APS new classification criteria and daily practice in laboratory diagnosis of APS

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Antiphospholipid syndrome (APS)

- Autoimmune disease
- Prevalence: 40-50/ 100 000 individuals
- Incidence: 1-5 new cases/100 000 individuals/year
- Younger patients (<50 year)

- 1/3 systemic lupus erythematosus (SLE)
- Primary APS: absence of other systemic autoimmune disorders

- Thrombotic APS, Obstetric APS, Catastrophic APS

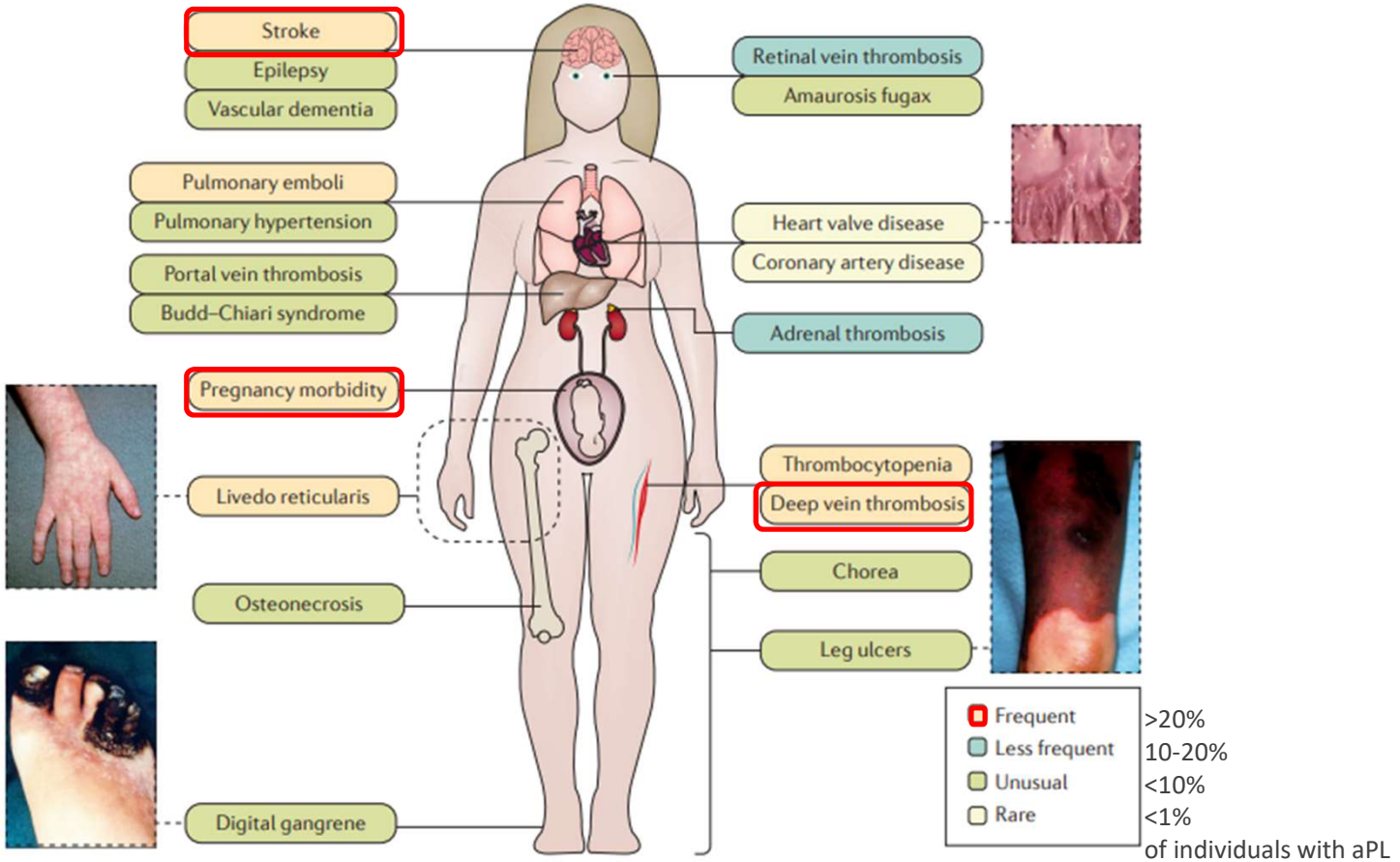
- Antiphospholipid antibodies (aPL)

***Miyakis S**. et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). J Thromb Haemst 2006; 4: 295-306.*
***Schreiber K**. et al. Antiphospholipid syndrome. Nature Reviews Disease Primers 4, 2018, Jan 11;4: 17103. doi: 10.1038/nrdp.2017.103.*
***Cervera R**. et al. Euro-Phospholipid Project Group. Antiphospholipid syndrome: clinical and immunologic manifestations and patterns of disease expression in a cohort of 1,000 patients. Arthritis Rheum 2002;46:1019-27. doi:10.1002/art.10187*

Antiphospholipid syndrome (APS)

Clinical manifestations

Increased risk for
- Thrombosis
- Pregnancy morbidity
- Autoimmune complications
- Inflammatory complications



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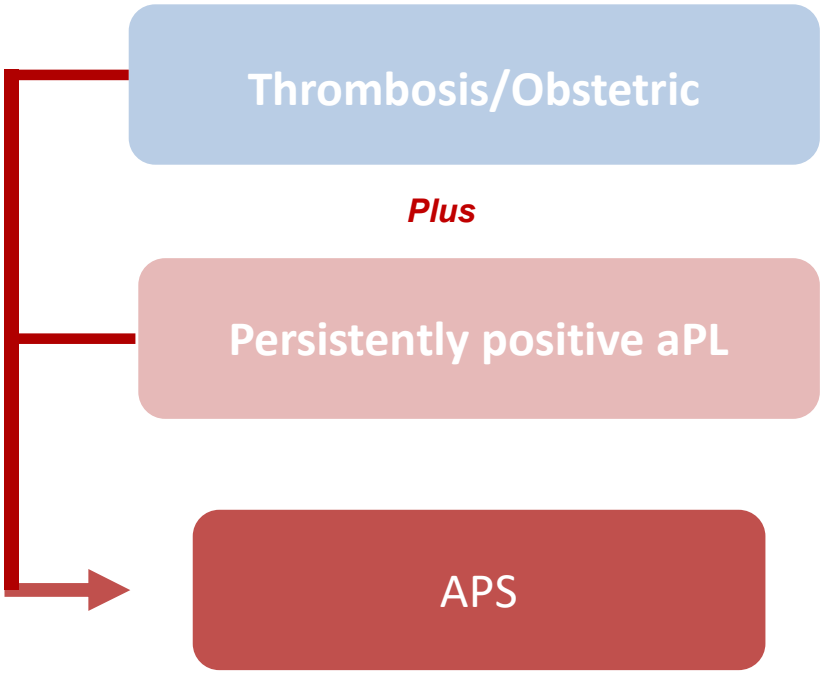
Diagnosis of Antiphospholipid syndrome (APS)

- Clinical symptoms
- Presence of antiphospholipid antibodies (aPL)



Clinical symptoms

Laboratory tests

***Miyakis S**. et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). J Thromb Haemst 2006; 4: 295-306*
***Barbhaiya M**. et al. 2023 ACR/EULAR Antiphospholipid Syndrome Classification Criteria. Arthr & Rheum 2023; 75:1687-702.*

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- Clinical symptoms
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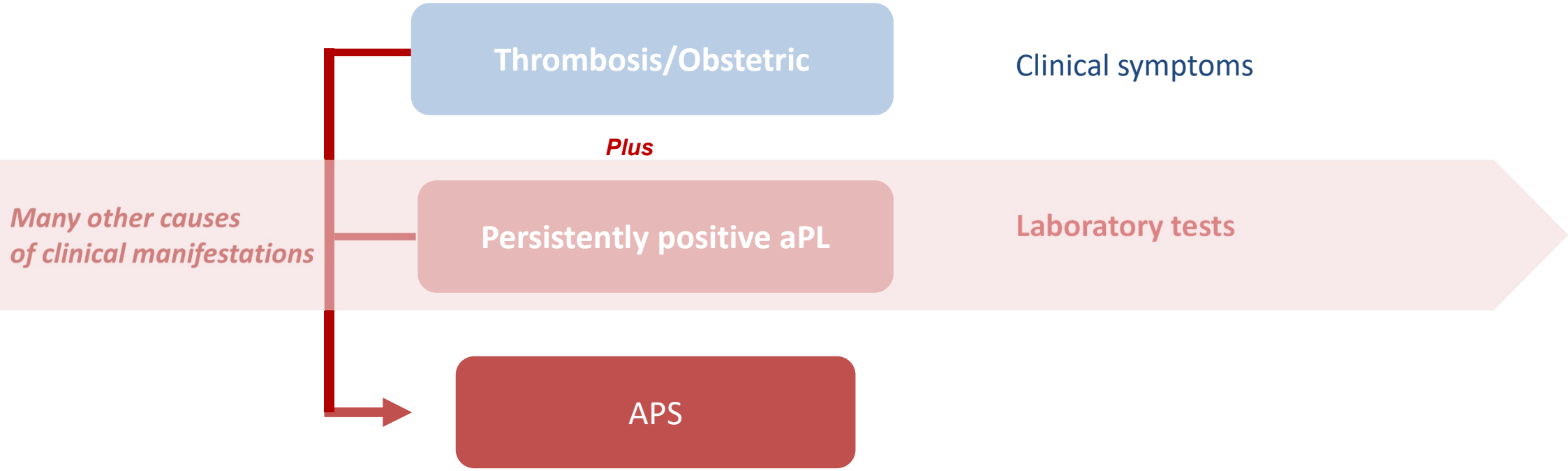

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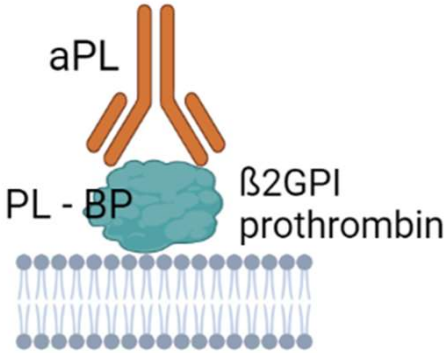
Role of aPL in APS

- aPL are part of the diagnostic criteria for APS
- Thrombotic/obstetric risk in APS
  - Clinical factors
    - Coexistence of predisposing thrombotic risk factors
    - Association with underlying autoimmune diseases (SLE)
  - Serological factors
    - Type and level of aPL
- The laboratory parameters in risk stratification for thrombotic and obstetric complications in APS

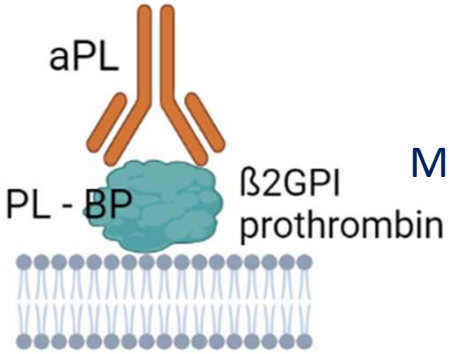
***Devreese KMJ**. Antiphospholipid antibodies: Evaluation of the thrombotic risk. Thromb Res. 2012 Oct;130 Suppl 1:S37-40*
***Devreese KMJ**, Ortel TL, Pengo V, de Laat B. Subcommittee on Lupus Anticoagulant/Antiphospholipid Anitbodies. Laboratory criteria for antiphospholipid syndrome: communication from the SSC of the ISTH. J Thromb Haemost. 2018;16: 809-813.*

Antiphospholipid syndrome (APS)

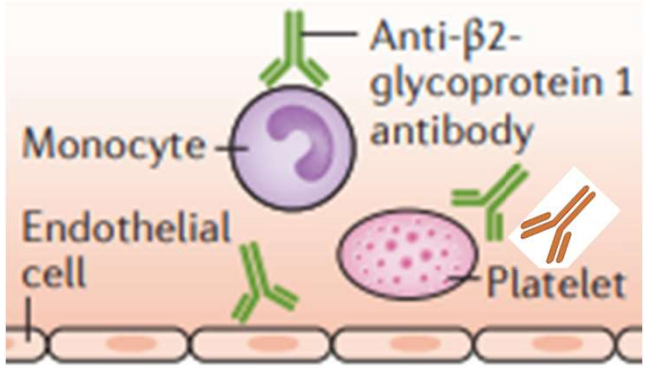


***Schreiber K**. et al. Antiphospholipid syndrome. Nature Reviews Disease Primers 4, 2018, Jan 11;4: 17103. doi: 10.1038/nrdp.2017.103.*
***Chayoua W**. et al. Antiprothrombin antibodies induce platelet activation: a possible explanation for anti-FXa therapy failure in patients with antiphospholipid syndrome?". J Thromb Haemost 2021, 19: 1776-1782. **Chinnaraj M**. et al. Discovery and characterization of 2 novel subpopulations of aPS/PT antibodies in patients at high risk of thrombosis. Blood Adv 2019, 3: 1738-1749*

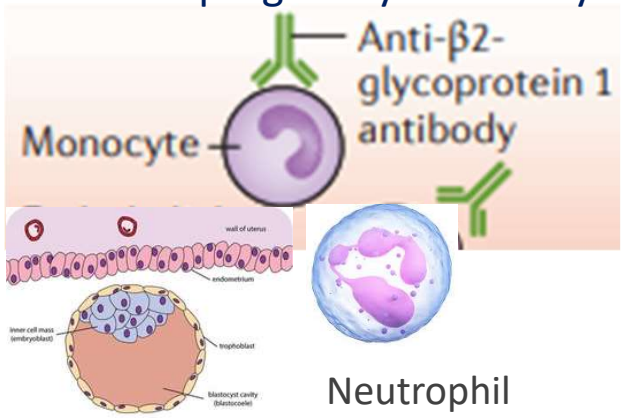
Antiphospholipid syndrome (APS)



Mechanism of thrombosis



Mechanism of pregnancy morbidity



Proinflammatory and
Prothrombotic phenotype

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***Chayoua W**. et al. Antiprothrombin antibodies induce platelet activation: a possible explanation for anti-FXa therapy failure in patients with antiphospholipid syndrome?". J Thromb Haemost 2021, 19: 1776-1782 doi: 10.1111/jth.15320**. **Chinnaraj M**. et al. Discovery and characterization of 2 novel subpopulations of aPS/PT antibodies in patients at high risk of thrombosis. Blood Adv 2019, 3: 1738-1749 DOI 10.1182/ bloodadvances.2019030932*

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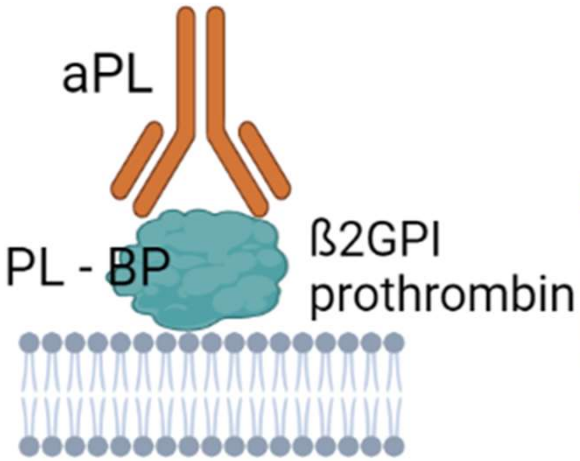

Relevant testing

Lupus anticoagulant (LA)
Anti-β2 glycoprotein I antibodies (aβ2GPI)
Anti-domain I β2 glycoprotein I antibodies (aDI)
Anticardiolipin antibodies (aCL)

Lupus anticoagulant (LA)
Antiphosphatidylserine/prothrombin antibodies (aPS/PT)

***Schreiber K**. et al. Antiphospholipid syndrome. Nature Reviews Disease Primers 4, 2018, Jan 11;4: 17103. doi: 10.1038/nrdp.2017.103.*
***Devreese KMJ**, Zuily S, Meroni PJ. Role of antiphospholipid antibodies in the diagnosis of antiphospholipid syndrome. J Transl Autoimm 2021, 4, doi.org/10.1016/j.jtauto.2021.100134*

Laboratory diagnosis of APS

Lupus anticoagulant (LA)

and/or

Anticardiolipin antibodies (aCL)IgG/IgM

and/or

Beta-2-glycoprotein I antibodies(aß2GPI)IgG/IgM

Classification criteria (2006, 2023)
ISTH-SSC **diagnostic** lab criteria (2018)

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Classification criteria
Restricted laboratory criteria to identify homogeneous APS patient population for **research**

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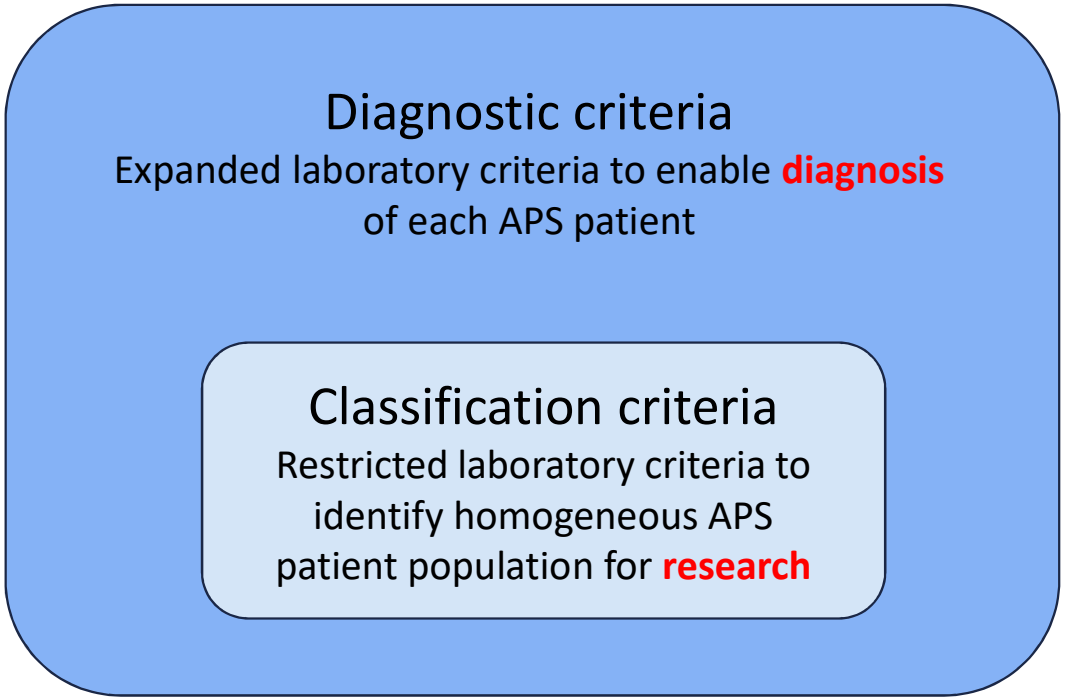

Diagnostic and classification criteria APS

➡ Three groups (LA, aCL, aβ2GPI) of aPL: concurrently measured

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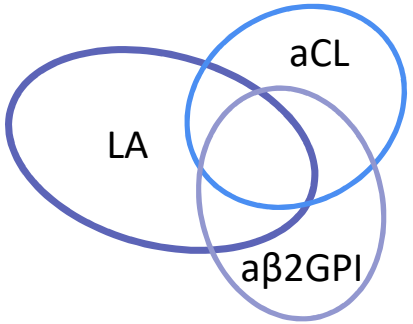
Pathogenicity of aPL



LA is a strong risk factor

	LA	aCL	aβ2GPI	Diagnostic value
Triple positive	**Pos**	**Pos**	**Pos**	**++++**
Double positive	Neg	**Pos**	**Pos**	**+++**
Single positive	**Pos**	Neg	Neg	++
Single positive	Neg	**Pos**	Neg	+
Single positive	Neg	Neg	**Pos**	+

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Laboratory diagnosis of APS

Diagnostic criteria

Lupus anticoagulant (LA)

and/or

Anticardiolipin antibodies (aCL)IgG/IgM

and/or

Beta-2-glycoprotein I antibodies(aß2GPI)IgG/IgM

Table 1 Recommended laboratory testing for the antiphospholipid syndrome

1. Lupus anticoagulant (LAC) present in plasma detected according to the Scientific Standardisation Subcommittee (SSC) on Lupus Anticoagulant/Phospholipid Antibodies recommendations [2]
2. β2GPI-dependent anticardiolipin antibodies (aCL) of IgG/IgM isotype in plasma or serum, present at higher levels (> 99th percentile of normal controls), measured by solid phase assays (ELISA or automated systems), according to the SSC on Lupus Anticoagulant/Phospholipid Antibodies recommendations [3]
3. β2GPI-antibodies (aβ2GPI) of IgG/IgM isotype in plasma or serum, present at higher levels (> 99th percentile), measured by solid phase assays (ELISA or automated systems), according to the SSC on Lupus Anticoagulant/Phospholipid Antibodies recommendations [3]
4. LAC, aCL and aβ2GPI should be positive on two or more occasions at least 12 weeks apart [1–3]
5. Laboratory results need to be reviewed and interpreted in a collaboration between a clinical pathologist and a clinician who is skilled at interpreting the data
6. Comprehensive aPL testing (LAC, aCL, and aβ2GPI IgG and IgM) should be carried out as triple aPL-positive patients are at high risk of thrombosis or aPL-related pregnancy morbidity.
7. Other antiphospholipid antibody tests are not recommended yet

ISTH-SSC **diagnostic** lab criteria (2018)

-sufficient if one group of aPL is positive
-persistently positive
-aCL and aβ2GPI (99th p)
-antibody profiles (triple positives)

***Devreese KMJ**, Ortel TL, Pengo V, de Laat B. Subcommittee on Lupus Anticoagulant/Antiphospholipid Anitbodies. Laboratory criteria for antiphospholipid syndrome: communication from the SSC of the ISTH. J Thromb Haemost. 2018;16: 809-813.*

Laboratory diagnosis of APS

Lupus anticoagulant (LA)

Anticardiolipin antibodies (aCL)IgG/IgM

Beta-2-glycoprotein I antibodies(aß2GPI)IgG/IgM

Classification criteria

ACR/EULAR classification criteria (2023)

Laboratory (aPL) domains and criteria[e]	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-β₂-glycoprotein-I antibody [aβ₂GPI] ELISA [persistent])**	
Positive LAC (single – one time)	1	Moderate or high positive (IgM) (aCL and/or aβ₂GPI)	1
Positive LAC (persistent)	5	Moderate positive (IgG) (aCL and/or aβ₂GPI)	4
		High positive (IgG) (aCL or aβ₂GPI)	5
		High positive (IgG) (aCL and aβ₂GPI)	7

3 points for the laboratory criteria

-different weight to type and titer of aPL with

-high score single persistent LA

-high score for single aCL IgG or aβ2GPI IgG in high titer

-low score for IgM even in moderate and high titer

***Barbhaiya M**. et al. 2023 ACR/EULAR Antiphospholipid Syndrome Classification Criteria. Arthr & Rheum 2023; 75:1687-702*

Laboratory diagnosis of APS

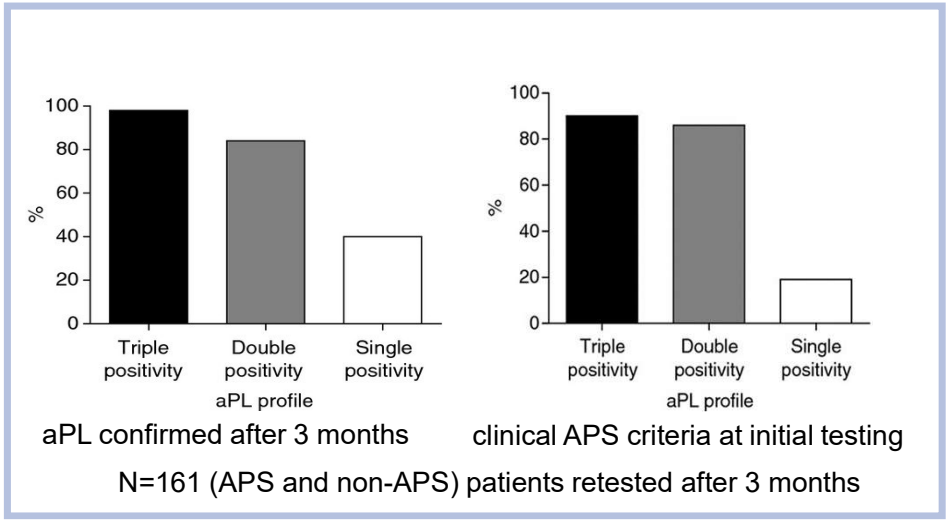
Diagnostic criteria

Classification criteria

Retesting
≥12 weeks

Persistent versus transient positivity of LA, aCL, aβ2GPI

- to avoid overdiagnosis of APS
- transient aPL without APS: infections, drugs
- single aPL not always associated with clinical APS
- reproducing the same result after 3 months and to confirm antibody profile



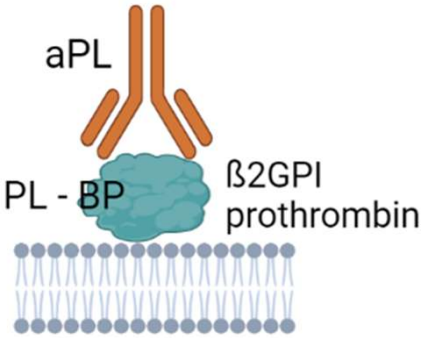
***Pengo V**. et al. Confirmation of initial antiphospholipid antibody positivity depends on the antiphospholipid antibody profile. J Thromb Haemost 2013; 11: 1522-1531.*
***Devreese KMJ** et al. Update of the guidelines for lupus anticoagulant detection and interpretation. J Thromb Haemost 2020; 18:2828–2839.*

Methodology for LA

Lupus anticoagulant (LA)

Phospholipid dependent coagulation tests

Functional antibodies: “all” aPL, independent of the cofactor of aPL = heterogenous group of aPL



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Methodology for LA

Diagnostic criteria

Classification criteria

Lupus anticoagulant (LA)

ISTH

Guidance from the Scientific and Standardization Committee for lupus anticoagulant/antiphospholipid antibodies of the International Society on Thrombosis and Haemostasis

Update of the guidelines for lupus anticoagulant detection and interpretation

jth

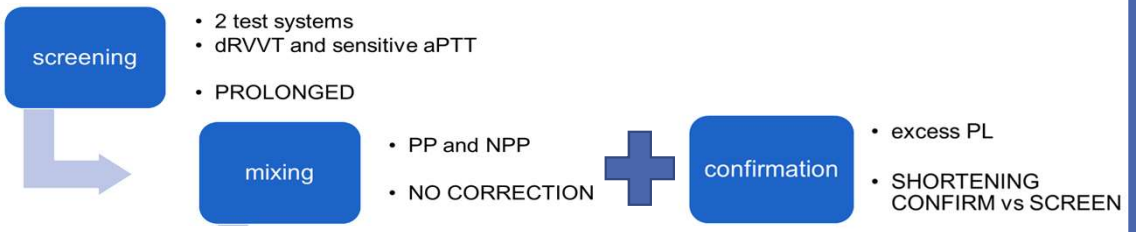
Katrien M. J. Devreese[1,2] | Philip G. de Groot[3] | Bas de Laat[3] | Doruk Erkan[4] | Emmanuel J. Favaloro[5] | Ian Mackie[6] | Marta Martinuzzo[7] | Thomas L. Ortel[8,9] | Vittorio Pengo[10] | Jacob H. Rand[11] | Armando Tripodi[12,13] | Denis Wahl[14,15] | Hannah Cohen[16,17]

Methodology for LA

Lupus anticoagulant (LA)

Phospholipid dependent coagulation tests

- Complex methodology
  - Two PL-dependent assays (aPTT, dRVVT)
  - LA = aspecific inhibitor : three step method



Mixing and confirmatory test is performed in every sample with a prolonged screening test, irrespective of the result of the mixing test

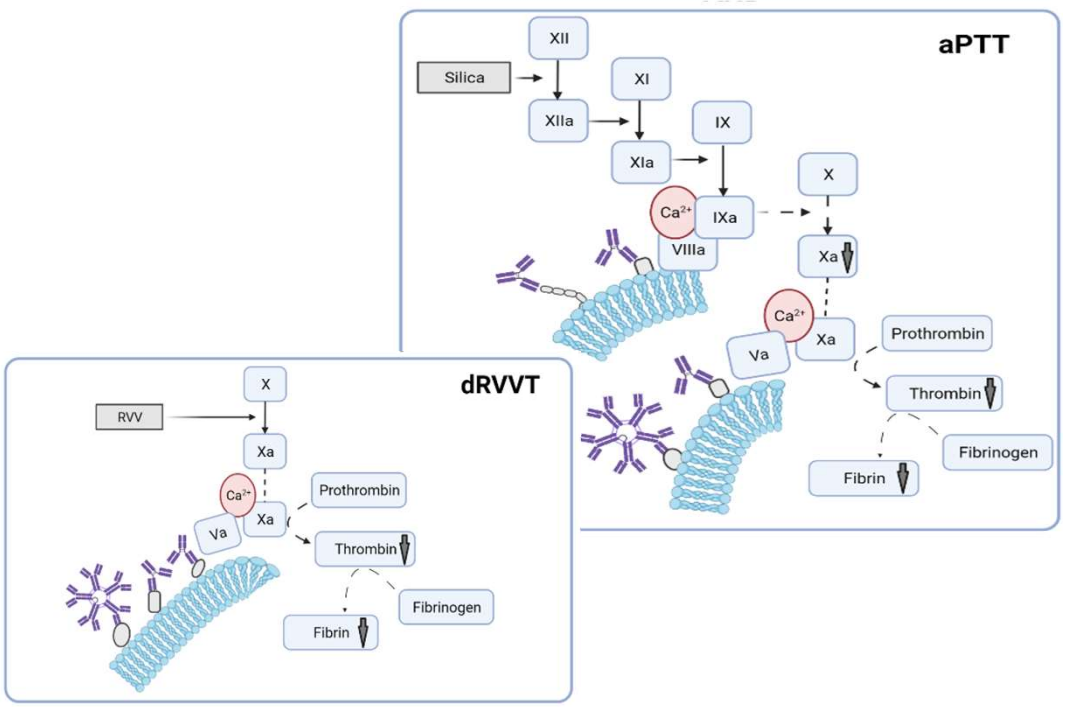
LA present if three steps in one test system positive

Devreese KMJ et al. Update of the guidelines for lupus anticoagulant detection and interpretation. Guidance from the ISTH-SSC J Thromb Haemost 2020; 18:2828–2839

Methodology for LA

Lupus anticoagulant (LA)

Phospholipid dependent coagulation tests



- LA "phenomenon" by competition with coagulation factors
- **Interferences: false negative/false positive results**
  - Acute phase proteins (FVIII, C-reactive protein)
  - Anticoagulant therapy

***Devreese KMJ** et al. Update of the guidelines for lupus anticoagulant detection and interpretation. Guidance from the ISTH-SSC J Thromb Haemost 2020; 18:2828–2839*
***Vandevelde A and Devreese KMJ**. Laboratory diagnosis of antiphospholipid syndrome: insights and hindrances. J Clin Med 2022; doi: 10.3390/jcm11082164*
***Barbhaiya M**. et al. 2023 ACR/EULAR Antiphospholipid Syndrome Classification Criteria. Arthr & Rheum 2023; 75:1687-702*

Methodology for LA

Interferences

Interference of anticoagulant therapies

Site of Thrombosis	aPL Positivity	Warfarin	DOACs
Venous	Single	First choice INR target 2–3	Can be considered *
	Double	First choice INR target 2–3	Can be considered *
	Triple	First choice INR target 2–3	Contraindicated
Arterial	Any	First choice INR target 3–4	Contraindicated

Tumian *NR and Hunt BJ, Clinical management in thrombotic APS. J Clin Med 2022, 11, 735.* ***Devreese KMJ*** *et al. Update of the guidelines for lupus anticoagulant detection and interpretation. Guidance from the Scientific and Standardization Committee for lupus anticoagulant/antiphospholipid antibodies of the ISTH. J Thromb Haemost 2020; 18:2828–2839.* ***Tripodi A.*** *et al. Lupus anticoagulant testing in anticoagulated patients. Guidance from the Scientific and Standardization Committee for lupus -anticoagulant/antiphospholipid antibodies of the ISTH. J Thromb Haemost 2020; 18:1569-1575*

Methodology for LA

Interferences

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	Triple	First choice INR target 2–3	Contraindicated
Arterial	Any	First choice INR target 3–4	Contraindicated

Testing during anticoagulation

- Blood should be collected before initiation of anticoagulation
- Duration of anticoagulation (long-term in APS)
- Choice of anticoagulant (no DOAC in triple positive APS patients)

Avoid false positives or false negatives:
DOAC removal (adsorbant, filter), antiXa measurement, VKA interpretation with care

__Tumian__ NR and Hunt BJ, Clinical management in thrombotic APS. J Clin Med 2022, 11, 735. __Devreese KMJ__ et al. Update of the guidelines for lupus anticoagulant detection and interpretation. Guidance from the Scientific and Standardization Committee for lupus anticoagulant/antiphospholipid antibodies of the ISTH. J Thromb Haemost 2020; 18:2828–2839. __Tripodi A.__ et al. Lupus anticoagulant testing in anticoagulated patients. Guidance from the Scientific and Standardization Committee for lupus -anticoagulant/antiphospholipid antibodies of the ISTH. J Thromb Haemost 2020; 18:1569-1575

Methodology for LA

Interferences

Testing during anticoagulation

Classification criteria

"Samples from patients receiving anticoagulants should be marked positive or negative on the LA assay only if reviewed/confirmed by an individual with expertise in performing/ interpreting the LA assay, e.g., expert laboratory personnel"

Interference of anticoagulant therapies

Site of Thrombosis	aPL Positivity	Warfarin	DOACs
Venous	Single	First choice INR target 2–3	Can be considered *
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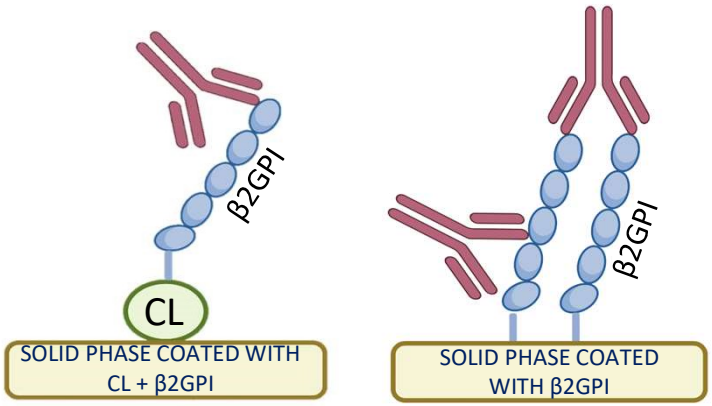
aCL and aβ2GPI

Anticardiolipin antibodies (aCL)IgG/IgM

Beta-2-glycoprotein I antibodies(aß2GPI)IgG/IgM



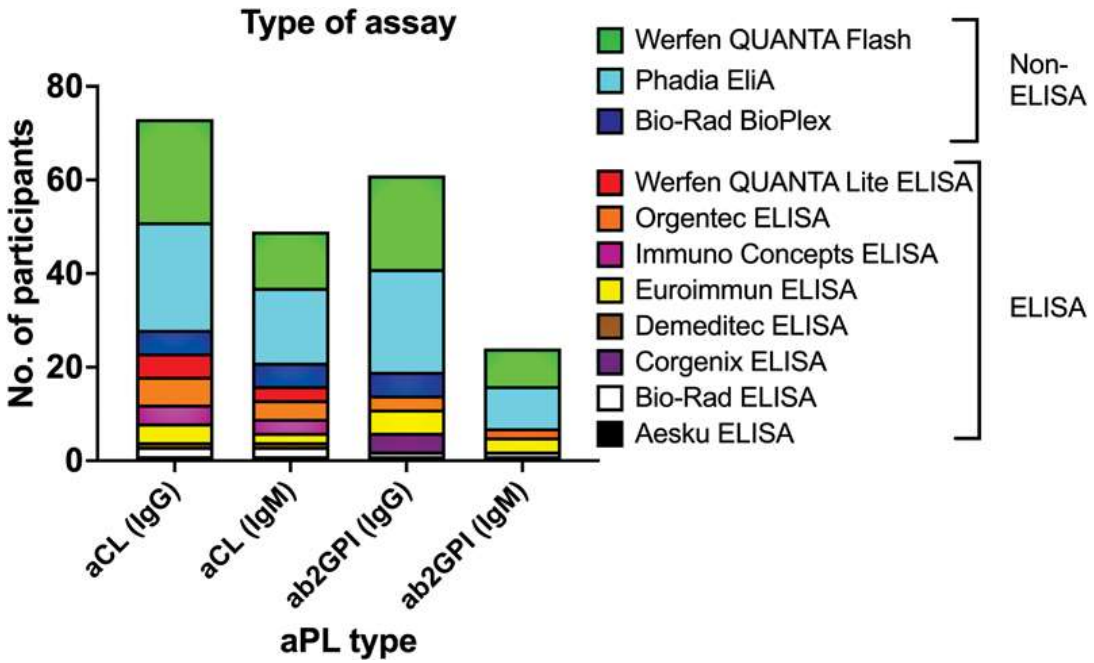
Solid phase assays

One group of aPL

- No interferences of acute phase proteins or anticoagulant therapy
- Methodological concerns: differences in assays (coating, antigens, source of β2GPI, calibration, …)

__Devreese KMJ__, Ortel TL, Pengo V, de Laat B. Laboratory criteria for antiphospholipid syndrome: communication from the SSC of the ISTH. J Thromb Haemost. 2018;16(4):809-813. __Devreese KMJ__ et al. Subcommittee on Lupus Anticoagulant/Phospholipid/Dependent A. Testing for antiphospholipid antibodies with solid phase assays: guidance from the SSC of the ISTH. J Thromb Haemost. 2014;12:792-795.

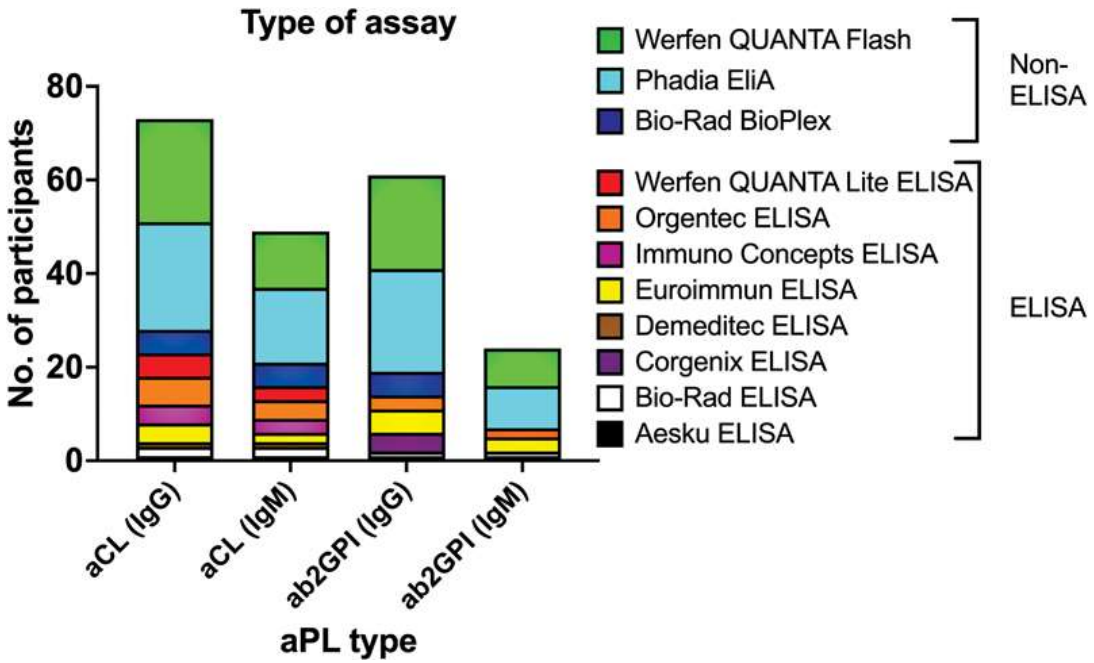
Methodology for aCL and aβ2GPI



2023 Royal College of Pathologists of Australasia Quality Assurance Program

Favaloro *et al. Classification criteria for the antiphospholipid syndrome: not the same as diagnostic criteria for antiphospholipid syndrome. Semin Thromb Hemost 2023, DOI https://doi.org/10.1055/s-0043-1776318.*

Methodology for aCL and aβ2GPI



2023 Royal College of Pathologists of Australasia Quality Assurance Program

IgG ECAT 2023-2 aCL IgG **n**

U/mL, µg/mL, GPL/MPL	143
Aeskulisa Diagnotic GmbH	7
Euroimmun	11
INOVA Quanta Lite	8
Orgentec (Alegria)	12
Orgentec (Elisa)	18
Thermo Scientific EliA	71
CU/mL	77
I.L. Acustar / INOVA Quanta Flash	76

>75% non-ELISA automated systems

Sciensano survey aCL IgG

84 % non-ELISA automated systems

Favaloro *et al. Classification criteria for the antiphospholipid syndrome: not the same as diagnostic criteria for antiphospholipid syndrome. Semin Thromb Hemost 2023, DOI https://doi.org/10.1055/s-0043-1776318.*

Methodology for aCL and aβ2GPI

Automated systems versus ELISA

- Automated systems have the advantage of performance simplicity, strict protocols
- Reduced human error (no manual pipetting)
- Rapid result of the four parameters by one test system
- Less labor-intensive

- Reduced inter-laboratory variation

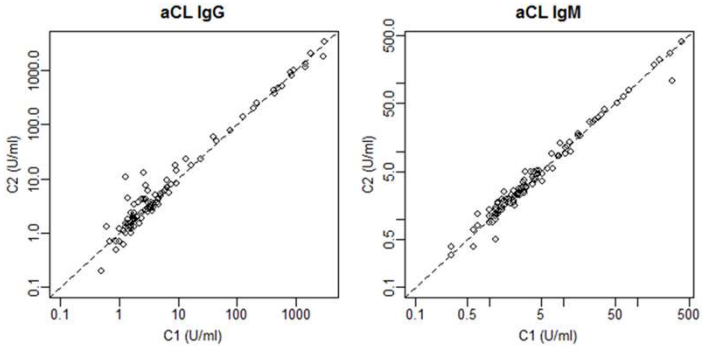
Devreese KMJ *et al. Subcommittee on Lupus Anticoagulant/Phospholipid/Dependent A. Testing for antiphospholipid antibodies with solid phase assays: guidance from the SSC of the ISTH. J Thromb Haemost. 2014;12:792-795.* ***Devreese KMJ*** *et al. A multicentre study to assess the reproducibility of antiphospholipid antibody results produced by an automated system. J Thromb Haemost 2017;15; 91-95.* ***Huisman A et al.*** *Antiphospholipid antibody solid phase–based assays: problems and proposed solutions for the 2023 ACR/EULAR classification criteria for antiphospholipid syndrome. J Thromb Haemost 2024; 22:874–876*

Methodology for aCL and aβ2GPI

Automated systems versus ELISA

- Automated systems have the advantage of performance simplicity, strict protocols
- Reduced human error (no manual pipetting)
- Rapid result of the four parameters by one test system
- Less labor-intensive
- Reduced inter-laboratory variation

AcuStar CLIA, samples by three centers C1, C2, C3 current batch of reagents



Anticardiolipin IgG										
					Automated platforms					
		Orgentec (ELISA)			IL ACUstar/INOVA Quanta flash			Thermo Scientific EliA		
					CU/mL			U/mL		
Survey	Sample	Mean	CV	Range	Mean	CV	Range	Mean	CV	Range
2022-L1	LA ratio ~ 2.0	41.4	38.4	8.2-91.6	174.7	11.5	34.8-936.5	26.5	15.5	12.7-35.0
2022-L2	LA ratio ~ 1.9	14.7	33.6	7.4-22.6	32.3	11.8	22.2-42.3	5.1	13.2	3.2-6.4
2022-L3	LA ratio ~ 1.4	14.0	37.3	7.3-24.8	72.6	10.2	6.9-103.8	10.4	11.5	6.6-13.0
2022-L4	LA ratio ~ 1.7	25.2	18.9	12.4-45.4	121.2	11.1	97.7-145.0	19.7	10.3	16.0-26.0
2023-L1	LA ratio ~ 1.7	13.4	20.7	9.6-22.0	61.2	11.6	43.9-253.8	6.5	15.4	4.0-9.6
2023-L2	LA ratio ~ 1.4	5.0	25.8	2.8-6.6	20.2	11.2	5.9-24.0	2.3	13.8	1.4-3.3
2023-L3	LA ratio ~ 2.2	14.4	22.2	9.9-32.7	70.9	10.4	56.8-85.6	6.8	14.8	1.4-9.9

Devreese KMJ *et al. Subcommittee on Lupus Anticoagulant/Phospholipid/Dependent A. Testing for antiphospholipid antibodies with solid phase assays: guidance from the SSC of the ISTH. J Thromb Haemost. 2014;12:792-795.* ***Devreese KMJ*** *et al. A multicentre study to assess the reproducibility of antiphospholipid antibody results produced by an automated system. J Thromb Haemost 2017;15; 91-95.* ***Huisman A et al.*** *Antiphospholipid antibody solid phase–based assays: problems and proposed solutions for the 2023 ACR/EULAR classification criteria for antiphospholipid syndrome. J Thromb Haemost 2024; 22:874–876*

Methodology for aCL and aβ2GPI

Anticardiolipin antibodies (aCL)IgG/IgM

Beta-2-glycoprotein I antibodies(aß2GPI)IgG/IgM

RECOMMENDATIONS AND GUIDELINES

Testing for Antiphospholipid antibodies with Solid Phase Assays: guidance from the SSC of the ISTH

K. M. J. DEVREESE,* S. S. PIERANGELI,† B. DE LAAT,‡ A. TRIPODI,§ T. ATSUMI¶ and T. L. Ortel,** FOR THE SUBCOMMITTEE ON LUPUS ANTICOAGULANT/PHOSPHOLIPID/DEPENDENT ANTIBODIES

*Coagulation Laboratory, Department of Clinical Chemistry, Microbiology and Immunology, Ghent University Hospital, Ghent, Belgium; †University of Texas Medical Branch, APLS Laboratory, Galveston, TX, USA; ‡Department of Biochemistry, Synapse BV, Maastricht University, Maastricht, the Netherlands; §Department of Clinical Sciences and Community Health, Angelo Bianchi Bonomi Hemophilia and Thrombosis Center, Università degli Studi di Milano and IRCCS Maggiore Hospital Foundation, Milan, Italy; ¶Department of Medicine II, Hokkaido University Graduate School of Medicine, Sapporo, Japan; and **Departments of Medicine and Pathology, Duke University Medical Center, Durham, NC, USA

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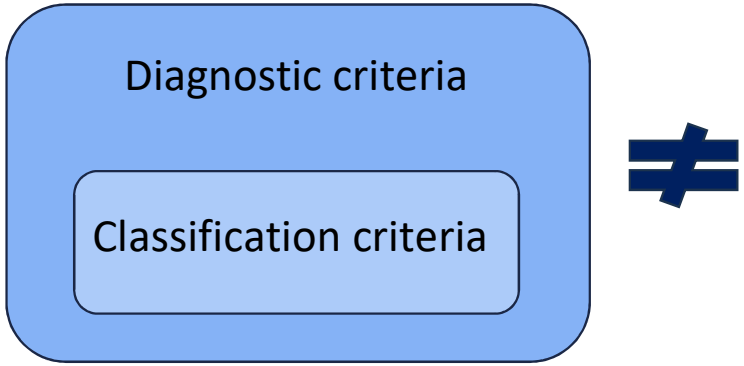
Harmonisation in measurement of aPL with solid phase assays, interpretation and reporting

***Devreese KMJ**, Ortel TL, Pengo V, de Laat B. Laboratory criteria for antiphospholipid syndrome: communication from the SSC of the ISTH. J Thromb Haemost. 2018;16(4):809-813;*
***Devreese KMJ** et al. Subcommittee on Lupus Anticoagulant/Phospholipid/Dependent A. Testing for antiphospholipid antibodies with solid phase assays: guidance from the SSC of the ISTH. J Thromb Haemost. 2014;12:792-795.*

Methodology for aCL and aβ2GPI



ISTH-SSC guidance on laboratory diagnosis of APS:
ELISA or automated systems

Sydney classification criteria (2006):

… aCL IgG/IgM levels, by ELISA

… aβ2GPI IgG/IgM, by ELISA

ACR/ EULAR classification criteria (2023):

… aCL and aβ2GPI IgG/IgM by ELISA

__Devreese KMJ__ et al. Subcommittee on Lupus Anticoagulant/Phospholipid/Dependent A. Testing for antiphospholipid antibodies with solid phase assays: guidance from the SSC of the ISTH. J Thromb Haemost. 2014;12:792-795. __Devreese KMJ__, Ortel TL, Pengo V, de Laat B. Laboratory criteria for antiphospholipid syndrome: communication from the SSC of the ISTH. J Thromb Haemost. 2018;16(4):809-813. __Barbhaiya M__. et al. 2023 ACR/EULAR Antiphospholipid Syndrome Classification Criteria. Arthr & Rheum 2023; 75:1687-702

Methodology for aCL and aβ2GPI

Multicenter solid phase assay study; n= 1168
APS thrombosis, non-APS thrombosis, AID, HC,
APS obstetric, non-APS obstetric, normal pregnancy

aCL and aβ2GPI IgG/IgM, measured with 4 platforms

Positive agreement (pos/neg)

Kappa agreement (**positive agreement**)	
1-0.80	very good agreement
<0.80-0.60	good agreement
<0.60-0.40	moderate agreement

aCL IgG	Bioplex	Phadia	Acustar	Inova
Bioplex		0.77	0.87	0.71
Phadia	0.77		0.81	0.79
Acustar	0.87	0.81		0.75
Inova	0.71	0.79	0.75	

aβ2GPI IgG	Bioplex	Phadia	Acustar	Inova
Bioplex		0.76	0.88	0.66
Phadia	0.76		0.70	0.80
Acustar	0.88	0.70		0.58
Inova	0.66	0.80	0.58	

aCL IgM	Bioplex	Phadia	Acustar	Inova
Bioplex		0.51	0.71	0.58
Phadia	0.51		0.51	0.57
Acustar	0.71	0.51		0.64
Inova	0.58	0.57	0.64	

aβ2GPI IgM	Bioplex	Phadia	Acustar	Inova
Bioplex		0.79	0.85	0.75
Phadia	0.79		0.86	0.78
Acustar	0.85	0.86		0.74
Inova	0.75	0.78	0.74	

-detection of patients positive for aCL and aβ2GPI antibodies is **assay dependent**
-good-very good **agreement** between methods for aCL/aβ2GPI IgG and aβ2GPI IgM positivity
-apart from Bioplex-Acustar Acustar-Inova,moderate agreement for aCL IgM positivity

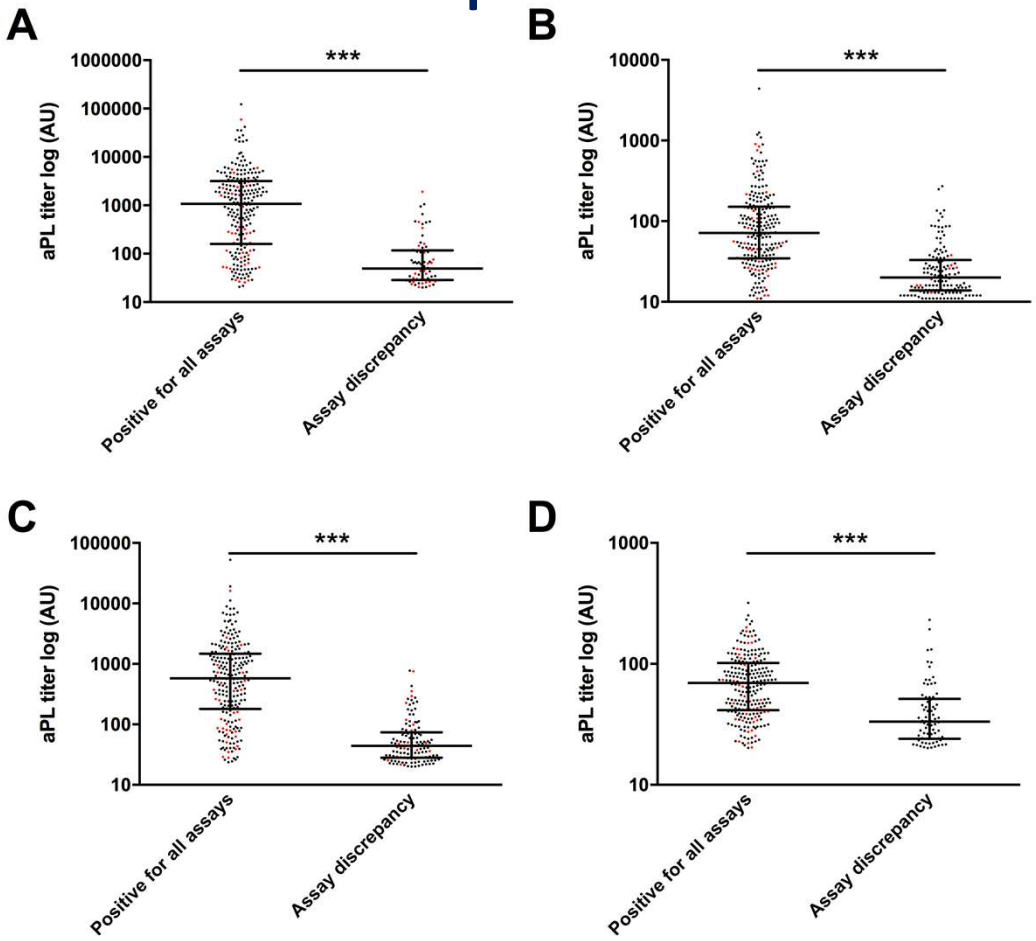
***Chayoua W**, Kelchtermans H, Moore GW, et al. Detection of anti-cardiolipin and anti-ß2glycoprotein I antibodies differs between platforms without influence on association with clinical symptoms. Thromb Haemost 2019, 19, 797-806*

Methodology for aCL and aβ2GPI

Multicenter solid phase assay study; n= 1168
APS thrombosis, non-APS thrombosis, AID, HC,
APS obstetric, non-APS obstetric, normal pregnancy

Agreement

Platform
A. BioPlex®2200
B. ImmunoCap®EliA
C. ACL AcuStar®
D. QUANTA Lite ELISA®



aPL positive samples not in agreement across the platforms were characterized by lower median aPL titers

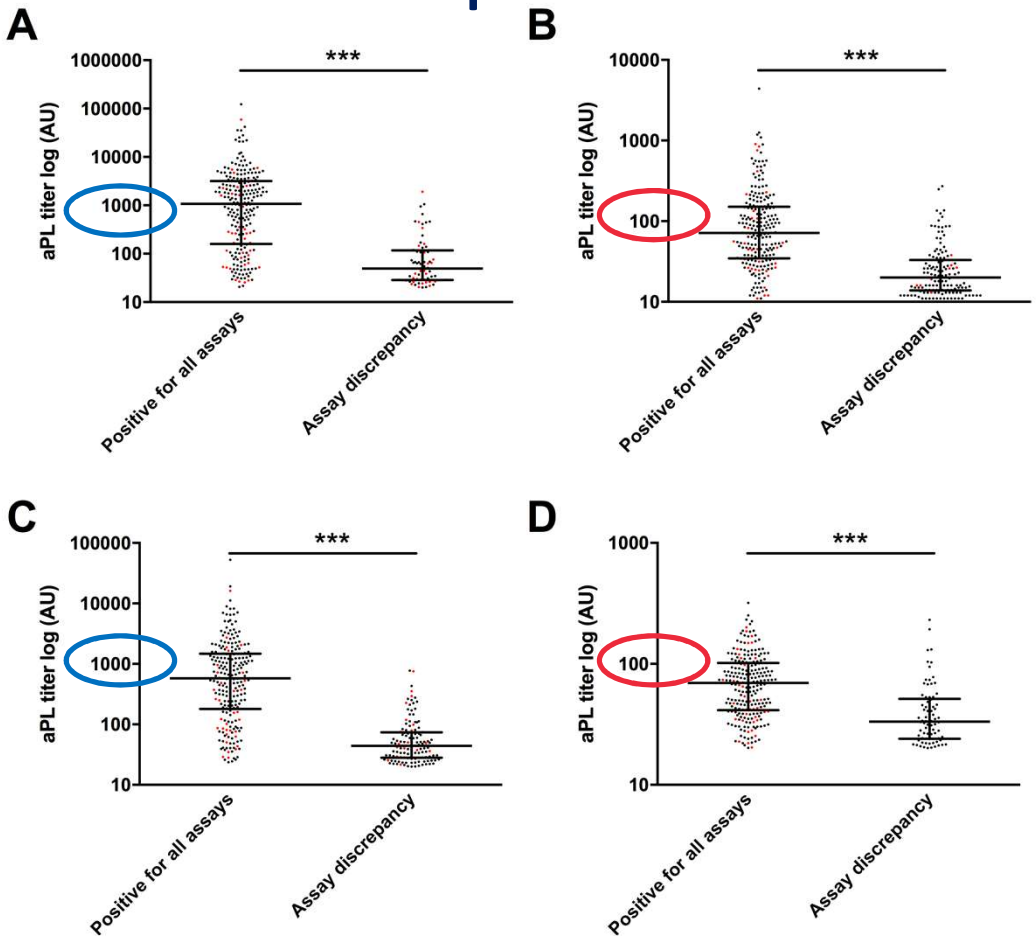
Chayoua W, Kelchtermans H, Moore GW, et al. Detection of anti-cardiolipin and anti-β2glycoprotein I antibodies differs between platforms without influence on association with clinical symptoms. Thromb Haemost 2019, 19, 797-806

Methodology for aCL and aβ2GPI

Differences in titer

Platform
A. BioPlex®2200 MFI
B. ImmunoCap®EliA FIA
C. ACL AcuStar® CLIA
D. QUANTA Lite ELISA®

CLIA: chemiluminescent assay
MFI: multiplex flow immunoassay
FIA: fluorescense enzyme immunoassay



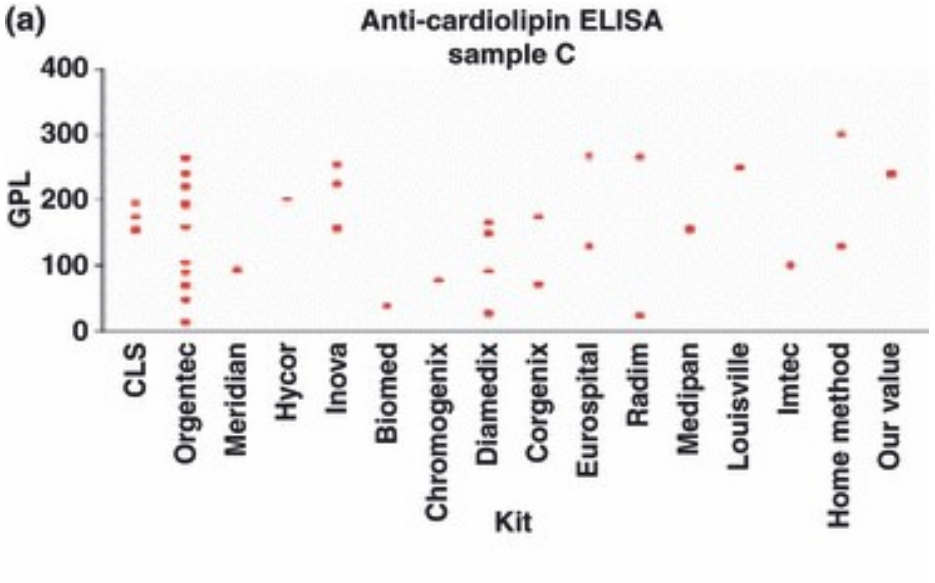
Differences in titer: CLIA and MFI higher titers compared to ELISA and EliA

__Chayoua W__, Kelchtermans H, Moore GW, et al. Detection of anti-cardiolipin and anti-β2glycoprotein I antibodies differs between platforms without influence on association with clinical symptoms. Thromb Haemost 2019, 19, 797-806

Methodology for aCL and aβ2GPI

Comparability of ELISA assays

Commercial ELISAs, same samples
tested in different labs



***Pengo V** et al. Italian Federation of Anticoagulation C. Antiphospholipid antibody ELISAs: survey on the performance of clinical laboratories assessed by using lyophilized affinity-purified IgG with anticardiolipin and anti-beta2-Glycoprotein I activity. Thromb Res. 2007;120:127-33.*

Methodology for aCL and aβ2GPI

Results expression

Diagnostic criteria

- aCL/aβ2GPI reported with **titer and local cut-off value**
- Value above the **cut-off value (99th percentile)= positive**
- Numerical values vary between test platforms: one numeric value cannot be recommended as a general criterion for positivity
- Semiquantitative reporting (L-M-H) is not recommended due to variability in titers between systems

***Devreese KMJ**, Pierangeli SS, de Laat B, Tripodi A, Atsumi T, Ortel TL. Subcommittee on Lupus Anticoagulant/Phospholipid/Dependent A. Testing for antiphospholipid antibodies with solid phase assays: guidance from the SSC of the ISTH. J Thromb Haemost. 2014;12:792-795. **Miyakis S** et al . International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). J Thromb Haemost. 2006;4 :295-306. **Barbhaiya** et al. 2023 ACR/EULAR Antiphospholipid Syndrome Classification Criteria. Arthr & Rheum 2023; 75:1687-702*

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Diagnostic criteria

Classification criteria

Sydney classification criteria (2006):

- 40 GPL/ MPL or > 99th p thresholds for medium/high aCL IgG/IgM levels, by ELISA
- > 99th p is positive for aβ2GPI IgG/IgM, by ELISA

ACR/ EULAR classification criteria (2023):

aCL and aβ2GPI thresholds of moderate (40–79 units) and high (>80 units), by ELISA

High-priority: Other aCL/anti-β2GPI testing platforms, e.g., automated laboratory systems, to determine the "moderate" and "high" thresholds corresponding to ELISA

***Devreese KMJ**, Pierangeli SS, de Laat B, Tripodi A, Atsumi T, Ortel TL. Subcommittee on Lupus Anticoagulant/Phospholipid/Dependent A. Testing for antiphospholipid antibodies with solid phase assays: guidance from the SSC of the ISTH. J Thromb Haemost. 2014;12:792-795. **Miyakis S** et al . International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). J Thromb Haemost. 2006;4 :295-306. **Barbhaiya** et al. 2023 ACR/EULAR Antiphospholipid Syndrome Classification Criteria. Arthr & Rheum 2023; 75:1687-702*

Methodology for aCL and aβ2GPI

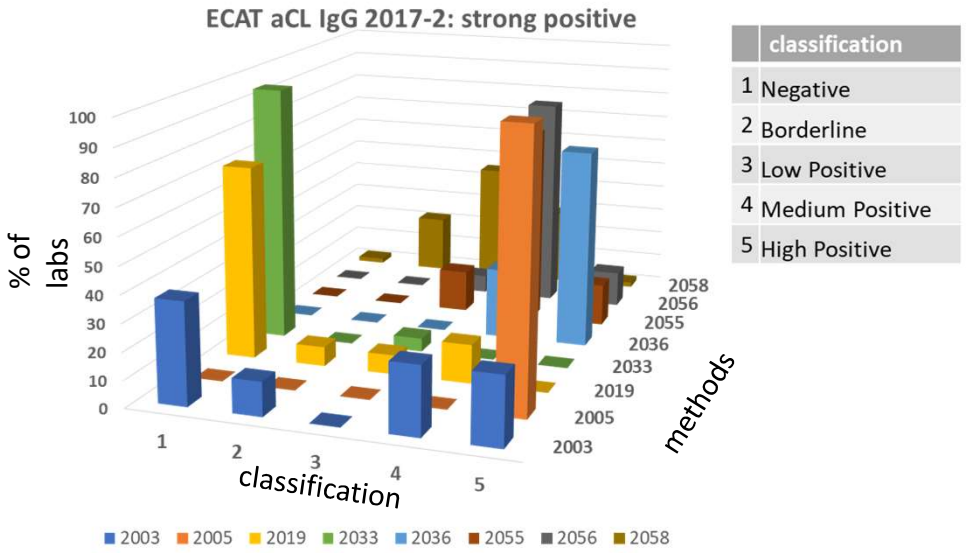
Results expression

Semiquantitative classification (**low-medium-high**)

Diagnostic criteria

Classification criteria

Harmonization to identify low-medium-high positive

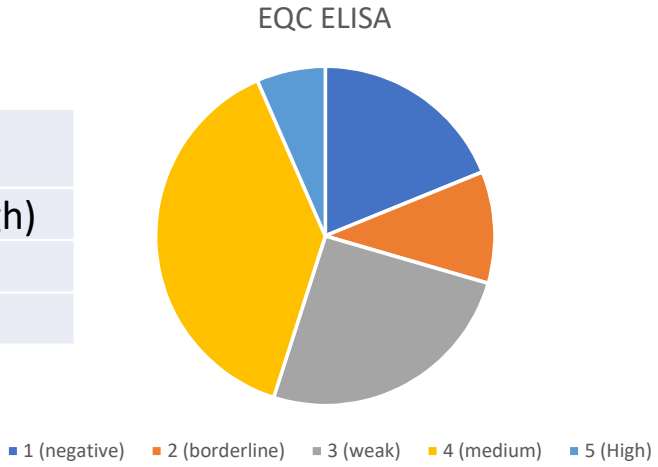


- EQC results: classification into low-medium-high positive depends on method and user
- No guidance on how to classify in ranges of L-M-H for non-ELISA methods

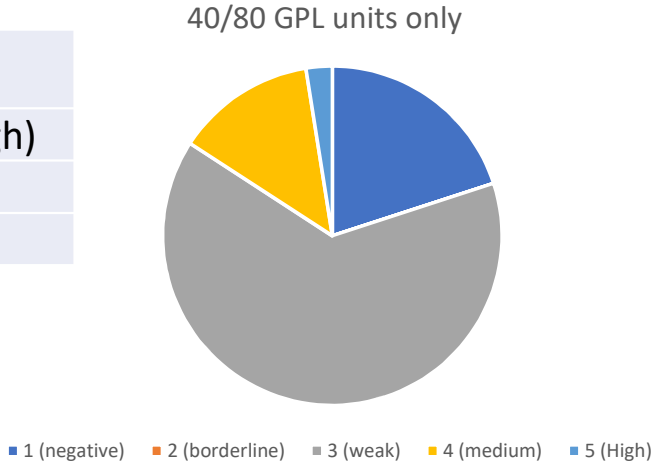
Semiquantitative interpretation of aCL and aβ2GPI

Results ELISA aCL IgG 2017-2

	Results reported by participants				
	1 (negative)	2 (borderline)	3 (weak)	4 (medium)	5 (high)
n	23	13	31	47	8
%	18,9	10,7	25,4	38,5	6,6



	Categorization based on thresholds 40/80				
	1 (negative)	2 (borderline)	3 (weak)	4 (medium)	5 (high)
n	24	0	77	16	3
%	19,7	0,0	64,8	13,1	2,5



=> Less variation in classification

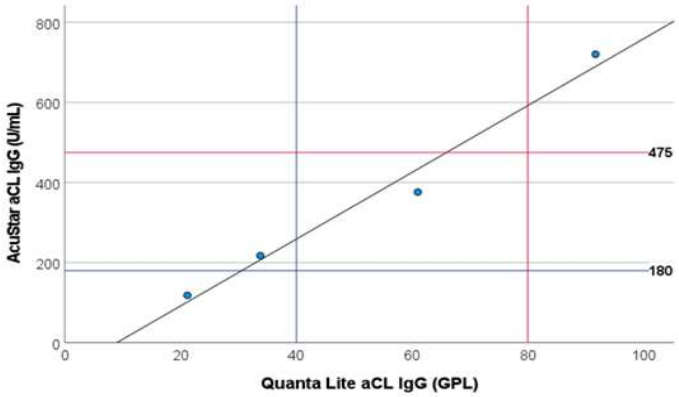
Methodology for aCL and aβ2GPI

Results expression

Semiquantitative classification (**low-medium-high**)

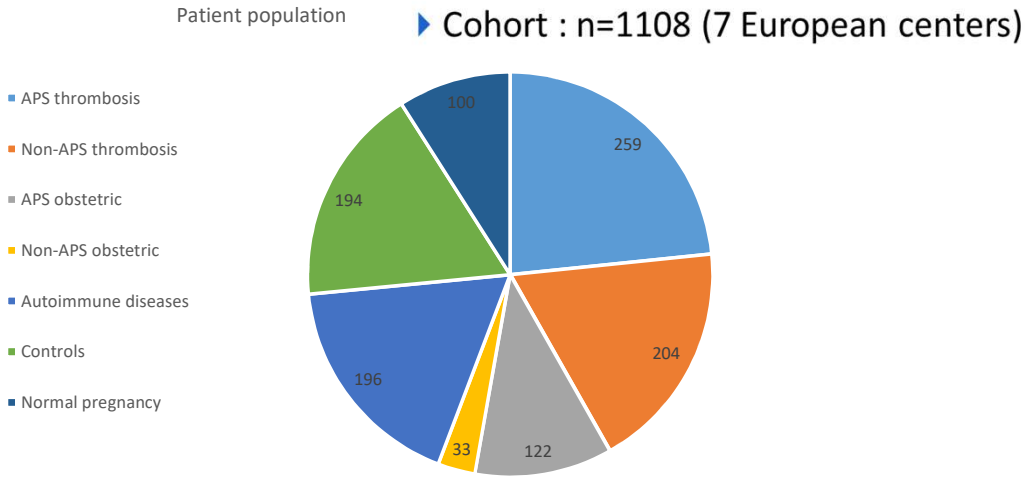
How to classify non-ELISA methods?

Standard materials



Sapporo HCAL dilution series
y=74,92+ 8,34x

ROC analysis



Tested with ELISA and other platforms
Corresponding threshold based on sensitivity or specificity

***Vandevelde A**. et al. Semiquantitative interpretation of anticardiolipin and antiß2glycoprotein I antibodies measured with various analytical platforms: Communication from the ISTH SSC Subcommittee on Lupus Anticoagulant/Antiphospholipid Antibodies. J Thromb Haemost 2022, 20: 508-524*

Semiquantitative interpretation of aCL and aβ2GPI

Results expression

Semiquantitative classification (**low-medium-high**)

- **Adapted thresholds** (ROC curve analysis) according to the solid phase method

N=853 TAPS	ELISA GPL/MPL	CLIA U/mL	MFI U/mL		ELISA GPL/MPL	CLIA U/mL	MFI U/mL
aCL IgG				**aβ2GPI IgG**			
Moderate	40	202	748	Moderate	40	1959	2300
High	80	492	1955	High	80	4904	5118
aCL IgM				**aβ2GPI IgM**			
Moderate	40	45	36	Moderate	40	31	47
High	80	170	121	High	80	66	83

moderate/high cutoff CLIA/MFI vs ELISA

- 40/80 is only applicable for ELISA
- is higher for CLIA and MFI
- higher for IgG vs IgM for CLIA and MFI
- is different for aCL and aβ2GPI for CLIA and MFI

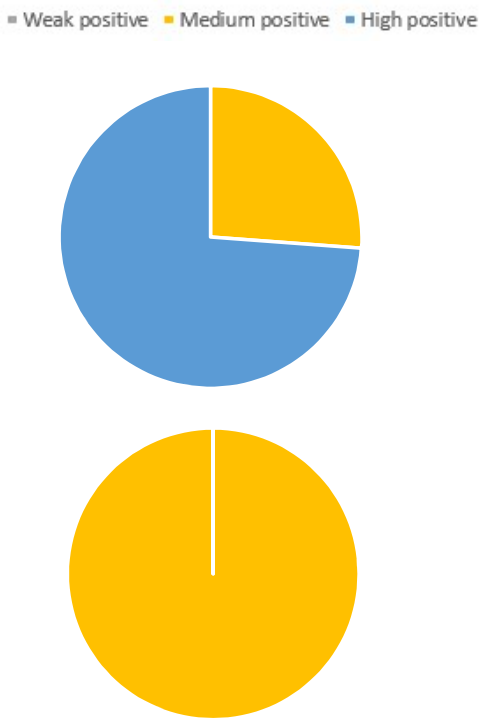
***Vandevelde A**. et al. Semiquantitative interpretation of anticardiolipin and antiß2glycoprotein I antibodies measured with various analytical platforms: Communication from the ISTH SSC Subcommittee on Lupus Anticoagulant/Antiphospholipid Antibodies. J Thromb Haemost 2022, 20: 508-524*

Semiquantitative interpretation of aCL and aβ2GPI

Results CLIA (Acustar) aCL IgG 2017-2

	2 (borderline)	3 (weak)	4 (medium)	5 (high)
	Results reported by participants			
n	0	0	11	31
%	0	0	26,2	73,8
	Based on ROC thresholds			
n	0	1	41	0
%	0	2,4	97,6	0

=> Less variation in classification



Semiquantitative interpretation of aCL and aβ2GPI

Results expression

Semiquantitative classification (**low-medium-high**)

- **Adapted thresholds** according to the solid phase method

Thresholds into L-M-H and clinical relevance?
likelihood ratio: appropriateness of laboratory testing

Vandevelde A. *et al. Semiquantitative interpretation of anticardiolipin and antiß2glycoprotein I antibodies measured with various analytical platforms: Communication from the ISTH SSC Subcommittee on Lupus Anticoagulant/Antiphospholipid Antibodies. J Thromb Haemost 2022, 20: 508-524*

Semiquantitative interpretation of aCL and aβ2GPI

Results expression → Semiquantitative classification (**low-medium-high**)

- **Adapted thresholds** according to the solid phase method

Thresholds into L-M-H and clinical relevance?
likelihood ratio: appropriateness of laboratory testing

aCL IgG	CLIA		ELISA		FEIA		MFI	
N= 1108	Level interval	IS-LR	Level interval	IS-LR	Level interval	IS-LR	Level interval	IS-LR
Low	20-89	**3.5**	20-32	**4.8**	10-21	**1.9**	20-180	**3.3**
Moderate	89-770	**12**	32-98	**9.0**	21-150	**9.8**	180-3000	**11**
High	≥770	**22**	≥98	**23**	≥150	**28**	≥3000	**22**

ELISA and non-ELISA adapted thresholds

- LR+ increase with higher levels of aPL and high titers indicate the highest risk

Vandevelde A. et al. unpublished data 2024

aCL and aβ2GPI: isotype

Diagnostic criteria

Classification criteria

aCL/aβ2GPI IgG/IgM		aCL/aβ2GPI IgA
▪ aCL and aβ2GPI IgM are correlated with thrombosis and pregnancy morbidity ▪ More significant correlations for IgG ▪ Significant associations for IgM also found with corresponding IgG	Literature	▪ aCL and aβ2GPI IgA antibodies are associated with thrombosis and pregnancy morbidity ▪ The added value of IgA aPL in APS is not clear ▪ In SLE aβ2GPI IgA associated with DVT and stroke
▪ Higher odds ratios for IgG compared to IgM positivity ▪ Single positivity for IgM is not associated with thrombosis, single positivity is more frequent in obstetric APS ▪ Addition of IgM (on top of IgG) aPL to the criteria panel increases the association with thrombosis	Multicenter study	▪ Single positivity for IgA is not associated with thrombosis or pregnancy morbidity ▪ Addition of IgA aPL to the criteria panel does not increase the association with thrombosis or pregnancy morbidity ▪ IgA aCL/aβ2GPI not included in diagnostic and classification critera

Devreese KMJ. *et al. Communication from the SSC of the ISTH J Thromb Haemost. 2018;16(4):809-813;* ***Devreese KMJ et al.*** *Testing for antiphospholipid antibodies with solid phase assays: guidance from the SSC of the ISTH. J Thromb Haemost. 2014;12:792-795.* ***Kelchtermans H.*** *et al. gG/IgM antiphospholipid antibodies present in the classification criteria for the antiphospholipid syndrome: a critical review of their association with thrombosis. J Thromb Haemost. 2016;14:1530-1548.* ***Chayoua W.*** *et al The (non-)sense of detecting anti-cardiolipin and anti-ß2glycoprotein I IgM antibodies in the antiphospholipid syndrome. J Thromb Haemost. 2020;18:169-179.* ***Chayoua W.*** *et al. Is There an Additional Value in Detecting Anticardiolipin and Anti-ß2 glycoprotein I IgA Antibodies in the Antiphospholipid Syndrome? Thrombosis and Haemostasis, 2020 120:1557-1568.*

Other antiphospholipid antibodies (aPL)

Criteria aPL

- Lupus anticoagulant (LAC)
- Anticardiolipin antibodies (aCL)IgG/IgM
- Beta-2-glycoprotein I antibodies(aß2GPI)IgG/IgM

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Diagnostic criteria

Classification criteria

other aPL

- Antiphosphatidylserine/ prothrombin (aPS/PT)
- Anti-domain I β2GPI

Solid phase assays

***Devreese KMJ**, Ortel TL, Pengo V, de Laat B. Subcommittee on Lupus Anticoagulant/Antiphospholipid Anitbodies. Laboratory criteria for antiphospholipid syndrome: communication from the SSC of the ISTH. J Thromb Haemost. 2018;16: 809-813.*

Other antiphospholipid antibodies (aPL)

Antiphosphatidylserine/prothrombin antibodies (aPS/PT)

- High prevalence in APS
  - IgG/IgM 58-72 %
  - aPS/PT more frequent in LA positives (55-100%)
  - in double/triple positive patients (71-100%)
- Association with clinical APS
  - Thrombotic APS 6 studies OR 2.6-14.0
  - Obstetric APS 2 studies OR 5.7-11.0
- No added value for diagnosis
  - Single aPS/PT is very rare
  - Tetrapositive patients have comparable Odd ratios

    TAPS: OR 5.9 [4.3-8.4]

    Triple positive 27.3 [16.4-45.5]

    Tetra positive 27.3 [16.1-46.2]

Zhu R *et al. Prevalence of aPhosphatidylserine/prothrombin antibodies and association with antiphospholipid antibody profiles in patients with antiphospholipid syndrome: a systematic review and metaanalysis. Thromb Res 2022; 214: 106-114.*
Vandevelde A *et al. Added value of antiphosphatidylserine/prothrombin antibodies in the workup of thrombotic antiphospholipid syndrome: Communication from the ISTH SSC Subcommittee on Lupus Anticoagulant/Antiphospholipid Antibodies. J Thromb Haemost 2022; 20: 2136-2150;* ***Vandevelde A*** *et al. J Thromb Haemost. 2023;21:1981–1994.*

Other antiphospholipid antibodies (aPL)

Antiphosphatidylserine/prothrombin antibodies (aPS/PT)

- High prevalence in APS
  - IgG/IgM 58-72 %
  - aPS/PT more frequent in LA positives (55-100%)
  - in double/triple positive patients (71-100%)
- Association with clinical APS
  - Thrombotic APS 6 studies OR 2.6-14.0
  - Obstetric APS 2 studies OR 5.7-11.0
- No added value for diagnosis
  - Single aPS/PT is very rare
  - Tetrapositive patients have comparable Odd ratios

    TAPS: OR 5.9 [4.3-8.4]
    Triple positive 27.3 [16.4-45.5]
    Tetra positive 27.3 [16.1-46.2]

Anti-domain I aβ2GPI IgG (aDI)

- Role of aDI in APS
  - Variable exposure of the specific epitope in commercial assays
  - Inconsistent results for correlation with thrombosis and added value of aDI
- High prevalence in triple positive patients, and higher titer of aDI
- No added value for diagnosis

  TAPS: OR
  Triple positive 2.8 [2.1-3.8]
  Tetra positive 2.9 [2.2-3.8]

__Zhu R__ et al. Prevalence of aPhosphatidylserine/prothrombin antibodies and association with antiphospholipid antibody profiles in patients with antiphospholipid syndrome: a systematic review and metaanalysis. Thromb Res 2022; 214: 106-114.
__Vandevelde A__ et al. Added value of antiphosphatidylserine/prothrombin antibodies in the workup of thrombotic antiphospholipid syndrome: Communication from the ISTH SSC Subcommittee on Lupus Anticoagulant/Antiphospholipid Antibodies. J Thromb Haemost 2022; 20: 2136-2150; __Vandevelde A__ et al. J Thromb Haemost. 2023;21:1981–1994.

__Yin D.__ et al. The clinical value of assays detecting antibodies against domain I of β2-glycoprotein I in the antiphospholipid syndrome. Autoimmunity Reviews 2018; 17: 1210-1218
__Yin D__. et al. Detection of anti-domain I antibodies by chemiluminescence enables the identification of high-risk antiphospholipid syndrome patients: a multicenter multiplatform study. J Thromb Haemost 2020; 18:463-478

Non-criteria aPL aPS/PT and aDI

Role of aPS/PT and aDI in APS

- aPS/PT cannot not replace LA in all APS patients

- aPS/PT and aDI frequently positive in triple positive patients, but do not increase the risk for thrombosis or pregnancy morbidity
- aPS/PT and aDI **confirm the patients at risk** but not essential for first-line diagnosis

aPS/PT and aDI can have added value in patients with an incomplete antibody profile:

- aPS/PT **add value** to aCL/aβ2GPI: could be used to consolidate a high risk aPL profile in patients with aCL and aβ2GPI positivity and LA negative/ unreliable
- aPS/PT can confirm single LA positivity
- aDI can confirm/exclude clinical risk in single LA or aβ2GPI positive patients

***Zhu R** et al. Thromb Res 2022; 214: 106-114. **Vandevelde A** et al. Added value of antiphosphatidylserine/prothrombin antibodies in the workup of thrombotic antiphospholipid syndrome: Communication from the ISTH SSC Subcommittee on Lupus Anticoagulant/Antiphospholipid Antibodies. J Thromb Haemost 2022; 20: 2136-2150. **Yin D.** et al. Detection of anti-domain I antibodies by chemiluminescence enables the identification of high-risk antiphospholipid syndrome patients: a multicenter multiplatform study. J Thromb Haemost 2020; 18:463-478.*

Laboratory diagnosis of APS

Cornerstone of laboratory diagnosis of APS

Lupus anticoagulant
Anticardiolipin antibodies IgG/IgM
Anti-β2-glycoprotein I antibodies IgG/IgM

Complex methodology

- aPL define the diagnosis of APS
- Perform all three assays **LA, aCL IgG/IgM, aß2GPI IgG/M** at the same time to increase diagnostic utility
- No routine testing for other aPL (aPS/PT, aDI)
- LA is reported with a final conclusion as positive/negative
- Report and aCL and aβ2GPI IgG/IgM with titer, along with local cut-off value
- Further efforts to harmonize ranges of low-medium-high positive aCL/aβ2GPI

- Only **persistently** positive results are clinically relevant
- Make an integrated interpretation of LA, aCL and aβ2GPI (**aPL profile**)
- Results should be interpreted in a **clinical context** and knowledge of the patient's anticoagulation status
- A report with an **explanation** of the results should be given with warning for interference
- Perform assays according to **guidelines** for more harmonisation

***Devreese KMJ**, Ortel TL, Pengo V, de Laat B. Subcommittee on Lupus Anticoagulant/Antiphospholipid Anitbodies. Laboratory criteria for antiphospholipid syndrome: communication from the SSC of the ISTH. J Thromb Haemost. 2018;16: 809-813. **Devreese KMJ** et al. Update of the guidelines for lupus anticoagulant detection and interpretation. Guidance from the ISTH-SSC J Thromb Haemost 2020; 18:2828–2839. **Devreese KMJ** et al. Subcommittee on Lupus Anticoagulant/Phospholipid/Dependent A. Testing for antiphospholipid antibodies with solid phase assays: guidance from the SSC of the ISTH. J Thromb Haemost. 2014;12:792-795.*

THANK YOU FOR YOUR ATTENTION

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