Síndrome antifosfolípido: Nuevas dianas diagnósticas y correlación clínica de las mismas

Dr. Pascual Marco

Hospital General Universitario de Alicante

RETOS en SAF

- **Diagnóstico :**
  - Aspectos Clínicos Especiales
  - Nuevos marcadores Biológicos
  - Pacientes asintomáticos
  - Pacientes seronegativos
- *Fisiopatología*
- *Tratamiento*

RECOMMENDATIONS AND GUIDELINES

Laboratory criteria for antiphospholipid syndrome: communication from the SSC of the ISTH

K. M. J. DEVREESE,* T. L. ORTEL,† V. PENGO‡ and B. DE LAAT§¶FOR THE SUBCOMMITTEE ON LUPUS ANTICOAGULANT/ANTIPHOSPHOLIPID ANTIBODIES

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Stago

Recomendaciones para optimizar la detección del Anticoagulante Lúpico

- **Extracción de sangre :**
- **1.- Evitar la interferencia de cualquier anticoagulante .**
- **2.- Sangre venosa sobre citrato de sodio 0.109 M a proporcion 9/1**
- **3.- Doble centrifugación para obtener un PPP (recuento < 10.000/mm3)**
- **4.- Realizar las pruebas con el plasma lo mas fresco posible (< 6 horas)**
- **5.- Si no es posible : Congelación inmediata**
- **6.- Descongelación rápida a 37ºC (Evitar la precipitación de fibrina)**

Stago

Recomendaciones para optimizar la detección del Anticoagulante Lúpico

- **Pruebas de Mezcla :**
- **1.- Usar "pool" de plasma normal . Si no es posible usar plasmas comerciales certificados**
- **2.- La mezcla debe ser al 1/1 y analizarla lo antes posible , sin preincubación .**
- **3.- Reactivo de APTT adecuado**
- **4.- No analizar muestras de pacientes con tiempo de trombina alargado (Heparina/Dabigatran)**
- **5.- Comparar con el valor de corte del percentil 99**
- **6.- Calcular el ICA : (b-a)/a x 100 . b: plasma mezcla , a: plasma paciente c: plasma normal**

Stago

Recomendaciones para optimizar la detección del Anticoagulante Lúpico

- **Pruebas de Confirmación:**
- **1.- Usar dos pruebas basadas en Fosfolípidos : Baja(búsqueda) y alta concentración(confirma)**
- **2.- Establecer punto de corte de estas pruebas**
- **3.- Resultado : (búsqueda-confirmación)/ búsqueda) 100**
- **4.- Resultado positivo si el % de correccion es superior al de valor de corte**
- **5.- Resultados deben ser interpretados como ratio entre PPPpaciente/PPPnormal**
- **(con el dRVVT ratio > 1.25 / con corección fosfolípidos hexagonales > 8 segundos)**

Stago

Pruebas Integradas (más práctico)

- **Incluir en la metódica de trabajo prueba de búsqueda y de confirmación**
- **Trabajar en paralelo con APTT y dRVVT con alta y baja concentración en fosfolípidos**
- **Estas pruebas pueden evitar las pruebas de mezclas**
- **Resultados se expresan por cocientes (APTT pobre Phs-APTT rico Phs)/ APTT pobre**
- **Resultado : Ratio de APTT Paciente/Control**

Stago

Medir el Anticoagulante Lúpico en la fase aguda de la trombosis

- **Considerar que la mayoría de las proteínas de la hemostasia son reactantes de fase aguda**
- **El Factor VIII:C y el Factor XI:C a niveles elevados acortan el APTT :falsos positivos**
- **Las muestras pueden estar contaminadas por heparinas o AVK**
- **En mujeres embarazadas con abortos o con trombosis**
- **Si no va a tener incidencia en el tratamiento : Evitar el estudio y demorarlo ¿?**

Stago

Medir el Anticoagulante Lúpico durante el tratamiento anticoagulante

- **Considerar que el alargamiento del APTT puede estar condicionado por Tratamiento**
- **El tratamiento con AVK : esperar al menos 2 semanas tras suspender**
- **Si el INR < 1.5 se puede realizar**
- **Si el INR 1.5-3 se puede optar por una dilución previa al 1/1 con plasma normal ¿?**
- **No se recomiendan otras pruebas por no estar normalizadas para interpretarlas**
- **Analizar simultáneamente con anticuerpos anticardiolipina o anti beta2GPI**
- **Valorar doble o triple positividad en pacientes de alto riesgo de trombosis**

Stago

Otras pruebas (guías Británica y CLSI)

- **Tiempo de coagulación con Kaolín (EXNER)** : Muy sensible. Precisa diluciones PPy PN
  - Poco reproductible
  - Reactivo con Kaolin en suspensión , que sedimenta
  - Resultados muy prolongados
- **Silica Clotting Time** : Automatizable , método óptico
  - Buena sensibilidad
  - Prueba integrada búsqueda y confirmación
- **Tiempo de Tromboplastina Diluida** : En desuso .
  - Gran variabilidad de las Tromboplastinas
  - Diferencias entre las tromboplastinas recombinantes y resto
  - En algunas publicaciones : ha detectado mas AL en cmbinacion con dos pruebas clásicas

Stago

Anticuerpos anti cardiolipina

- Técnica de Enzimainmunoensayo
- Técnica por Quimioluminiscencia
- Isotipo IgG / Isotipo IgM / IgA
- Si resultado con significado clínico , repetir a las 12 semanas
- Establecer percentiles de la población normal vs población con Trombosis
- Linealidad de la técnica

Anticuerpos anti β2-GPI

- Técnica de Enzimainmunoensayo
- Técnica por Quimioluminiscencia
- Isotipo IgG / Isotipo IgM
- Anticuerpos anti-Dominio I Isotipo IgG
- Si resultado con significado clínico , repetir a las 12 semanas
- Establecer percentiles de la población normal vs población con Trombosis
- Linealidad de la técnica

Anticoagulante lúpico y Trombosis

- "Potencia del Anticoagulante lúpico" y Trombosis
  - Ratio del aPTT
  - Ratio del dRVVT : > 1.5
  - Diferencia en la prueba del STK-LA : > 20 seg.
  - Asociación a anticuerpos anti-β_2-GPI isotipo IgG
  - Asociación a anticuerpos anti- β_2-GPI dominio I
  - "Cuantificación" de la Actividad del Anticoagulante Lúpico:
    - Anticuerpo monoclonal con actividad anti-β_2-GPI y anti-Protrombina
    - Estándar de Calibración de la actividad del Anticoagulante Lúpico

Faltan datos en la literatura para la asociación de Trombosis y aPL

Necesidad de Estardarización

- Variables pre-analíticas
  - De los reactivos
  - Del plasma
- Sistemas de medición
- Protocolos experimentales
- Métodos adaptados para parámetros específicos

Stago

Journal of Thrombosis and Haemostasis, 14: 1779–1787 DOI: 10.1111/jth.13389

ORIGINAL ARTICLE

Role of anti-domain 1-$\beta_2$glycoprotein I antibodies in the diagnosis and risk stratification of antiphospholipid syndrome

A.-S. DE CRAEMER,* J. MUSIAL† and K. M. J. DEVREESE*
*Coagulation Laboratory, Department of Clinical Chemistry, Microbiology and Immunology, Ghent University Hospital, Ghent, Belgium; and †Department of Medicine, Jagiellonian University Medical College, Krakow, Poland

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Conclusion

The strong association between a positive aDI IgG result and the triple-positive antibody profile emphasizes its value in a patient's risk stratification. However, because the majority of aβ_2GPI IgG antibodies measured through HemosIL® AcuStar aβ_2GPI IgG target domain 1, the clinical performance characteristics are highly comparable between the two assays. Consequently, aDI IgG did not add diagnostic power to the aPL panel used in this study or act as an independent predictor of clinical complications in this study population. Hence, the contribution of aDI IgG in the diagnosis and risk stratification of APS strongly depends upon the solid phase assays used for aCL and aβ_2GPI detection.

Stago

New insight into antiphospholipid syndrome: antibodies to $\beta_2$glycoprotein I-domain 5 fail to induce thrombi in rats

Paolo Durigutto,[1] Claudia Grossi,[2] Maria Orietta Borghi,[2,3] Paolo Macor,[1] Francesca Pregnolato,[2] Elena Raschi,[2] Michael P. Myers,[4] Philip G. de Groot,[5] Pier Luigi Meroni[2] and Francesco Tedesco[2]

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PD and CG contributed equally to this work. PLM and FT contributed equally to this work.

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Hui Shi[a], Hui Zheng[a], Yu-Feng Yin[a], Qiong-Yi Hu, Jia-Lin Teng, Yue Sun, Hong-Lei Liu, Xiao-Bing Cheng, Jun-Na Ye, Yu-Tong Su, Xin-Yao Wu, Jin-Feng Zhou, Gary L. Norman, Hui-Yun Gong, Xin-Ming Shi, Yi-Bing Peng, Xue-Feng Wang* and Cheng-De Yang*

Antiphosphatidylserine/prothrombin antibodies (aPS/PT) as potential diagnostic markers and risk predictors of venous thrombosis and obstetric complications in antiphospholipid syndrome

Variables	APS (n=186)	SNAPS (n=48)	p-Value
Gender (female/male)	164/22	41/7	0.786
Mean age (years ± SD)	34.2 ± 13.9	38.9 ± 18.0	0.867
Onset type			
PAPS, n (%)	67 (36.0)	N/A	
SAPS, n (%)	119 (64.0)	N/A	
Clinical manifestations			
Thrombosis only, n (%)	113 (60.7)	36 (75.0)	0.096
AT only, n (%)	53 (28.5)	20 (41.7)	0.114
VT only, n (%)	68 (36.5)	12 (25.0)	0.182
AT + VT, n (%)[a]	9 (4.8)	8 (16.7)	0.012
Pregnancy morbidity only, n (%)	56 (30.1)	8 (16.7)	<0.01
Thrombosis + pregnancy morbidity, n (%)[b]	17 (9.1)	4 (8.3)	0.999

APS, antiphospholipid syndromes; PAPS, primary antiphospholipid syndrome; SAPS, secondary antiphospholipid syndrome; SNAPS, sero-negative APS, patients with clinical manifestations highly suggestive of APS, but with persistently negative LAC, IgG/IgM aCL and IgG/IgM anti-β2-GPI antibodies; AT, arterial thrombosis; VT, venous thrombosis. [a]Including AT + VT. [b]Including thrombosis + pregnancy morbidity.

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Hui Shi[a], Hui Zheng[a], Yu-Feng Yin[a], Qiong-Yi Hu, Jia-Lin Teng, Yue Sun, Hong-Lei Liu, Xiao-Bing Cheng, Jun-Na Ye, Yu-Tong Su, Xin-Yao Wu, Jin-Feng Zhou, Gary L. Norman, Hui-Yun Gong, Xin-Ming Shi, Yi-Bing Peng, Xue-Feng Wang* and Cheng-De Yang*

Antiphosphatidylserine/prothrombin antibodies (aPS/PT) as potential diagnostic markers and risk predictors of venous thrombosis and obstetric complications in antiphospholipid syndrome

Table 2: Prevalence of aPS/PT in the study groups.

	No.	IgG or IgM aPS/PT, n (%)	IgG aPS/PT, n (%)	IgM aPS/PT, n (%)	Dual positivity, n (%)[a]
APS	186	160 (86.0)	134 (72.0)	125 (67.2)	99 (53.2)
PAPS	67	61 (91.0)	47 (70.1)	53 (79.1)	39 (58.2)
SAPS	119	99 (83.2)	87 (73.1)	72 (60.5)	60 (50.4)
SNAPS	48	25 (51.0)	14 (28.6)	17 (34.7)	6 (12.2)
SLE	79	30 (38.0)	10 (12.7)	26 (32.9)	6 (7.6)
SS	29	9 (31.0)	1 (3.4)	8 (27.6)	0 (0)
RA	38	0 (0)	0 (0)	0 (0)	0 (0)
AS	30	3 (10.0)	0 (0)	3 (10.0)	0 (0)
HC	90	7 (8.2)	0 (0)	7 (8.2)	0 (0)

aPS/PT, antiphosphatidylserine/prothrombin antibody; SLE, systemic lupus erythematosus; SS, Sjogren syndrome; AS, ankylosing spondylitis; RA, rheumatoid arthritis; HC, healthy controls. [a]IgG and IgM aPS/PT are both positive.

Stago

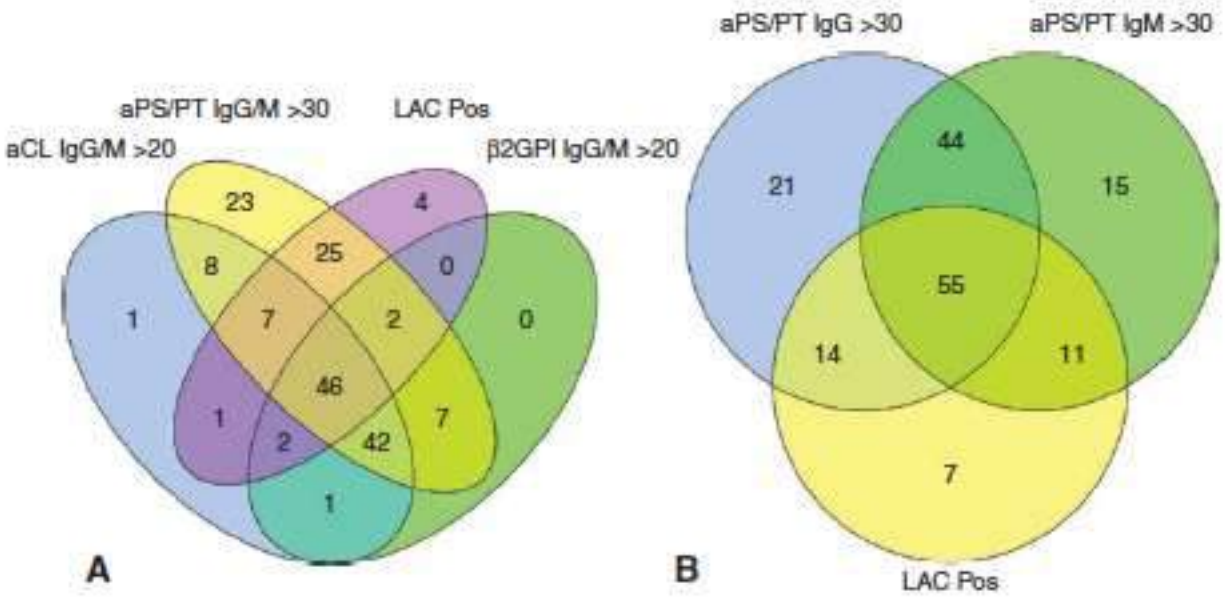

Figure 4: Venn diagram of the aPLs.

Venn diagram of serum reactivity of patients with APS. Serum was tested for aPS/PT and criteria aPLs by ELISA or by LAC. Numbers in individual fields indicate positive cases for a given reactivity or combinations of reactivities. (A) Venn diagram of aPS/PT IgG/M, aCL IgG/M, aβ2GPI and LAC. (B) Venn diagram of aPS/PT IgG, aPS/PT IgM and LAC.

Reliability of Lupus Anticoagulant and Anti-phosphatidylserine/ prothrombin Autoantibodies in Antiphospholipid Syndrome: A Multicenter Study

Savino Sciascia[1,2†], Massimo Radin[1,3†], Irene Cecchi[1,3], Elena Rubini[1,3], Anna Scotta[1,3,4], Roberta Rolla[4], Barbara Montaruli[5], Patrizia Pergolini[4], Giulio Mengozzi[5], Emanuela Muccini[6], Simone Baldovino[1,3], Michela Ferro[3], Antonella Vaccarino[7], Michael Mahler[8], Elisa Menegatti[3] and Dario Roccatello[1,3]*

Conclusion: Despite the progress in the standardization of aPL testing, we observed up to 45% of overall discrepant results for LA, even higher in patients on VKA. The introduction of aPS/PT testing might represent a further diagnostic tool, especially when LA testing is not available or the results are uncertain.

Frontiers in immunology 2016

Stago

Table 4: Relationship of aPL with thrombosis and/or obstetric manifestations.

aPL assay	Thrombosis		Arterial thrombosis		Venous thrombosis		Pregnancy loss	
	OR (95% CI)	p-Value	OR (95% CI)	p-Value	OR (95% CI)	p-Value	OR (95% CI)	p-Value
aCL IgG/M (≥40 PL)	7.72 (4.42–14.05)	<0.001	3.76 (2.13–6.66)	<0.001	3.78 (2.23–6.44)	<0.001	3.74 (2.10–6.67)	<0.001
aCL IgG (≥40 GPL)	9.49 (5.15–18.61)	<0.001	3.98 (2.22–7.15)	<0.001	4.18 (2.41–7.26)	<0.001	3.23 (1.76–5.91)	<0.001
aCL IgM (≥40 MPL)	3.93 (1.61–10.55)	0.004	1.38(0.44–3.72)	0..546	3.27 (1.32–7.92)	<0.001	4.26 (1.70–10.75)	<0.001
aβ2GPI IgG/M	6.21 (3.80–10.37)	<0.001	3.16 (1.85–5.39)	<0.001	3.96 (2.40–6.54)	<0.001	4.36 (2.54–7.49)	<0.001
aβ2GPI IgG	7.50 (4.24 13.84)	<0.001	3.95 (2.21–7.06)	<0.001	3.61 (2.09–6.20)	<0.001	3.37 (1.86–6.06)	<0.001
aβ2GPI IgM	3.22 (1.72– 6.24)	<0.001	1.62 (0.76–3.27)	0.192	2.68 (1.38–5.11)	<0.001	4.87 (2.48–9.60)	<0.001
LAC	7.85 (4.50–14.23)	<0.001	2.72 (1.53–4.78)	<0.001	4.56 (2.70–7.74)	<0.001	5.13 (2.92–9.07)	<0.001
aPS/PT IgG/M	9.10 (5.73–14.81)	<0.001	6.30 (3.58–11.57)	<0.001	5.58 (3.27–9.94)	<0.001	10.41 (5.47–21.63)	<0.001
aPS/PT IgG	10.50 (6.54–17.23)	<0.001	4.62 (2.76–7.88)	<0.001	6.42 (3.91–10.76)	<0.001	5.66 (3.35–9.75)	<0.001
aPS/PT IgM	4.24 (2.78–6.56)	<0.001	3.12 (1.89–5.23)	<0.001	3.24 (2.02–5.29)	<0.001	4.71 (2.79–8.12)	<0.001
aCL IgG + aβ2GPI IgG	9.36 (4.81–19.79)	<0.001	4.07 (2.18–7.58)	<0.001	4.09 (2.27–7.36)	<0.001	3.33(1.73–6.37)	<0.001
aCL IgG + aβ2GPI IgG + LAC	6.33 (2.79–16.27)	<0.001	3.99 (1.83–8.58)	<0.001	2.33 (1.07–4.88)	0.011	4.06 (1.77–9.35)	<0.001
aCL IgG + aβ2GPI IgG + aPS/PT IgG	8.90 (4.44–19.49)	<0.001	3.77 (1.97–7.19)	<0.001	4.27 (2.32–7.89)	<0.001	3.31 (1.67–6.51)	<0.001
Double (aCL + aβ2GPI)	6.93 (3.87–12.98)	<0.001	3.55 (1.96–6.40)	<0.001	3.68 (2.12–6.39)	<0.001	4.31 (2.36–7.88)	<0.001
Double (aCL + LAC)	6.38 (3.14–14.11)	<0.001	3.96 (1.99–7.87)	<0.001	2.36 (1.20–4.56)	0.002	3.97 (1.94–8.14)	<0.001
Double (aCL + PS/PT)	7.05 (4.03–12.85)	<0.001	4.03 (2.27–7.16)	<0.001	3.28 (1.91–5.60)	<0.001	3.79 (2.11–6.81)	<0.001
Double (aβ2GPI + LAC)	7.11 (3.52–15.67)	<0.001	3.12 (1.57–6.10)	<0.001	3.21 (1.68–6.06)	<0.001	4.47 (2.23–9.03)	<0.001
Double (aβ2GPI + PS/PT)	7.05 (4.21–12.15)	<0.001	3.72 (2.16–6.45)	<0.001	3.84 (2.31–6.40)	<0.001	4.95 (2.86–8.63)	<0.001
Double (PS/PT + LAC)	7.07 (4.02–12.94)	<0.001	3.22 (1.80–5.76)	<0.001	3.79 (2.21–6.49)	<0.001	4.90 (2.75–8.76)	<0.001
Triple (aCL + aβ2GPI + LAC) "Triple Pos"	5.32 (2.58–11.85)	<0.001	3.63 (1.77–7.36)	<0.001	2.21 (1.08–4.38)	0.025	5.29 (2.50–11.35)	<0.001
Triple (aPS/PT + aβ2GPI + LAC)	6.54 (3.22–14.43)	<0.001	3.32 (1.67–6.57)	<0.001	2.82 (1.45–5.38)	<0.001	4.48 (2.20–9.20)	<0.001
Triple (aCL + aβ2GPI + aPS/PT)	6.30 (3.51–11.81)	<0.001	3.83 (2.11–6.97)	<0.001	3.16 (1.79–5.53)	<0.001	4.42 (2.39–8.18)	<0.001
Quadruple(aCL + aβ2GPI + aPS/PT + LAC)	4.83 (2.33–10.80)	<0.001	3.93 (1.90–8.09)	<0.001	1.86 (0.88–3.78)	0.092	5.39 (2.50–11.84)	<0.001

Multivariate models are controlled for age and sex.

Papel de los anticuerpos anti anti β2-GPI

	Lupus Anticoagulant	Anti-cardiolipin ab	Anti β2-Glycoprotein I ab	
Triple positive*	Positive	Positive	Positive	NO
Double positive*	Negative	IgG Positive	IgG Positive	YES
Single positive	Positive	Negative	Negative	NO
Single positive	Negative	Positive	Negative	NO
Single positive	Negative	Negative	IgG Positive	NO/YES

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Papel de los anticuerpos anti PS/PT

	Lupus Anticoagulant	Anti-cardiolipin ab	Anti β2-Glycoprotein I ab	
Triple positive*	Positive	Positive	Positive	NO/YES
Double positive*	Negative	Positive	Positive	NO
Single positive	Positive	Negative	Negative	NO/YES
Single positive	Negative	Positive	Negative	?
Single positive	Negative	Negative	Positive	?

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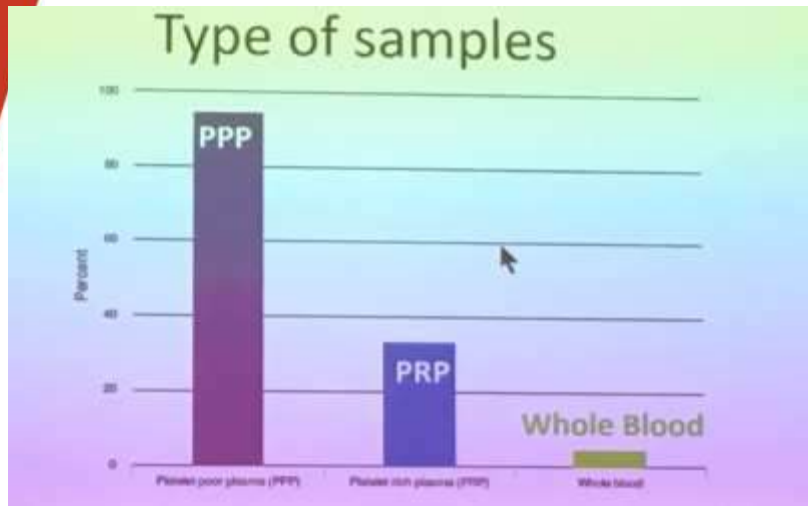
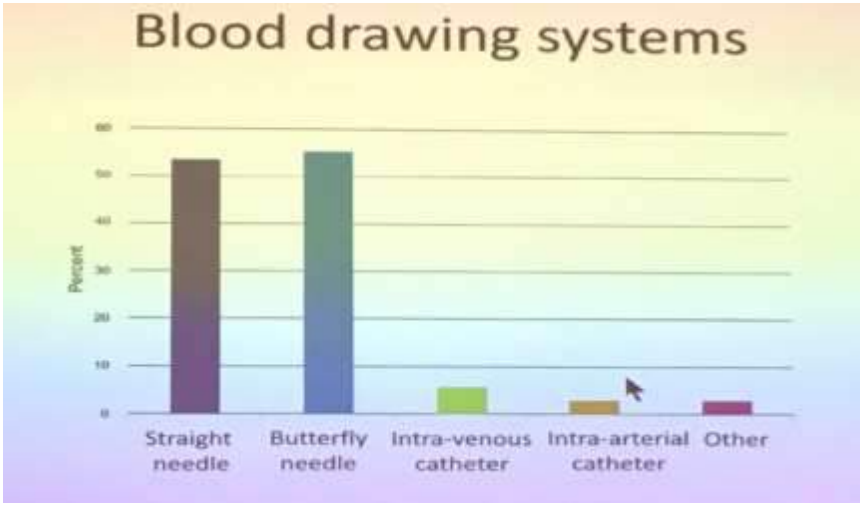
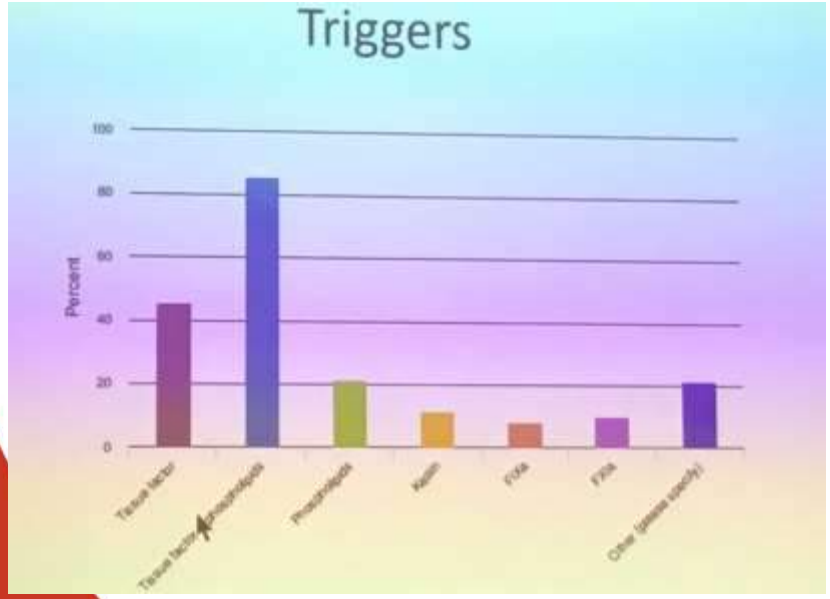
Generación de Trombina en SAF

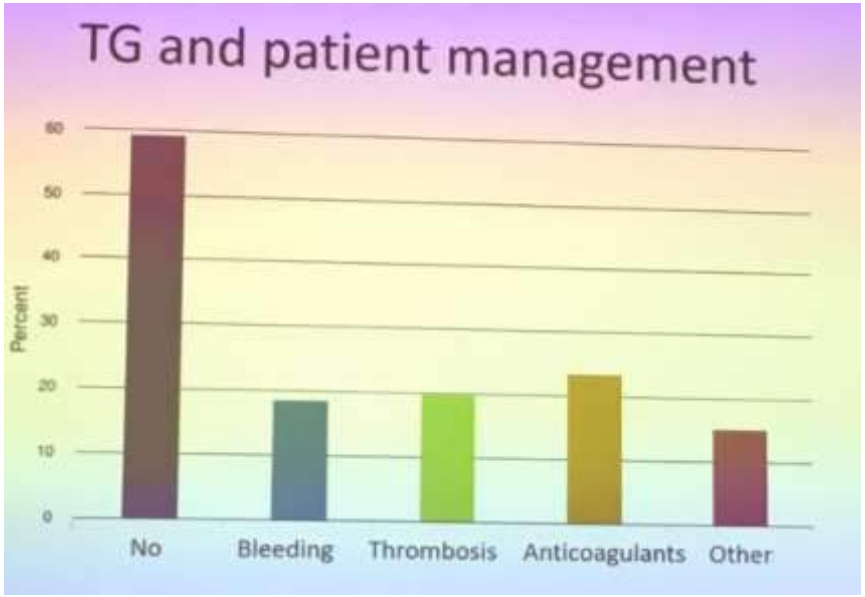
- Desarrollo de nuevos protocolos y algoritmos para identificar a los pacientes de alto riesgo de trombosis

- Desarrollo de un sistema de inteligencia artificial que informe sobre el riesgo trombótico individual del paciente

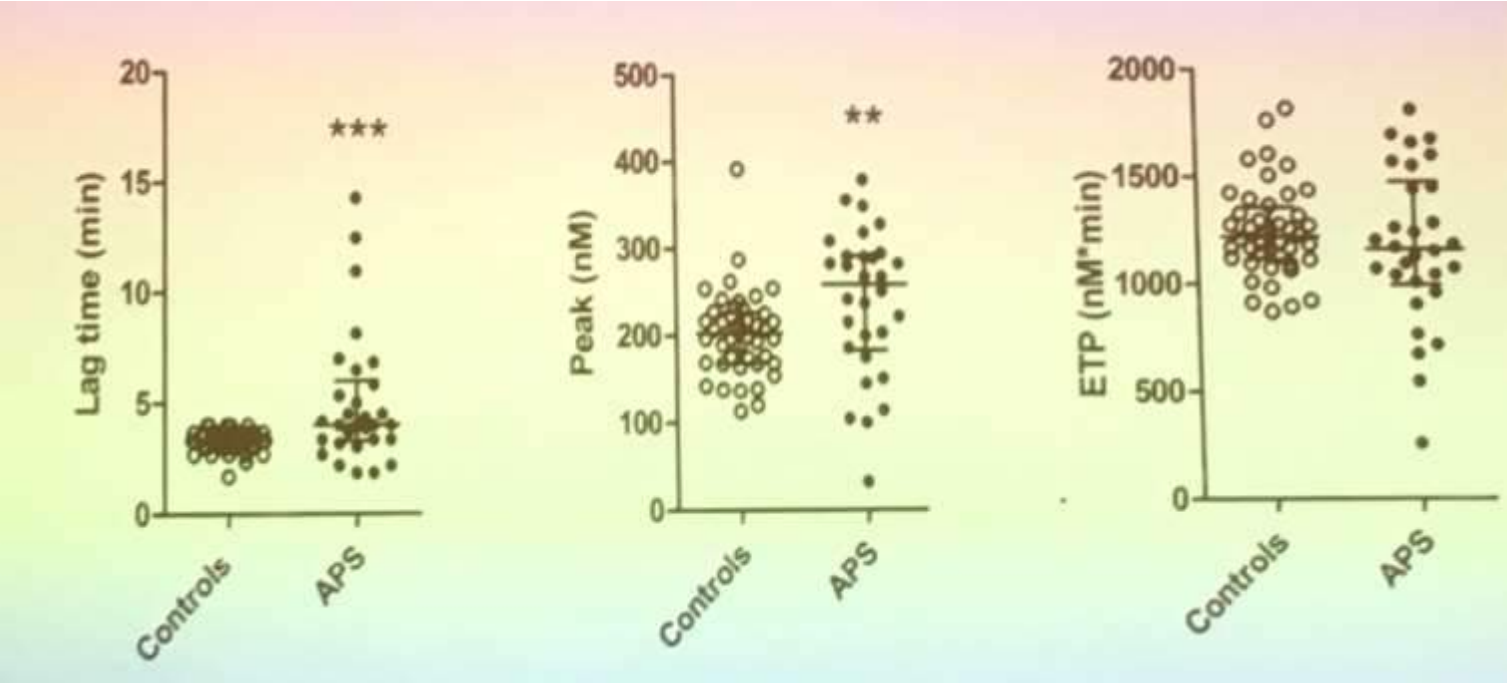

Type of samples
Percent
PPP
PRP
Whole Blood


Blood drawing systems
Percent
Straight needle
Butterfly needle
Intra-venous catheter
Intra-arterial catheter
Other


Triggers
Percent


TG and patient management
Percent
No
Bleeding
Thrombosis
Anticoagulants
Other

Generación de Trombina y AL



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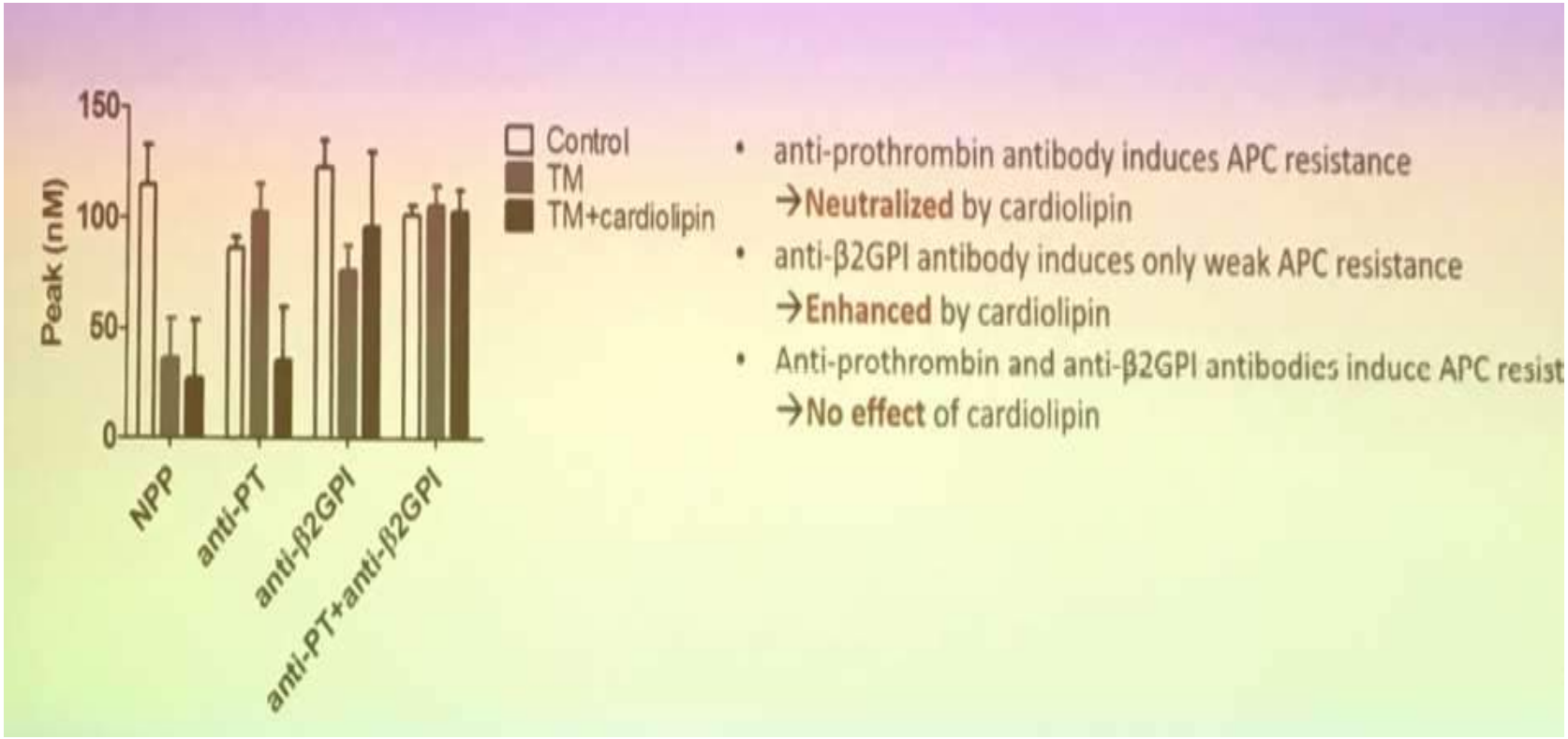
Pico de Trombina en SAF



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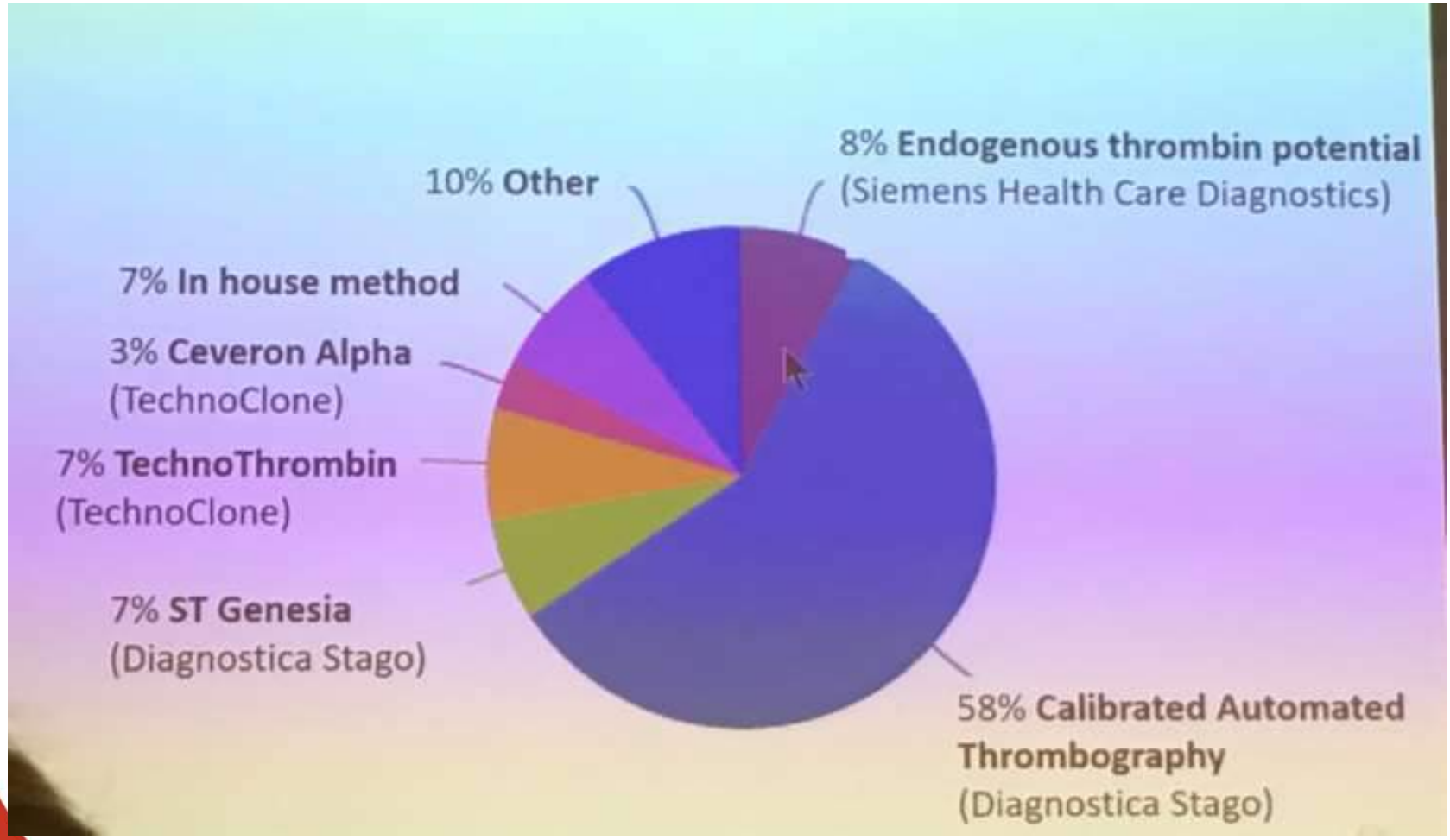
Metodologías



Stago

RHEUMATOLOGY

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Advance Access publication 12 January 2013

Original article

GAPSS: the Global Anti-Phospholipid Syndrome Score

Savino Sciascia[1,2], Giovanni Sanna[1,3], Veronica Murru[1], Dario Roccatello[2], Munther A. Khamashta[1,2] and Maria Laura Bertolaccini[1]

TABLE 3 Multivariate logistic regression analysis for the development cohort and scoring system

	β-coefficient	GAPSS[a]
Hyperlipidaemia	1.73	3
Arterial hypertension	0.54	1
aCL IgG/IgM	2.63	5
Anti-β2GPI IgG/IgM	2.02	4
aPS/PT IgG/IgM	1.78	3
LA	2.35	4

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RHEUMATOLOGY

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Original article

GAPSS: the Global Anti-Phospholipid Syndrome Score

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FIG. 1 GAPSS in development and validation cohorts.

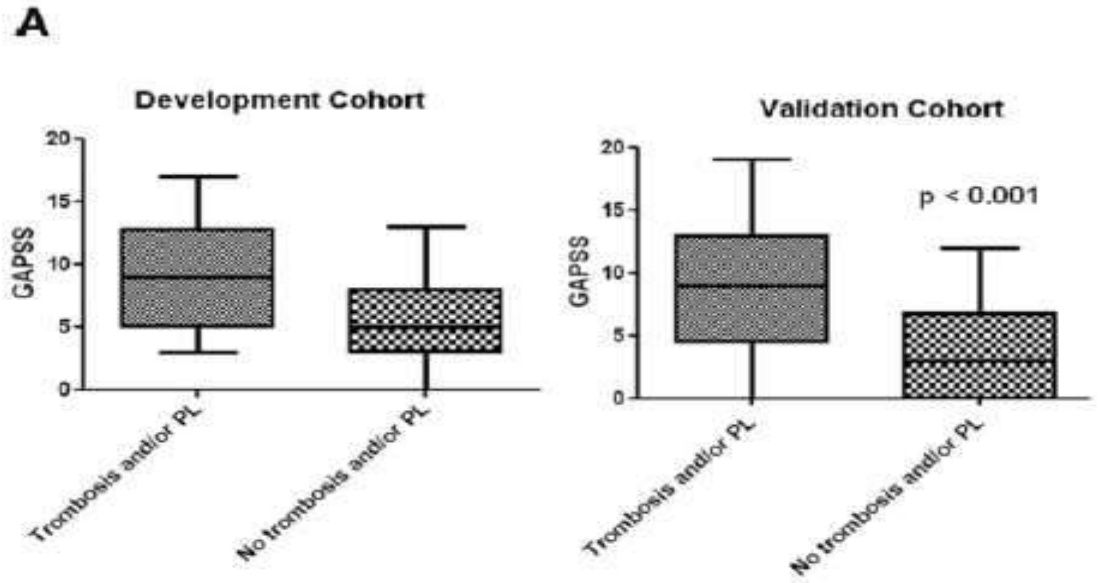

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TABLE 4 Diagnostic accuracy including sensitivity, specificity, PPV and NPV for different cut-off values of GAPSS

	AUC	Sensitivity	Specificity	NPV	PPV	*P*-value
GAPSS cut off = 10	0.736	0.709	0.793	0.7705	0.7045	0.000
GAPSS cut off = 12	0.697	0.578	0.817	0.7206	0.7027	0.001
GAPSS cut off = 15	0.664	0.378	0.950	0.6706	0.8500	0.004

Rheumatology key messages

- GAPSS is based upon combinations of positive aPL tests and conventional cardiovascular risk factors.
- A combination of aPL tests should be considered when assessing the risk of thrombosis/PL in SLE.
- GAPSS represents an improvement in assessment of the risk of thrombosis/PL in SLE patients.

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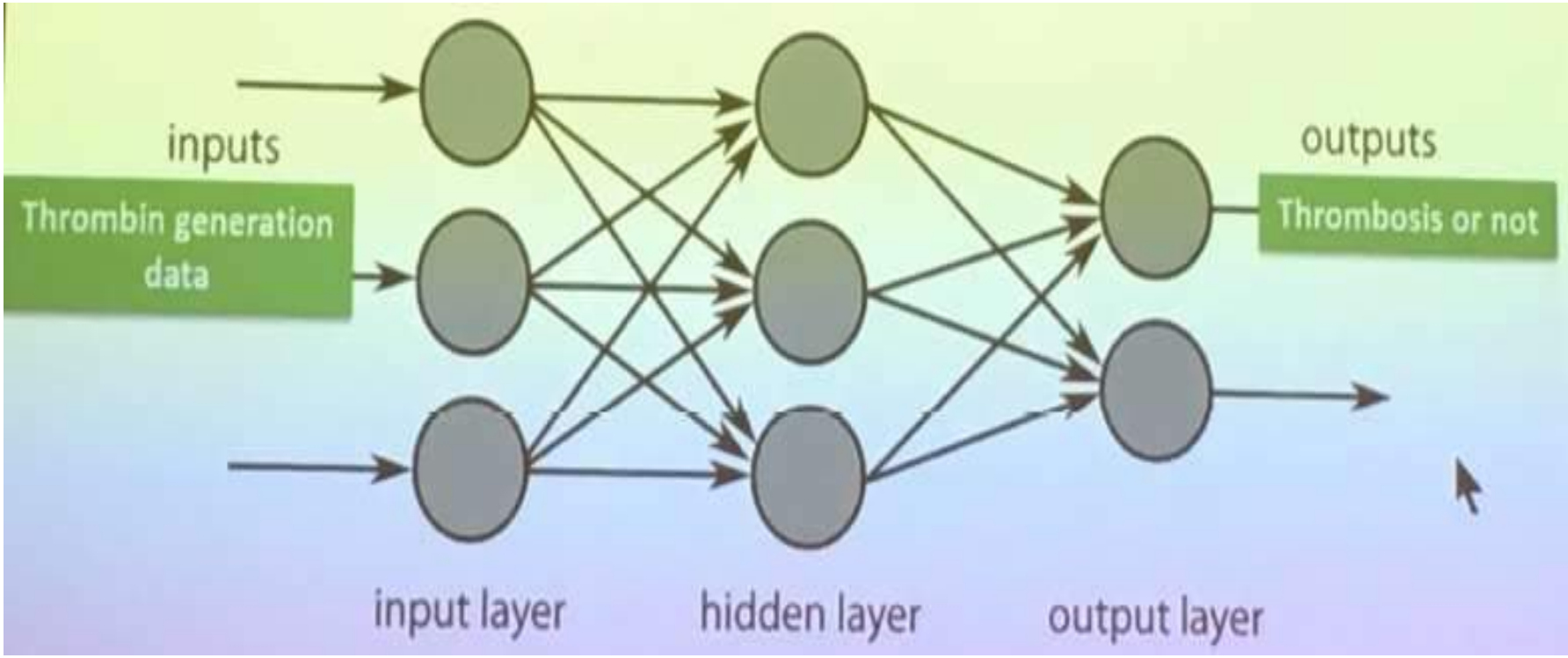
Inteligencia Artificial



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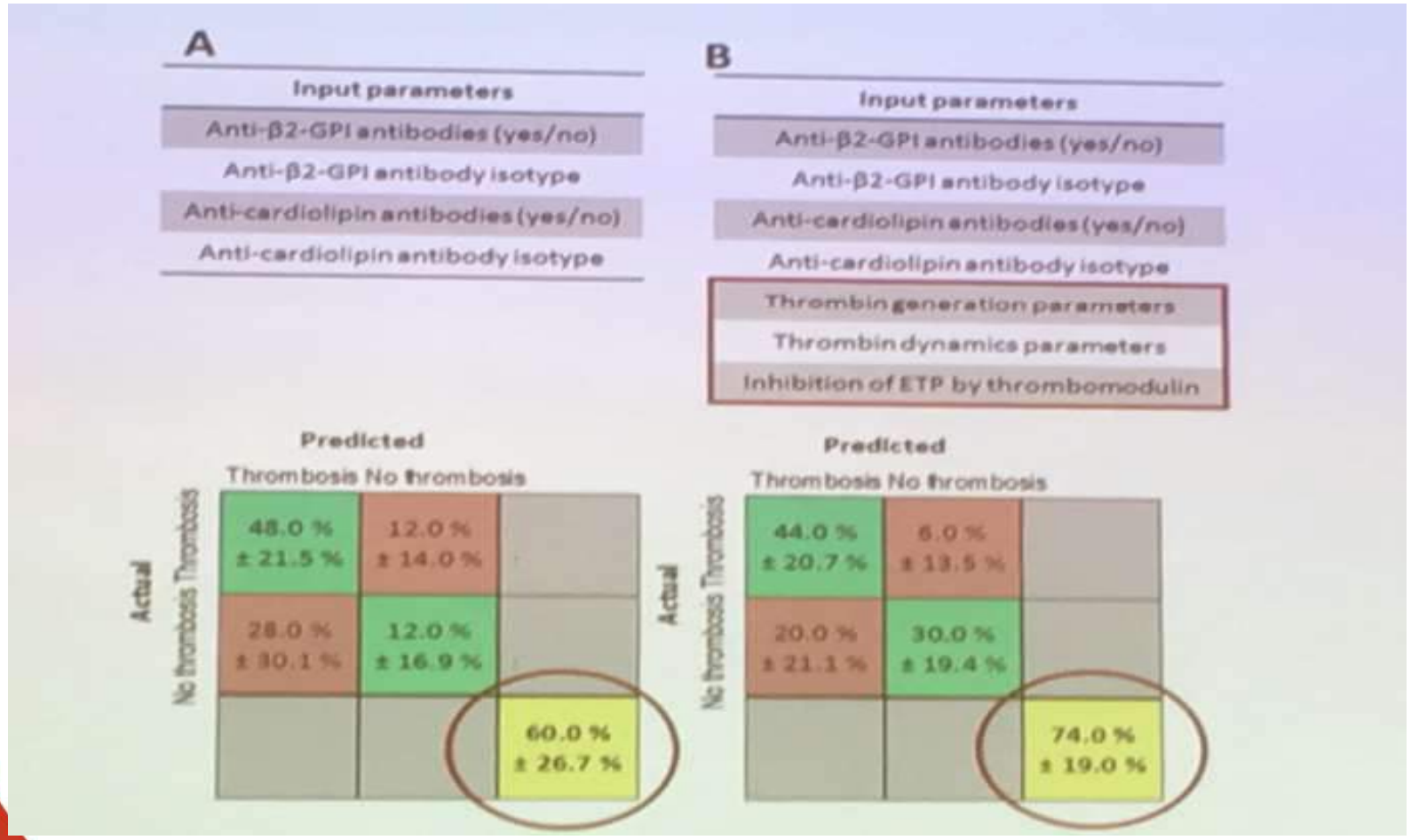
Predicción de Trombosis en SAF



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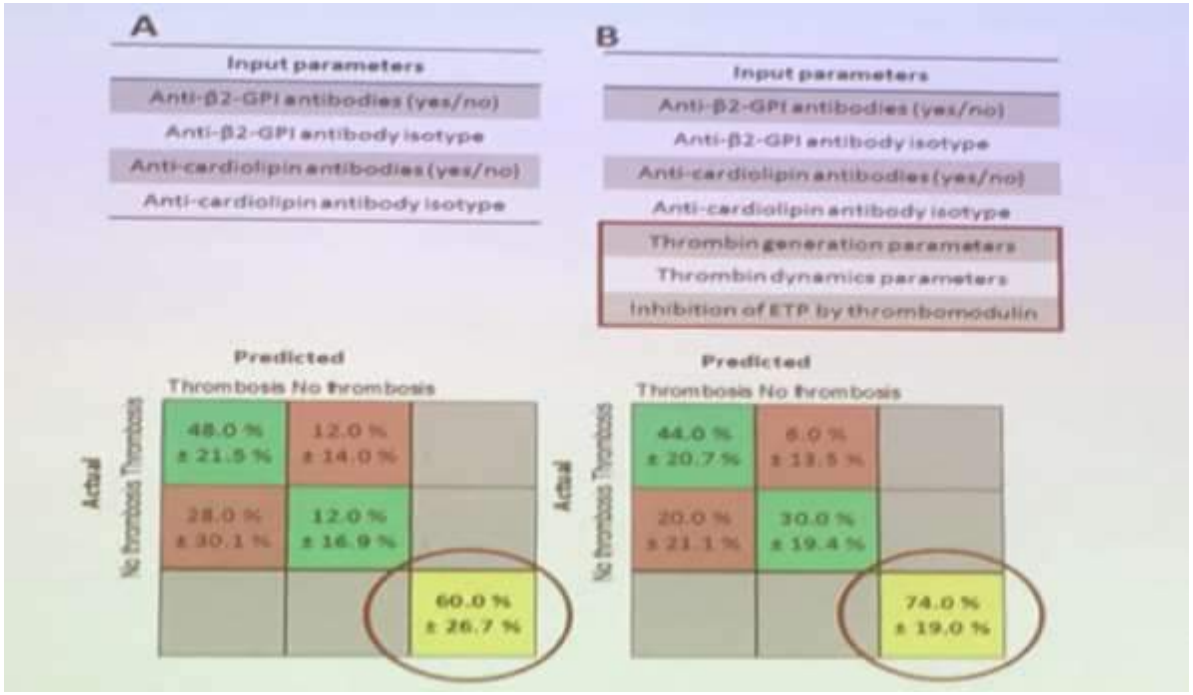
Predicción de Trombosis (Big Data)



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The antiphospholipid syndrome: still an enigma

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Diagnosis and management of the antiphospholipid syndrome

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Abstract

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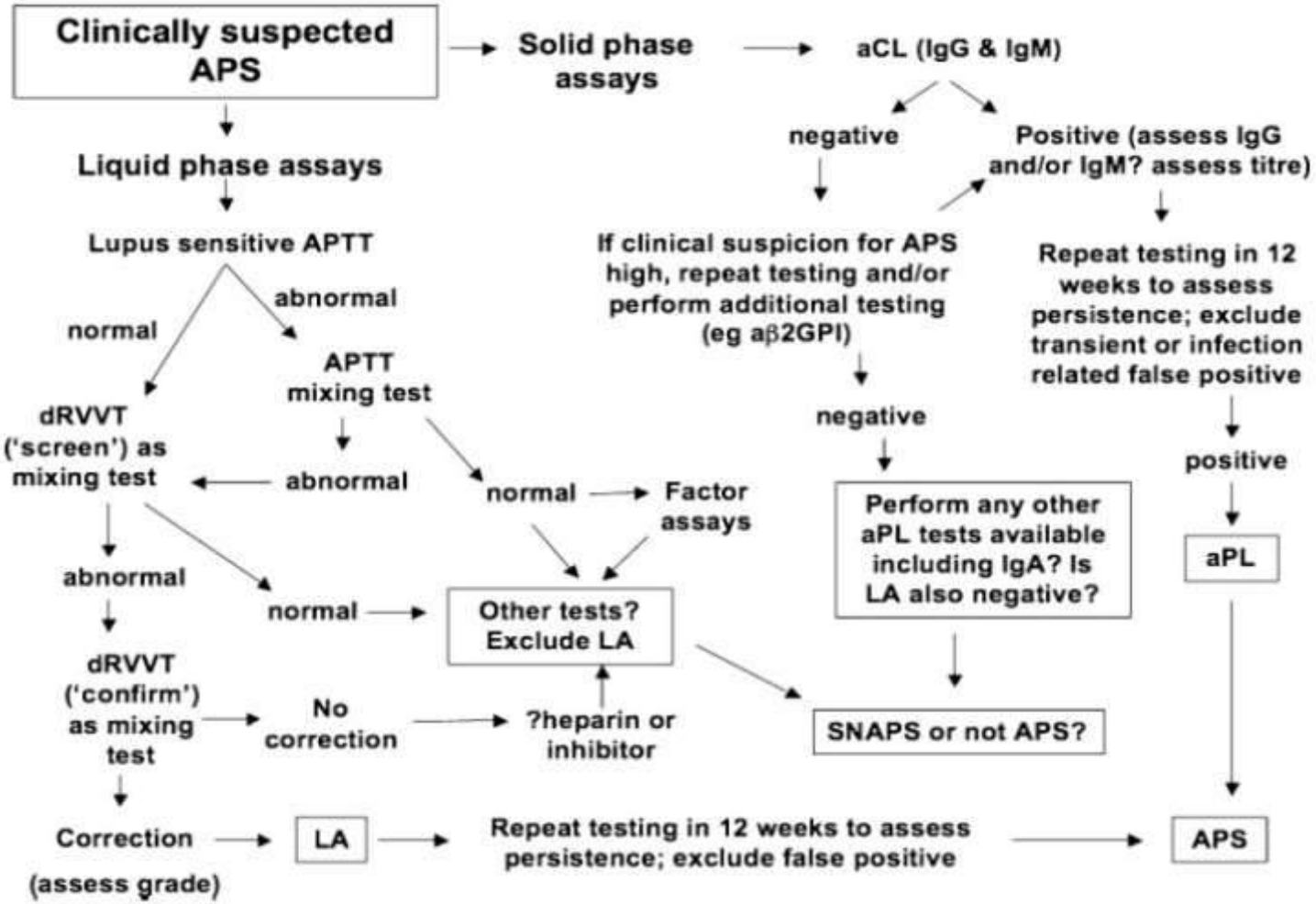
Clinically suspected APS
Solid phase assays
aCL (IgG & IgM)
negative
Positive (assess IgG and/or IgM? assess titre)
Liquid phase assays
Lupus sensitive APTT
abnormal
normal
APTT mixing test
dRVVT ('screen') as mixing test
abnormal
normal
Factor assays
abnormal
normal
Other tests? Exclude LA
dRVVT ('confirm') as mixing test
No correction
?heparin or inhibitor
Correction (assess grade)
LA
Repeat testing in 12 weeks to assess persistence; exclude false positive
APS
If clinical suspicion for APS high, repeat testing and/or perform additional testing (eg aβ2GPI)
negative
Perform any other aPL tests available including IgA? Is LA also negative?
SNAPS or not APS?
Repeat testing in 12 weeks to assess persistence; exclude transient or infection related false positive
positive
aPL