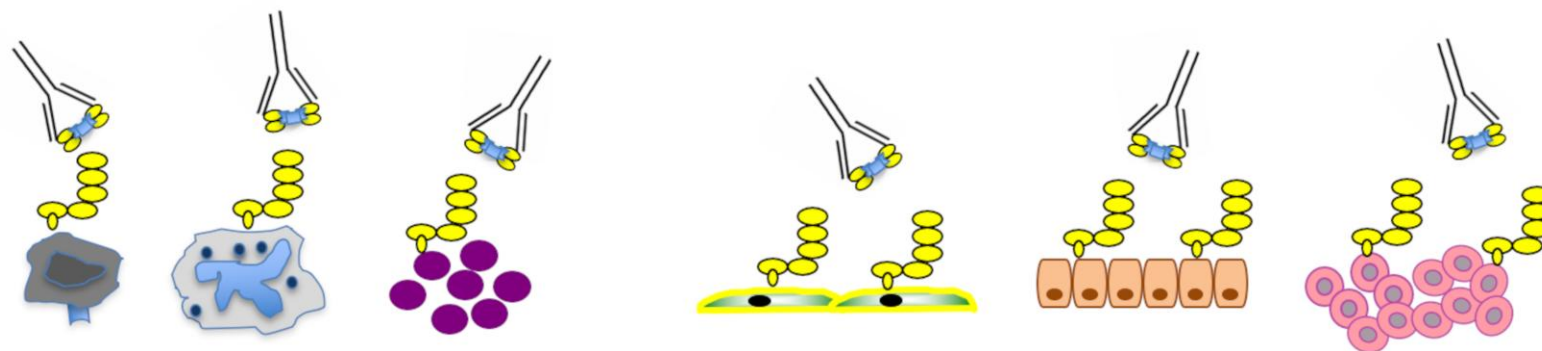
C



D



E



monocyte



neutrophil



platelets



endothelial
cells



decidual
cells



extra-villous
trophoblasts



β 2GPI



β 2GPI-dependent
aPL



complement
non-fixing aPL



anti-DV
aPL



TIFI



heparin



pegylated DI
immunodominant
epitope

An update on laboratory detection and interpretation of antiphospholipid antibodies for diagnosis of antiphospholipid syndrome: guidance from the ISTH-SSC Subcommittee on Lupus Anticoagulant/Antiphospholipid Antibodies

Katrien M. J. Devreese¹  | Maria Laura Bertolaccini²  | D. Ware Branch³  |
 Bas de Laat⁴  | Doruk Erkan⁵  | Emmanuel J. Favaloro⁶  | Vittorio Pengo⁷  |
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J Thromb Haemost. 2025

What is known

- ✓ Variability in aCL/aβ₂GPI results of ELISA and non-ELISA assays
- ✓ No «gold standard» assay
- ✓ No universal international reference material
- ✓ Qualitative agreement suboptimal
- ✓ Positivity in one assay >> negativity in another or if tested in another lab by the same assay

What is recommended

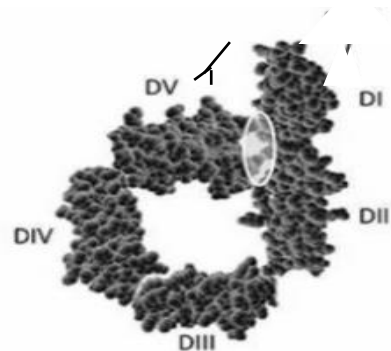
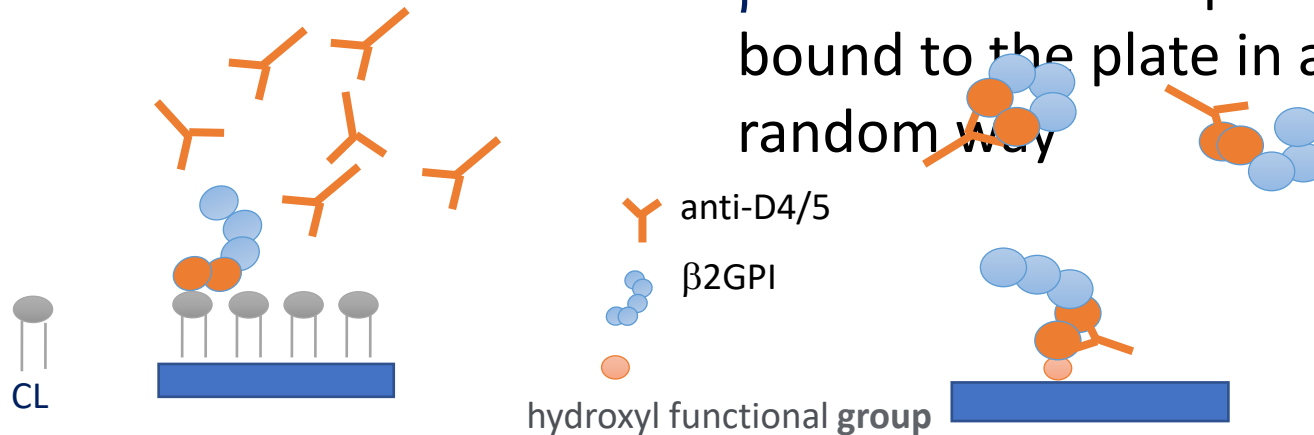
- Measuring aCL/aβ₂GPI IgG/IgM by solid phase assay (ELISA/non-ELISA)
- Reporting aCL/aβ₂GPI with their levels (pos >99th percentile HC)
- Low-medium-high positivity method-dependent >> no grading at present
- **Efforts at harmonising methods with adapted level intervals**

• Do not trust “isolated aPL positivities”

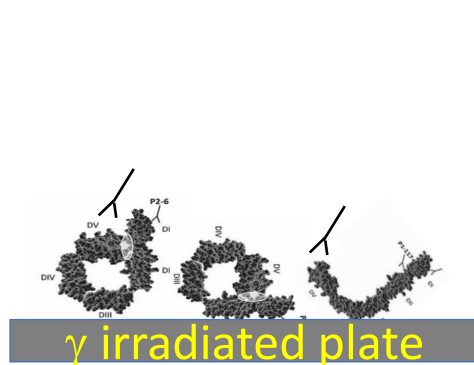
Isolated anti- β 2GPI Abs:

anti-D4,5 IgG do not recognize β 2GPI bound to CL

anti-D4,5 IgG interact with β 2GPI in the fluid phase or bound to the plate in a random way

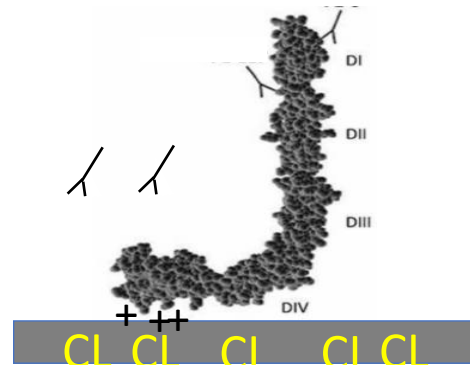


circulating blood



γ irradiated plate

anti- β 2GPI assay



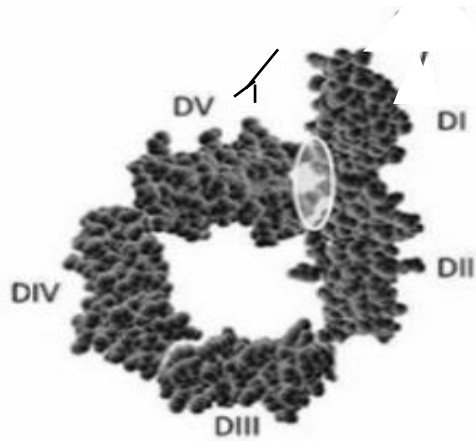
CL-coated plate

aCL assays

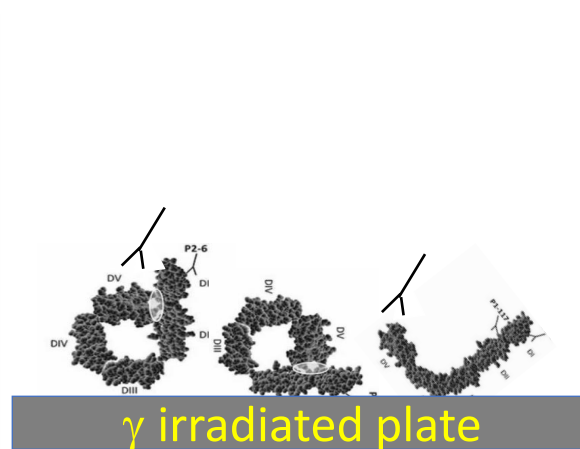
Anti-D4,5 β 2GPI Abs:

- NOT associated with APS
- detectable in infectious diseases
- Not thrombogenic in animals

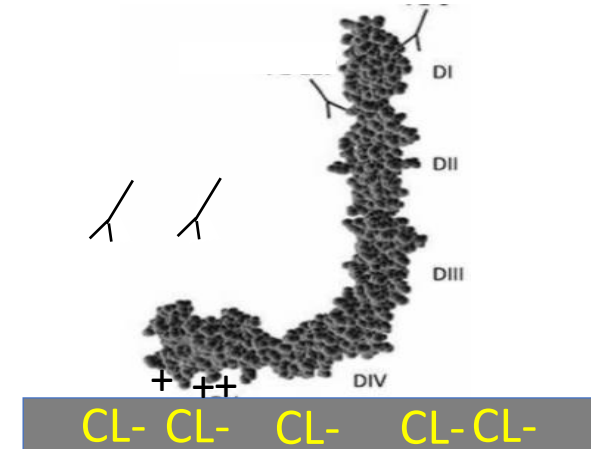
- IgG from anti-D4/5 pos sera react with recombinant D5
- IgG from anti-D4/5 pos sera react with soluble beta2GPI
- **IgG from anti-D4/5 pos sera do not react with beta2GPI bound to CL**



circulating blood



anti- β 2GPI assay

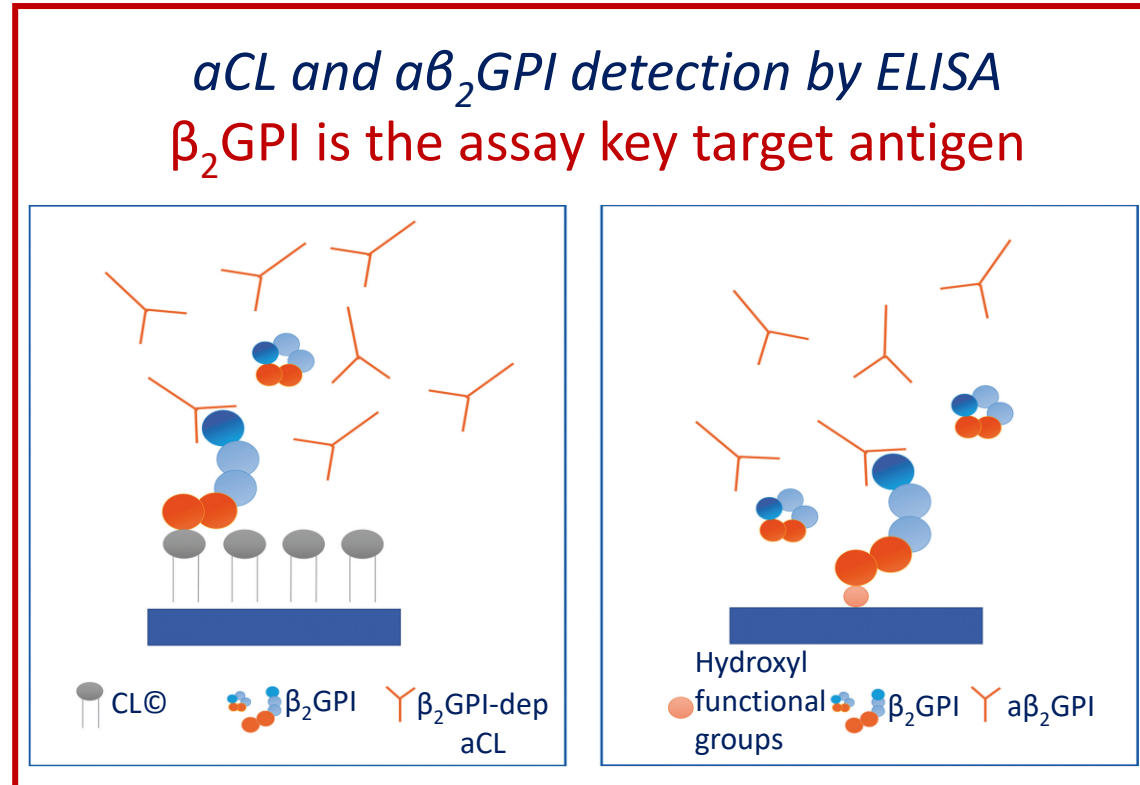


CL-coated plate

aCL assays

2023 APS classification criteria: from the steering committee....

- aCL and a β_2 GPI IgG positivity should be evaluated in combination

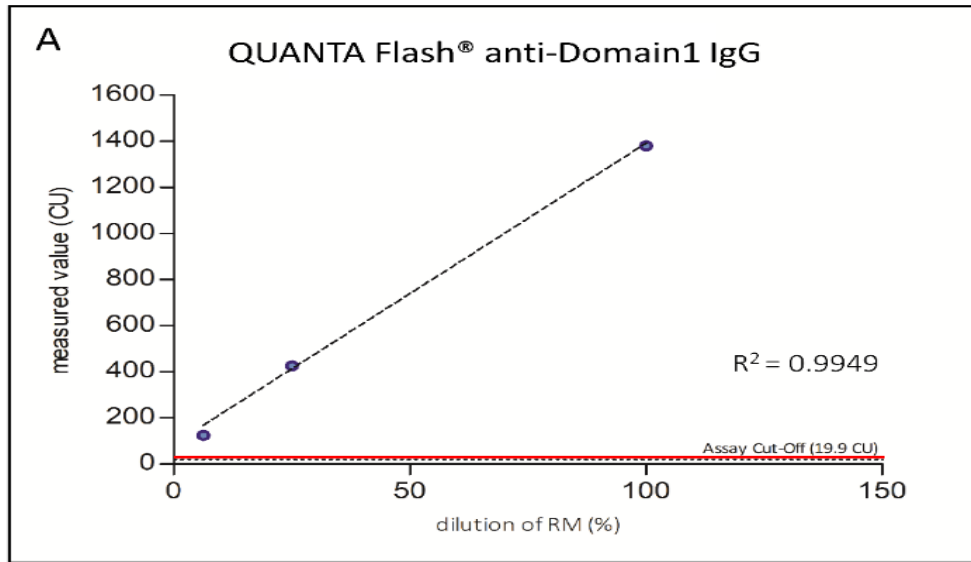


Main role of β_2 GPI-dependent IgG antibodies

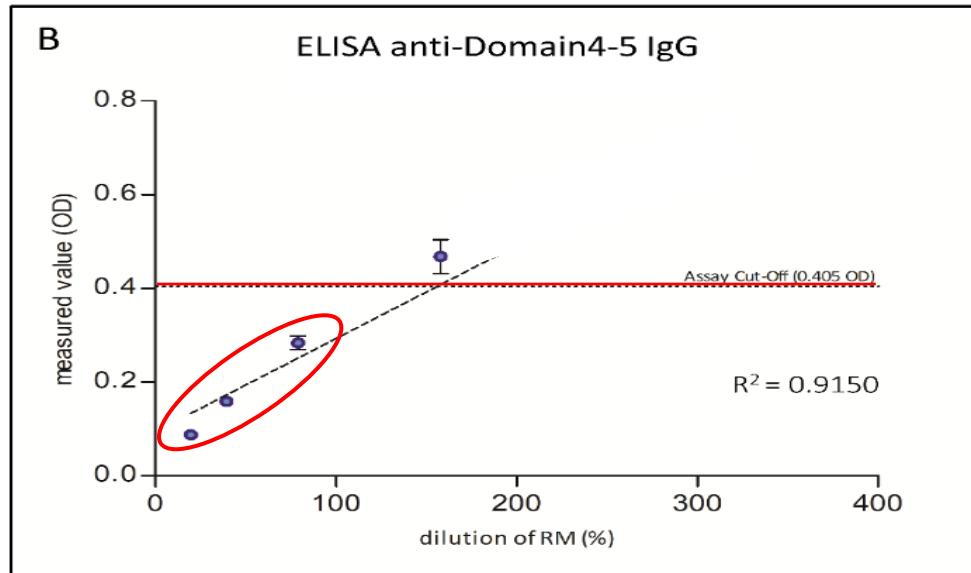
- IgG and IgM isotypes should not be additively considered

IgM for aCL/a β_2 GPI confer lower APS likelihood and specificity than IgG

CRM aPL profile characterization: β_2 GPI domain-specific reactivity



- High reactivity against β_2 GPI D1 dilution-dependent



- Negligible reactivity against β_2 GPI D4-5 at recommended test dilutions