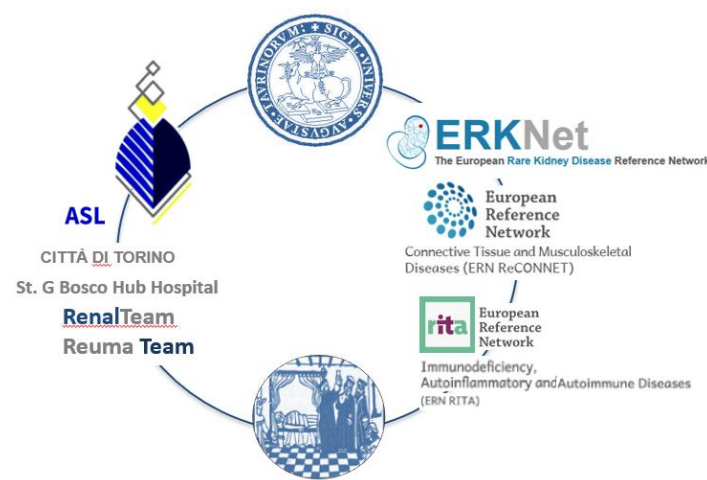




How do we manage APS patients when the aPL profile turns negative?

Savino Sciascia

***University Center of Excellence on Nephrologic, Rheumatologic and Rare Diseases (ERK-net, ERN-Reconnect and RITA-ERN Member) with Nephrology and Dialysis Unit and Center of Immuno-Rheumatology and Rare Diseases (CMID), Coordinating Center of the Interregional Network for Rare Diseases of Piedmont and Aosta Valley, San Giovanni Bosco Hub Hospital, and Department of Clinical and Biological Sciences of the University of Turin, Turin, Italy
Director Roberta Fenoglio***

Case: what to do when aPL turn negative?

Giorgio is a 54-year-old male who attends your clinic for a first consultation.

He is a mechanic and **ten years ago he had an episode of DVT** after a long day of intense physical work and dehydration.

- Congenital thrombophilia was ruled out
- No significant additional CV risk factors
- **Positive for LA**
- Started on long-term anticoagulant therapy with VKA (target INR 2-3).

He came to my clinic, he repeated the aPL screening testing:

Negative result for aCL and a β 2GPI antibodies and LA

Giorgio wants to know if he could **interrupt the anticoagulant treatment**

- 
- 
- Is the case of Giorgio a rare exception?
 - What is aPL negativization?
 - What evidence to support stopping VKA?

Is the case of Giorgio a rare exception?

Study, year	Criado-García et al. 2008	Medina et al. 2017	Comarmond et al. 2017	Bazàn et al. 2017
Study's design	Prospective	Retrospective	Retrospective	Retrospective
Patients	6 Primary APS	24 Primary APS	10 APS	7 Primary APS
Previous LA positivity (%)	16,70%	N/A	N/A	86%
Previous aCL (IgG/IgM) positivity (%)	100%	87,50%	N/A	28,60%
Previous anti-β2GPI (IgG/IgM) positivity (%)	0%	N/A	N/A	0%
Non Criteria aPL tested	N/A	anti-annexin A5 antibodies	N/A	N/A
Time of aPL positivity (months)	10-53	109,4 ± 80,7	N/A	At least two aPL determinations, performed 12 weeks apart
Mean time of anticoagulation therapy (months)	25 ± 18	N/A	21 (9–118)	111 ± 52,4
Definition of aPL negativization	2 consecutive negative determinations	≥2 subsequent negative aPL determinations, retested after 5 years	N/A	At least nine negative determinations
Follow up after anticoagulation discontinuation (months)	21 ± 12	60	19 (4–66.75)	18
Recurrences at follow-up	None	45.8%: DVT in 37,5%, ischemic stroke in 4,2%	One out of 10 patients (10%) relapsed developing PE	None

What evidence to support stopping VKA?

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Concise report

Prevalence, outcome and management of patients with SLE and secondary antiphospholipid antibody syndrome after aPL seroconversion

Margherita Zen¹, Marta Loreda Martinez², Francesco Benvenuti¹,
Mariele Gatto¹, Francesca Saccon¹, Maddalena Larosa¹, Luca Iaccarino¹ and
Andrea Doria ¹

Fifty-five out of 513 (10.7%) SLE patients had vascular SAPS.
Sixteen patients (**29.1%**) became aPL seronegative during follow-up.

Immunosuppressive therapy predicted aPL
negativization

APS diagnosis prior to that of SLE & triple-positive profile
→ negative predictors of aPL negativization.

OAC was discontinued in 13/55 patients (23.6%)
→ No thrombotic recurrences mean follow-up time of 44 months



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journal homepage: www.elsevier.com/locate/autrev

Review

Deciphering the clinical significance of longitudinal antiphospholipid antibody titers

Cecilia B. Chighizola^{a,*}, Rohan Willis^b, Gabriella Maioli^c, Savino Sciascia^d, Laura Andreoli^e, Olga Amengual^f, Massimo Radin^d, Maria Gerosa^c, Tatsuya Atsumi^f, Guilherme de Jesus^g, Laura Trespidi^h, D. Ware Branchⁱ, Roberto Caporali^{a,c}, Danieli Andrade^j, Robert Roubey^k, Michelle Petri^l, Maria Laura Bertolaccini^m

Rates of seroconversion of antiβ2 glycoprotein I antibodies in available studies.

Author, year [REF]	Follow-up	N of patients	Study cohort composition	Rate of seroconversion*
Amory, 2016 [16]	24 months	147	Anti-β2GPI +	16.3%
Yelnik, 2017 [8]	13 years	39	Anti-β2GPI +	23%
Frodlund, 2021 [17]	36 months	50	Recent-onset SLE	8%
Chighizola, 2023 [4]	4 years	170	aPL+	Antiβ2GPI IgG: 7.1% Positive → negative: 6.5% Negative → positive: 0.6%

N: number; aPL: antiphospholipid antibodies; SLE: systemic lupus erythematosus; antiβ2GPI: antiβ2 glycoprotein I antibodies.

* If not otherwise detailed, the rate of seroconversion refers to aPL-positive patients turning negative.

- **Single aPL** positivity are more prone to experiencing aPL negativization Vs triple positive individuals
- aCL or antiβ2GPI **at low titers**, tests are also more likely to become negative in subsequent assays
- Seroconversion is more likely seen in **asymptomatic aPL carriers** Vs full-blown APS



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- **Single aPL** positivity are more prone to experiencing aPL negativization Vs triple positive individuals
- aCL or antiβ2GPI **at low titers**, tests are also more likely to become negative in subsequent assays
- Seroconversion is more likely seen in **asymptomatic aPL carriers** Vs full-blown APS

Very few studies have addressed the stability of LA.

Among 98 aPL carriers (59 with baseline positive LA) a repeat LA assay turned out negative in **22% of cases**.

In a cohort of 53 patients: fluctuating LA was in **32%**.

Prevalence of Antiphospholipid Antibodies Negativisation in Patients with Antiphospholipid Syndrome: A Long-Term Follow-Up Multicentre Study

Massimo Radin^{1,*} Karen Schreiber^{2,3,*} Savino Sciascia¹ Dario Roccatello¹ Irene Cecchi¹
María Ángeles Aguirre Zamorano⁴ Maria Jose Cuadrado⁵

DEFINITION OF aPL NEGATIVIZATION

Subsequent to APS diagnosis, negativization of aPL antibodies defined as:

1. At least **two** negative aPL consecutive tests
 2. At least **12 weeks** apart
 3. With a follow-up of at least **one year** since aPL firstly turned negative.
-

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259 patients with definite APS:

we observed a rate of **9% (N=23) of aPL negativisation**

- Most of patients (78.3%) had a single aPL positivity
 - No triple positive patients
 - Only 2 patients had aPL at high titres (IgG/M $\geq$ 80 U/ml)
-

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→ aPL negativization

- It is not a negligible fact in the routine clinical practise
- It mainly occurs in patients with **low-risk aPL profile** at diagnosis.

What evidence to support stopping VKA?

Treatment and Follow-up

- At the time of data collection, after aPL negativization:
- 15 patients $\longrightarrow$ still on anticoagulation
- 8 patients $\longrightarrow$ anticoagulation was suspended
(according to treating physicians' judgement)

Treatment and Follow-up

All 8 patients in whom anticoagulation was stopped:

- History of thrombotic **venous** events
- VKA was stopped and low-dose aspirin started
- After a median follow up time of 3.2 years (± 1.5) after withdrawal of anticoagulation, **no recurrence** of thrombotic events was observed

(nor now after 5,5 years additional years of F/U)

Limits and Strengths

Limits

- Retrospective design
- Potential heterogeneity in laboratory testing on three different centres
- Changes of sensitivity of different assays during time

—————→ *standardization of aPL testing*

Strengths

- Sample size
- Stringent inclusion criteria and the precise definition of aPL negativization
- Length of follow-up before and after aPL negativization

What is known about this topic?

- The rate of antiphospholipid antibody (aPL) negativization in antiphospholipid syndrome (APS) patients is uncertain, but it is estimated to be as high as 8%.
- A consensus definition of aPL negativization is lacking, as well as international recommendations on how to approach treatment in patients with a persistent aPL-negative seroconversion.

What does this paper add?

- SIR-APS (APS Study Group of the Italian Society for Rheumatology) committee agrees on defining aPL negativization as the presence of two negative determinations, 1 year apart.
- Pragmatic clinical scenarios on how to approach APS patients with aPL negativization.
- Type of previous thrombotic event, number of previous aPL positivity, presence of cardiovascular risk factors, and evaluation on “*extra criteria*” aPL positivity are important variables to consider before deciding to interrupt vitamin K antagonist therapy.

What is aPL negativization?

Accepted Manuscript online: 2022-03-15 Article published online: 2022-06-28

1612 Stroke, Systemic or Venous Thromboembolism

Clinical Delphi on aPL Negativization: Report from the APS Study Group of the Italian Society for Rheumatology (SIR-APS)

Savino Sciascia^{1,*} Silvia Grazietta Foddai^{1,*} Cristiano Alessandri² Alessia Alunno³ Laura Andreoli⁴ Alice Barinotti¹ Antonia Calligaro⁵ Valentina Canti⁶ Francesco Carubbi³ Irene Cecchi¹ Cecillia B. Chighizola⁷ Fabrizio Conti² Giacomo Emmi⁸ Antonella Fioravanti⁹ Fabio Fischetti¹⁰ Franco Franceschini⁴ Maria Gerosa⁷ Ariela Hoxha¹¹ Maddalena Larosa¹² Maria-Grazia Lazzaroni⁴ Cecilia Nalli⁴ Giulia Pazzola¹³ Massimo Radin¹ Bernd Raffener¹⁴ Veronique L. Ramoni¹⁵ Elena Rubini¹ Gian Domenico Sebastiani¹⁶ Simona Truglia² Maria Letizia Urban⁸ Dario Roccatello¹ Angela Tincani⁴

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What do to before considering stopping anticoagulation?

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Risk assessment & new antibody specificities

aCL IgG/M
anti- β 2GPI IgG/M

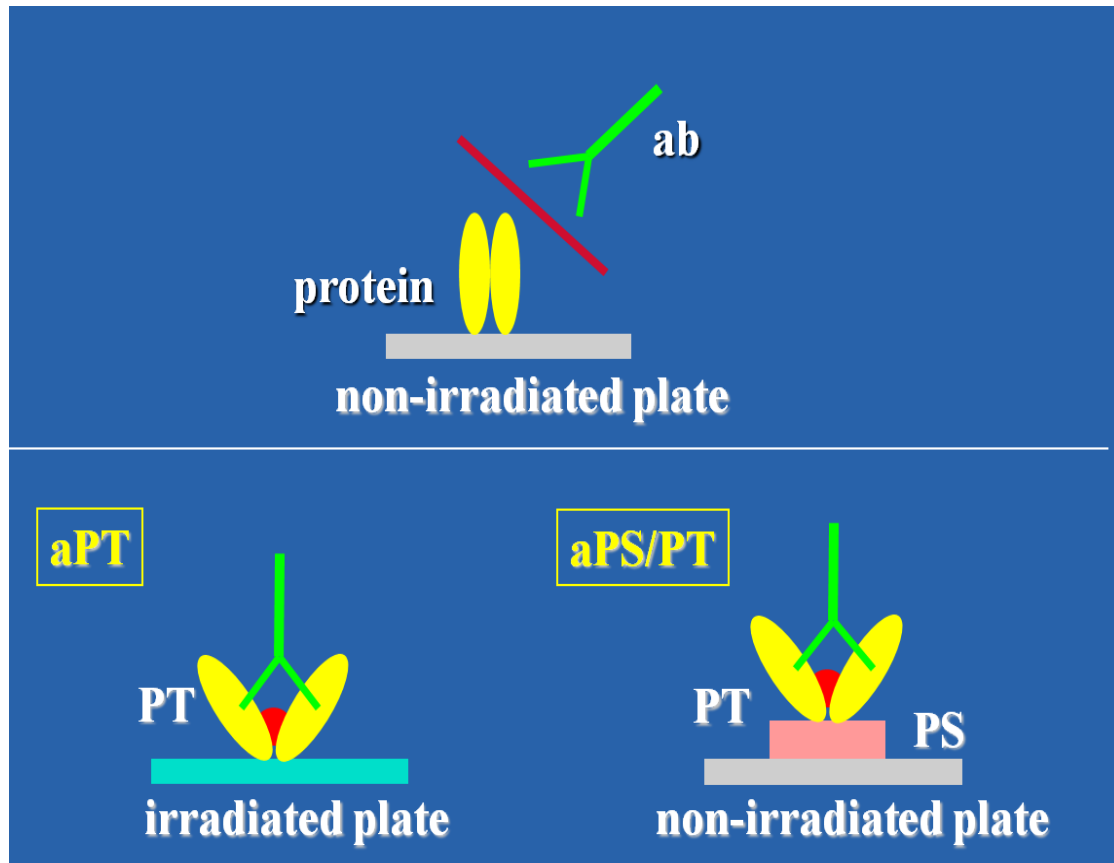
LA

aCL IgA
anti- β 2GPI IgA

anti-phosphatidylinositol
anti-phosphatidylserine
anti-phosphatidylethanolamine
anti-phosphatidic acid
anti-prothrombin
anti-phosphatidylserine-prothrombin
anti-vimentin/cardiolipin complex
APhL ELISA assay

Annexin A5 resistance

Anti-prothrombin Antibodies

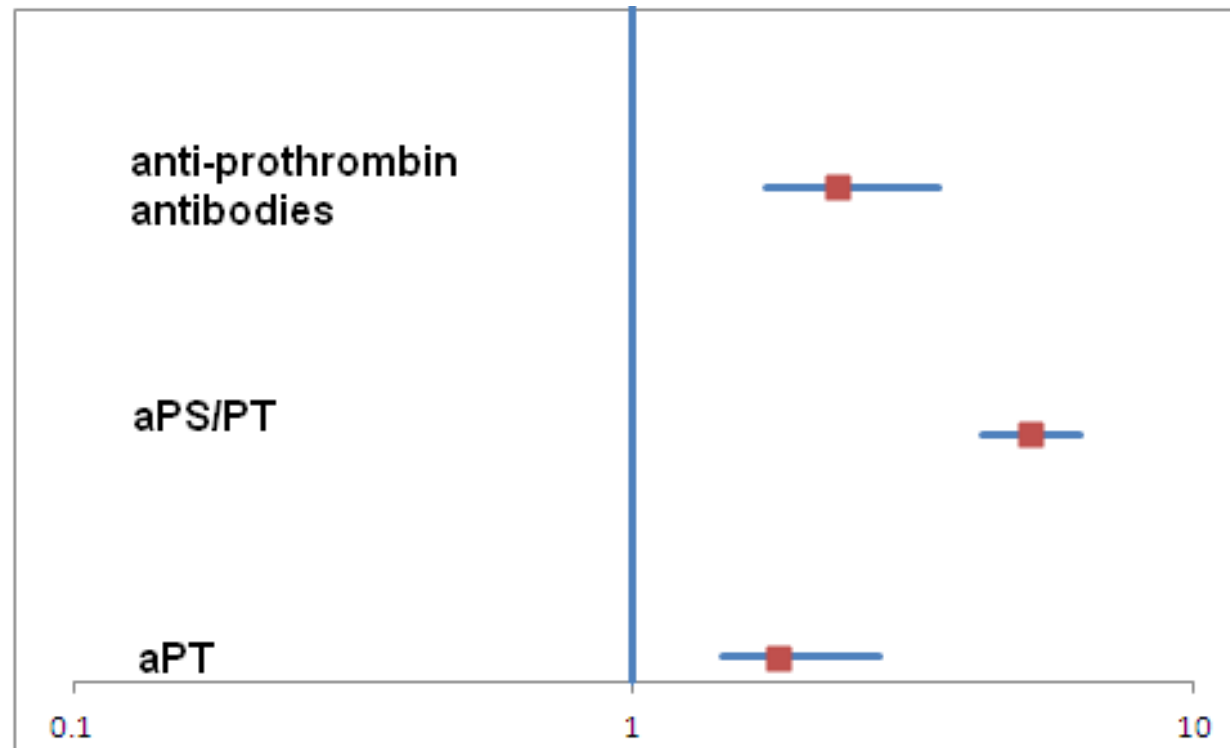


Detected by two systems:

- directly coating prothrombin on irradiated ELISA plates (**aPT**)
- using phosphatidylserine/prothrombin complex as antigen (**aPS/PT**)

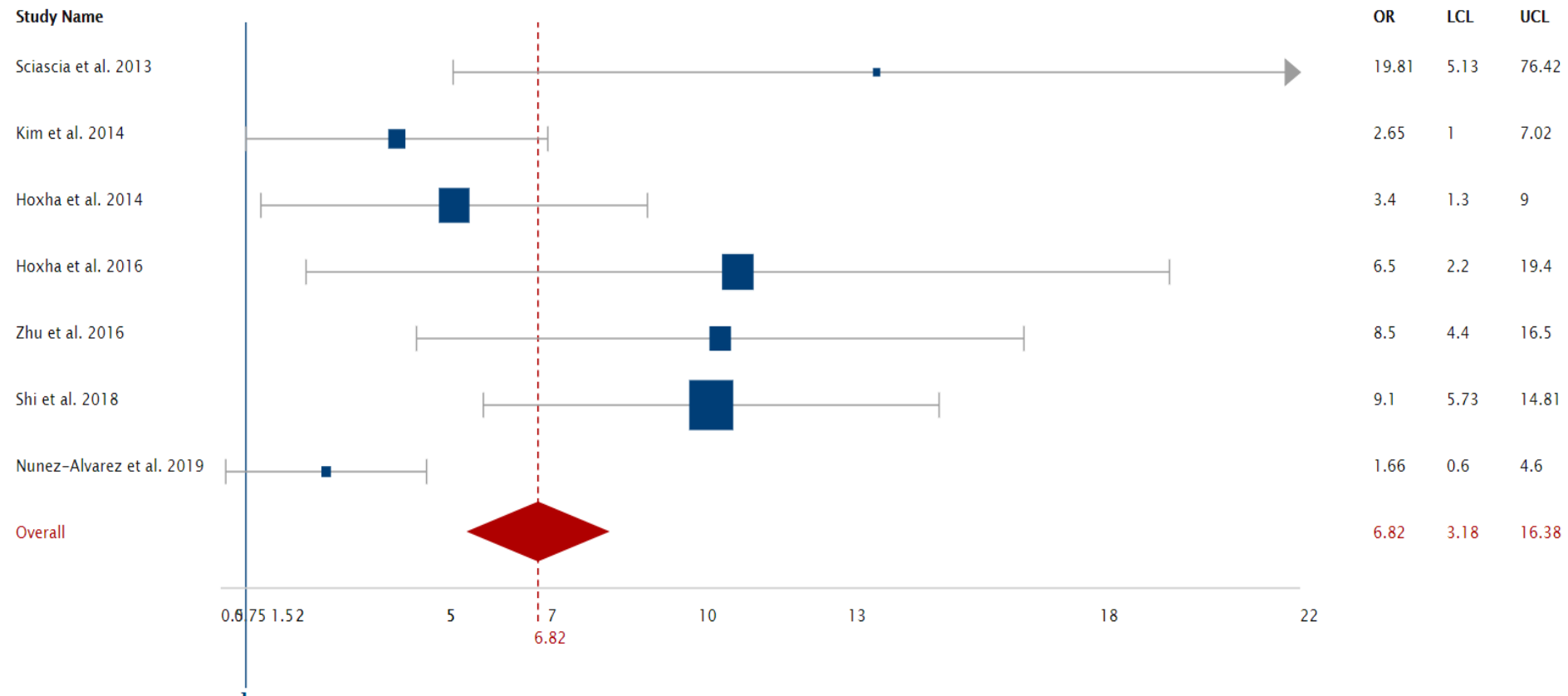
aPT and aPS/PT in thrombosis

- Analysed studies provided information on 6006 patients and 1422 controls.
- Four prospective studies contributed with 417 patients.



aPT and aPS/PT in thrombosis

Thrombosis



Review Article

Prevalence of aPhosphatidylserine/prothrombin antibodies and association with antiphospholipid antibody profiles in patients with antiphospholipid syndrome: A systematic review and meta-analysis

Rui Zhu ^{a,b,1}, Chun-Yan Cheng ^{c,1}, Yan Yang ^b, Gentian Denas ^c, Vittorio Pengo ^{c,d,*}

^a International PhD Program in Arterial Hypertension and Vascular Biology (ARHYVAB), University of Padua, Padua, Italy

^b Department of Endocrinology, Sichuan Academy of Medical Sciences & Sichuan Provincial People's Hospital, Chengdu, China

^c Thrombosis Research Laboratory, Department of Cardio-Thoracic-Vascular Sciences and Public Health, University of Padua, Padua, Italy

^d Arianna Foundation on Anticoagulation, Bologna, Italy



IgG OR: 2.7-12.7
IgM OR: 3.1-36.0
IgG/M OR: 2.6-14.0

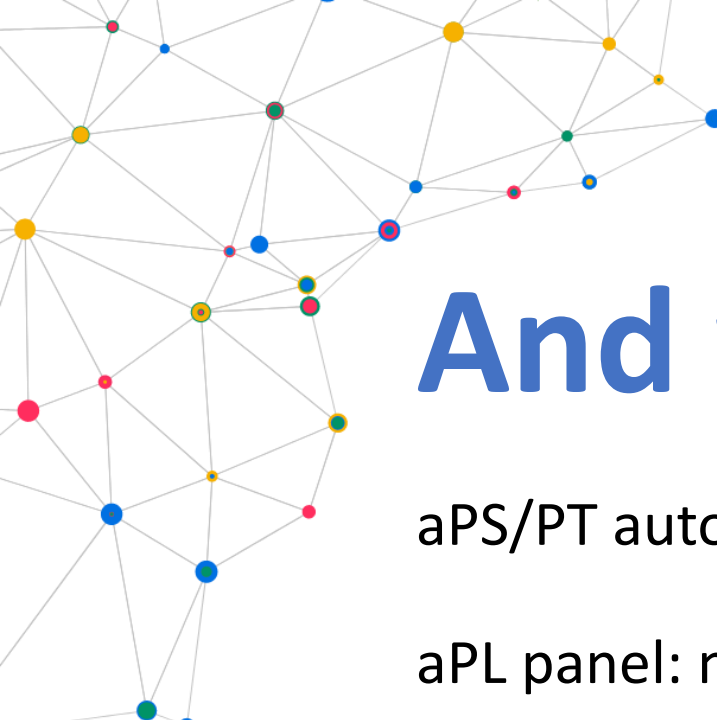
Table 5
Association of aPS/PT and clinical manifestations in APS.

Author, year	Clinical manifestations	APS vs controls	aPS/PT IgG			aPS/PT IgM			aPS/PT IgG/M		
			Positivity	OR	P	Positivity	OR	p	Positivity	OR	p
Amengual, 2017 [10]	Thrombosis	APS (n = 59) vs non-APS (n = 58)	30 (51%) vs 4 (9%)	11.0	<0.001						
	-Arterial	APS (n = 30) vs non-APS (n = 58)	13 (43%) vs 4 (9%)	8.1	<0.001						
	-Venous	APS (n = 33) vs non-APS (n = 58)	18 (55%) vs 4 (9%)	12.7	<0.001						
	Obstetric complications	APS (n = 40) vs non-APS (n = 58)	20 (50%) vs 4 (9%)	10.6	<0.001						
Atsumi, 2000 [29]	All clinical complications	APS (n = 62) vs SAD (n = 203)	13 (21%) vs 16 (8%)	3.1	0.008				16 (26%) vs 18 (9%)	3.6	0.001
Bertolaccini, 2005 [20]	Thrombosis	APS-SLE (n = 56) vs SLE (n = 56)	26 (46%) vs 5 (9%)	9.0	<0.001	22 (48%) vs 1 (2%)	36.0	<0.001	35 (63%) vs 6 (11%)	14.0	<0.001
Hoxha, 2017 [23]	Thrombosis	TAPS (n = 111) vs OAPS (n = 56)	37 (33%) vs 4 (7%)	6.5	<0.05	62 (56%) vs 14 (25%)	3.8	<0.05			
Kim, 2014 [25]	Thrombosis	APS (n = 25) vs non-APS (n = 109)	11 (44%) vs 30 (28%)	2.7	<0.05	10 (40%) vs 15 (14%)	3.1	<0.05	14 (56%) vs 30 (28%)	2.6	<0.05
Shi, 2018 [32]	Thrombosis	APS (n = 186) vs non-APS (n = 224)	N.A.	10.5	<0.001	N.A.	4.2	<0.001	N.A.	9.1	<0.001
	Obstetric complications	APS (n = 186) vs non-APS (n = 224)	N.A.	5.7	<0.001	N.A.	4.7	<0.001	N.A.	10.4	<0.001

APS, antiphospholipid syndrome; aPS/PT, anti-phosphatidylserine/prothrombin antibodies; N.A., not available; OR, odds ratios; OAPS, APS patients with obstetric complications; SAD, systemic autoimmune diseases; TAPS, APS patients with thrombosis alone.

aPS/PT pathogenicity





And what about Giorgio?

aPS/PT autoAb IgG/M negative

aPL panel: negative (both in ELISA and CLIA). LA neg.

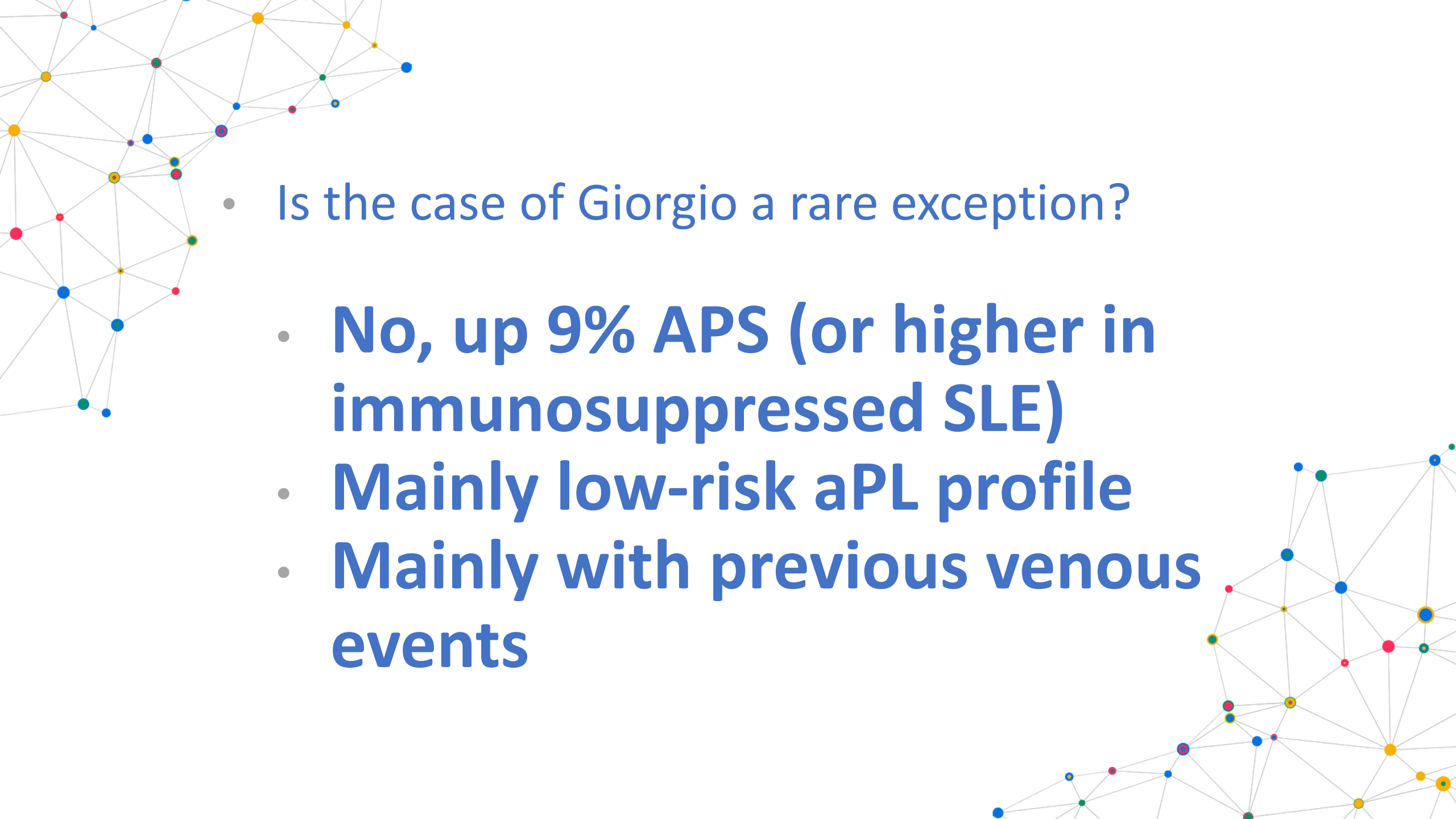
48 months after stopping VKA

Giorgio is well, did not experience any further DVT

He is still in follow-up and he is monitored for CV risk factors

He is aware that in he should received LMHW in case of high-risk situations



- 
- Is the case of Giorgio a rare exception?
 - **No, up 9% APS (or higher in immunosuppressed SLE)**
 - **Mainly low-risk aPL profile**
 - **Mainly with previous venous events**



What is aPL negativization?

- **At least two negative aPL consecutive tests at least 12 months apart**
 - **Heterogeneity in aPL assays exists**
- 



What evidence to support stopping VKA?

- **Limited, BUT**
 - **No consistent trend for recurrences in recent studies (the opposite)**
- 



What evidence to support stopping VKA?

- **Consider CV risk profile**
 - **Consider extra-criteria aPL**
 - **LMHW in high-risk situations**
 - **Consider hemorrhagic risk on VKA**
- 