Antiphospholipid Antibody results and clinical implications

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ECAT symposium
15-16/9/2022

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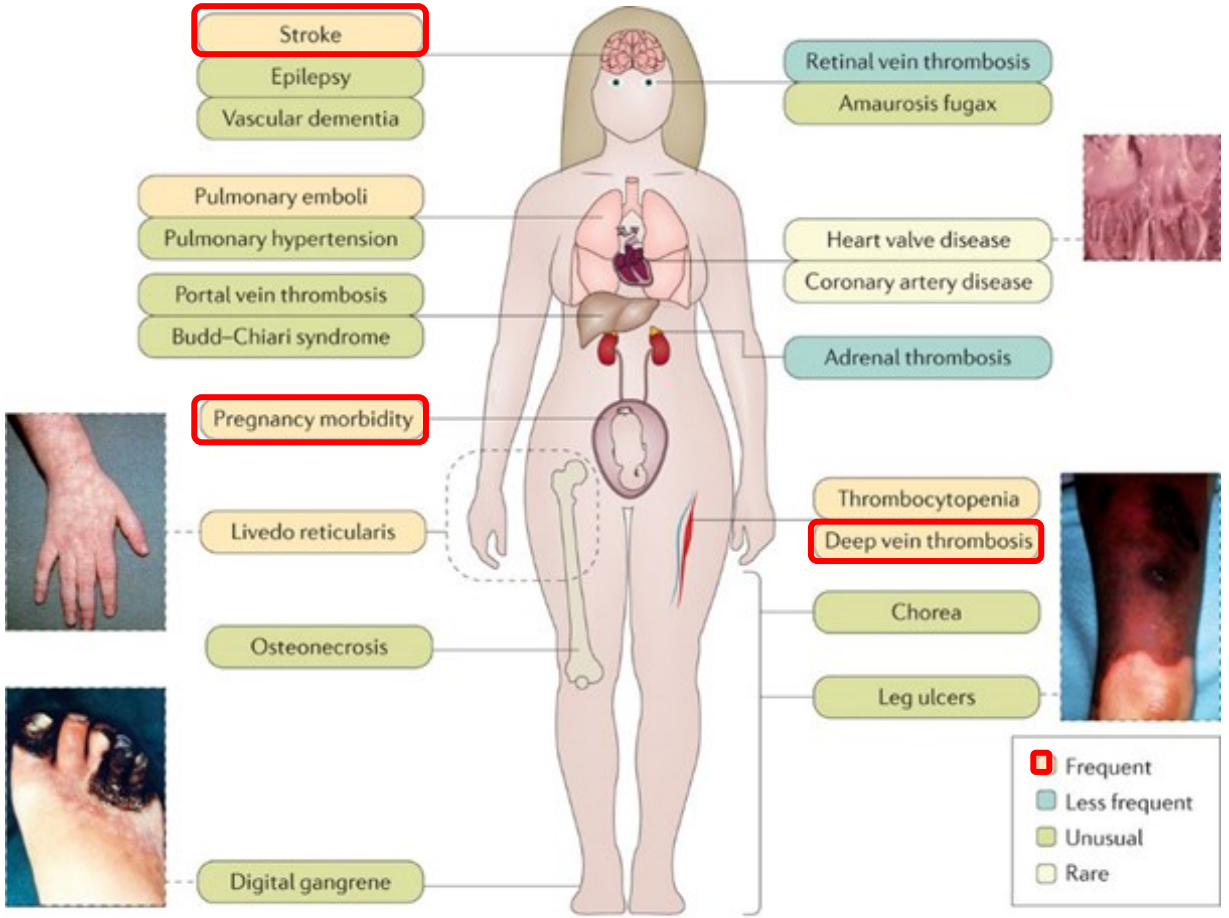
Antiphospholipid syndrome (APS)

Clinical manifestations

Prevalence: 40-50/ 100 000 individuals
Incidence: 1-5 new cases/100 000 individuals/year



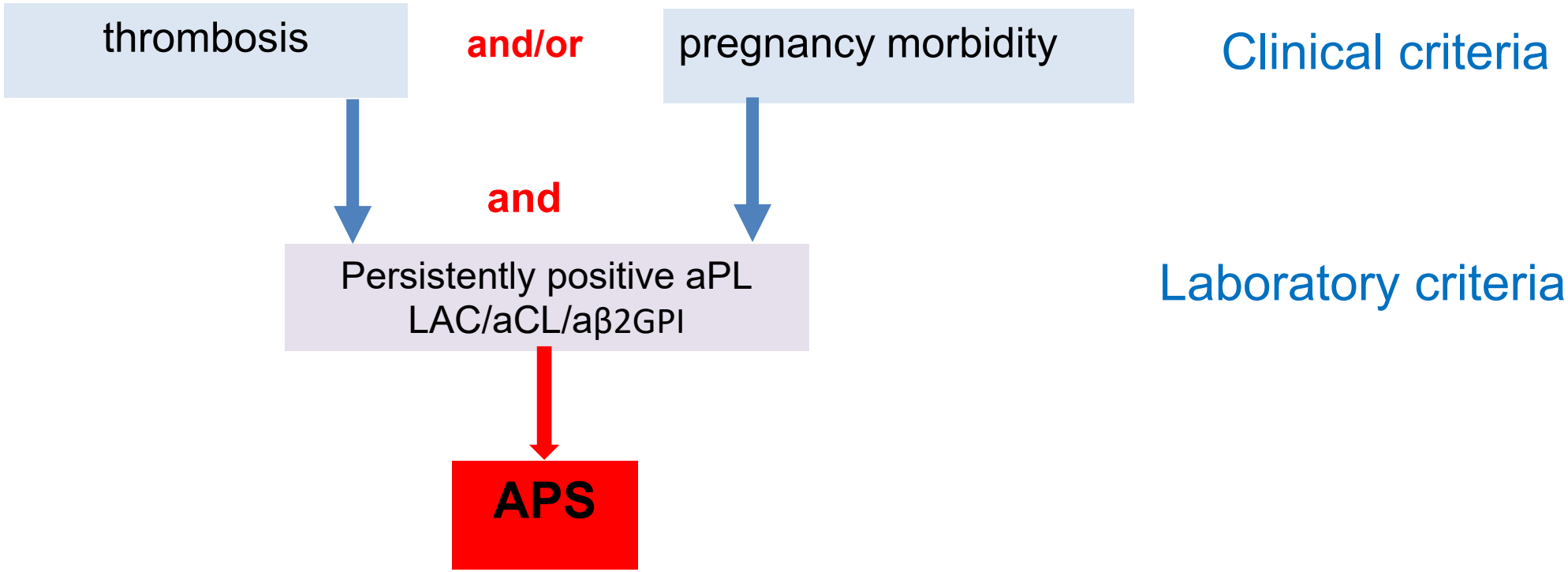
Images courtesy of Y. Shoenfeld

>20% of individuals with aPL
10-20%
<10%
<1%

Miyakis 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.

Diagnosis of Antiphospholipid syndrome (APS)

- Clinical symptoms
- Presence of **antiphospholipid antibodies** (aPL)



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Antiphospholipid syndrome (APS)

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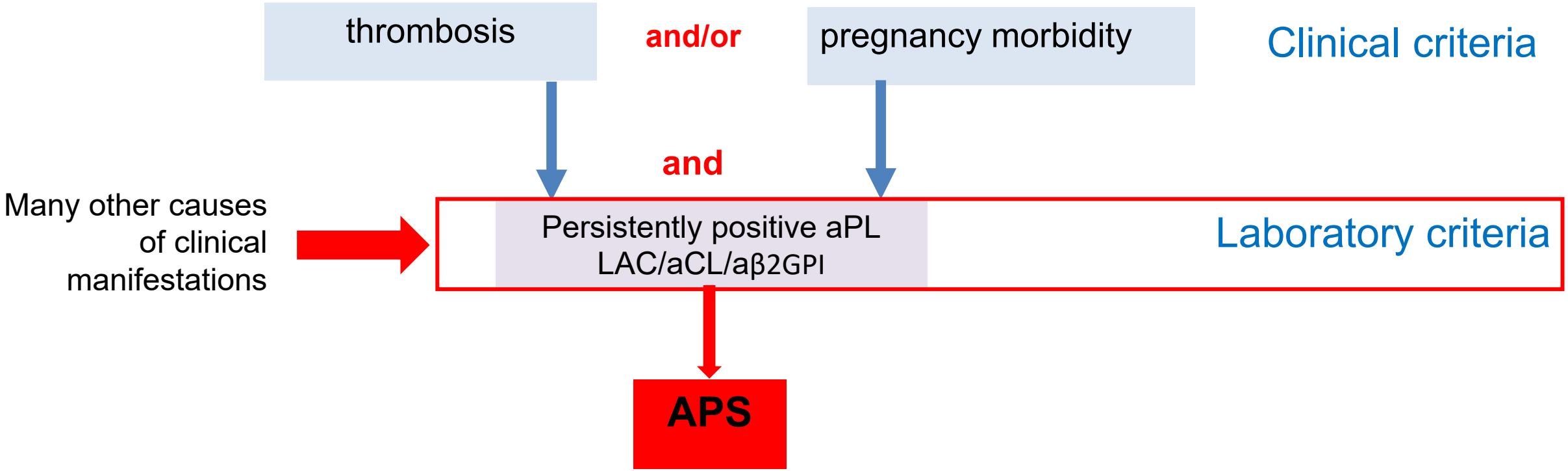
- Presence of **antiphospholipid antibodies** (aPL)



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Patient selection for testing for aPL

-focus on patients who are likely to have APS

-younger patients (<50 years) with unprovoked venous or arterial thrombosis
-thrombosis at unusual sites

-pregnancy morbidity
-thrombosis and/or pregnancy complications in patients with autoimmune disease

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 International Society on Thrombosis and Haemostasis. J Thromb Haemost 2020; 18:2828–2839.
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-recurrent VTE unexplained by subtherapeutic anticoagulation, patient nonadherence, or malignancy

-younger patients (<50 years) with noncriteria clinical manifestations, eg cognitive dysfunction, valvular heart disease, thrombocytopenia with presence of other systemic autoimmune diseases

-younger patients (<50 years) following provoked VTE when the provoking environmental factor is mild

-patients with unexplained prolonged aPTT as incidental finding

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 International Society on Thrombosis and Haemostasis. J Thromb Haemost 2020; 18:2828–2839.
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Laboratory criteria of APS

Lupus anticoagulant (LAC)

and/or

Anticardiolipin antibodies (aCL)IgG/IgM

and/or

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

Sydney classification criteria (2006)
~ Diagnostic criteria

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AMERICAN COLLEGE of RHEUMATOLOGY
Empowering Rheumatology Professionals

Development of a New International Antiphospholipid Syndrome Classification Criteria Phase I/II Report: Generation and Reduction of Candidate Criteria

Medha Barbhaiya,[1] Stephane Zuily,[2] Yasaman Ahmadzadeh,[3] Mary-Carmen Amigo,[4] Tadej Avcin,[5] Maria Laura Bertolaccini,[6] D. Ware Branch,[7] Guilherme de Jesus,[8] Katrien M. J. Devreese,[9] Camille Frances,[10] David Garcia,[11] Francis Guillemin,[12] Steven R. Levine,[13] Roger A. Levy,[14] Michael D. Lockshin,[1] Thomas L. Ortel,[15] Surya V. Seshan,[16] Maria Tektonidou,[17] Denis Wahl,[2] Rohan Willis,[18] Ray Naden,[†] Karen Costenbader,[19] and Doruk Erkan,[1] on behalf of the New APS Classification Criteria Collaborators

LAC, aCL and aβ2GPI are retained for the laboratory part, no other aPL

Miyakis et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). J Thromb Haemst 2006; 4: 295-306.
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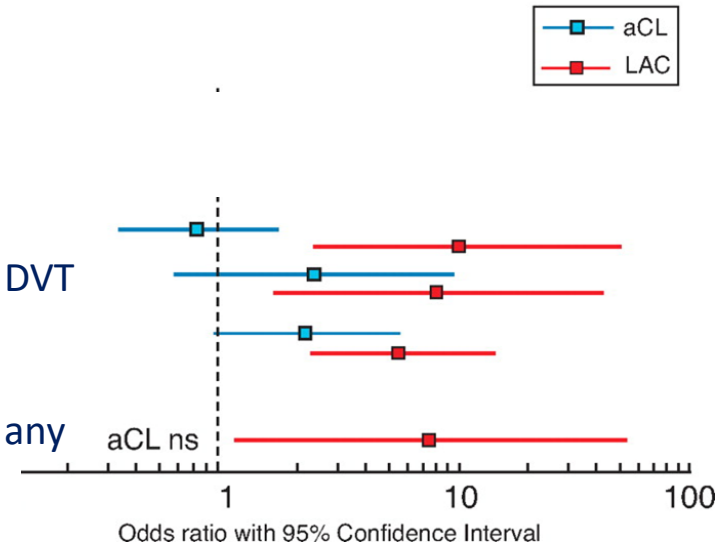
Role of aPL in APS

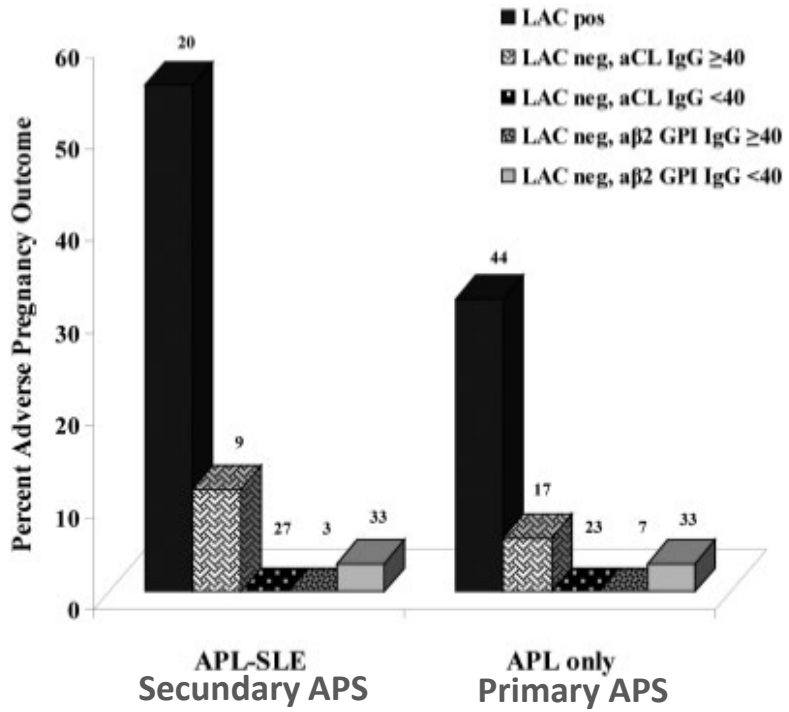
- aPL are part of the diagnostic criteria for APS
- Thrombotic risk in APS
  - Clinical factors
    - Coexistence of predisposing thrombotic risk factors
    - Association with underlying autoimmune diseases (SLE)
  - Serological factors
    - Type and level of aPL
- The laboratory parameters in risk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

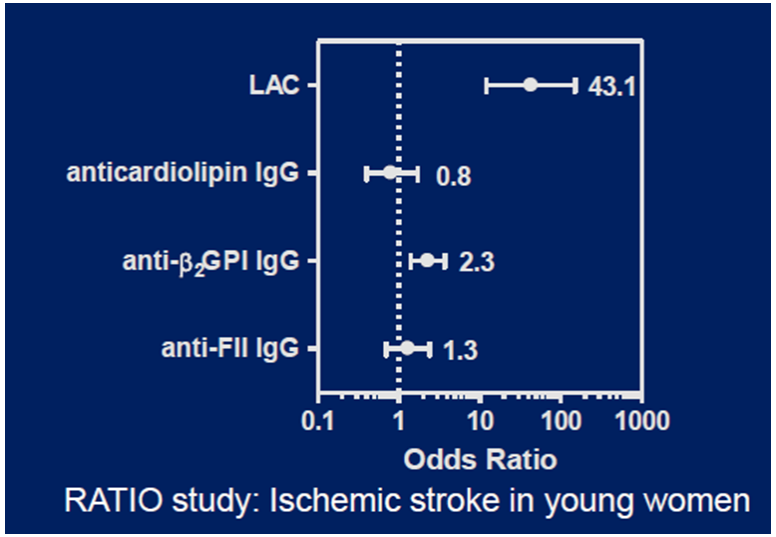
Devreese. Antiphospholipid antibodies: Evaluation of the thrombotic risk. Thromb Res. 2012 Oct;130 Suppl 1:S37-40
Devreese, Ortel, Pengo, de Laat. Laboratory criteria for antiphospholipid syndrome: communication from the SSC of the ISTH. J Thromb Haemost 2018; 16: 809-813

Pathogenicity of LAC

- stronger risk factor for thrombosis and adverse pregnancy outcome than aCL and aβ2GPI
- risk factor for venous and arterial thrombosis







Galli et al. Blood 2003; 101: 1827-32

Lockshin et al. Arthritis Rheum 2012; 64: 2311-8

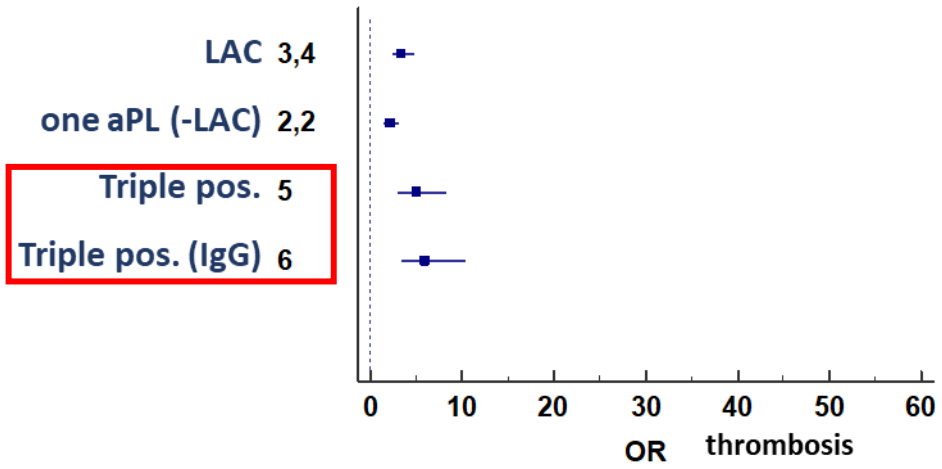
Urbanus et al. Lancet Neurology, 2009, 8: 998-1005

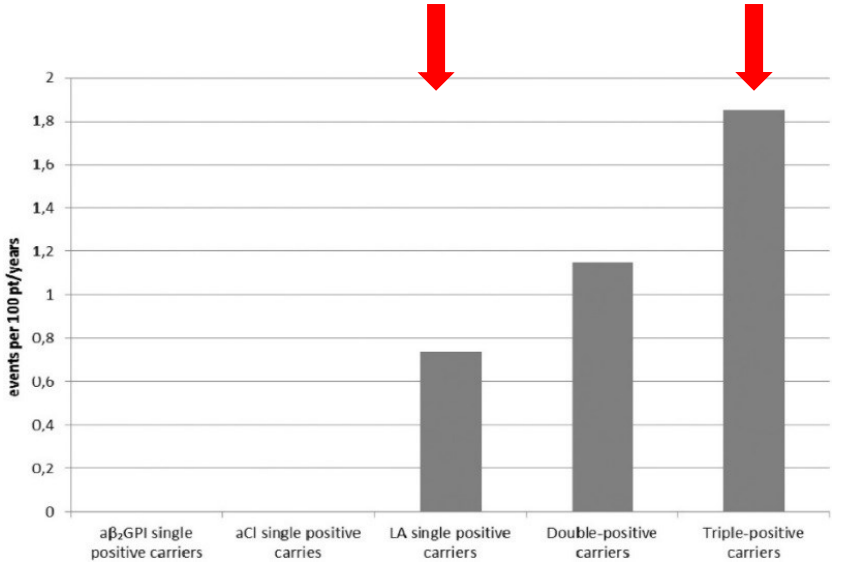
Pathogenicity of LAC

Triple positivity

-triple positivity (LAC/aCL/aβ2GPI) is associated with an increased risk of thrombosis and pregnancy morbidity

-Carriers are at risk for a first event





CHAYOUA ET AL, J THROMB HAEMOST. 2018; 16,2016-23

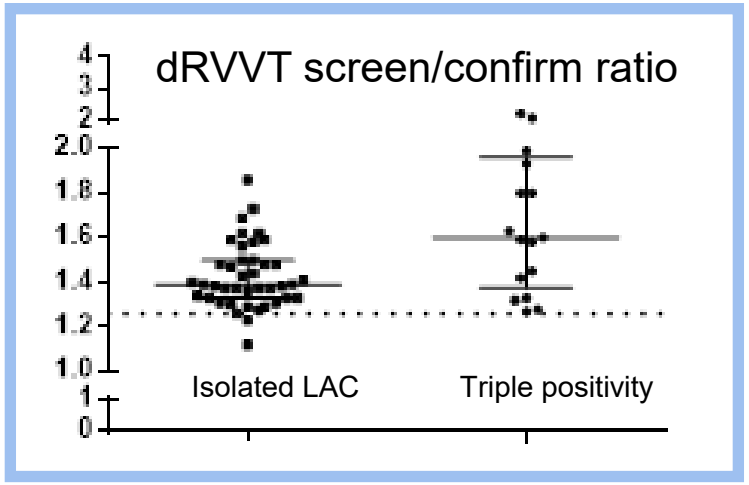
P MUSTONEN ET AL. LUPUS 2014, 23: 1468-1476

Pathogenicity of LAC

Isolated positivity for LAC

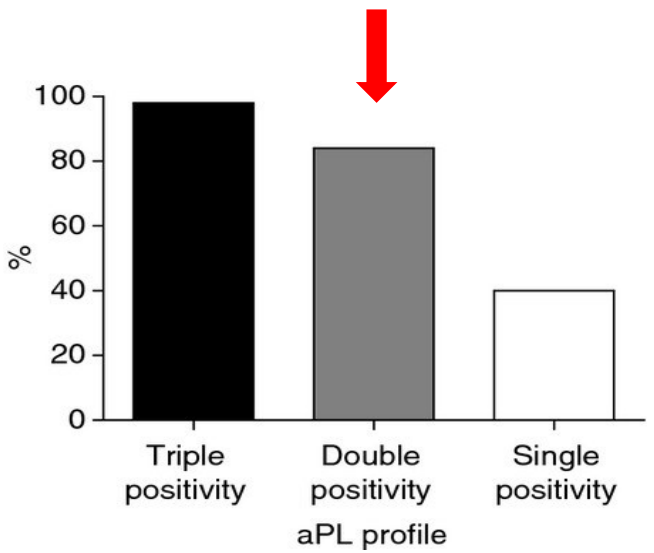
- In absence of clinical symptoms
- In elderly patients
- On a first occasion, not confirmed after 12 weeks
- Lower association with thrombosis, except for myocardial infarction and stroke

- Recent multicentre study:
  - Isolated LAC is associated with thrombosis
    OR 7.3 (3.3–16.1) (n=456)
  - Isolated LAC shows weaker activity than LAC
    in triple positive patients

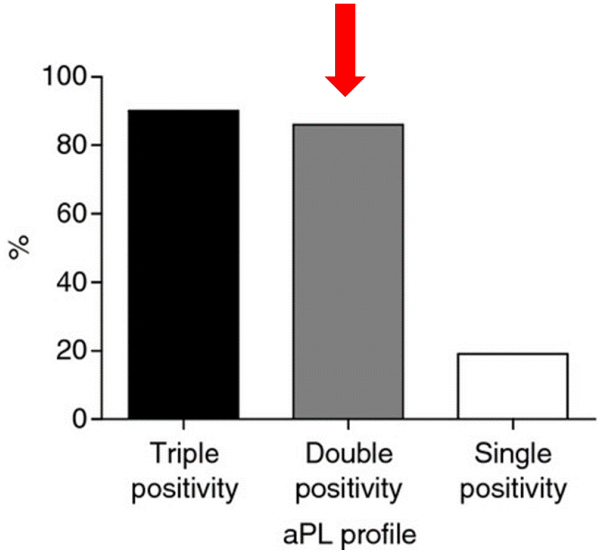


Pengo et al, Thromb Res 2018;
Yin D et al. Clinical Relevance of Isolated Lupus Anticoagulant Positivity in Patients with Thrombotic Antiphospholipid Syndrome. Thromb Haemost 2021; 121: 1220-7

Pathogenicity of aCL and aβ2GPI

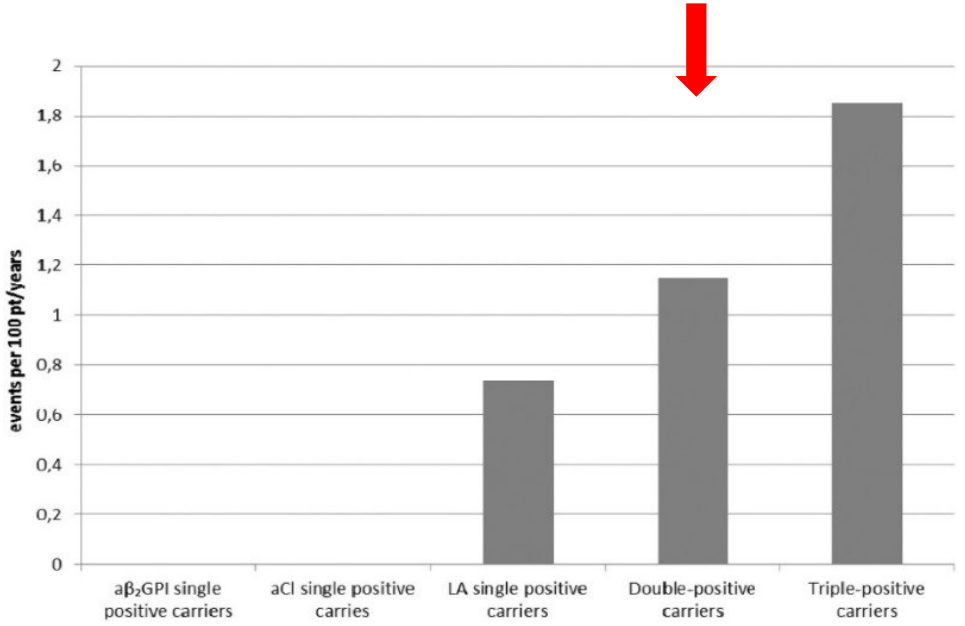


aPL confirmed after 3 months



clinical APS criteria at initial testing

N=161 (APS and non-APS) patients retested after 3 months



risk for first event in asymptomatic carriers N=119

Pengo et al. J Thromb Haemost 2013; 11: 1522-31

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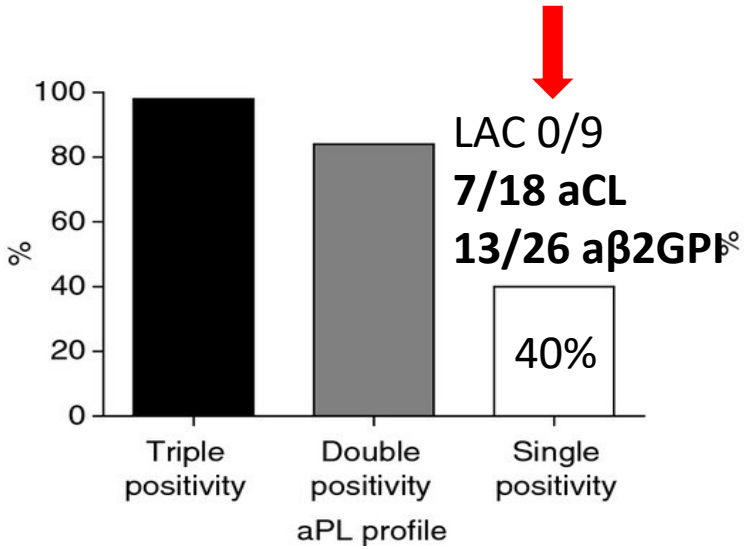
Pathogenicity of aCL and aβ2GPI



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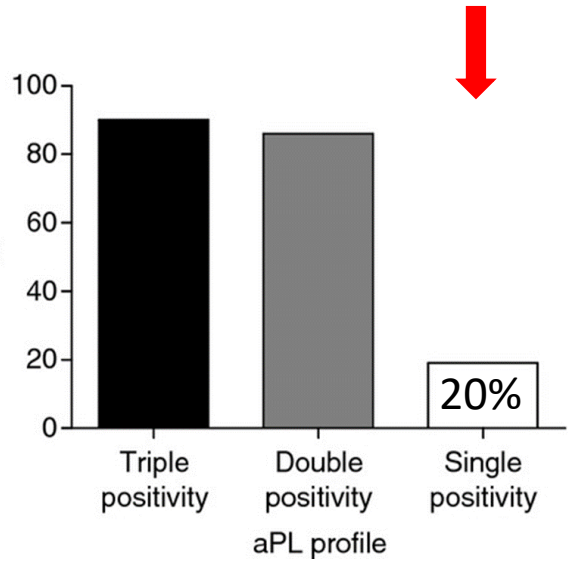

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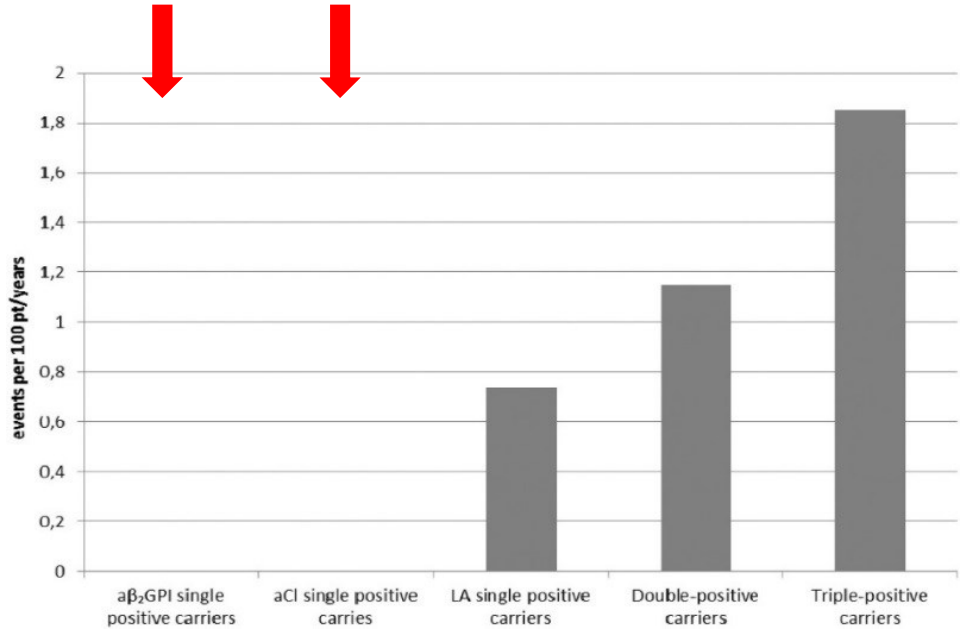

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Laboratory criteria of APS

Methodology for aPL

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

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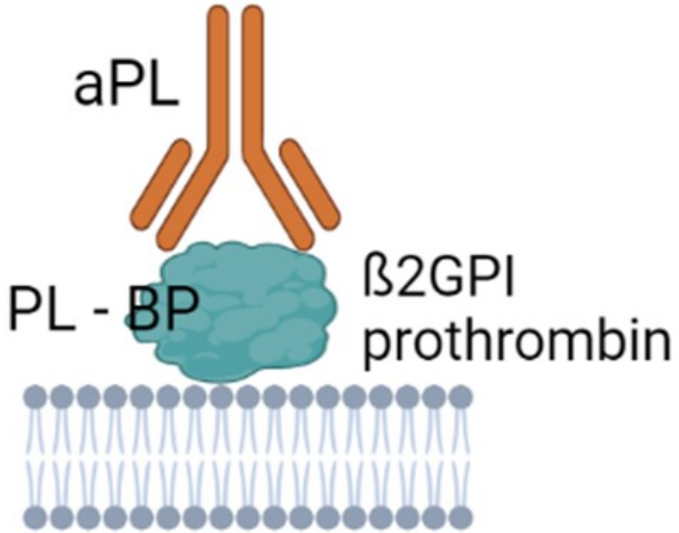
Methodology for aPL

Lupus anticoagulant (LAC)

Phospholipid dependent coagulation tests

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



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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 LAC

Lupus anticoagulant (LAC) → **Phospholipid dependent coagulation tests**

- Complex methodology
  - Two PL-dependent assays (aPTT, dRVVT)
  - LAC= aspecific inhibitor : three step method (screen, mix and confirm)
- False negative/false positive results
  - Acute phase proteins
  - Anticoagulant therapy

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Methodology for LAC

Lupus anticoagulant (LAC)

TOPICS

- Patient selection and timing of testing
- Sample preparation and quality
- Interferences
- Choice of assays, three step procedure
- Calculation and expression of results
- Cut-off values
- Confirmation of persistent LAC

J Thromb Haemost 2020; 18: 2828-2839

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

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Harmonisation in LAC measurement, interpretation and reporting

PRACTICAL GUIDANCE FOR LABORATORY SCIENTISTS AND CLINICIANS

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Lupus Anticoagulant- Interferences

Pre-analytical phase → 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 International Society on Thrombosis and Haemostasis. J Thromb Haemost 2020; 18:2828–2839; Tripodi et al. Lupus anticoagulant testing in anticoagulated patients. Guidance from the Scientific and Standardization Committee for lupus - anticoagulant/antiphospholipid antibodies of the International Society on Thrombosis and Haemostasis. J Thromb Haemost 2020; 18:1569-1575

Lupus Anticoagulant- Interferences

Pre-analytical phase → Interference of anticoagulant therapies

-blood for LAC detection should be collected before initiation of anticoagulation, whenever possible

-testing during anticoagulation: avoid FP and FN

↕

- duration of anticoagulation (long-term in APS)
- choice of anticoagulant (no DOAC in triple positive APS patients)

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Lupus Anticoagulant- Interferences

Pre-analytical phase → Interference of anticoagulant therapies

-blood for LAC detection should be collected before initiation of anticoagulation, whenever possible

-**testing during anticoagulation**: avoid FP and FN

- comment/warning on the report
- antiXa for heparins: LAC is reliable in therapeutic range
- DOAC removal (adsorbant, filter)
- during VKA: difficult interpretation, further study on alternative testing (TSVT/ECT)

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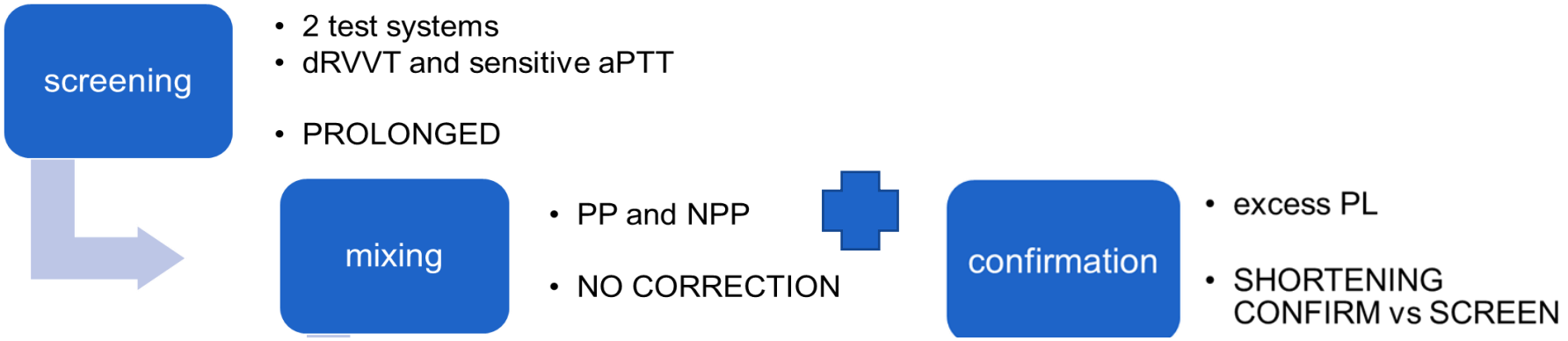
Lupus Anticoagulant- Analytical procedure

Analytical phase

Multiple step procedure

confirmatory test to be performed if the screening test suggests LA presence, irrespective of the result of the mixing test with screening reagent



LAC positive if at least one of the two test systems gives a positive result in the three steps

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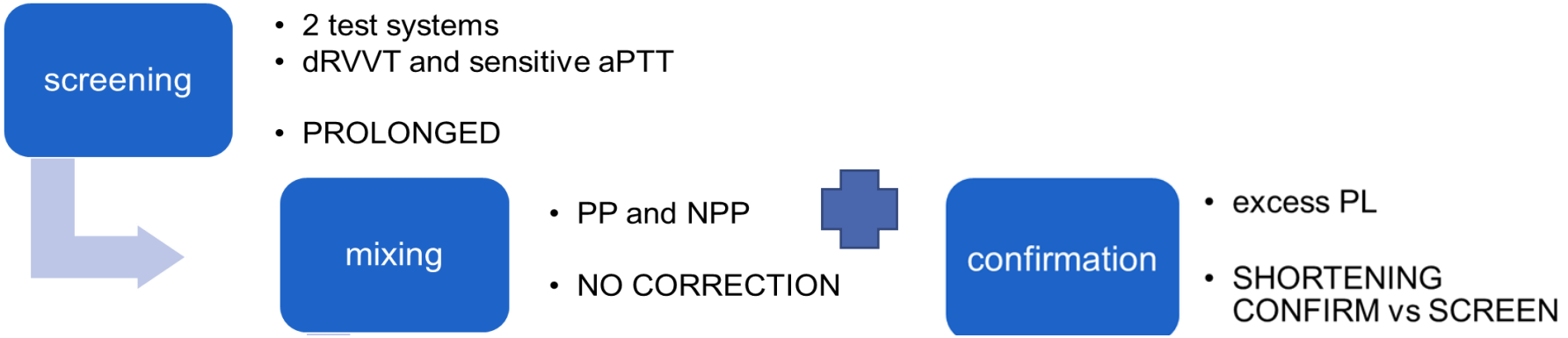
Lupus Anticoagulant- Analytical procedure



Positive	Positive	Positive	LAC present
Positive	Negative	Negative	LAC negative

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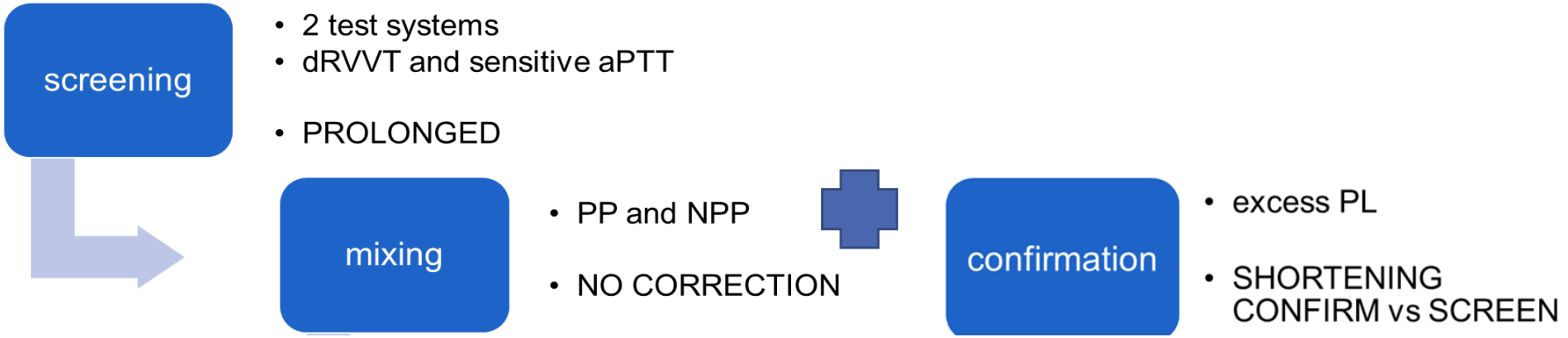
Lupus Anticoagulant- Analytical procedure



Positive	Positive	Positive	LAC present
Positive	Negative	Negative	LAC negative
Positive	**Negative**	**Positive**	**LAC negative with comment!**

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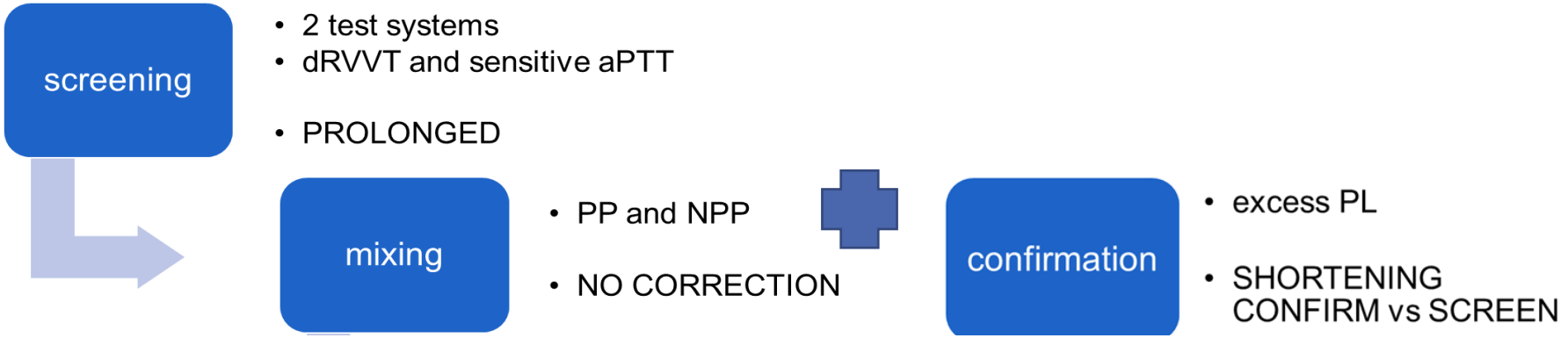

Positive	Positive	Positive	LAC present
Positive	Negative	Negative	LAC negative
Positive	**Negative**	**Positive**	**LAC negative with comment!**

-anticoagulated (VKA) patients
-no anticoagulants: measurement of coagulation factors
-comment on LAC result, repeat LAC testing, interpretation along with aCL and aβ2GPI

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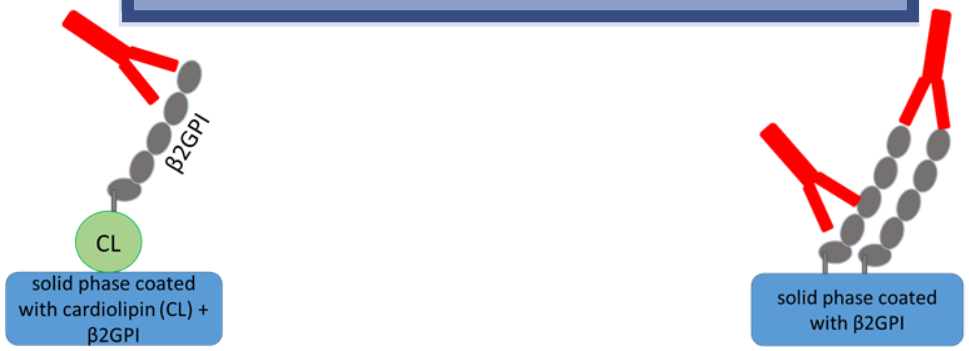
Methodology for aCL and aβ2GPI

Lupus anticoagulant (LAC)

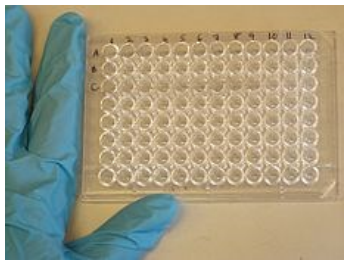
Anticardiolipin antibodies (aCL)IgG/IgM

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



Solid phase assays

One group of aPL



Methodological concerns

-differences in calibration
-differences in assays

variability in results

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

Methodology for aCL and aβ2GPI

Agreement between solid phase assays

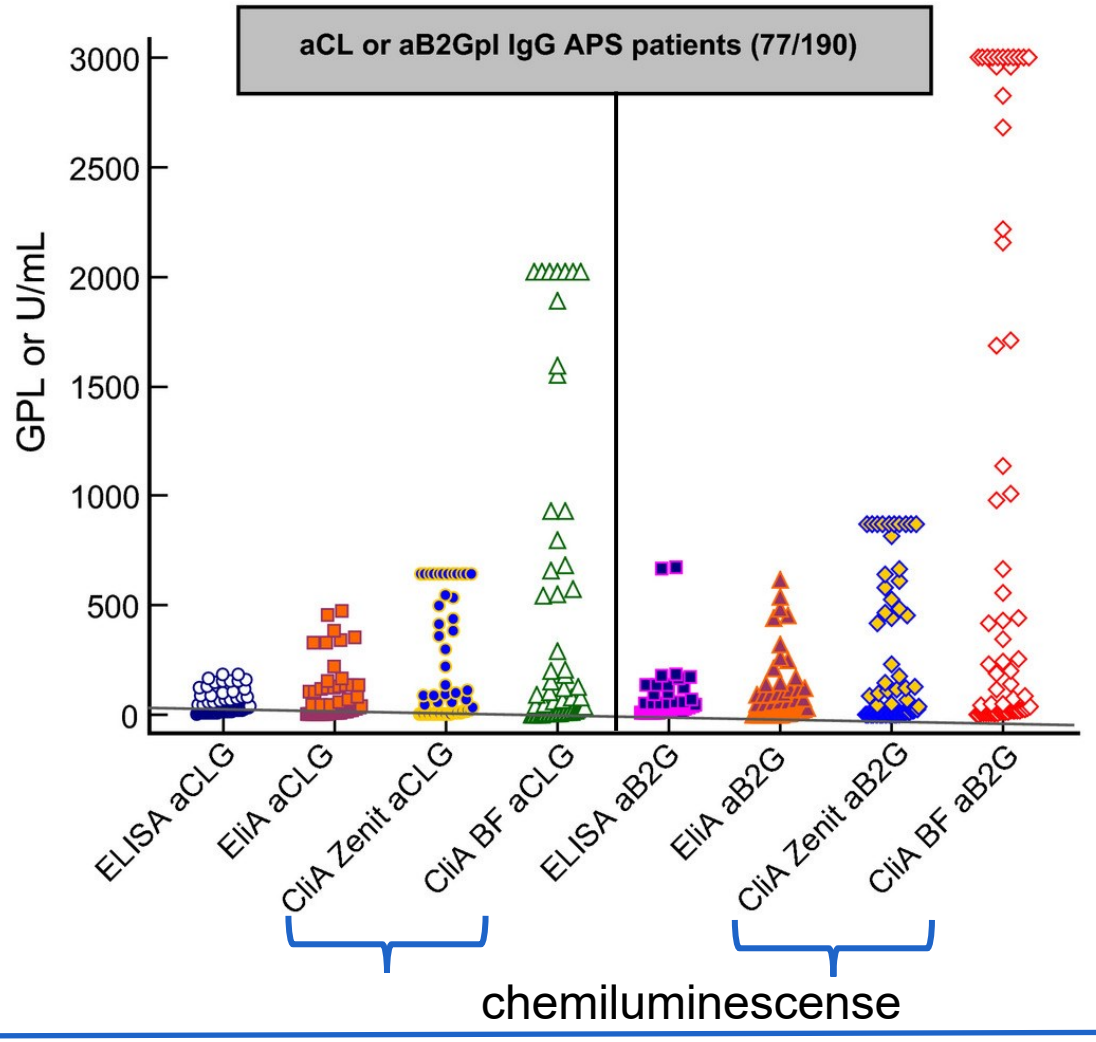
-differences in positive/negative agreement

-differences in titer

Comparison of different immunoassays in APS and non-APS patients

-ELISA (Inova)

-automated systems (Phadia, Zenit, QuantaFlash)



Montaruli B, De Luna E, Erroi L, et al. Analytical and clinical comparison of different immunoassay systems for the detection of antiphospholipid antibodies. Int J Lab Hematol . 2016;38(2):172-182.

Methodology for aCL and aβ2GPI

- Numerical values vary between test platforms: one numeric value (> 40 GPL/MPL, Sydney criteria) cannot be recommended as a general criterion for low/medium-high positivity.
- aCL/aβ2GPI reported with titer and local cut-off value
- Value above the cut-off value (99th percentile) = positive

Devreese KM, 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(5):792-795.

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- aCL/aβ2GPI reported with titer and local cut-off value
- Value above the cut-off value (99th percentile) = positive

- Semiquantitative classification (**low-medium-high**)
  - Useful for the clinicians
  - Benefit the uniformity in interpretation of results
  - Is not recommended due to variability in titers between systems
  - A model of defining the ranges for classification

Devreese KM, 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(5):792-795.

aCL and aβ2GPI: semiquantitative classification

Semiquantitative thresholds

40 and 80 GPL/MPL (Sydney criteria for ELISA): medium/high

aCL IgG	Thrombotic test population (n=853)		
	Range	LR+	95% CI
ELISA	40-80		
ELISA	>80		
aCL IgM			
ELISA	40-80		
ELISA	>80		

Arne Vandevelde, Walid Chayoua, Bas de Laat, Jean-Christophe Gris, Gary W. Moore, Jacek Musiał, Stéphane Zuily, Denis Wahl and Katrien M. J. Devreese. 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

aCL and aβ2GPI: semiquantitative classification

Semiquantitative thresholds

40 and 80 GPL/MPL (Sydney criteria for ELISA): medium/high

aCL IgG	Thrombotic test population (n=853)			
	Range	LR+	95% CI	
ELISA	40-80	**6.2**	3.0	13
ELISA	>80	**27**	9.8	74
aCL IgM				
ELISA	40-80	**5.4**	2.8	10
ELISA	>80	**5.2**	2.2	13

ELISA threshold

Calculation of likelihood ratios (LR) confirms that 80 **G**PL **aCL and aβ2GPI** for ELISA indicates the highest risk

Arne Vandevelde, Walid Chayoua, Bas de Laat, Jean-Christophe Gris, Gary W. Moore, Jacek Musiał, Stéphane Zuily, Denis Wahl and Katrien M. J. Devreese. 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

aCL and aβ2GPI: semiquantitative classification

Semiquantitative thresholds for non-ELISA systems

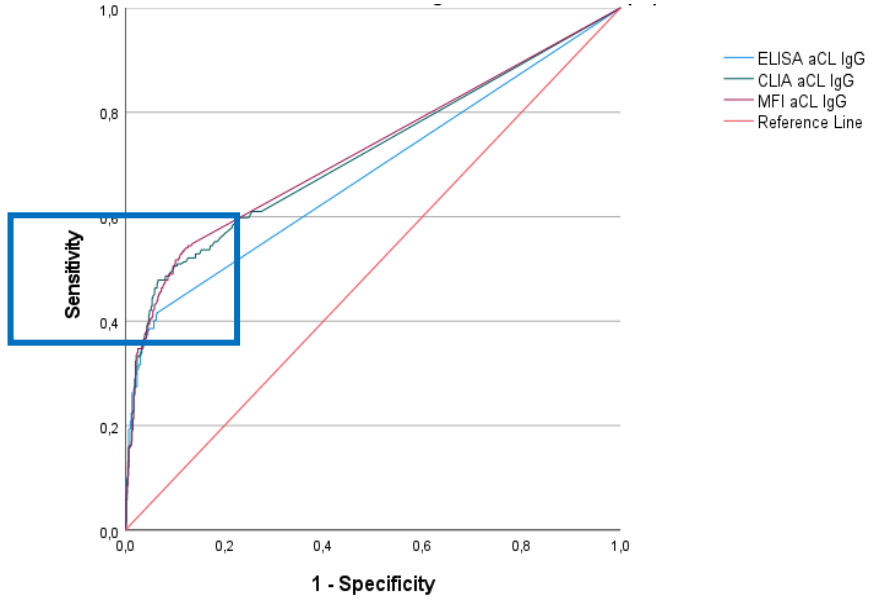
I. **Threshold levels for ELISA GPL/MPL**

- Low 20-40 Moderate: 40-80 High: >80

II. **Thresholds by ROC curve analysis patient population (n=853)**

- 1 = APS trombosis
- 0 = AID, HC, non-APS thrombosis
- Cut-off based on sensitivity

		Sensitivity (%, 95% CI)	Specificity (%, 95% CI)
Thrombosis			
$N = 853^b$	ACL AcuStar	35.85 (31.48–40.41)	79.74 (75.41–83.62)
	QUANTA Lite ELISA	31.10 (26.91–35.54)	84.62 (80.65–88.05)



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aCL and aβ2GPI: semiquantitative classification

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- Low 20-40 Moderate: 40-80 High: >80

II. **ROC curve analysis on patient population**

- 1 = APS trombosis
- 0 = AID, HC, non-APS thrombosis
- Cut-off based on sensitivity

	cutoff	sensitivity	
ELISA aCL IgG	19,80	0,37	Low
	39,1	0,29	Moderate
	78,3	0,19	High
CLIA aCL IgG	45,1	0,37	Low
	201,6	0,29	Moderate
	491,7	0,19	High

Arne Vandevelde, Walid Chayoua, Bas de Laat, Jean-Christophe Gris, Gary W. Moore, Jacek Musiał, Stéphane Zuily, Denis Wahl and Katrien M. J. Devreese. 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

aCL and aβ2GPI: semiquantitative classification

	ELISA	CLIA
	GPL/MPL	U/mL
	Thrombotic test population	
aCL IgG		
Moderate	39	202
High	78	492
aCL IgM		
Moderate	40	45
High	82	170
aβ2GPI IgG		
Moderate	39	1959
High	80	4904
aβ2GPI IgM		
Moderate	40	31
High	79	66

Thresholds calculated by ROC analysis

moderate/high cutoff CLIA

- is higher for CLIA vs ELISA
- higher for IgG vs IgM
- is different for aCL and aβ2GPI for CLIA

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aCL and aβ2GPI: semiquantitative classification

Kappa agreement of thresholds

Cohen's Kappa (level of agreement)			
<0,21	none	0,60-0,79	moderate
0,21-0,39	minimal	0,80-0,90	strong
0,40-0,59	weak	>0,90	almost perfect

identical **classification of samples as low/moderate/high** based on
Range 1: 20/40/80 Range 2 ROC sensitivity-based cut-off

		THROMBOTIC TEST POPULATION			
		Range 1	**Kappa 1**	**Range 2**	**Kappa 2**
Level	**System**	**aCL IgG (n=105)**			
Low	ELISA	20-40	**0.23**		
	CLIA	20-40			
Moderate	ELISA	40-80	**-0.06**		
	CLIA	40-80			
High	ELISA	>80	**0.18**		
	CLIA	>80			

Vandevelde, 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

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Low	ELISA	20-40	**0.23**	20-39	**0.60**
	CLIA	20-40		**20-202**	
Moderate	ELISA	40-80	**-0.06**	39-78	**0.36**
	CLIA	40-80		**202-492**	
High	ELISA	>80	**0.18**	>78	**0.66**
	CLIA	>80		**>492**	

Ranges L- M- H

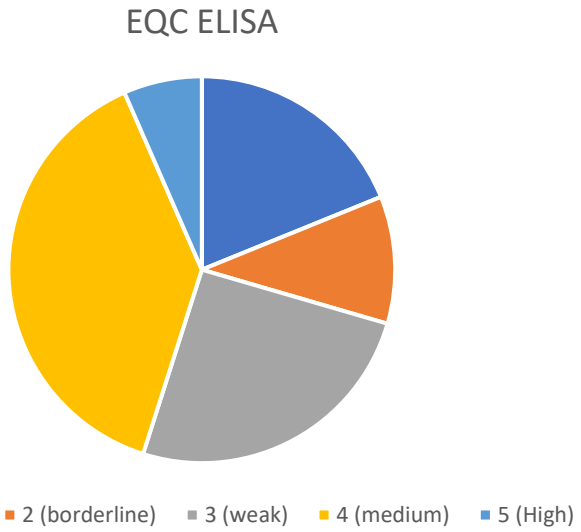
Ranges for classification into low-moderate-high applied for ELISA cannot be transferred to other platforms, and should be calculated per system

Vandevelde, 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

aCL and aβ2GPI: semiquantitative classification

Results ELISA aCL IgG 2017-2

	Classification reported by participants				
	negative	borderline	weak	medium	high
n	23	13	31	47	8
%	18,9	10,7	25,4	38,5	6,6



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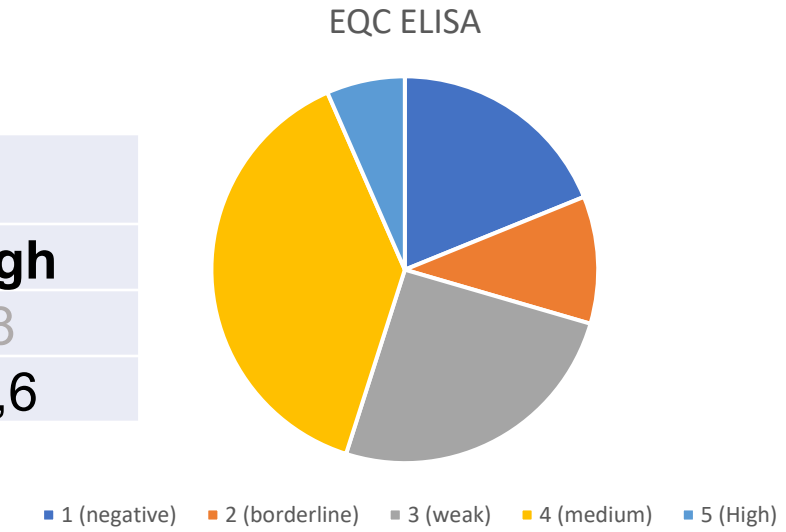
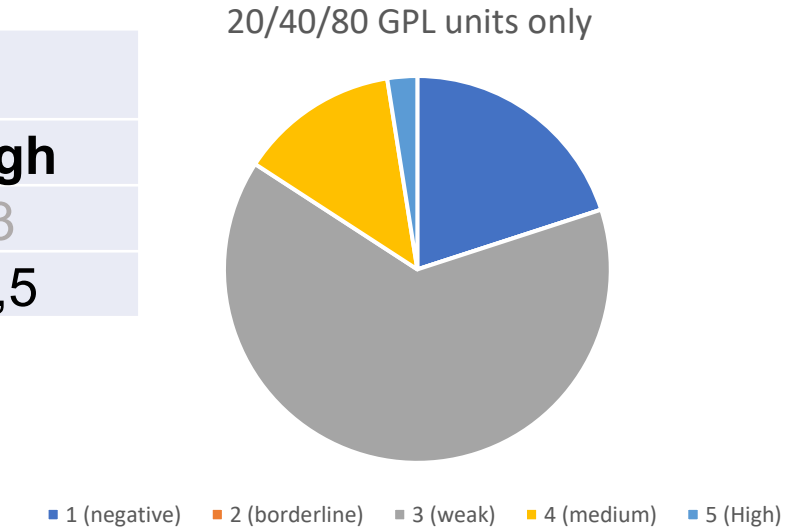


	Categorization based on thresholds 40/80				
	negative	borderline	weak	medium	high
n	24	0	77	16	3
%	19,7	0,0	64,8	13,1	2,5

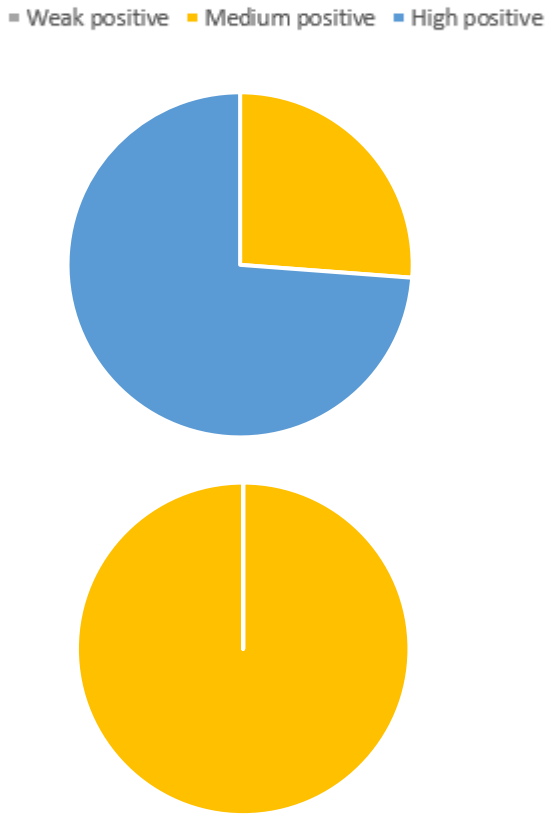


=> Less variation in classification

aCL and aβ2GPI: semiquantitative classification

Results CLIA (Acustar) aCL IgG 2017-2

	negative	borderline	weak	medium	high
	Classification reported by participants				
n	0	0	0	11	31
%	0	0	0	26,2	73,8
	Classification based on ROC thresholds				
n	0	0	1	41	0
%	0	0	2,4	97,6	0



=> Less variation in classification

Predefined thresholds harmonize reporting of results

Other antiphospholipid antibodies (aPL)

Criteria aPL

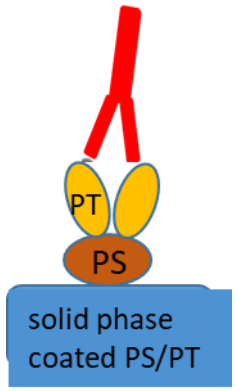
Lupus anticoagulant (LAC)

Anticardiolipin antibodies (aCL)IgG/IgM

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

Non-Criteria aPL

Antiphosphatidylserine/ prothrombin (aPS/PT)



Solid phase assays

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

Antiphosphatidylserine/prothrombin antibodies (aPS/PT)

Prevalence of aPS/PT

in APS

- IgG/IgM 65.0 (57,7-72) %

in LA positives

- aPS/PT IgG/IgM 55-100%
- aPS/PT more frequent in LA positives compared to LA negatives

in double/triple positive patients

- aPS/PT IgG/IgM 71-100%

Zhu R et al. Thromb Res 2022; 214: 106-114

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- aPS/PT more frequent in LA positives compared to LA negatives

in double/triple positive patients
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Conclusion on added value aPS/PT

❖ aPS/PT cannot not replace LAC

Zhu R et al. Thromb Res 2022; 214: 106-114

Antiphosphatidylserine/prothrombin antibodies (aPS/PT)

Association of aPS/PT with clinical manifestations

Thrombosis 6 studies

- OR 2.6-14.0

Obstetric APS 2 studies

- OR 5.7-11.0

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Obstetric APS 2 studies

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Crude odds ratios (OR) thrombotic APS	
n= 197	OR [95%CI]
Triple positive	27.3 [16.4-45.5]
Tetra positive	27.3 [16.1-46.2]

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Arne Vandevelde, Walid Chayoua, Bas de Laat, Gary W. Moore, Jacek Musiał, Stéphane Zuily, Denis Wahl and Katrien M. J. Devreese. 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; 10.1111/jth.15785

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Conclusion on added value aPS/PT

- OR for triple and tetra positive patients is comparable
- aPS/PT **confirm the patients at risk** for TAPS, but not essential for first-line diagnosis TAPS

Zhu R et al. Thromb Res 2022; 214: 106-114
Arne Vandevelde, Walid Chayoua, Bas de Laat, Gary W. Moore, Jacek Musiał, Stéphane Zuily, Denis Wahl and Katrien M. J. Devreese. 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; 10.1111/jth.15785

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Crude odds ratios (OR) thrombotic APS	
n= 197	OR [95%CI]
Triple positive	27.3 [16.4-45.5]
Tetra positive	27.3 [16.1-46.2]

Adjusted for	aOR [95%CI]
LAC	0.69 [0.38-1.26]
aCL IgG	2.20 [1.42-3.40]
aCL IgM	4.91 [3.41-7.06]
aβ2GPI IgG	2.04 [1.29-3.20]
aβ2GPI IgM	4.60 [3.19-6.65]
aCL and aβ2GPI	2.30 [1.50-3.52]

Conclusion on added value aPS/PT

- 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 LAC negative/ unreliable

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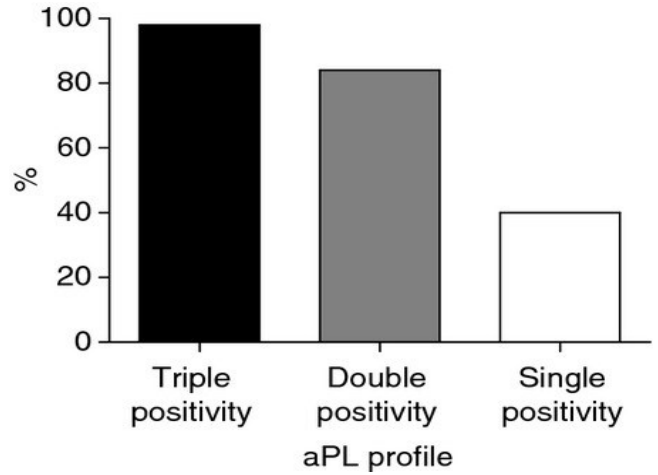
Arne Vandevelde, Walid Chayoua, Bas de Laat, Gary W. Moore, Jacek Musiał, Stéphane Zuily, Denis Wahl and Katrien M. J. Devreese. Added value of antiphosphatidylserine/prothrombin antibodies in the workup of thrombotic antiphospholipid syndrome: Communication from the ISTH SSC Subcommittee on Lupus Anticoagulant/Antiphospholipid Antibodies J Thromb Haemost 2022; 10.1111/jth.15785

aPL- Post-analytical procedure

Retesting

Persistent versus transient positivity of LAC, aCL, aβ2GPI

- to avoid overdiagnosis of APS
- transient aPL without APS: infections
- single aPL not always associated with clinical APS



aPL confirmed after 3 months

N=161 (APS and non-APS) retested after 3 months

Pengo et al. J Thromb Haemost 2013; 11: 1522-31,
Devreese KMJ et al. Update of the guidelines for lupus anticoagulant detection and interpretation. J Thromb Haemost 2020; 18:2828–2839.

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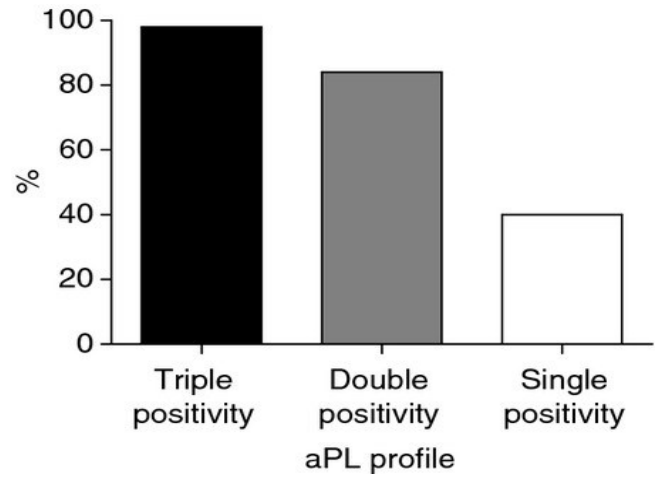
Persistent versus transient positivity of LAC, aCL, aβ2GPI

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



aPL confirmed after 3 months

N=161 (APS and non-APS) retested after 3 months

Multicenter study
aPL profile (n) in thrombotic APS n=197

Triple IgG positive (n=94)

Triple positive IgM (n=40)
Double positive (n=5)

Single LAC (n=70): 35%

OR for thrombotic APS

Single LAC 10,9 (6,7-17,7)
Triple positives 29,2 (16,7-50,9)

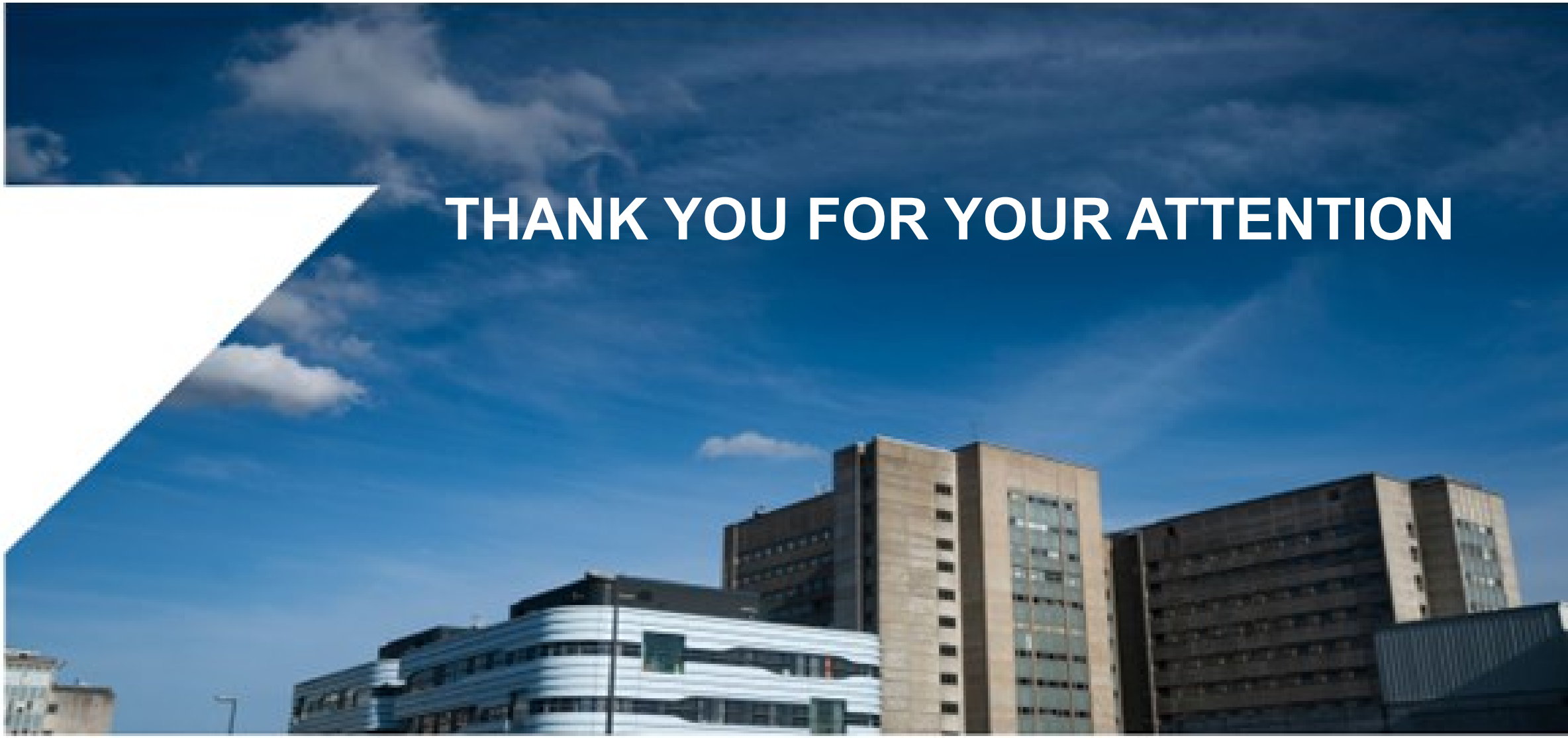
Pengo et al. J Thromb Haemost 2013; 11: 1522-31, Vandevelde et al. J Thromb Haemost 2022; DOI: 10.1111/jth.15785, Devreese KMJ et al. Update of the guidelines for lupus anticoagulant detection and interpretation. J Thromb Haemost 2020; 18:2828–2839.

Conclusions aPL and clinical implications

- aPL define the diagnosis of APS
- Test for antiphospholipid antibodies in selected patients
- Perform all three assays **LAC, β2GPI-dependent aCL IgG/IgM, aß2GPI IgG/M** on the same blood sampling at the same time to increase diagnostic utility
- No routine testing for other aPL (aPS/PT)
- LAC is reported with a final conclusion as **positive/negative**
- aCL and aβ2GPI IgG/IgM are reported with **titer**, along with local cut-off value, semiquantitative reporting is not harmonized yet

- Only **persistently** positive results are clinically relevant
- Make an integrated interpretation of LAC, aCL and aβ2GPI (**aPL profile**)
- Results to 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 interferences

- A close interaction between the laboratory and the clinician is mandatory!
- Perform assays according to guidelines for more harmonisation



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